## 1) Protocol Title (Version # and/or Version Date)

Hepatitis: Treatment and Integrated Prevention (H-TIPS)

v12Mar15

## 2) IRB Review History

NA

## 3) Objectives

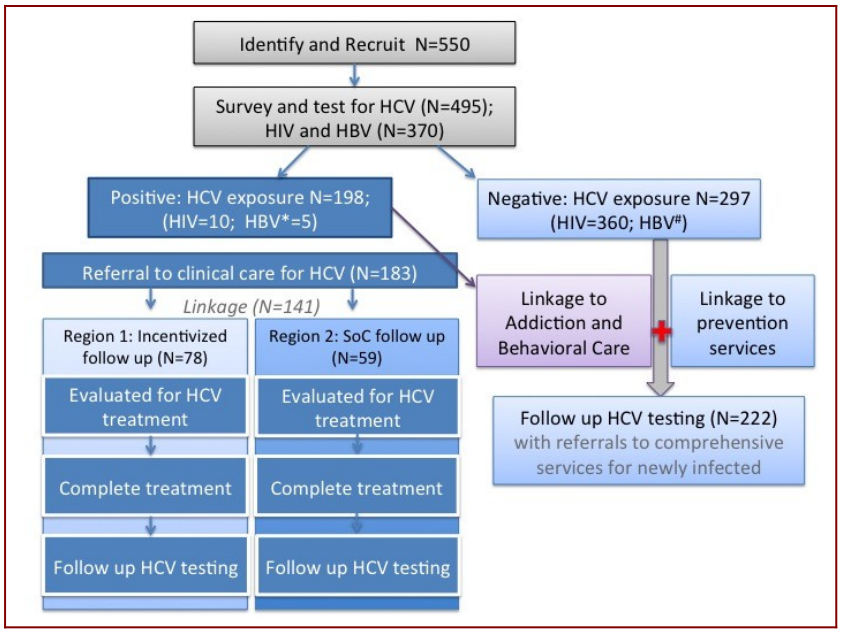
1. To conduct an epidemiological study of HCV prevalence, incidence and risk factors in young adult (≤ 30 years) people who inject drugs (PWID) in non-urban areas of New Mexico. Participants will be tested for HCV, and other viruses (HIV and HBV), and surveyed regarding prevention and risk exposures, drug use patterns, and injecting relationships. We will also assess health service utilization, including primary care, drug treatment, mental health, and HIV care. Viral genotype distribution will be assessed among those who are HCV positive.

2. To determine and compare the proportion of HCV infected young adult PWID who are successfully linked to HCV care who are participating in a contingency management (CM) HCV care program to those participating in a standard of care (SoC) management program. Secondary analyses will assess treatment cascade outcomes including the proportion: (i) evaluated, (ii) initiated, (iii) complete, and (iv) achieve SVR.

3. To examine factors that may contribute to non-treatment, poor adherence, and failure to achieve SVR among young adult PWID with chronic HCV infection.

4. To assess rate and factors associated with HCV reinfection PWID treated for HCV who achieve SVR.

To achieve these aims we will conduct an epidemiological study of HCV in young adult PWID in two areas of New Mexico. We anticipate that ≥550 young adult PWID will be recruited (~275/year), of whom 90% or 495 will be enrolled and surveyed. Of those tested: 297 (60%) will be HCV negative; 167 (33.7%) will have existing (chronic) HCV infection; 16 (3.2%) will be detected with acute HCV (anti-HCV negative/RNA positive), and 15 (3%) will have serological evidence of cleared infection (anti-HCV+/RNA-). We anticipate successful 6-month follow up of 75% of HCV negatives, and with an anticipated 18% incidence rate, we could detect up to 30 incident infection. Referrals will be provided to all HCV infected participants (N=183) and successful linkage will be achieved for total of 141; 78 participants in Region 1, where CM will be implemented, and 63 participants in Region 2, where SoC management will be implemented. If 40% of those with chronic HCV are successfully treated and reach SVR, reinfection risk will be assessed in 56 participants, of whom 3 may show evidence of HCV reinfection. The figure below illustrates the study plan.




## 4) Background

Significance

The HCV epidemic in the U.S. is concentrated in people who inject drugs (PWID); young and recent initiates to injecting have the highest risk for infection for HCV [1-9]. Outbreaks of HCV in young adult PWID have recently reported by the U.S. Centers for Disease Control and Prevention (CDC) [4, 6-9], as well as new ongoing investigations in non-urban locales including Wisconsin, Indiana, Virginia, Pennsylvania, Florida and the Northern Plains (American Indian community) [10]). These have raised serious concerns regarding an expanding epidemic, notable for also for the linkage to extraordinary increases in prescription opiate use in the U.S. Young adults in particular are using more prescription opiates, especially in non-urban areas of the U.S. [11-13], and are also the population with the highest rates of heroin use, which appears to be fueling this newly emergent HCV epidemic [14]. After only one year of injecting, about 20% of PWID will become HCV positive; and after five years, 45% will be infected [15]. HCV incidence in many urban studies has been shown to be stable but extremely high. In the few studies done in rural areas, prevalence has been shown to be in excess of 50% in young adults [16]. To effectively address HCV prevention in young adult PWID multiple approaches are needed, including enhancing access to HCV testing and counseling, and critical prevention services including education, harm reduction services, and drug treatment including opiate agonist therapy [17, 18]. Increasing uptake of clinical treatment services including for effective HCV antivirals as well as drug treatment and mental health services also have potential to impact HCV infection rates in this population [19-21], similar to the Treatment as Prevention (TasP) model promoted for HIV, and perhaps even more so, since HCV infection can be cured (with viral eradication).

