Protocol For A Smartphone Based Automated Directly Observed Treatment Improves Adherence and SVR to Fixed-Dose Elbasvir and Grazoprevir in PWIDs: A Randomized Controlled Trial

People who Inject Drugs (PWIDs) constitute 60% of the approximately 5 million people in the United States infected with hepatitis C virus (HCV). Successful HCV treatment leading to sustained viral response (SVR) is associated with increased survival, but to date successful treatment of PWIDs has been limited. Treatment of PWIDs is complex due to addiction, mental illness, poverty, homelessness, lack of positive social support, poor adherence-related skills, low motivation and knowledge, and poor access to and trust in the health care system. At Albert Einstein College of Medicine, we have developed a multidisciplinary model of HCV care that integrates on-site primary care, substance abuse treatment, and HCV-related care within opiate agonist treatment clinics. To optimize HCV treatment outcomes, we have introduced directly observed therapy (DOT). In our DOT model, one daily dose of oral HCV medication is administered with methadone. However, DOT is not feasible for PWIDs who are not enrolled in methadone maintenance treatment programs, and is less effective for methadone-maintained PWIDs who do not attend the methadone clinics every day. In addition, DOT has been used for decades both to measure and maximize adherence for treatment of tuberculosis infection, but the cost and logistical complexity of administering DOT for large HCV clinical programs would be prohibitive.

Automated DOT (a-DOT), a smartphone app that uses facial recognition software and advanced features to detect noningestion, combines the accuracy of in-person DOT with the convenience of real-time centralized data collection and monitoring. Adding a daily side effect diary to a-DOT will further allow precise tracking of timing of both medication ingestion and side effects which may be compromising adherence. Zepatier (elbasvir and grazoprevir) is a new once-daily fixe-dose combination tablet which has achieved high rates of SVR ranging from 94 to 97 percent in genotype-1 infected patients including those with HIV/HCV coinfection and renal impairment. Zepatier is administered for 12 to 16 weeks, depending on HCV genotype, prior treatment history, and the presence of certain baseline NS5A polymorphisms (1a only). By administering Zepatier via this innovative a-DOT platform, we hypothesize that PWIDs treated in real-wrold settings can be successfully treated with high rates of adherence and SVR.

In this proposed 18-month trials, 75 PWIDs enrolled in opiate agonist treatment (genotypes 1a and 1b) with chronic HCV will be enrolled over a 12-month period, and randomized to either aDOT or treatment as usual (TAU). **We will recruit PWIDs from diverse community settings include a syringe exchange program (NYHRE), federally-qualified health center (Comprehensive Health Care Center), homeless shelter (The Living Room), and a methadone maintenance treatment program (Montefiore Wellness Centers).** All patients (inlcuding treatment-experienced and HIVV/HCV coinfected subjects) will be treated with Zepatier-based regimens as per the standard of care. Rigorous data are necessary to judge the contribution of a-DOT to the success of HCV treatment in PWIDs. By performing a randomized trial of a-DOT HCV therapy (Zepatier with and without ribavirin), we will evaluate the efficacy of a-DOT for improving HCV treatment outcomes among PWIDs.

1. **To determine in a randomized trial whether HCV treatment delivered via a-DOT (Zepatier with and without ribavirin) provided on-site at community treatment programs during a 12-week study period is more efficacious than self-administered HCV treatment for enhancing adherence and SVR in PWIDs.** 75 subjects will receive Zepatier will be randomized to take medications by either treatment as usual (self-administration), automated directly observed therapy (a-DOT), or a-DOT with gamification (25 subjects in each arm). Those in the a-DOT arm will be observed taking their Zepatier dose by the smart-phone based interface. We hypothesize that adherence and SVR will be higher in a-DOT versus TAU subjects, and that SVR in a-DOT arm will be equivalent to SVR seen in registration trials.
2. **To evaluate the feasibility and acceptability of a-DOT to both participants and HCV providers in tracking longitudinal patterns of adherence and providing adherence feedback in real-time.** We hypothesize that a-DOT will be highly acceptable to both participants and medical providers.
3. **To determine whether gaming features added to the aDOT platform enhance adherence compared to standard aDOT.** For the 25 subjects randomized to the aDOT + gamification arm, subjects will compete with other subjects within this arm for modest cash incentives. Those with highest levels of adherence measured at monthly research visits compared to their peers will earn additional incentives.

