Intensive Models of HCV Care for Injection Drug Users
PREVAIL Study

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Injection drug users (IDUs) constitute 60% of the approximately 5 million people in the U.S. infected with hepatitis C virus (HCV). HCV is the leading cause of liver failure and transplantation in the U.S., and mortality and health care costs due to HCV are expected to increase over the next two decades. Successful HCV treatment leading to sustained viral response (SVR) is associated with decreased progression of liver disease and increased survival, but to date successful treatment of IDUs has been limited.

Although past HCV therapies have been relatively ineffective in genotype-1 infected patients (the most common genotype in the U.S.), newer regimens are substantially improved. With the addition of direct-acting antiviral agents, HCV treatment delivered within large clinical trials leads to SVR or cure in over 90% of genotype-1 infected patients, compared to 45% with previous regimens. However, SVR rates are as low as 14% in real-world settings (pegylated interferon and ribavirin). Initial triple therapy HCV regimens were associated with increased dosing frequency (three times daily), pill burden (up to 20 pills daily), and side effects. Newer regimens such as fixed-dose ledipasvir and sofosbuvir are dosed once daily and have minimal side effects. Nevertheless, IDUs may still have lower adherence and high rates of treatment discontinuation, and many of those who fail to attain an SVR will develop drug resistance.

If HCV treatment continues to be delivered within current models of care, most IDUs will not only fail treatment and develop resistance, but may transmit drug resistant viruses to others, leading to new reservoirs of drug resistant virus. Though a growing number of studies now provide support for using interferon-based HCV treatment regimens in IDUs, none have determined the best model for delivering treatment, and this lack of data has contributed to physician reluctance to offer HCV treatment to IDUs. To reduce HCV prevalence, decrease HCV transmission leading to new infections, decrease mortality and health-care costs, and eliminate disparities in HCV-related care, effective HCV treatment must be provided to IDUs.

Treatment of IDUs 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. Although treatment for addiction and access to multidisciplinary teams likely play important roles in successfully treating HCV-infected IDUs, it is unknown which specific psychosocial and/or structural interventions are needed. Each patient's course of HCV treatment may cost over $90,000, but may not be cost-effective with our current models of care. The life- and cost-saving benefits of new HCV treatments will not be realized unless we determine optimal models of care for the majority of HCV-infected patients.

We have developed a multidisciplinary model of HCV care which integrates substance abuse treatment, on-site primary and psychiatric care, and HCV-related care within opiate agonist treatment clinics. To maximize HCV treatment outcomes, we have also piloted two models of intensive care: directly observed therapy (DOT), and concurrent group therapy (CGT). In our DOT model, one daily dose of oral medication is administered with methadone. Though we have shown that DOT is associated with increased adherence, we do not know how DOT will extend to new DAA therapy, or what impact DOT will have on resistance. In our CGT model, groups initiate and complete HCV treatment in a once weekly treatment group which provides powerful social support to mitigate fears of side effects and promotes efficient education. While CGT has also been associated with good pilot outcomes, we do not know whether either model is better or more cost-effective than standard care.

In the proposed study, 150 IDUs with chronic HCV (genotype 1) will be recruited from opiate agonist treatment clinics and randomized to one of three models of care: DOT; CGT; or standard on-site care. We hypothesize that either intensive model will be superior to standard on-site care. One-hundred will initiate treatment with fixed-dose ledipasvir and sofosbuvir. Our specific aims are:

1. **To determine in a randomized trial whether either of two intensive on-site HCV treatment models (DOT or concurrent group treatment) provided at a methadone program is more efficacious than standard on-site treatment for enhancing adherence and virological outcomes, and decreasing drug resistance.** We will compare the proportion of subjects in each arm who: a) adhere to antiviral treatment; b) complete antiviral treatment; c) attain SVR (cure); and d) develop drug resistance.
2. **To determine the incidence and factors associated with the development of drug resistance in IDUs initiating HCV treatment.** In a pooled analysis of all subjects, we will determine what proportion of subjects develops resistance, and examine associations between adherence and resistance.
3. **To perform cost and cost-effectiveness analyses of each model of intensive on-site HCV care.** We will use empirical data to determine the total costs of providing intensive on-site or standard on-site care. A computer simulation cost-effectiveness model combining empirical and published data will be used to determine dollars per quality-adjusted life-year gained associated with intensive versus standard care.

B. SIGNIFICANCE

B.1. HCV epidemic in IDUs. HCV prevalence in injection drug users (IDUs) ranges from 70-90%, and HCV incidence ranges from 10–26 per 100 person-years.[1-4] IDUs comprise 60% of all HCV-infected persons in the U.S., and genotype-1 infections are the most prevalent (74%).[5] In the U.S., approximately 35,000 acute HCV infections occur each year, and a 4-fold increase in the number of adults with chronic HCV is projected from 1990-2015.[6] HCV causes up to 15,000 deaths annually, and is the leading cause of liver transplantation in the U.S.[7-9] Until recently (6/11), HCV treatment was effective in less than 50% of patients in registration trials,[10-12] and much less effective (14%) in real-world urban populations.[13] Treatment effectiveness among IDUs is crucial because IDUs remain the leading risk group for HCV infection.[14]

B.2. Treatment of chronic HCV. Sustained viral response (SVR), defined as the absence of detectable virus 24 weeks after completion of therapy, reflects elimination of HCV infection because >95% of patients with such responses remain persistently free of detectable virus up to 10 years later.[15,16] Combination pegylated interferon (IFN) and ribavirin therapy also reduces progression of liver fibrosis,[17-22] reduces portal hypertension,[23] prevents development of liver cancer,[24-26] improves quality of life,[27-29] and lengthens survival.[30-32] Treatment is complex, however, because treatment limiting side effects are extremely common.[10-12, 33-35] These include flu-like syndromes,[36] cytopenias[10-12] which may require reduction or discontinuation of medications or the administration of growth factors,[37, 38] and neuropsychiatric side effects.[39-45] Other common side effects are anorexia, nausea, skin rash, diarrhea, arthlagias, headaches, dizziness, and impaired thought.[10, 45] Support for side effect management is a crucial feature of HCV care.

B.3. Efficacy of new HCV regimens for genotype-1 infected patients. Treatment with IFN and ribavirin has been associated with SVR rates of 40-50% in treatment-naive patients with genotype 1. In the ADVANCE trial, patients who were treated with IFN, ribavirin, and telaprevir achieved an SVR of 75%, compared to 44% in the IFN and ribavirin arm.[46] Rates of SVR were higher in telaprevir-treated patients regardless of stage of liver disease, race, or ethnicity. However, there was a two-fold higher incidence of adverse effects, including rash, nausea, and anemia,with telaprevir-based regimens compared to IFN and ribavirin.[46-48] When patients discontinue treatment prior to 20 weeks, the SVR rate is markedly decreased - only 23%.[47] Support for keeping patients on treatment is also crucial to maximize rates of SVR. The FDA has recently approved treatment of genotype-1 infected patients with 12 – 24 weeks of fixed-dose (ledipasvir and sofosbuvir), and this is associated with SVR rates of >95% (www.hcvguidelines.org).