HCV among young adult PWID in New Mexico: As in many areas of the U.S., New Mexico has seen a disproportionate increase in the number of acute HCV cases identified and reported to the CDC between 2007 to 2011 (http://www.cdc.gov/hepatitis/Statistics/index.htm). Of special concern is that in these "non-urban" areas, limited data exist to fully characterize the problem. There is significant worry that these emergent high-risk groups may have less access to and utilization of prevention, treatment and primary care services [10, 16]. Much of what is known about risk factors, including drug use patterns, transitions to injecting, injection exposures and other characteristics are from studies conducted in urban settings [22-28]. Few studies have been done in non-urban areas, with the exception of rural Appalachia, where HCV is now an emerging public health crisis [12, 13, 16, 29-31]. Our research program will address and inform several critical areas and gaps in information regarding the HCV epidemic in young adult PWID in New Mexico and the U.S.

Surveillance by the New Mexico Department of Health (NMDoH; collaborators in this study) demonstrates troubling increases in the number of newly reported HCV cases between 2006 and 2012. Over this period, the average number of HCV cases reported annually has been stable, averaging 3634 annually, but the proportion of cases among those age 14-34 had steadily increased. With enhanced surveillance, the number of newly detected confirmed cases has increased from1879 cases in 2006 to 3575 cases in 2012. In 2012, over one third of infections are detected in those age 14-34 years of age, a group that is potentially also at high risk of other blood borne infections including HIV and HBV. Among sites participating in the CDC Emerging Infections Program (EIP), Hepatitis Surveillance Demonstration Sites project, in 2011, New Mexico ranked first among all states (2nd to San Francisco) for the number and rate of HCV cases reported [43]. Accessible and proximal outreach to young adult PWID in in non-urban settings is a priority for the NMDoH HIV and viral hepatitis prevention efforts.

This group has demonstrated capacity to reach young PWID in the regions (non-urban) proposed for the research in this application. The NMDoH Public Health Division and Epidemiology Response Division conducted a pilot project of HCV among PWID ≤ 30 years of age. The "U30 HCV Enhanced Surveillance Pilot Project (U30 Pilot)" identified and surveyed young adults who reported potential exposure to HCV via injection drug use, or who self-reported being HCV positive at harm reduction sites, including SSPs (where our research sites are proposed). Through March 2014, 211 cases were identified, the majority (52%) were Hispanics, ages 21 to 25 (40%) and half (51%) were female. There remains a lack of information regarding the epidemiologic characteristics of HCV among young adult PWID in New Mexico, as well as for HIV and HBV, and it is essential to characterize not only infection distributions, but also injection behaviors, networks for this risk group in New Mexico.

HCV incidence is highest in young and recent initiates to injecting: Over the past decade, numerous studies conducted in urban areas, including San Francisco, Chicago, New York, and other cities have demonstrated that young adult PWID

have extremely high risk for HCV [22-24, 48]. In these cities, HCV prevalence has ranged from 35% to 65%, and incidence from 9% to 34%. Although the rate at which young PWID acquire HCV has declined in the two decades accompanying widespread HIV prevention efforts, HCV incidence remains remarkably high, eclipsing HIV infection rates in the same group[49-51]. It is now well established that in addition to needle and syringe sharing, ancillary drug preparation equipment sharing contributes significantly to transmission [2, 22, 23, 52-56]. Since equipment sharing is common [61], and confers excess risk for HCV acquisition [57], harm reduction and syringe access programs must incorporate messaging, training, and equipment for injecting clients regarding single use containers, sterile water, filters and syringes [62]. Young adult PWID in non-urban areas may be at increased risk of infection resulting from the combination of high viral infectivity and high prevalence of HCV in injecting groups, coupled with a lack of knowledge regarding these other infection routes [10].

Emergent risk factor: prescription opioid use: Prescription opioid use is a key feature emerging in contemporary studies of injection initiation among young adults [12, 46, 47, 64]. Injection of prescription opioids has been shown to be associated with several HCV outbreaks, and with increased risk of HCV [65]. In studies of rural injectors in Kentucky, Havens et al, have shown high HCV prevalence (54.6%), and that injection of prescription opioids is associated with over two-fold higher odds of HCV 2.22 (95% CI=1.13, 4.35) [16]. In New Mexico, as in other states prescription opioid use has increased significantly; however the state has been recognized for implementing a wide range of evidence informed prevention policies to combat the trend [44].