4. **To determine the impact of ongoing drug use (cocaine, opiates, or benzodiazepenes) and on HCV virologic outcomes in subjects receiving Zepatier by aDOT.** We hypothesize that ongoing drug use during HCV treatment will not be associated with adherence in subjects randomized to a-DOT.

B. APPROACH

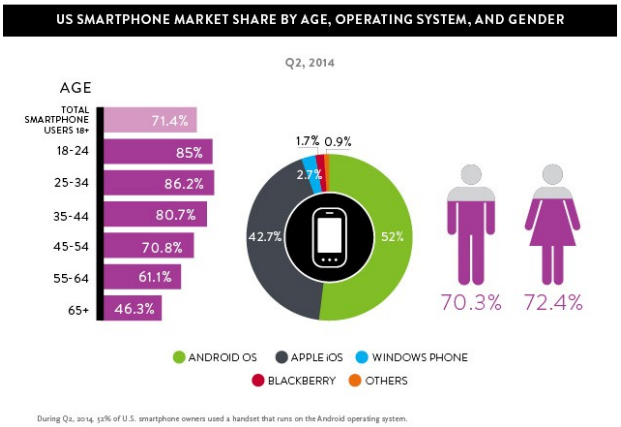
B.1. Preliminary Studies

B.1.1. Overview of the research team. Dr. Alain Litwin has focused on defining optimal models of HCV care for PWIDs over the last 15 years, and is expert in treating HCV in PWIDs, methadone and buprenorphine-maintained patients, and active drug users.

Monitoring and improving adherence to antiviral therapy in real world settings requires methods that address varied challenges in treating high-risk populations. While accuracy is paramount, cost, ease of deployment, desirability, scalability, privacy, and flexibility are also important for ensuring wide-scale utility.

AiCure's HIPAA-compliant platform uses artificial intelligence software to automate DOT on smartphones (see aicure.com/video). The system works through a webcam to automatically confirm that the right patient is taking the right medication at the right time, using security features to identify evidence for cheating; biometrics used to confirm patient identity also protect against duplicate enrollment and multiple registration of users with same or similar names. Unlike video dosing, no human review is needed. Medication adherence data are automatically transferred to a centralized cloud-based dashboard for real-time analysis. These data are encrypted, blurred, and stored, creating a real-time audit trail of every dosing; all protected health information (PHI) is encrypted and withheld from view on the dashboard. Secure communications (voice over IP, text messaging, email) are systematically logged. The software platform can also be used for training and intervention, tailored to individual adherence profiles, and translated into other languages.

D² leverages existing and desirable consumer-grade technology to accurately collect data and provide a 2-way communication platform between study staff and participants. Unlike other measurement tools that require additional hardware (e.g., electronic pill bottles) or microchip-embedded pills, a-DOT uses software that can be downloaded onto smartphones, making it scalable, cheap, and easily integrated into everyday life. Smartphone penetration has doubled in the last three years to 75% in the US. Younger people, African Americans, and Latinos are most likely to own a smartphone, and more likely to download apps than other groups. Globally, smartphones will account for two out of every three mobile connections by 2020.

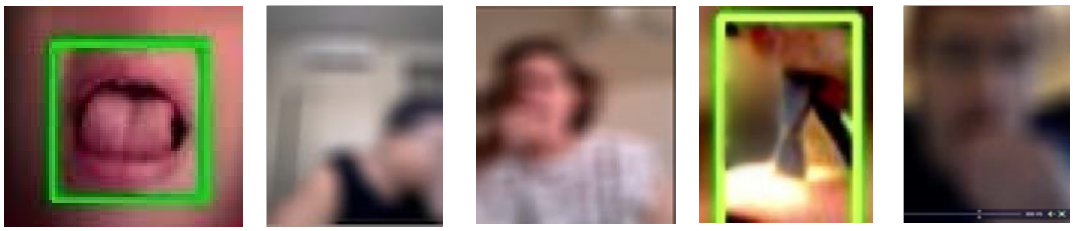


a-DOT software will integrate collection of side effects with measurement of adherence. A-DOT software is easily tailored to collect side effects that may decrease adherence and lead to treatment interruptions.