B.4. Is HCV treatment feasible in IDUs? Despite the central role IDUs occupy in the HCV epidemic, the 1997 NIH Consensus Statement on the Management of Hepatitis C, citing concerns about adherence and toxicity, recommended not treating patients who were using illicit drugs unless they had stopped for at least 6 months.[49] After advocacy by Dr. Edlin and colleagues,[50,51] the 2002 Consensus Panel altered this stance and affirmed that active IDUs can be successfully treated for HCV. The Panel further stated that active drug use in and of itself is not a reason to exclude patients from antiviral therapy, and that treatment decisions for active IDUs be made case-by-case. [52] Subsequently, the 2004 AASLD Guidelines recognized that patients with co-occurring alcohol or drug abuse or psychiatric illness may be effectively treated for HCV infection.[53]

Nearly 10 years later, few data are available on optimal methods of treating IDUs. Most physicians, reluctant to engage an already challenging patient group in a complex and difficult treatment regimen, continue to adhere to old guidelines.[54-60] Consequently, IDUs are still rarely offered treatment for HCV,[61, 62] and registration trials of new triple therapy regimens still exclude active drug users and rarely enroll patients on opiate substitution treatments, including methadone. Although a large proportion of IDUs with HCV is willing to undergo treatment, few actually receive therapy.[63-67] We expect that physician reluctance to treat IDUs and disparities in access to HCV care will increase markedly with newer HCV regimens that are associated with increased side effects, higher rates of treatment discontinuation, and, for the first time, with drug resistance.[68]

A growing number of new studies provides support for IFN-based HCV therapy in drug using and methadone-maintained patients.[69-85] Though on-site multidisciplinary models of care have demonstrated good outcomes for IDUs, optimal models of care must be studied.[84] By performing a randomized trial of 2 models of intensive on-site HCV care - modified directly observed therapy and concurrent group therapy - we will be able to evaluate whether either on-site model is optimal for delivering state of the art therapy to drug users.

B.5. HCV treatment in minority populations. A disproportionately high number of African-American and Latino persons in the U.S. are infected with HCV,[5, 86, 87] yet evidence suggests that HCV treatment is more effective in Whites than in Latinos or African Americans.[88-93] Prior studies of genotype-1 infected patients treated with IFN and ribavirin have shown lower rates of SVR among Latinos compared to non-Latino whites (34% v. 49%),[91] and among African Americans compared to non-Hispanic Whites (19% v. 52%).[92] In a recent effectiveness study from our liver clinic, rates of SVR for genotype-1 infected patients were even lower: 11% for Latinos, 14% for African Americans, and 25% for Whites.[13] While some rural programs are reducing

disparities in HCV care between Latinos and non-Latino Whites using telemedicine,[94] active drug users have been excluded.[95] Treatment differences among Latinos, African Americans and Whites are explained to a large extent by differences in DNA sequences near the interferon lambda 3 gene, and the favorable IL28B genotype (C/C vs. C/T or T/T) is more prevalent in Whites than in Latinos or African Americans.[96, 97] Clinical trial data suggest that disparities may be less pronounced with telaprevir-based treatment: the ADVANCE trial demonstrated SVR rates of 62% in African Americans and 74% in Latinos.[46] With fixed-dose (ledipasvir and sofosbuvir), there does not appear to be differences in rates of SVR based on race and ethinicty. However, there may be differences seen in real-world studies. Additional intensive interventions are needed to optimize treatment outcomes for Latino and African American IDUs. Because our substance abuse treatment program serves predominantly Latinos and African Americans, we have the opportunity to test such interventions.

B.6. What is known about adherence to HCV treatment? Strict adherence to IFN and ribavirin therapy is necessary to optimize SVR rates. Studies have shown that patients who adhere to at least 80% of the intended treatment schedule (taking at least 80% of the total dose of both IFN and ribavirin for at least 80% of the intended duration) are more likely to achieve an SVR (44% v. 7%).[98, 99] Among patients with genotype 1, greater adherence has been associated with SVR at 48 weeks.[100] Some studies have suggested that ribavirin exposure may be particularly important in determining response to HCV treatment, supporting the concept that adherence to daily oral medications requires unique interventions.[101, 102] There are currently little data describing associations between DAA adherence and virological outcomes, making optimal levels of adherence to DAA-based regimens unknown. However, because of the risk of resistance observed with protease inhibitor treatment for HIV, optimal adherence may be as high as 90%. Adherence support is particularly important for active drug users, because active drug use has been associated with nonadherence.[103-111]

Electronic monitors measure adherence most accurately, and have the advantage of continuously assessing doses taken and temporal regularity.[112] Med-ic® electronic monitors are an innovative method of assessing adherence that uses an electronic monitoring system applied directly to weekly blister packs.[113] This system allows patients to continue to take medications from blister packs, which are associated with improved adherence to complex regimens. In the proposed trial, we will take advantage of this new technology to monitor adherence, and we will also use self-report adherence measures. Self-reported adherence to HCV treatment has been shown to be correlated with (though higher than) electronic monitoring estimates.[114]

B.7. Direct-acting antiviral HCV agents and resistance. Emergence of antiviral resistant variants during PI-based therapy has been observed during all trials, and is associated with both virological failure and relapse.[115] In clinical trials, resistance-associated mutations were seen in 62% of patients who failed to achieve SVR. However, only 5% of patients in telaprevir trials had baseline HCV substitutions/variants, and these were not associated with SVR.[115] Treatment-emergent substitutions have been demonstrated to reduce the anti- HCV activity of NS3/4A protease inhibitors.[116-118] Additional mutations have been seen in patients treated with fixed-dose (ledipasvir and sofosbuvir). In the proposed trial, we will assess development of resistance, and determine the association between adherence level and development of resistance.

B.8. Cost of HCV treatment. A 48-week course of IFN, ribavirin, and telaprevir, including the use of growth factors (and exclusive of physician visits, laboratory tests, or care for complications) may be over $50,000.[119,177-179] Cost of fixed-dose (ledipasvir and sofosbuvir) may be over $90,000. A small increment in the overall cost of treatment that appreciably increases patients' likelihood of successfully completing the regimen could substantially improve its cost-effectiveness. To assess this, we will estimate the cost of each model of on-site care (mDOT, CGT, and standard care). While intensive on-site interventions such as mDOT and CGT may require additional provider time, we expect the incremental cost of this effort will be relatively small compared to the current cost of treatment.