Drug treatment: an essential component of HCV prevention for PWID: Providing medication-assisted treatment (MAT) for substance use disorders is one strategy for reducing injection drug use and the spread of HCV. Injection cessation effectively removes risk for HCV [22]. Opioid agonist therapy (OAT) is one form of MAT that may facilitate injection cessation and thus eliminate risk for HCV acquisition [22]. Two studies, a meta- and a pooled-analysis reported reduced HCV incidence in association with OAT, ranging from 40% to 60% [18, 83]. However, many of those prior studies were conducted older patients and prisoners. We have recently shown that young PWID in San Francisco who get maintenance OAT have a significantly and independently reduced HCV incidence (AHR=0.40; 95% CI: 0.19-0.88) (Tsui J et al, in press JAMA IM). Two other groups from Australia and Canada, are also publishing similar results with almost identical effect sizes. This evidence demonstrating the efficacy of buprenorphine for treatment of opioid dependence in youth [84, 85] compel us to include referrals for drug treatment in our proposed study. Many young adult PWID encounter significant barriers to receiving OAT for the treatment of moderate to severe opioid use disorders [86]. An essential part of our proposal includes linking participants where possible with the highly successful Project ECHO Integrated Additions and Psychiatry (IAP) program. We will track and assess the rate of successful referrals to drug treatment in H-TIPS participants.

Project ECHO and HCV care: Project ECHO has improved both capacity and access to specialty care for rural and underserved populations, notably for hepatitis C treatment. This low-cost, high-impact intervention is accomplished by linking expert interdisciplinary specialist teams with primary care clinicians through teleECHO clinics, in which the experts co-manage patient cases and share their expertise via mentoring, guidance, feedback and didactic education. We will take advantage of the key strength of Project ECHO: developing specialty care capacity in rural underserved communities – for young adult PWID participating in the H-TIPS study. Project ECHO will help increase the likelihood that young adult PWID can obtain care in their own communities with providers that they may know and with whom they may already have established relationships with the goal of increasing the likelihood of successful HCV treatment.

The Treatment as Prevention (TasP) model applied to HCV infection: New direct acting antivirals (DAAs) which involve shorter and more tolerable therapeutic regimens are also likely to improve treatment response rates, including in people who inject drugs (PWID). The "Treatment as Prevention" (TasP) paradigm may be possible due to efficacy, low toxicity and shorter regimens, which could result in higher uptake, better adherence and completion of treatment, offering potential to help overcome the barriers that interferon treatment posed to HCV treatment in drug using populations [89-91]. The potential impact of HCV therapy on HCV infection in PWID populations has been explored in several mathematical models that collectively show that treatment of chronic infection in PWID could impact HCV prevalence and transmission at the population level [19, 92-94]. Research on HCV treatment in PWID using treatments that pre-date newly approved DAAs has shown that PWID can be successfully treated for HCV (reviewed in [95, 96]), although numerous clinical, social and structural factors have resulted in low uptake of HCV treatment in this population [97-99]. With these new treatments there is a need to assess implementation models for successful delivery and adherence to treatment in this high-risk population. For these reasons, we propose to assess the feasibility and impact of a contingency management program on successful linkage to care among young adult PWID.

Contingency management: a model for promoting positive treatment outcomes: Building on the behavioral principles of operant conditioning, contingency management (CM) involves the systematic application of positive reinforcement [102], most commonly incentives to promote behavior change that can have positive impacts on clinical and treatment outcomes. Financial and or material incentives may be used to promote adherence to treatment, or behavior consistent with treatment goals and consequently enhance the benefits of treatment. In the drug abuse treatment field, an extensive literature has examined the efficacy of CM for treatment of drug addiction and to promote drug abstinence and utilized to promote HIV-related health behavior change among substance users [103-105]. CM has been successfully used to promote adherence among PWID to other clinical care programs, including to multi-dose HBV vaccine schedules [106-109], tuberculosis [110-112] and HIV treatments [105]. Most of these studies use modest incentives and show effects on average of 30% or greater on adherence outcomes. Significantly, many also were conducted in integrated conditions-within drug treatment or primary care, demonstrating the feasibility of leveraging CM

within existing programs. We aim to assess the potential effectiveness of CM in promoting the successful linkage to care among young PWID in non-urban areas of New Mexico, comparing outcomes in a CM program offering escalating incentives for on-time attendance at milestone HCV treatment visits in one region, to HCV treatment without incentive (standard of care; SoC) in the 2nd region.

## 5) Inclusion and Exclusion Criteria

Subjects. Young adult PWID age 18-30 years.

- Inclusion criteria: Understand spoken English or Spanish; able to provide informed consent; provide contact information including: name, 'street name' or nickname; and address, email, or phone number of a housed friend or relative who would know their whereabouts.
    - (Aim 1) Age 30 years or younger; history of injection drug use in the past 12 months;
    - (Aim 2) Evidence of existing or acute HCV infection: (i) Existing HCV infection; Positive anti-HCV test and reactive HCV RNA; (ii) Acute HCV infection: Negative anti-HCV test and reactive HCV RNA test.
- Exclusion criteria: Over age 30; planning to leave or travel outside the region in the next 3 months; intoxicated or otherwise impaired to undergo informed consent or to complete a 45-minute questionnaire.

## 6) Number of Subjects (Recruitment Target)

We anticipate recruiting 550 young adult PWID, of whom 495 will be surveyed at baseline. We anticipate following 197 HCV negatives and 141 HCV positive participants prospectively.