The accuracy of a-DOT has been previously evaluated by AiCure in two medication trials: a 6-month study of schizophrenic patients and a 12-week study of substance users. In each trial, the artificial intelligence system automatically analyzed the visual data to confirm correct medication dosing. Face tracking was used to ensure the patient did not leave the visual field, and face recognition was used to check for duplicate enrollment and substitute pill-takers. To evaluate accuracy, human reviewers manually inspected the results generated by the system and classified each as correct or incorrect. **In an analysis of 8700 separate dosings, a-DOT demonstrated >97% accuracy across multiple steps of the algorithm** (Tabl). A-DOT adherence rates were consistent with pharmacokinetic (PK) data, with lower a-DOT adherence among those with low or no detectable drug at one or more visits. A-DOT was also able to identify able to identify patients with evident patterns of cheating, including curving the tongue, leaving the field of view, putting hand to mouth, or having tampered with or spitting out medication (Figure 6). On the basis of these data, AiCure has developed a second generation system incorporating additional surveillance and learning technologies to further increase sensitivity to cheating.

Step (Accuracy of a-DOT - N=53)	Accuracy
Face tracking	98.0%
Patient consistency check	97.8%
Patient duplicate check	97.8%
Pill identification	97.3%
Pill in mouth confirmation	97.6%
After drinking water, no pill visible in mouth	98.9%

Figure 6. Examples of "cheating" in pill ingestion detected by a-DOT



B.1.2. Study of HCV treatment in IDUs. In 2001, Dr. Litwin collaborated on a multi-site study of the safety and efficacy of thrice-weekly IFN and ribavirin in PWIDs. The model of care included multidisciplinary treatment with on-site HCV care, substance abuse treatment, and psychiatric care. Subjects self-administered both medications, and 28% achieved SVR. We concluded that PWIDs can be safely and effectively treated despite multiple barriers to treatment. However, SVR was lower than would be expected in a large registration trial where projected SVR would be 51%, given the same proportion of genotypes.

B.1.3. Study of HCV treatment in methadone patients. In 2003, we adapted our on-site multidisciplinary HCV program to include directly-administered weekly pegylated IFN in addition to screening, assessment of treatment eligibility, psychiatric services, and on-site antiviral therapy. Of 73 patients, most were Latino (67%) or African-American (12%), nearly half (49%) had used illicit substances in the 6 months before initiating treatment, 32% were HIV-infected, and current psychiatric illness was common (67%). Most (86%) completed 12 weeks of HCV treatment and 45% achieved SVR, including 40% of genotype-1 patients. Though 30% used illicit drugs during HCV treatment, there was no association between illicit drug use and virological outcomes. These results demonstrate that IDUs with complex medical and psychiatric comorbidities can be effectively treated for HCV with co-located on-site care. However, it is unknown which interventions (multidisciplinary on-site care v. DOT injections) contributed to the observed outcomes.

B.1.4. Pilot RCT of directly observed HCV treatment in methadone patients. In 2008 we began a pilot RCT (K23 DA022454, PI: Litwin) of modified DOT (mDOT) which extended our DOT strategy to the oral medication ribavirin. We designed this trial to test the efficacy of 2 versions of mDOT. Our primary objective was to determine whether enhanced DOT with both IFN plus ribavirin is more efficacious than standard DOT with weekly provider-administered IFN and self-administered ribavirin for improving adherence. We have completed the study (n=80), and we observed significant differences in pill count adherence between the treatment arms (88% in mDOT arm vs. 77% in the treatment as usual, or TAU arm, p=0.02). In addition, 81%

of mDOT subjects achieved ≥ 80% adherence v. 53% in the TAU arm (p=0.09). Only 16% discontinued treatment, and among genotype-1 infected patients, 55% achieved SVR (half active drug users). We have an ongoing NIH-funded study of all-oral HCV treatment delivered by DOT at the methadone program; SVR has exceeded 80% with sofosbuvir-based regimens in combination with ribavirin (with and without IFN).

B.2. Overview of study approach. In the proposed study, 75 HCV-infected genotype-1 infected PWIDs eligible for on-site HCV treatment with Zepatier will be recruited from diverse community settings, and randomized to either aDOT (n=25), aDot + gamification (n=25), or TAU (n=25). We will measure adherence with pill counts in both arms and with the a-DOT interface in the a-DOT arm. All subjects will be treated with the standard regimens for 12 weeks based on subtype, baseline NS5a polymorphisms and treatment history. For this study we will not enroll patients taking Ribavirin.