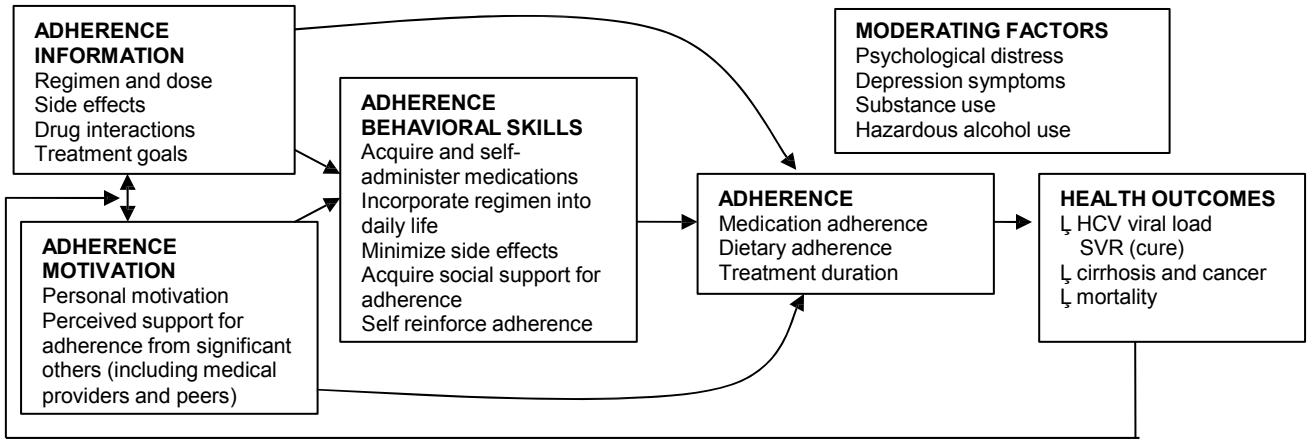
B.9. Theoretical frameworks for the proposed trial.

Information, Motivation, Behavior (IMB) model of adherence. The proposed mDOT and CGT interventions are guided by Fisher's IMB model.[120-122] The IMB model asserts that information, motivation, and behavioral skills are fundamental determinants of adherence.[120] According to the IMB model, information and motivation work through behavioral skills to effect adherence. Behavioral skills are a critical prerequisite of adherence, and determine whether even well-informed and motivated individuals are able to adhere. The IMB model further specifies that personal and situational characteristics, such as poor psychologic health, substance abuse, unstable housing, or inadequate access to medical care, may moderate these relationships and impact adherence.[120] In extreme cases, strong negative effects on adherence are expected, and interventions aimed at improving information and motivation may not be effective without adjuvant support.

Both interventions - mDOT and CGT - focus on enhancing information, motivation, and behavioral skills, and provide adjuvant support to lessen negative impacts of moderating factors. The mDOT strategy, in which adherence to HCV treatment is linked to an established behavioral skill, specifically methadone clinic

attendance, addresses adherence skills: acquisition and administration of HCV medications; incorporation of HCV treatment into daily routines; coping with side effects (through side effect assessment and management protocols); and acquisition of social support. While primarily operating on behavioral skills, the mDOT

intervention also enhances both information and motivation (through support from nurses and other clinic staff). Our proposed CGT intervention addresses information (through education), motivation (through peer and providers support), and behavioral skills (by dispensing medications during group).



Theory of Fundamental Cause and disparities in HCV care. Disparities related to HCV care can be expected to increase with the introduction of more efficacious treatments, just as was observed with HIV. Initially, HIV did not discriminate based on race, ethnicity, or socioeconomic status (SES), but as effective treatments became available, African Americans, Latinos, and those with low SES began to have poorer treatment outcomes. Link and Phelan proposed that socioeconomic status is a "fundamental cause" of mortality disparities, and that socioeconomic disparities endure despite availability of more effective treatments.[123] This is because SES embodies an array of resources such as money, knowledge, prestige, power, and beneficial social connections, all of which protect health. In the U.S., although health care is fragmented for all people, patients with high SES are able to mobilize resources to minimize the effect of fragmented care on poor health. Effective models of care which mobilize resources for low SES patients, or for all patients across the SES spectrum equally, have the greatest potential to minimize or eliminate disparities.[94]

Intensive models of HCV care which mobilize resources normally available to patients with high levels of SES (such as knowledge, social networks, prestige, or power) may decrease associations between SES and HCV-related morbidity and mortality. To optimize HCV prevention and control, it is essential to eradicate racial and ethnic disparities, as well as disparities based on SES and IDU-status in HCV-related healthcare. Our proposed models may be an important step towards eliminating disparities in HCV care.

B.10. Generalizability of mDOT and CGT approaches. IDUs are at the heart of the HCV epidemic, and the majority of all cases in the U.S. and other developed nations are related to illicit drug use. There are several reasons for initiating this research in the methadone treatment setting: (1) drug users must attend their methadone program frequently because methadone take-home doses are linked to absence of illicit drug use; (2) methadone treatment is a congregate setting in which patients are already present nearly daily to receive methadone; and (3) drug users may have particular difficulty adhering with HCV treatment, in part because the side effects of IFN mimic the symptoms of opiate withdrawal. If proven effective, our mDOT model could be applied in other programs that serve the approximately 180,000 HCV-infected methadone patients in the U.S.[124-125] as well as in other settings in which drug users are present nearly daily (e.g. correctional facilities, homeless shelters, day treatment programs, and residential substance abuse settings). DOT can be extended in the community through nurses and community health workers.[126-127] If proven effective, our CGT model could be applied to many diverse clinical settings in which patients are able to attend clinic once weekly.

C. INNOVATION

- First randomized trial to test innovative intervention strategies for providing HCV-care to IDUs in the U.S.
- Concurrent group treatment (CGT) is an innovative model of care allowing groups of patients to concurrently initiate HCV treatment, leading to informed and activated patient groups with enhanced social support and trust in the healthcare team.
- Adherence monitoring of blister packs with Medi-ic® technology allows us to combine a state of the art electronic adherence monitoring system with weekly blister packs.
- First study to provide data on factors associated with resistance to HCV direct-acting antiviral drugs in IDUs, and to define associations between adherence and development of resistance.
- Innovative techniques for modeling cost, including quality adjustment for treatment failure and development of resistant-virus.[128]
- First study to evaluate cost effectiveness of HCV treatment in a methadone clinic in a randomized trial.

D. APPROACH

D.1. Preliminary Studies

D.1.1. Overview of the research team. We have assembled a strong team of investigators with expertise conducting research to improve health outcomes among HCV-infected and drug-using populations. Dr. Litwin has focused on defining optimal models of HCV care for IDUs, and is expert in treating HCV in IDUs, methadone-maintained patients, and active drug users. Dr. Arnsten is a nationally recognized expert on adherence to antiviral therapy and treatment of HIV and HCV in substance users. Dr. Edlin is expert in epidemiologic studies of and interventions for infectious complications of drug use, particularly HCV. Dr. Schackman is expert in cost studies of models of care for screening and treatment for diverse populations, and has extensive experience conducting economic analyses in collaboration with the NIDA Clinical Trials Network and the NIAID AIDS Clinical Trials Group. Dr. Linas has expertise in modeling the impact of care systems on HCV- and HIV-related outcomes. This team has successfully conducted epidemiological, clinical, behavioral, and cost studies of HCV-infected and drug-using populations, and together has published over 300 peer-reviewed papers.