## 7) Recruitment Methods

Recruitment will be primarily direct and in-person by partnering with New Mexico Department of Health Harm Reduction sites. [125, 148]. The study mobile van will be located next to these sites and any one utilizing the Harm Reduction program who meets the target demographic for the study will be referred to the study. By being on-site this allows potential study participants to receive full information regarding the study immediately and to be able to make an informed decision. Study staff will have recruiting materials, such as information flyers regarding the study with study contact information listed. There will also be flyers with future dates and locations that interested parties will be able to enroll in the study, in case they are not interested at that time and would like further time to consider participation. A full listing of locations, hours and services can be found at NMDoH website: http://nmhealth.org/about/phd/idb/hrp. By locating the study van near the Harm Reduction programs, this allows for ease of access for interested parties, but also allows for a separation of the two programs, so that potential participants will not feel coerced into participating in the study. They will be free to decline participation if they are not interested. The study will partner with outreach workers who are familiar with the region and services therein, including existing syringe exchange program (SEP) and harm reduction services, as well as locations and venues where young adult PWID congregate. We will also target drug treatment providers in the two areas, as well as specialty housing ("halfway houses" or "sober living environments"). Young adult PWID will be recruited directly and in person; study invitation cards and flyers will also be used at service locations, with community providers and by word of mouth. As part of study recruitment, outreach workers will map outreach areas (street, locale, venue) and number of contacts and study invitations. Regular review of this data will guide subsequent outreach locations and hours.

## 8) Study Timelines

See Appendix 3 of the study protocol.

## 9) Study Endpoints

Aim 1:

Primary outcomes: (1) Prevalent HCV infection; (2) Incident HCV infection;

Secondary outcomes: (1) injecting risk behaviors (e.g. injection equipment sharing; injection frequency); (2) prevention practices (e.g. SEP use); (3) HCV disclosure to an injecting partner; (4) types of drug used (prescription opiates; heroin, benzodiazepines; etc.)

Aim 2:

Outcomes: Primary outcome: Successful Linkage to care, defined as successful evaluation appointment, complete screening, and diagnostic testing for active HCV infection. Secondary outcomes within the HCV treatment cascade: (i) % evaluated; (ii) % initiated; (iii) % complete; (iv) % who achieve SVR

Aim 3:

Outcomes: Primary outcomes: (i) Patient willingness to be evaluated for HCV; views on HCV care, health priorities, stages of change; % adherence to clinical treatment plan, including: (1) proportion of prescribed medication taken; and (2) number and proportion of clinical visits attended as scheduled.

Aim 4:

Outcome: Phylogenetically confirmed HCV reinfection.

## 10) Research Setting

We will operate the H-TIPS study out of a mobile clinical research van, working side to side with collaborating prevention and harm reduction service providers in two "health regions" of New Mexico, including the Northeast and Southwest. Service Program locations throughout the state, including both the two targeted regions offer syringe exchange, overdose prevention education with Naloxone distribution, HIV and HCV testing, and referral to other services. Additional services are offered at many locations, including food, clothing, suboxone treatment, primary medical care, and STD testing. A full listing of locations, hours and services can be found on the program website: http://nmhealth.org/about/phd/idb/hrp. The mobile clinical research van will outfitted for laboratory procedures associated with point of care HIV and HCV testing, as well as blood specimen collection, processing and storage. The van will also have a private interview room. Study procedures will be conducted in association with NMDoH harm reduction activities, which take place at mobile or stationary sites. With the exception of recruitment, no study activities will take place at NMDoH service locations, so as not to interfere with the provision of services. The study van will have regular schedule with afternoon and evening hours at these locations two to three days per week. A field supervisor, interviewers, counselors, phlebotomist/lab manager will staff the van. Appointments will be available, but not required for participation.

## 11) Study Methods

Eligible young adult PWID will be undergo an informed consent process in private area with trained research staff members. The research staff will review all elements of the study: provide an overview of the study, explain its purpose, procedures, risks and benefits, alternatives, research-related procedures (described in further detail in Section 27). Names and contact information will be collected; all of this information will be entered into a secure database. We will also use a digital fingerprint technology (PersonID; 360 Biometrics) system which works by converting an individual fingerprint into a digital image and then into a Unique Testing Code (UTC) that is recognized later, to easily allow for verification of unique individual identities and tracking of unduplicated participants. The digital finger printing protects participant confidentiality by creating a unique identifier that will allow us to identify the participant without using identifying information. The fingerprint scan is saved only as the digital number on a secure UNM server, so there is no scan of the actual fingerprint saved anywhere. This technology has been utilized by the PID in the United States, Cambodia and Africa with great success and acceptance by participants. Utilizing this technology will also protect the study from participants who attempt to receive extra incentives by re-enrolling using false information.

Questionnaires will be administered by trained interviewers. Interview results will be captured electronically on tablets. The questionnaire will capture multiple domains of information summarized in the table below. A survey previously used by the investigators is attached, however we expect that changes may be made to it in collaboration with collaborators at the Center for Disease Control (CDC) Appendix 1. If the survey is modified we will submit it for review to the IRB prior to implementation.