- G1a: Treatment-naïve or PegIFN/RBV-experienced without baseline NS5A polymorphisms: Zepatier for 12 weeks

- G1b: Treatment-naïve or PegIFN/RBV-experienced: Zepatier for 12 weeks

B.3. Setting: Montefiore and Einstein Division of Substance Abuse (DoSA). DoSA is a clinical, research, and teaching division of Einstein's Department of Psychiatry and Behavioral Sciences. DoSA operates a comprehensive substance abuse treatment program providing pharmacotherapy and related services to about 4200 adults (≥18 years) with current narcotic addiction (typically heroin). The primary focus is treatment of opiate dependence with methadone, and the average methadone pick-up schedule is 5 times per week. At present, DoSA operates three large clinics in three Bronx communities. The treatment paradigm relies on integrating general and HCV- and HIV-related medical, substance abuse, and mental health services under one roof. Multiple RCTs have been conducted in DoSA. Both recruitment and research visits will occur at DoSA. With Dr. Litwin (HCV Medical Director), participant recruitment and private office space for research visits will be ensured. We have established treatment programs and/or partnerships with three additional programs: **syringe exchange program (New York Harm Reduction Educators - NYHRE), federally-qualified health center (Comprehensive Health Care Center), homeless shelter (The Living Room), and a methadone maintenance treatment program (Montefiore Wellness Centers).**

B.4. Participants. Most DoSA patients are Hispanic (59%) or black (24%), male (62%), and live under the federal poverty line (81%). Mean age is 47 years. Approximately 65% (n=2730) are HCV-infected, and 75% of those have chronic HCV (n=2048); 70% have genotype-1 (n=1434), and 80% of those are HIV-negative (n=1147). We will check HBV serologies for all patients and exclude those who are HBsAg positive. We will monitor those that are HBN core Ab positive and treat as medically appropriate.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• **HCV-infected (HCV RNA test above the limit of quantification at baseline)** • **Genotypes/Subtypes: G1a or G1b** • **Eligible for HCV treatment per 2016 AASLD/IDSA guidelines** • **Willing to receive HCV treatment on-site at DoSA clinics** • **Health care provider decision to treat patient with Zepatier-based therapy based on 2016 AASLD/IDSA guidelines** • **Using illicit drugs (either opiates, cocaine, or benzodizepenes) within the last 6 months** • **Age 18 or older** • **Able to provide informed consent** • **English or Spanish speaking**	• **Known hypersensitivity (allergy) to elbasvir, grazoprevir** • **Pregnant or breast-feeding**

B.5. Recruitment. Recruitment (as with other successful studies conducted in this setting) will be both active and passive; for active recruitment DoSA medical providers will inform HCV-infected subjects about the study and assist with referral, and for passive recruitment subjects will self-refer. Self-referred subjects will meet with their provider to determine whether starting HCV treatment is appropriate. In addition to DoSA, we will recruit from three other settings which serve PWIDs: 1) primary care at Montefiore Comprehensive Health

Care Center; 2) syringe exchange program – New York Harm Reduction Educators; 3) homeless shelter with on-site HCV care – The Living Room. Potential subjects will be tested on-site with rapid HCV test kit (ongoing NYC DOHMH and CDC rapid testing project). Determination of chronic hepatitis C will be done at Montefiore Medical Center through Roche TaqMAN assay, and HCV NS5A Drug Resistance Assay through LabCorp as a send-out.

Determination of eligibility.

Initial screening visit and informed consent: • Obtain oral consent for brief screening using Einstein Committee on Clinical Investigations (IRB) screening consent template • Brief screen in private room in clinic to determine eligibility • Discuss study procedures, risks and benefits of study participation • Obtain written consent for 1) clinical trial participation; 2) study staff to use protected health information from methadone clinic records; 3) study staff to disclose protected health information in event of psychiatric distress
HCV clinic chart review: ▪ Laboratory test results: HCV Ab, HCV viral load, HIV, HCV genotype/subtype, IL28B, APRI and FibroSURE (biomarker tests for liver fibrosis), absence of advanced cirrhosis (labs within 3 months - biliribin, albumin, PT/INR), CBC, PT/INR, AFP, ANA, and GFR (for obese patients – adjusted GFR) • Methadone or buprenorphine dose if applicable
Second screening visit (medical and psychiatric eligibility): ▪ Review of HCV-related labs (as above) and staging by liver biopsy/fibroscan (if available) ▪ Review of HCV Treatment Evaluation Flow Sheet to confirm planned on-site treatment regimen: Zepatier with or without ribavirin as per 2016 AASLD/IDSA HCV guidelines ▪ Participants who meet all eligibility criteria scheduled for a baseline visit