D.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 IDUs.[70] 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 IDUs 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.[10]

D.1.3. Study of HCV treatment in methadone patients. In 2003, we adapted our on-site multidisciplinary HCV program to include directly-administered weekly IFN in addition to screening, assessment of treatment eligibility, psychiatric services, and on-site antiviral therapy.[79] 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.[78-80]

D.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 enrollment (n=80), with 74 initiating HCV treatment. 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).[129] 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 (n=22), 55% achieved SVR (half active drug users).[129] Of the 1st 4 subjects on telaprevir-based triple therapy randomized to DOT, pill count adherence at 4 weeks was 98%, and 3 of 4 had 4 week VL<43 IU/ml, with one subject discontinuing treatment.

The above data demonstrate: (1) our ability to enroll and retain HCV-infected IDUs; (2) efficacy of enhanced mDOT v. standard mDOT; and (3) promising early outcomes with telaprevir-based therapy. However, because this pilot RCT was not powered to demonstrate increased SVR with mDOT (and both arms included some degree of DOT), we now propose a definitive study to determine if DOT is associated with increased SVR for genotype-1 patients, and whether DOT is cost-effective.[129] We will have sufficient power to answer this question as treatment for genotype-1 patients is more effective (SVR=75%),[46] we will include only genotype-1 patients, and all medications will be self-administered in the proposed TAU arm.

D.1.5. Concurrent Group Treatment (CGT). In 2009, we implemented a group treatment model of HCV care. To date, 39 patients have initiated CGT (including 34 enrolled in the mDOT study described above). Early treatment outcomes are promising, with 89% of patients completing at least 80% of planned treatment duration, and only 2 patients discontinuing treatment because of side effects. Of the first 20 patients who initiated CGT, 80% achieved an end of treatment response and 55% achieved SVR, including 57% of those with genotype-1 (half active drug users).[130] Eight CGT patients have initiated telaprevir-based regimens, 7 of 8 had 4 week HCV VL <43 IU, 5 out of 8 had undetectable VL, with one discontinuing treatment. These data demonstrate that CGT is a promising model of care for treating IDUs. However, since patients were not randomized, it is possible that CGT patients were more motivated than others. The 2 x 2 figure demonstrates the effects of each intervention (mDOT and CGT), as well as of their interaction. When subjects were treated individually with mDOT, or when the subjects were treated with CGT (without mDOT), adherence and virological outcomes were better than without either intervention. However, the additive effects of mDOT and CGT appear modest. For this reason, as well as to increase generalizability, in the proposed study we will evaluate 2 models of intensive care: mDOT (both IFN and oral medications) and CGT (IFN directly-administered and oral meds self-administered). Both models must be rigorously tested to determine whether intensive models of care are superior to standard on-site care for achieving SVR.

N=54	Arm	CGT	Indiv
Adherence 4 wks	mDOT	92% (n=13)	87% (n=16)
Adherence 12 wks		92%	86%
HCV VL↓ at 12 wks		2.5 log ↓	2.4 log ↓
ETR		69%	63%
SVR		45%	56%
Adherence 4 wks	TAU	92% (n=11)	68% (n=14)
Adherence 12 wks		86%	69%
HCV VL↓ at 12 wks		2.6 log ↓	2.0 log ↓
ETR		82%	54%
SVR		56%	36%

D.1.6. RCT of directly observed HAART in methadone patients. We conducted an RCT of DOT with HAART in HIV-infected drug users in methadone clinics. Seventy-seven participants were randomized to a 24-week DOT intervention or treatment as usual (TAU), with 86% study retention at 24 weeks. Participants randomized to DOT (v. TAU) had greater adherence (mean adherence: 86% v. 56%, p<0.0001) and VL

decreased by 0.52 log10 copies/ml in the DOT group while it remained stable in the TAU group ($p<0.01$). More DOT than TAU participants had undetectable viral load (71% vs. 44%, $p=0.03$). Active drug use decreased adherence, but the negative impact of drug use on adherence was eliminated by DOT. By 3 months after DOT ended, differences in both adherence and viral load between DOT and TAU had extinguished. These data demonstrate that DOT is associated with improved HIV virological outcomes among methadone-maintained patients, including active drug users, and that it should be continued long-term for durable effect. It is unknown whether virological outcomes will improve with HCV DOT.[131-134]

D.1.7. Effect of adherence and DOT on development of resistance. We explored the impact of DOT on the development of new antiretroviral resistance mutations in subjects enrolled in the above RCT. To determine if increases in adherence associated with DOT would affect drug resistance, we examined the development of new resistance mutations among 21 participants who had a detectable HIV VL at both baseline and a second time point. Of these, 9 developed new drug resistance mutations not seen at baseline (3 in DOT and 6 in TAU, $p=0.27$). Overall, 5 TAU subjects developed major mutations correlating with their current antiretroviral regimen, while no DOT subjects developed such mutations. These data demonstrate that improved HIV adherence associated with DOT does not lead to increased resistance. In the proposed study, we will investigate associations between HCV treatment adherence and development of drug resistance.[135]

D.1.8. Cost pilot data. Drs. Schackman and Litwin conducted a retrospective chart review of costs of HCV treatment for patients treated in a methadone maintenance program. Mean treatment costs were $40,600 for patients with SVR and $31,400 for patients without SVR. Drs. Linas and Schackman conducted a study of health care services utilization by HCV-infected patients in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials Cohort[136] in which they described the additional use of hospital and emergency department services associated with HCV infection in this cohort after adjusting fro demographic and clinical factors. Dr. Schackman has also assessed the cost of HIV medication adherence support interventions.[137]

D.2. Overview of study approach. In the proposed study, 150 HCV-monoinfected IDUs (genotype 1) eligible for on-site HCV treatment will be recruited from opiate agonist treatment clinics and randomized to one of 3 models of care: modified directly observed treatment (mDOT); concurrent group treatment (CGT); or standard on-site treatment which represents the treatment as usual arm (TAU). We will compare the proportion of patients in each arm who optimally adhere (>80%), complete treatment, achieve SVR, and develop resistance. We hypothesize that both intensive models of care (mDOT and CGT) will be superior to TAU. Participants on 48 week regimens (e.g. telaprevir) will be followed for 72 weeks (up to 48 weeks of HCV treatment + 24 weeks of follow-up), with visits occurring every 4 weeks for the first 24 weeks, followed by 4 additional visits at 12 week intervals. Participants (n=100) on 12 – 24 weeks regimens (fixed-dose ledipasvir and sofosbuvir) will be followed up to 48 weeks (up to 24 weeks of HCV treatment + 24 weeks of follow-up) with visits occurring every 4 weeks for the first 12 weeks, week 24 (if necessary), end of treatment, and follow-up weeks (4, 12 and 24). Data sources will include blood tests (HCV viral load and resistance tests), urine toxicology tests, questionnaires, medical records, electronic monitors for assessing adherence, and staff logs and direct observation (for cost-effectiveness analysis). In pooled analyses of all subjects (n=150), we will determine associations between adherence and development of resistance. We will also assess cost and cost-effectiveness of all 3 models.