**Categories of information and outcome data to be collected in quantitative surveys**

| AIM 1 - Domain | Data to be collected (See Appendix 1) |
|---|---|
| Demographics and socioeconomic | Age, education, housing status, mobility history, sources of income, family structure; |
| Medical history and health services use | Utilization of health services: primary care, STI; drug treatment: MMT, buprenorphine, 12-step, etc.; HIV and HCV prevention (harm reduction, testing, SSP); previous HAV, HBV vaccine; hospitalizations; overdose; mental health; |
| Drug use | Injection related: types of drugs, frequency, quantity, binge use, routes of administration; Initiation of injection: age, type of drug; Use of clean/sterile equipment; frequency, re-use, sharing; Non-injection drug use history; alcohol use and abuse (modified Audit-C); |
| Sexual behavior | Number, sex and type of sexual partners (steady, casual) frequency of sexual practices, condom use. |

| | |
|---|---|
| Social/relationship | Injecting partnerships, duration number; sexual partnerships; overlapping sex/injecting partnerships, behaviors in partnerships |
| **AIM 3 - Domain** | Data to be collected: |
| Patient | Willingness to be evaluated for HCV care and treatment*; Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES8D); From Aim 1 (above): Substance use measures; alcohol use (modified Audit-C); medical history and health services use - including use of prevention services and drug treatment, housing, mobility and incarceration |

Blood specimens will be collected by trained phlebotomists into two five mL EDTA tubes on visits with HCV RNA and HBV testing. Procedures for specimen transportation will be in compliance with US Department of Transportation Hazardous Materials Guidelines. One blood sample will be delivered the United Blood Services for confirmatory HCV RNA testing. One will be delivered to the CLIA certified NMSLD laboratory (New Mexico State Lab Division) for anti-HBc, HBsAG, and anti-HBs testing. Remaining samples will be stored for five years in a secure lab at the University of New Mexico Cancer Center to be used to compare HCV genotypes for any participant who becomes re-infected with HCV during the study.

Viral testing: All participants in the study will receive HBV, HCV and HIV tests. This group is at high risk for HBV and HIV, and testing them for these diseases allows for an enhanced epidemiological profile, as well as offering the participants a valuable service. All viral testing will be done with appropriate pre-and post-test counseling. HBV, HCV, and HIV are reportable diseases in New Mexico, and positive cases will be reported to the New Mexico Department of Health. Participants who test positive for any of these infections will receive appropriate referrals to care. Those that test positive for HIV will be linked to Department of Health Infectious Disease specialists and local organizations that provide services for HIV positive individuals. The study will only collect data on HBV and HIV infection, it will not be collecting data on HBV and HIV treatment. Information and referrals will be available as part of the SOC.

HCV testing: We will test for both anti-HCV and HCV RNA. Anti-HCV testing will be done using a rapid point-of-care test that uses a finger stick to test capillary blood (OraQuick HCV Rapid Antibody Test (OraSure Technologies)). This test has high sensitivity and specificity [133] and has been shown to be well accepted for HCV screening in young adult PWID [137]. We have experience and Standard Operating Procedures (SOPs) for this test. All participants will also be asked to undergo phlebotomy for HCV RNA testing. Dry-blood spot (DBS) specimens will be collected at check-in visits and stored for future HCV RNA testing [124]. We will use a sensitive qualitative HCV RNA test (Gen-Probe (San Diego, CA)/Chiron (Emeryville, CA) that uses transcription mediated amplification (TMA) to identify positive RNA results. This test offers the advantage of low cost and highly sensitive detection of HCV RNA. Using this testing algorithm we will be able to provide participants with knowledge of their infection status, including acute, cleared, or existing infection. Rapid anti-HCV testing

will enable our proposed study participants to get their anti-HCV results immediately. Participants will be asked to return in one week for HCV RNA results.

HIV testing: HIV testing will be voluntary and will be completed using the Trinity Biotech Uni-Gold Rapid HIV test, using either venipuncture or a finger stick to test blood for HIV antibodies. This test is a single use rapid immunoassay and detects antibodies to HIV-1 and HIV-2 with high sensitivity (99.3% (95% CI=97.1%, 99.9%). This test has been used in New Mexico since 2006. Confirmatory testing is completed with the use of a 4th generation assay blood test and a multi-spot test which test for both antigens and antibodies to HIV-1 and HIV-2. These confirmatory tests are collected by the testing agency and then sent to NMSLD (New Mexico State Lab Division) for processing. The procedures take a total of 30 minutes: results from the Uni-Gold Rapid HIV test take 10 minutes, and counseling takes an additional 20 minutes. Participants are asked to return for confirmatory tests in two weeks.