B.6. Participant tracking and retention. We have extensive experience following HCV- and HIV-infected drug users in studies. In our completed RCT of directly observed HCV treatment, 24-week follow-up was 92%. In our completed RCT of directly observed HAART, 24-week follow-up was 86%. At enrollment and subsequent visits, we will record: 1) participants' address, phone number, and social security number; 2) contact information of family or friends; 3) contact information of participants' community-based organizations; 4) contact information of case managers; and 5) locations where participants "hang out".

B.7. Assignment to Interventions. Participants will be assigned to either control or treatment arms via computer-generated random numbers. The mechanism used to generate the random numbers will be REDCap, which provides a blinded randomization feature for participant assignment. The allocation sequence will be generated and input into REDCap by in-house Biostatisticians. The Research Assistant will enroll participants without prior knowledge of allocation sequence.

B.8. Treatment arms: a-DOT and TAU. HCV care will be delivered on-site at three clinical settings (methadone clinic, community health center, and homeless clinic) and via linkage to either the methadone program or community health center for subjects recruited at the syringe exchange program. Central pharmacists will deliver the study medications to the respective clinics. In both arms (a-DOT and TAU), Zepatier will be dispensed monthly at the clinical visit by the provider (2 bi-monthly packs).

Subjects randomized to the a-DOT arm will be instructed on using the a-DOT platform at the baseline research visit, and will take the first dose with a-DOT smartphone device in front of the HCV provider at the treatment initiation clinical visit. Prior to ingesting each daily Zepatier dose, subjects will take a brief side effect survey on the a-DOT app which rates the severity of key side effects as none, mild, moderate or severe. If subjects do not ingest Zepatier within 2 hours of scheduled dose, they will receive a friendly reminder to take the medication. Subjects who do not ingest Zepatier within 4 hours of scheduled time will receive a call from research staff during day-time hours, and the next morning if evening dose is missed. For a-DOT subjects further randomized to the gamification feature, subjects will receive real-time feedback regarding ranking of their adherence to Zepatier as compared to their peers (unnamed) leading to friendly competition for additional modest incentives to be collected at monthly research visits. Patients will return the medication packs (including any uningested tablets) at all research visits. Standard clinical visits include 2 baseline visits, and week 0, 2, 4, 8, 12, and follow up 12, and follow up 24. Additional clinical visits are scheduled as needed by either provider or patient. HCV-related labs (including LFTs) are drawn prior to each of these clinical visits as per our standard clinical protocol. In particular, hepatic laboratory testing will be performed prior to therapy, at treatment weeks 8 and 12, and as clinically indicated. Patient are instructed to consult their HCV provider without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or

discolored feces. HCV providers will discontinue Zepatier if ALT levels remain persistently greater than 10 times the ULN, or if ALT elevation is accompanied by signs or symptosm of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR. Patients with decompensated cirrhosis (Child-Pugh B or C) will not be eligible for treatment with Zepatier.

B.9. Data sources and collection.

B.9.1. Overview. Sources of data will include: medical charts, pharmacy database and packaging (biweekly packs)

B.9.2. Research visits. Research visits will occur every 4 weeks during the 12 - 16 weeks of treatment. Participants will receive $25 for each research visit and an additional $10 for each returned biweekly pack.

Baseline visit (Table 3). At baseline we will conduct chart review using standardized tool (Protocol: "HCV Clinical Registry").

Follow-up visits (Table 3). Follow up visits will occur at weeks 4, 8, 12, and 16 (if necessary). Adherence to all medications will be evaluated by pill counts. Weeks on treatment will be determined by chart review (including pharmacy database). HCV viral load and virological endpoints (see below) will be obtained by chart review.