D.3. Setting: Einstein and Montefiore 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 12 clinics in 5 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), Dr. Arnsten (DoSA Research Director), and Dr. Cohen (DoSA Medical Director), participant recruitment and private office space for research visits will be ensured.

D.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 anticipate 800 new admissions over the 3-year recruitment period, representing another 216 HCV-monoinfected genotype-1 patients.

Table 1. Inclusion and Exclusion Criteria (also see Human Subjects)

Inclusion Criteria	Exclusion Criteria
• **HIV-negative** • **Willing to receive HCV treatment on-site** • **Initiating treatment with fixed dose (sofosbuvir and ledipasvir)** • **Receiving methadone in clinic at least once per week** • **Age 18 or older** • **Able to provide informed consent** • **English or Spanish speaking**	• **Pregnant or breast-feeding**

D.5. Recruitment. Recruitment (as with other successful studies conducted in this setting)[129,132,142] will be both active and passive; for active recruitment DoSA medical providers will inform genotype-1 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.

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 methadone 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

Methadone clinic chart review:
- Laboratory test results: HCV Ab, HCV viral load, HIV (within 1 year), HCV genotype/subtype, IL28B, APRI and FibroSURE (biomarker tests for liver fibrosis)
- Methadone clinic attendance and dose

Second screening visit (medical eligibility determination by Dr. Litwin):
- Review of HCV-related labs (as above) and fibroscan or liver biopsy (if available)
- Review of HCV Treatment Evaluation Flow Sheet to confirm no previous HCV treatment and planned on-site treatment regimen: fixed dose (sofosbuvir and ledipasvir)
- Participants who meet all eligibility criteria scheduled for a baseline visit
- Randomization (stratified, blocked) generated by centralized computer program

D.6. Participant tracking and retention. We have extensive experience following HCV- and HIV-infected drug users in studies. In our ongoing RCT of directly observed HCV treatment, 24 week follow-up was 92%.[129] In our completed RCT of directly observed HAART, 24-week follow-up was 86%.[142] 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".

D.7. Randomization. We will recruit 150 patients (100 on fixed-dose sofosbuvir and ledipasvir), with patients randomized to mDOT, CGT, or TAU in a 1:1:1 ratio (50 subjects in each group) in variable block sizes of 3-6 via central, computer-generated randomization. Two special randomization strategies (stratification and blocking) will be used to avert imbalances in prognostic factors, and to ensure comparison

groups of approximately equal size. Because of the historical importance of IL28B genotype and stage of liver disease (cirrhosis v. no cirrhosis) in determining virologic outcomes,[46] we will stratify by these 2 factors. All subjects will have the IL28B genetic test performed as per our standard clinical algorithm. To determine presence of cirrhosis, all subjects will have 2 biomarker tests (APRI and Fibrosure) performed at baseline,[143-144] per our standard clinical algorithm (Appendices A and D). Liver biopsy / Fibroscan is not required but will be performed if 1) biomarker tests are inconclusive for determination of cirrhosis as per the SAFE algorithm (<20%),[145] 2) to rule out co-occurring liver disease, or 3) if the result will influence the decision to initiate treatment. Results of liver biopsy / Fibroscan (if done) will be used for stratification instead of biomarker tests. Since IL28B explains much of the variability in response between African Americans and non-African Americans,[96,146] and rates of SVR with DAAs may be equivalent in Latinos and non-Latino Whites,[46] we will not stratify by race or ethnicity, but will adjust in the analyses if necessary.

D.8. Treatment arms: TAU, mDOT, and CGT. All 3 models of care include co-located on-site care including HCV care, primary care, and substance abuse treatment. Table 2 summarizes similarities and differences between the 3 models. Subjects randomized to TAU will receive all medications monthly at the clinic from the clinic nurse, packaged in 7-day blister packs (oral medications)

Table 2: Element	IMB Model	TAU	mDOT	CGT
Co-located care	Information Motivation	X	X	X
Enhanced social support by providers	Motivation		Nurse – individual	Medical provider - group
DOT Interferon	Behavioral Skills		Nurse - individual	Medical provider - group
DOT telaprevir and ribavirin	Behavioral Skills		DAA 1-6 doses/week	
DOT snack (if telaprevir or RBV only)	Behavioral Skills		Nurse - individual	
Enhanced social support by patients	Motivation			Peers – group
Enhanced education	Information			Weekly educational sessions
Enhanced side effect management	Information Motivation		Nurse - individual	Weekly group treatment

D.8.1. Intensive treatment intervention arms (mDOT and CGT)

Modified directly observed treatment (mDOT). Since DOT of HCV medications will be linked to methadone visits, the number of directly observed oral doses will vary based on the number of days the patients attends the clinic to receive directly observed methadone (pick-up schedule). This intervention is considered modified DOT (mDOT) since only 1-6 out of up to 24 weekly oral medication doses will be observed. Subjects in the mDOT arm will receive: 1) 1 to 6 directly observed oral medication doses per week at the same time as they receive methadone, and 2) individually packaged take-home doses for self-administration on days not in the clinic. In addition, methadone clinic nurses will: 3) notify clinicians when doses are declined, 4) assess for side effects using a standard script; and 5) refer subjects to onsite clinicians as necessary. Since some medications must be taken with food, subjects will also be provided with a high-fat snack (20 grams of fat) when necessary.

Concurrent group treatment (CGT). We developed this model by adapting models linking HCV support groups with treatment[70,77-78] and models of group medical visits across many chronic conditions.[180-182] Weekly CGT meetings will have 6 components: 1) brief physical exams; 2) psychosocial support from peers and providers; 3) education; 4) direct administration of pegylated interferon medication in the group setting (if applicable); 5) side effect management; and 6) closing meditation on positive health. Six to 12 patients will receive treatment concurrently. Other intervention elements will be as follows.

ORIENTATION MEETINGS. The orientation will be the first opportunity for subjects to meet as a group and interact with each other and the treatment team (physician and physician assistant). Subjects will introduce themselves and share concerns about HCV. The treatment team will present an overview of the HCV epidemic and its impact on drug users, natural history of HCV, and risks, benefits, and efficacy of HCV treatment. The group treatment protocol and schedule will be discussed, and time allowed for questions and discussion. A second orientation will be scheduled the following week to discuss medication side effects and general strategies for managing them. A group treatment contract, including a confidentiality agreement, will be read aloud by subjects and signed. At the third weekly group, all members will initiate treatment concurrently and receive the first IFN injection directly administered in the group setting (if applicable).