HBV testing and vaccination: HBV testing will be done through venipuncture by a licensed phlebotomist or nurse. All HBV testing will be conducted by the New Mexico State Lab (NMSLD). NMSLD conducts anti-HBc, HBsAG, and anti-HBs testing to determine the presence of HBV infection. HBV test results will be available within five days of NMSLD's receipt of the blood specimen. Once the HBV test specimen has been collected from the individual, they will be offered a first dose of Twinrix ® vaccine. This will be offered to all study participants that have not had the vaccine. The individual's vaccine information will be entered into the New Mexico Statewide Immunization Information System (NMSIIS). NMSIIS is a confidential, web-based, information system that keeps immunization records of people vaccinated in New Mexico. Using NMSIIS, medical providers can obtain up-to-date, accurate immunization records for patients immunized in New Mexico, even if that patient is new to the practice. (As of July 1, 2014, all persons who have received any type of vaccination must, by law, be entered into the NMSIIS.) Once entered into NMSIIS the individual can be notified when to receive their one (1) month and six (6) month doses to complete the series.

Following HCV negatives: All HCV uninfected participants will be followed up with check-in and study visits at regular intervals. Check-ins at months 3 and 9 will include optional anti-HCV testing and collection of DBS for future HCV RNA testing. Check-in visits may be done by phone or in person. Study visits at month 6 and 12 will include survey and blood testing procedures.

Incentives: We will provide cash incentives and opportunities for regular contact in order to enhance retention and attendance at check-in and follow-up visits. This table summarizes the proposed incentive scheme.

| **Remuneration for study visits for New Mexico H-TIPS prospective study of HCV incidence** | | |
|---|---|---|
| **Visit** | Procedure | Amount |
| | Baseline interview | 10 |
| **1** | Anti-HCV test and blood draw for RNA | 5 |

| | | |
|---|---|---|
| **1.1** | HCV RNA results | 15 |
| **2** | 3-month check-in (optional anti-HCV testing) | 5 |
| **3** | 6-month follow-up visit with interview and HCV testing | 10 |
| **4** | 9-month check in (optional anti-HCV testing) | 5 |
| **5** | 12-month follow up visit with interview and HCV testing, and results | 10 |
| **Total remuneration possible** | | 60 |

Retention: We will make every effort to retain cohort participants in the study using methods described below.
(1) Thorough explanation of the study visit schedule and procedural requirements during the informed consent process, and re-emphasis at each study visit.
(2) Compilation of detailed contact tracing and locator information at the study screening visits including phone and SMS (texting) numbers, locations where they may be found, and people who may be contacted to help locate them (eg., friends, family). The information will be actively reviewed and updated at study check-ins and follow-up visits.
(3) Use of appropriate and timely visit reminder mechanisms (e.g., Facebook, telephone and e-mail) (See appendix 4).
(4) Immediate and multi-targeted follow-up on missed visits.
(5) Use of trained outreach workers to complete in-person contact with participants at community locations, homes, venues, etc.
(6) Regular communication with the service and community based organizations to increase awareness of the purpose of HCV prevention research and the importance of completing research study visits. The study team will generate weekly reports on the number and percentage of participants completing the follow-up visits throughout the course of the study. Study investigators and outreach staff will track retention rates closely and work with the study site as needed to take any required action to address below-target retention rates.

Referrals to HCV care and tracking linkage: We anticipate identifying 198 participants with HCV infection.

HCV Education: All participants identified with HCV infection will be offered participation in a one-on-one HCV education session. This session will be led by the H-TIPS counselor, and will include information on key areas including: (1) the natural history of HCV, (2) reducing risk of transmission, (3) reducing risk of progressive liver disease, and (4) current anti-viral therapy based on national guidelines [152] and modified based on existing resources that have been developed for outreach in this younger population (http://www.ufomodel.org/about) with previous support from the CDC National Center for HIV, Viral Hepatitis, STDs and TB Prevention.

Referrals to clinical care: HCV-infected participants will be referred to a Project ECHO linked provider in their region. These participants will be assigned to one of two groups, one that will receive SOC, the other that will also be enrolled in the Contingency

Management Intervention. The CMI is that one group of the HCV-infected participants will receive incentives for attending their HCV treatment appointments, while the other group will not. Incentives will be in the form of money, which will be loaded onto a pre-paid debit card after each visit, once the visit has been confirmed by study staff. This is summarized in the following table:

| **Follow up milestones for HCV+ young PWID referred to HCV care: CM and SoC management** | | | |
|---|---|---|---|
| Visit | | Region 1: CM $ | Region 2: SoC $ |
| 1 | HCV Infection education session | 25 | 25 |
| 2 | Initial assessment | 5 | 0 |
| 3 | Laboratory visit | 5 | 0 |
| 4 | Follow up assessment #1 | 5 | 0 |
| 5 | **If HCV treatment*:** | | 0 |
| 6 | HCV Rx follow-up –week 2 | 10 | 0 |
| 7 | HCV Rx follow-up- week 4 | 10 | 0 |
| 8 | HCV Rx follow-up –week 8 | 15 | 0 |
| 9 | HCV Rx follow up – week 12 | 10 | 10 |
| **Total remuneration possible** | | **105** | **35** |
| ***** This schedule is based on 12-week treatment, such as for genotype 1. The schedule will be modified for those requiring 24 weeks of follow up such that the total remuneration is still $70. | | | |

The groups will be determined by geography, Dona Ana county vs. Rio Arriba County. It has not yet been determined which county will receive the CMI. Study staff will be contacting the physician's offices to verify that study participants ( both the CMI group and the SOC group) have attended their appointments. All HCV positive participants will receive incentives for participating in the education session with study staff and for returning at the 12-month mark for a follow-up HCV test.