Table 3. Overview of Data Collection by Aims

Aim & Hypothesis	Construct	Measure	Research visit (week)	Source
Outcome Measures				
All	Adherence	Pill count	4,8,12	RA
All	Completion	≥ 80% of planned treatment duration	NA	Chart and Pharmacy Database
All	Viral Load	Roche TaqMAN assay	0, 4, 8, 12, follow up 4, follow up 12	Chart
Other covariate measures*				
All	Demographics	Age, race/ethnicity	0	Chart
All	HCV-related clinical information	HCV VL, HIV, HCV genotype/subtype, IL28B, APRI and FibroSURE (biomarkers of liver fibrosis), liver tests (AST, ALT, total bilirubin, direct bilirubin, albumin), PT/INR, liver biopsy (if available), and fibroscan	0	Chart
All	Substance use	Urine toxicology	0,4,8,12	Chart
All	Addiction treatment	Methadone or buprenorphine dose (if applicable)	0,4,8,12	Chart

B.9.3. Definitions of outcome measures.

AICure missed dose adherence. For Zepatier, adherence will be calculated based on pills left in Med-ic blister pack where X=number of blisters with missing doses and Y=14. If packs are not brought back for pill count, we will assume conservatively that X=0, and also impute adherence based on other time periods in which packs have been returned (total of 6 – 8 observation periods).

HCV treatment completion**.** Subjects will be considered to have completed treatment if they have completed at least 80% of the planned treatment course (e.g. at least 10 weeks of 12 week course)

Sustained viral response (SVR). SVR is defined as undetectable HCV viral load 12 weeks after treatment completion or discontinuation.

B.9.4. Data Sources. There will be four data sources: medical record, pharmacy database, pill counts, and a-DOT dashboard,

Medical record. HCV viral load will be obtained by chart review. As per standard clinical protocol, HCV viral loads are done at weeks 4, 8, 12, and follow-up weeks 4, 12, and 24.

Pharmacy database. Information on dose changes, treatment interruptions and discontinuation will be obtained from clinical pharmacy database - updated weekly. This database includes dosages (updated weekly) of all HCV-related medications (Zepatier), treatment start and end dates, and dates of temporary discontinuation.

Adherence by pill count. Adherence by pill count will be calculated by research assistants at all research visits when treatment packs are returned using standardized forms as we have done with previous studies.

B.9.5. Data and safety monitoring plan. Because this study involves pilot testing an intervention that will enroll a relatively small number of participants over a short period of time, in each phase of the project, Dr. Arnsten will regularly monitor data and safety. We will not have a data safety and monitoring board due to the low risk and pilot nature of the study. Dr. Arnsten will: 1) identify the concern, 2) activate appropriate response to minimize the adverse event, and 3) ensure the adverse event is reported to the responsible authority in a timely manner.

All adverse events will be compiled and reported in summary form every 6 months and at the conclusion of the study. Unanticipated, non-serious adverse events will be documented on the Einstein IRB Adverse Event Form, and reported by Dr. Arnsten to the IRB within 30 days. Serious adverse events will be reported by Dr. Arnsten to the IRB within 48 hours by phone, email, or fax. All deaths will be reported by Dr. Arnsten to the IRB within 48 hours. We will use the FDA definition of serious adverse events (SAEs). In the event that a research subject either withdraws from the study or the investigator decides to discontinue a patient due to a SAE, the patient will be monitored by the investigator via ongoing status assessment until: (1) a resolution is reached, i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected, (2) the SAE is determined to be clearly unrelated to the study intervention, or (3) the SAE results in death.

B.9.6. Subject Compensation. Subjects will receive $25 for each research visit and $10 for each returned blister pack. Subjects randomized to the a-DOT arm (n=50) will receive additional incentives based on adherence measured at monthly visits: $10 for 50% adherence; $20 for 80% adherence; and $30 for 95% adherence. For the subjects further randomized to the a-DOT + gamification intervention, the second-most adherent participant will receive an additional $35 incentive, while the top-most adherent patient will receive a $50 incentive at their subsequent study visit. Should the top two participants be tied, the participant with the most adherent time of dosing will be awarded the first-place prize. In total, participants may earn up to $453, including metrocards and incentives.

B.9.7. Data Management/Confidentiality. Data will be stored with study ID codes in locked filing cabinets, separate from name-based files, which will be stored in a different locked cabinet. All study information and name-based information will be kept in separate, password protected, HIPAA compliant REDCap databases online. All name-based information will be destroyed at the end of the study, while study-ID-based information will be deleted if participants decline to allow storage of their records for future research of 50 years. All participants will be informed of the data management and confidentiality plan at the time of consent to participate.