WEEKLY TREATMENT GROUPS. Each group will last one hour. Prior to the group, one clinician will review labs and make decisions regarding ribavirin dose adjustments (if applicable) and initiation or adjustment of growth factors (if applicable) to manage adverse effects (cytopenias). When group members arrive, they will fill out weekly side effect inventory sheets. During the first 30 minutes, 2 providers will conduct brief individual

visits to check vital signs and address lab values, adherence to medications, and adverse effects. IFN injections and growth factors as needed will be administered in the group setting if needed, and the medical visit will be charted using a template. In the second 30 minutes, one provider will conduct a group discussion while the second provider completes individual visits. Facilitated group discussion will begin with an informal hand raising survey of how participants are faring in treatment from "terrible" to "no problem". The group will end with a 5-minute guided meditation exercise. The total time demand for the treatment team is 90 minutes. All subjects will receive metrocards (2 ride value of $5.00) for each of the first 12 weeks as an incentive for arriving within a 15 minute grace period. At the completion of treatment, a ceremony is held and certificates of appreciation are given out.

FREQUENCY OF CGT CYCLES. New cycles begin at each of 3 sites 3 times per year; therefore there is a new cycle starting nearly every month. To facilitate rapid entry into a group, trial subjects may elect to wait until a cycle is starting at their "home" clinic site, or travel to a different site. In addition, they may join a group that is already in its first month. (Appendix C for group treatment protocols)

D.9. Specific study design considerations.

D.9.2. Why not include an off-site treatment by referral arm? Our study is urgently needed because off-site referral is the current prevailing model of HCV care, and alternative approaches are needed. Dr. Reinus has studied outcomes from Montefiore's liver clinic and found that only 15% were eligible for HCV treatment, and SVR rates for genotype-1 were 14% (compared to 40% in our on-site cohorts).[13] These suboptimal outcomes on referral from our methadone clinics to our liver clinic motivated us to develop our on-site treatment program, in collaboration with Dr. Reinus.

D.9.3. Why another study of DOT for HCV treatment? To date, no HCV DOT study has demonstrated improved virological outcomes, the most important clinical outcome. Our currently funded study has a heterogeneous population and was powered for adherence, not virological outcomes. This study demonstrates that there is increased adherence with DOT and is the foundation for the proposed trial.

D.9.4. Why use weekly blister packs instead of the standard packaging? Weekly pill boxes and blister packs have been shown to be associated with increased adherence and improved virological outcomes.[147-149] The proposed design will maximize adherence in the control arm and eliminate the chance that suboptimal packaging could be responsible for any effect of the intensive interventions. Since any increase in adherence from blister packaging will be observed in all three arms, it will not contaminate intervention effects.

D.9.6. Future developments in HCV treatment. Study participants will receive state-of-the-art treatment (IFN in combination with telaprevir and ribavirin). As additional regimens become available with either more convenient dosing, fewer side effects, or increased efficacy, participants in all 3 arms will receive treatment according to best available practices. On October 10, 2014, the FDA approved fixed-dose (ledipasvir and sofosbuvir). Because rates of SVR are >95% in patients initiating treatment with fixed-dose (ledipasvir and sofosbuvir), all newly enrolled subjjects will initiate treatment with this regimen. It is likely that our intensive models of care will be generalizable to IFN-sparing regimens which include only oral therapies. We recognize that HCV treatment has been greatly simplified, but issues with adherence, resistance, side effects, and cost will remain.

D.10. Data sources and collection.

D.10.1. Overview. Sources of data will include: blood and urine tests, participant interviews, medical charts, staff activity and expense logs, direct observation of staff, and electronic adherence monitors (Table 3).

D.10.2. Research visits. Research visits will occur at baseline, then every 4 weeks during the first 12 weeks of treatment, then at week 24 (if necessary), a "Final Treatment Week visit" will be conducted after the last day of treatment, and then post-treatment visits after 4, 12, and 24 weeks, for a total of up to 9 research visits. Participants will receive $25 for each visit and an additional $20 for visits with blood draws.

Baseline visit (Table 3). At baseline we will assess: sociodemographic and HCV clinical factors, potential mediating variables based on the IMB model, potential moderators (including psychiatric status, substance use, and unstable housing), and additional psychosocial factors hypothesized to predict adherence. The baseline visit will take approximately 3 hours. Blood will be collected at the first visit and stored for possible HCV viral load and resistance testing, and for future studies.

Follow-up visits (Table 3). Follow up visits will occur at weeks 4, 8, 12, and 24 (if necessary). Adherence to all medications will be evaluated by electronic monitors and self-report. Weeks on treatment will be determined by electronic monitors and chart review. HCV viral load, virological endpoints, and resistance results will be obtained by chart review and blood draw, if unavailable by chart review. IMB model mediators will be assessed at weeks 8 and 12. Potential moderators will be assessed at each monthly visit.

Table 3. Overview of Data Collection by Aims				
Aim & Hypothesis	**Construct**	**Measure, source**	**Research visit (week)**	**Source**
Outcome Measures				
Aim 1, H1	Adherence	Med-ic® and MEMS® Electronic Monitors	4,8,12	Electronic
Aim 1, H2	Completion	Medical record	NA	Chart
Aim 1, H3	Viral load (SVR)	HCV VL by Roche TaqMAN assay	0,4,8,12, 24, FU 4, FU12, FU24	Chart, Blood
Aim 1/2, H4	Resistance	HCV GenoSURE NS3/4A, NS5A, NS5B (Monogram)	4, 8, 12, 24, FU4, FU12, FU24	Chart, Blood
Aim 3	Cost	HCV treatment mDOT and CGT interventions Non-HCV treatment health services	NA NA 12,24,FU4. FU12. FU24	Chart Logs, Direct Observation Q
Other covariate measures*				
All	Demographics	Age, race/ethnicity, education, income, housing	0	Q
All	HCV-related clinical information	HCV VL, HIV, HCV genotype/subtype, IL28B, APRI and FibroSURE (biomarkers of liver fibrosis)	0	Chart
All	Substance use	Addiction severity Index-Lite (ASI-lite) (152,153) Alcohol use (AUDIT) (154) Urine toxicology EMIT assay	0,4,8,12, 24, FU4, FU12, FU24	Q, Urine
All	Methadone dose opiate withdrawal	Methadone dose; Subjective and Objective Opiate Withdrawal Scales (SOWS and OOWS) (155)	0,4,8,12, 24, FU4, FU12, FU24	Q
All	Neuropsychiatric	MINI (138-140)	0	Q
All	Information , motivation, and behavioral Skills	Health Beliefs Model (161) HCV Motivation (161) Adherence Self-Efficacy (161)	0, 12	Q
All	Social support	Medical Outcomes Scale (162)	0,4,8,12,24, FU4, FU12, FU24	Q
All	DAA levels	GC-MS (if additional funding obtained)	4	Blood
All	Depression, anxiety, and hostility	Depressive symptoms (BDI-II) (156-157) Brief Symptom Inventory (BSI) anxiety subscale (158) BSI hostility subscale (158-160)	0,4,8,12,24, FU4, FU12, FU24	Q
All	Pychosocial factors	Stages of readiness for HCV treatment (183) Trust in physician (184)	0 0,4,8,12,24, FU4, FU12, FU24	Q
All	Quality of life	HCV QOL and EQ-5D (163-166)	0,4,12, 24, FU4, FU12, FU24	Q
All	Med side-effects	Adult ACTG adherence instrument – revised (167)	0,4,8,12, 24, FU4, FU12, FU24	Q
All	Adherence (self report)	Adult ACTG adherence instrument (167) Visual Analogue Scale (VAS) (168) 24 hour dietary recall instrument	0,4,8,12,24	Q
Q=Questionnaire		*All measures used in Dr. Litwin's pilot K23 HCV DOT study or Dr. Edlin's current R01 study		

D. 10.3. Definitions of outcome measures.

Med-ic® or MEMS® missed dose adherence. For DAA and ribavirin (if applicable), adherence will be calculated as Med-ic blister pack dose openings divided by total number of prescribed doses in time interval. For example, Med-ic adherence for one week would be X/7Y, where X=number of Med-ic dose openings recorded in one week and Y=number of doses prescribed per day.