All HCV clinical care will be managed by providers and tracked by Project ECHO using the iHealth data system. Participating providers will be fully informed regarding the H-TIPS Study. The H-TIPS Project Director will work with providers to track H-TIPS participants' scheduling and participation in clinical care and to facilitate implementation of the CM incentives. In general, patients may have the following visits for HCV treatment evaluation/planning; 1-2 visits for initial evaluation and follow to review laboratory results; 1 visit at start of treatment. Depending on genotype/duration and whether or not the patient receives interferon their follow-up will vary. For those on 12 weeks of therapy the general follow-up is at weeks: 1, 2, 4, 8, 12 and then 12 weeks later to check for SVR. For those on 24 weeks of therapy the general follow up adds weeks: 16, 20, 24 and then 12 weeks later to check for SVR. All participants will be asked to sign release of medical information forms and HIPAA compliance will be disclosed and observed.

Participant/patients will be surveyed regarding their views on HCV treatment (Aim 3). Participant/Patients will be surveyed regarding willingness for treatment following the HCV education session.

HIV, and HBV referrals as well as HBV vaccine delivery will be tracked using clinical records and the NMDoH Vaccine registry.

Reinfection determination: HCV Core-E1 sequences will be obtained from samples collected at baseline (1st observed viremic sample) and the visit with a new positive viremic test following HCV treatment. Procedures for RNA extraction, sequencing, amplification, and interpretation have been described in detail by Osburn et al.,[154]. Viral sequences will be identified as unique when the Core-E1 divergence between two sequences was ≥0.05. Genotypes will be determined by comparing Core-E1 sequences to HCV genotype reference sequences using the Los Alamos National Laboratories HCV Phylogenetic Placement Service with pairwise distance analysis [155]. Sequencing results will be compared to genotyping results obtained using a commercial genotyping assay (LiPA Line Probe Assay (Bayer Diagnostics, Tarrytown, NY). Viral sequencing will be done in the laboratory of Dr. Andrea Cox M.D., Ph.D., at Johns Hopkins University (See letter of support). All samples sent to JHU will be de-identified, with the link residing with Dr. Page at UNM. Dr. Cox is a longstanding collaborator with Dr. Page and has independent funding (U19AI066345) to do this testing.

## 12) List of Appendices

1. Behavioral survey (Quantitative Questionnaire)
2. Reinfection interview (Qualitative questions)
3. Timeline
4. Text for use on phone (SMS), email and/or Facebook reminders
5. References

## 13) Data and Specimen Banking

N/A

## 14) Data Management

Data will be stored and managed on a secure server at UNM operating an SQL Server database. The database will be populated using both electronic and paper source systems. At the study site, paper forms will be used to collect eligibility and contact tracing information with an option for online data entry. Data will be coded with a digital study number (generated by the electronic fingerprint system). Survey data will be captured electronically by interviewers using netbooks operating Entryware 6.0 (Techneos Systems). Both Interview and clinical data will be saved into electronic files using Tablet PCs, with options for wireless or cabled data transfers. Laboratory data will be transferred from paper source forms to the server via online data entry. Programming skip

patterns, ranges and logicals with alerts to deviations, will reduce missing data. Identifying information will be stored in a password-secured file. The database will be secured and accessed via a Citrix Secure Gateway via secured link. Control of users and privileges, as well as local and remote backup of the database will be in accordance with UNM Epi/Biostat data management procedures. Our group is experienced in connecting this database with several other commercial programs, including Excel, Access, SAS and Stata. Paperwork will be stored in locked file cabinets at UNM. All personal data and identifiers will be maintained in accordance with HIPAA regulations.

For all data sets, preliminary analyses will include checking for missing values, range checking, and outlier checking. Periodically, we will examine distributions of demographic variables such as age, and sex and risk exposures including frequency of risk behaviors assessing consistency and temporal trends. Continuous variables will be examined for normality using Q-Q plots, and transformations including categorizations will also be examined.

*Statistical analyses*

Aim 1: This aim will use descriptive statistics for all outcomes, independent measures and covariates of interest. Analyses of prevalent HCV will use variables collected in baseline interviews. Logistic regression will be used assess factors independently associated with the odds of prevalent HCV. For prospective analyses, we will use Cox regression analyses to assess factors associated with incident infection.

In cross sectional analyses a sample size of 495 will provide a minimum effect size (W) of 0.13. For prospective study of incidence, we anticipate follow up in N=222 (of 297 identified HCV negative). The 222 will contribute 5 (1 baseline and 4 quarterly) visits. We will observe 39 new infections, based on a conservative 18% annual incidence rate.

Power: (1) With a total of 495 individuals at baseline and an estimated 40% prevalence of HCV infection, 95% CI will be 35.7% to 44.5%. With this sample size we will have 80% power with alpha=0.05 to detect effect sizes of 0.13 or greater and a minimum OR of 1.77 if the prevalence of the risk exposure of interest ($P_0$) = 0.50. (2) We conservatively estimate HCV incidence will be an annualized rate of 18%, with 95% CI of 12.5% to 24%. In multivariable models for HCV incidence, we will have 80% power to detect a hazards ratio (HR) of 2.4-3.1 or greater for exposures with prevalence of 30% (for instance RNS or drug preparation equipment), at significance level of 0.05 in proportional hazards model including covariates with an $R^2$ ranging from 0 to 0.4.