B.10. Analytic plan.

First, the success of randomization will be checked by comparing the a-DOT and TAU groups on key variables, such as age, gender, race, HCV viral load, advanced liver disease, psychiatric, and active drug use. Continuous variables will be compared between study arms using the Student's t or Wilcoxon test, and

categorical variables will be compared using chi-square or Fisher's exact tests. Variables that are not equally distributed will be included in multivariate models if they are also associated with the study outcome.

Adherence to Zepatier (continuous measure) will be determined as the amount of medication taken by each patient during the first 12 weeks will be expressed as a percentage (with a 0-100% range) of the target dose. Subjects will be classified as "adherent" if they receive at least 80% of the total dose of Zepatier. Subjects who receive less than 80% of the total dose of Zepatier will be classified as "non-adherent." Analyses using self-reported adherence will also be conducted. Self-report is more accessible to clinicians than pill count, and there is added value in performing analogous analyses using the self-report measure.

Because adherence will be measured two ways (pill counts and self-report) *concordance correlation coefficients* will be calculated and performed to evaluate agreement between the measures We will also test if the means of the two measurements are equal. Because adherence will be measured monthly, mixed-effects linear models for repeated measures that account for within-subject correlation will be used. In addition, we will examine the adherence data using a dichotomous cut-off (adherence ≥ 80%), and determine the proportion of subjects who were sometimes, always, or never adherent during the 12-week treatment period. To this end, separate analyses will be performed for pill count and self-report adherence data.

For subjects randomzied to the a-DOT arm, association between active drug use during treatment and the continuous adherence will be tested using Student's t or Wilcoxon signed rank test, depending on normality of the data. Bivariate analysis of dichotomous adherence data with categorical variables will be performed with chi-square and Fisher exact tests. We will conduct multivariate logistic regression analyses based on findings from the univariate analysis, but recognize that our modest sample size will limit such models.

Based on our pilot data, if we conservatively assume that 80% of subjects in the a-DOT will achieve ≥80% adherence (v. 50% in the TAU arm), we will have >80% power to find a statistically significant difference. With the application of mixed-effects logistic regression to the repeatedly measured binary adherence outcome, power will be greater than 80% no matter how large the within-subject outcome correlation or intraclass correlation (ICC).

In our previous DOT study, mean adherence in the mDOT group was 87% (SD=12%, n=21), and mean adherence in the TAU group was 77% (SD=20%, n=19) which translates into a standardized effect size or Cohen's d = 0.6. Based on this effect size, the power of the mixed effects linear model for the repeatedly measured continuous adherence outcome will be greater than 80%, even if anticipated ICC is as high as 0.5.

We will determine the proportion (and Wald or exact 95% CI) of subjects randomized to aDOT arm (n=50) who achieve SVR. For example, if SVR is achieved in 70% of the 50 study participants, the 95% confidence interval around that proportion will be: 57%, 83%. If SVR is achieved in 80%, the 95% confidence interval will be: 69%, 91%. If SVR is achieved in 90%, the 95% confidence interval will be: 82%, 98%. The overall SVR for all subjects will be compared to historical controls to demonstrate feasibility of treating real-world injection PWIDs with Zepatier-based regimens. Although our study lacks power to definitively answer the question of whether a-DOT improves SVR, our study will provide an estimated effect size to be used in future R01-funded studies examining the efficacy of a-DOT.

We used power calculations for Fisher's exact test (with 80% power and 5% significance level in a two-tailed test) to find the minimum detectable difference between the percentage of "adherent" subjects in the favorable group (e.g. not actively using drugs) vs. unfavorable group (e.g. actively using drugs). We would be able to find that a characteristic is significantly associated with adherence if there are 71% "adherent" subjects in the favorable group vs. no more than 41% "adherent" subjects in the unfavorable group (3.55 in terms of odds ratio). When using adherence as a continuous measure, we will have greater power to show correlations between continuous predictor variables and adherence. We calculated the minimum detectable correlation coefficient with 80% power and 5% significance level to be 0.33 which represents a small to medium correlation effect size. Therefore, we expect to have sufficient power to detect some associations that are likely to exist.

We will determine an effect size with respect to the outcome of adherence in the aDOT + gamification arm vs. a-DOT arm which will inform future R01 interventions.

C. References

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