HCV treatment completion**.** Subjects will be considered to have completed treatment if they have completed at least 80% of the planned treatment course (at least 10 weeks of 12 week course, or at least 20 weeks of 24 week course) based on response guided therapy approach.[98,115]

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

Resistance. Subjects will be considered to have new drug resistance if they have a telaprevir- associated mutation (any substitutions at V36, T54, R155, A156) at any time point during the study, and the specific mutation did not exist at baseline. Subjects will be considered to have new drug resistance if they have a ledipasvir- associated mutation (K24R, M28T/V, Q30E/H/K/L/R, L31V/M/I, and Y93H/N) during the study, and the specific mutation did not exist at baseline. Subjects will be considered to have new drug resistance if they have a sofosbuvir- associated mutation (S282T) at any time point during the study, and the specific mutation did not exist at baseline.

Cost. Costs of HCV treatment will be collected using the same methods as in the pilot analysis (see Section D.1.8 above), by conducting chart reviews and assigning unit costs to all provider visits, lab tests, and medications based on Medicare fee schedules. The cost of the mDOT intervention will be determined by conducting observational time studies of the additional medical provider and patient time required for mDOT,

using prevailing national wage rates to determine the cost of the time, and applying this cost to each DOT interaction. Patient time costs will be valued based on the minimum wage, because most patients are likely to be unemployed. The cost of the CGT intervention will be similarly determined through observational studies, as well as staff member time and activity logs, and expense logs will be maintained for transportation and other incidental costs. Provider time spent on research activities, such as conducting research visit assessments, will be excluded. We will also examine the cost of health care services received outside of the study (emergency department visits, hospitalizations, substance abuse treatment) based on quarterly patient self-reports.

D.10.4. Data Sources. There will be 6 data sources. Results will not be provided to participants' medical providers unless participants specifically request (in writing) that study staff release this information.

Medical record. HCV viral load and resistance assays (if no SVR) will be obtained when possible by chart review. HCV viral load is measured by the Roche TaqMAN assay and HCV resistance is measured by the Monogram HCV GenoSURE NS3/4A assay, which is automatically run on any HCV viral load which is •2000 IU/ml. Information on treatment interruptions and discontinuation will be obtained from medical records.

Blood. Three tubes of blood will be drawn at weeks 0, and 4, and stored at Einstein's Clinical Research Center (CRC). HCV viral load and resistance assays will be performed if not available by chart review. For subjects who fail to achieve SVR, resistance testing will be performed on post-treatment specimen. All testing will be performed at Montefiore's laboratories.

Urine toxicology. Participants will provide urine specimens at each research visit, which will be tested for cocaine and opiates (and pH to ensure validity) using enzyme multiplied immunoassay technique.

Adherence by electronic monitors (Med-ic® and MEMS®) and self-report.

ADHERENCE TO DAAs AND RIBAVIRIN will be measured in all three arms by electronic compliance monitoring for blistered medications for the first 12 weeks of treatment with an attached Med-ic® device. Med-ic® is an innovative stick-on paper label for medication blisters that provides a disposable method to measure adherence.[185] Med-ic® packages yield 99.6% event accuracy (time of dose removal correctly recorded within ±2 minutes). This technology will allow tracking of medication usage from weekly blister packs prepared by our local pharmacist. Blister packs will be pre-fitted with labels and electronic tags, which can be recycled up to five times to save cost.

In the TAU arm, subjects will receive monthly packages of 4 blister packs, delivered at their methadone clinic by nurses. Blister packs will be returned at research visits for downloading adherence data. In the CGT arm, subjects will receive weekly blister packs at group meetings and used packs will be collected at each group. Unreturned packs will be returned at research visits.

In the mDOT arm, subjects will take observed doses from weekly blister packs, but the packs will be modified to contain only observed doses. Individual take-home doses will be taken in weekly blister packs given on Monday. Blister packs will be collected weekly.

SELF-REPORT ADHERENCE will be measured using a modified ACTG questionnaire, adapted for IFN, DAAs, and ribavirin, as well as a single-item visual analogue scale (VAS) which has been shown to correlate well with both pill counts and virological outcomes in HIV-infected patients taking HAART.[167,168] Adherence to dietary recommendations will be conducted by 24 hour dietary recall. Fat content of each meal will be determined with available software (www.nutritionco.com).

Participant surveys. At baseline and every research visit, participants will answer surveys using Audio Computer-Assisted Self-Interview (ACASI) technology. The ACASI system displays each question on a computer monitor while playing an audio recording of the question. Participants enter responses directly on the computer, which may result in more accurate reporting of sensitive behavior than other survey methods.[170]

D.11. Analytic plan. First, the success of randomization will be checked by comparing the mDOT, CGT and TAU groups on key variables, such as age, gender, ethnicity, race, HCV viral load, HCV subtype (1a vs. 1b), BMI, psychiatric history, active drug use, and social support.[46] By design, IL28B and stage of liver disease will be represented equally in each arm. Continuous variables will be compared between arms using the ANOVA or Kruskal-Wallis 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. In primary analysis, we will use the intention-to-treat principle, which preserves the advantages of a randomized design.

D.12.1. Hypotheses for Aim 1. We hypothesize that in the intensive intervention arms, compared to the control arm, rates of adherence, treatment completion, and SVR will be significantly higher, and that rates of resistance will be lower. We further hypothesize that the proportion of subjects in the intensive models of care arms who achieve an SVR will be equivalent to that observed in large registration trials.

D.12.2. Analytic plan for Aim 1. Adherence to DAAs, ribavirin, and IFN will be determined using electronic monitors and self report, as described above. Initially, adherence will be calculated as a single outcome for each subject, evaluated at the end of the study. We will use Chi-square tests or Fisher's exact test to compare the proportion of subjects who achieve high adherence rate (≥ 80%) complete treatment, achieve SVR, and develop resistance in the three arms (mDOT, CGT, and TAU). If the omnibus equality test of adherence across the 3 groups is rejected, we will conduct the following 2 specific post-hoc pairwise tests with a Bonferroni adjusted 2-sided alpha= 0.025: mDOT vs. control, and CGT vs. control. This strategy will be applied to multivariable logistic regressions if any potential confounding variables not equally distributed between the study arms at baseline are identified.

For the analysis of repeatedly measured adherence (using 6 post-baseline time points and adherence as a continuous measure), we will apply mixed effects linear model to test if the 3 groups are significantly different. This model accounts for within-subject longitudinal outcome correlation by taking the subject-level intercept as random. The model will include potential confounding variables. If the omnibus equality test is rejected, we will conduct the 2 post-hoc pairwise tests described above. Concerning potential clustering effects in the CGT arm, we used pilot data (5 groups) to examine whether clustering influenced adherence. Between cluster variation was not significant, as tested by application of a random effects repeated-measure ANOVA model. Clustering in the GCT arm will be minimal, and we will not adjust for it in statistical or power analysis.

We will also apply mixed effects logistic regression to test the significance of mDOT and CGT on repeatedly-measured undetectable HCV VL throughout the intervention period, adjusting for substance use. Changes in illicit drug use will be analyzed using urine toxicology data from each visit, counting the "person-month" as a unit of analysis, and analyzing the proportion of person-months that are positive for use of illicit drugs using a chi-square analysis.

As secondary analyses, we will examine if mDOT and CGT effects, v. TAU, will be mediated by IMB components. We will assess IMB model mediators of adherence at baseline, and during the intervention, and will analyze changes in those variables from the baseline to the intervention period. The indirect effects of IMB mediators will be tested by assessing changes in coefficients of the intervention effect (mDOT or CGT) with and without IMB component(s) in mixed effects models. Confidence intervals of the mediated effects will be calculated by bootstrapping, and mediation assumed if confidence intervals do not include zero.

D.12.3. Hypotheses for Aim 2. We hypothesize that only a minority (~20%) of IDUs will develop resistance, and that the relationship between adherence and resistance will be quadratic.

D.12.4. Analytic plan for Aim 2. The proportion of participants (n=150) who develop resistance will be determined with 95% confidence interval (CIs) calculated using exact binomial methods. The proportion of participants with resistance will then be determined within each of 4 groups determined by quartiles of adherence measured at the final time point in the study. We will apply logistic regression models to estimate odds ratios for resistance in each quartile. To examine whether the relationship between adherence and resistance is quadratic, we will test a linearity of trends in odds ratios. If this linear trend is rejected, we will identify a quartile group that is associated with the highest odds of resistance. Potential covariates will be entered in regression models if found by univariate analysis to be associated ($p<0.2$) with resistance.

D.12.5. Hypotheses for Aim 3. We hypothesize that the total cost of delivering the CGT intervention will be lower than delivering the mDOT intervention, and that the incremental cost-effectiveness ratios for CGT v. TAU and mDOT v. TAU will each be less than $100,000/QALY.

D.12.6. Cost and Cost-effectiveness Analyses. To project future HCV costs and life expectancy, we will adapt to the study population a computer simulation model of HCV disease progression that has been developed by Dr. Linas based on published data using empiric calibration methods.[171-172]The model is currently being updated with data on disease progression and resource utilization from a racially diverse cohort of over 600 HCV-infected individuals cared for at Boston Medical Center, an urban public hospital system, including IDUs in methadone treatment and active IDUs.[173] The model simulates chronic HCV with fibrosis progression through 3 stages of liver fibrosis including: mild to moderate fibrosis, cirrhosis, and decompensated cirrhosis. At all stages, HCV infection is associated with increased resource utilization and decreased quality of life (QOL).[136,186-187] When HCV infection reaches the stage of cirrhosis, individuals begin to experience increased mortality attributable to liver disease.[188] With successful HCV therapy, disease progression halts, and mortality, resource utilization, and quality of life returns to that of HCV un-infected individuals.[189] HCV-related QOL is stratified by fibrosis stage, and costs of chronic HCV care (such as hospitalizations, ED visits, and clinic visits) are identified separately for patients with and without cirrhosis and stratified by age and sex.

We will use the model to assess the cost-effectiveness of the 3 interventions: TAU, mDOT, and CGT. Primary outcomes will be projected life-expectancy, quality-adjusted life-expectancy (QALYs), lifetime costs, and incremental cost-effectiveness ratios measured in $/QALY. We will forecast health and cost outcomes of each intervention for a hypothetical cohort of HCV patients using baseline study data on fibrosis, age, sex, and alcohol use, and study outcome data for each intervention including SVR, resistance, and retention in care. We will explore the potential impact of resistance mutations by varying the efficacy of subsequent HCV retreatment for patients with resistance who choose to be retreated. Lifetime costs will include the costs of the intervention received as well as projected future costs of HCV care depending on treatment effectiveness. Incremental cost effectiveness ratios will be calculated for TAU compared to no treatment and for mDOT and CGI compared to the next most expensive intervention, with costs and QALYs discounted at 3% annually according to standard practice.[173] The resulting ratios will be compared to a threshold of $100,000 per QALY.[174-175] To explore uncertainties in our results, we will perform one and 2-way sensitivity analyses on key input variables (e.g. probability of SVR and intervention cost) and probabilistic sensitivity analyses (PSAs) using second order Monte Carlo simulation on multiple variables.[176] For PSAs we will perform 1,000 simulations of a cohort of 100,000 individuals. The result will be a distribution of 1,000 model-based outcomes with a median and inter-quartile range that reflects underlying uncertainty in critical model parameters.

D.13 Power considerations Assuming a conservative attrition rate of 20%, 50 subjects per arm will begin the study, but 40 subjects per arm will complete it. For power calculations for repeatedly measured continuous or binary adherence outcomes, we will use the expected number of observations per subject. The power analysis is conducted based on the omnibus testing of equality across the three groups. It follows that at least one of the post-hoc pair-wise tests is powered to be rejected by this study design.

Adherence. Based on our pilot data, if we conservatively assume that 80% of subjects in both mDOT and CGT arms will achieve ≥80% adherence (v. 50% in the TAU arm), we will have >87% 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 87% 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 90%, even if anticipated ICC is as high as 0.5.

Treatment completion. Based on our pilot data, if we assume treatment completion rates of 85% in CGT, 60% in mDOT, and 50% in TAU, we will have >80% power to detect this difference.

SVR. We anticipate that SVR rates in the mDOT and CGT arms will be 70%, and ≤40% in the TAU arm.[13,70,82] The statistical power will be >80%. These are conservative estimates of effect sizes, as actual effect sizes will likely be larger because regimens now contain telaprevir which is taken 3x daily. Effects size for fixed-dose (ledipasvir and sofosbuvir) is likely to be lower.

Resistance. We estimate that 16% of intervention arm subjects v. 30% of TAU subjects will develop resistance. We are underpowered to detect this difference, and consider this an exploratory analysis.

Effectiveness of intensive models of care. We will determine the proportion (and 95% CI) of subjects in each of the intensive intervention arms to achieve SVR, and compare to results from large registration trials.

D.14. Limitations. In addition to the considerations noted in Section D., our results may not be generalizable to HCV-infected drug users not enrolled in methadone clinics. However, we believe that the intensive models we are testing, if efficacious, can and should be adopted in diverse settings and populations.