Aim 2: For this aim we will compare proportions between CM and SoC groups using chi-square analyses. Multivariable analyses will be done using unconditional logistic regression. Of the 198 identified with HCV infection we anticipate that 183 (92%) will attend an HCV infection & care education session and be referred for evaluation, and 141/198 (71%) will be successfully linked. For secondary outcomes, we anticipate: 165/183 (90%) will present for 1st

evaluation appointment; and of 141 people successfully linked, 40% or 56 people may initiate treatment and potentially achieve SVR.

Power: (1) With a total of 92 evaluated for treatment in the CM group and 91 in the SoC group, we will have power to detect effect sizes (W) of 0.21 or greater. Assuming a 71% completion rate overall and "successful linkage" rates of 85% in incentivized vs. 65% in SoC groups, the 95% CIs for completion will be 0.76-0.92 and 0.54-0.75 respectively. (2) With 78 in the incentivized group being successfully "linked" and 59 in the SoC group, we will have power to detect effect sizes of 0.27 or greater and minimum OR of 3.1 (assuming 50% $P_0$).

Aim 3: Measures of central tendency (means, medians and proportions with corresponding with standard deviation, and range) will be tabulated. Participant demographic and risk behavior information will be obtained from surveys administered as part of Aim 1. Chi-squared and logistic regression will be used to analyze (i) association with willingness to be evaluated for HCV treatment, and HCV treatment outcomes; Multivariable analyses will be done using unconditional logistic regression.

Of the 198 identified with HCV infection we anticipate that 183 (92%) will attend an HCV infection care and education session and be willing to attend a clinical appointment for evaluation. Analyses will be don on the estimated 165/183 (90%) who present for 1st evaluation appointment; 141 people successfully linked, and 56 or (40%) who initiate treatment and potentially achieve SVR.

Power: With 183/198 with chronic HCV infection willing to be evaluated, we will have 80% power to detect a minimum difference in proportions of 0.16, 95% CI: 0 – 0.33, if the proportion of the exposure of interest (e.g., daily injection, alcohol use; in/not OAT program) in the willing to be evaluated group is 50% and 66% in the unwilling. We will be able to detect a minimum effect size of 0.23 for difference in adherence in those who initiated treatment. Comparing the 56/141 (40%) who achieve SVR to the 85 without SVR, we will have 80% power to detect a minimum difference in proportions of 0.16, 95% CI: 0.05– 0.27, if the proportion of the exposure of interest (e.g., drug use, incarceration) in the SVR group is 50% and 66% in the non SVR group.

Aim 4: If 40% of those in the both CM (n=78) and SoC (N=59) groups are treated and achieve SVR, this will total 54 successfully treated young adult PWID. With 5% rate of reinfection, we will observe 3 reinfections.

The small number of anticipated reinfections will preclude rigorous statistical analyses to quantify risk exposures associated with reinfection. For this aim we will conduct qualitative interviews (See appendix 2) with patients who demonstrate reinfection. We will query regarding injecting partnerships and social relationships, disclosure of HCV infection status with partners, and injection risk exposures, including sharing injecting equipment, drug treatment history, and prevention practices.

## 15) Provisions to Monitor the Data to Ensure the Safety of Subjects

Statement of PI responsibility for DSMP: Dr. Page is an experienced investigator in the design and conduct of research protocols with marginalized and underserved populations in the United States as well as in international settings. Dr. Page has been conducting research with people who inject drugs for over 14 years. Dr. Page will assume responsibility for implementing the data safety and monitoring plan detailed below.

**Data security and quality assurance:**
Procedures for data collection, entry transfer, management, storage and handling/disposal after completion of the study: S*urveys:* Study outcome data will be collected through a series of surveys and biological specimen collection with young adult PWID in New Mexico. Survey data will be collected in English and Spanish using electronic data capture methods. We have previous experience with this technology in other studies of PWID. Survey data will be downloaded and stored in a study database at UNM HSC/Division of Epi/Biostat/PrevMed (DEBPM). We will collect self-reported identifying information (name and birthdate), and also will use a fingerprint biometric system (360 Biometrics' PersonID, San Jose, CA, USA) to identify unique and repeat visits by participants. Each individual is first entered into the system by capturing one digit's fingerprint, which is assigned to a random number. Data collected from individuals will be coded with a study ID corresponding to the assigned number. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified using Fingerprint biometric data are captured on a fingerprint reader using an optical sensor. Individuals who participate in data collection (survey, interviews and specimen collection) will be matched by the captured fingerprint against the stored data and the unique number displayed. Biometric data will provide a confidential and secure means of identifying unique visits; it is encoded and cannot be graphically downloaded, ensuring safety and confidentiality. These procedures allow for participation in the study and collection of unique visits while collecting the minimum amount of identifying information on each participant to maintain confidentiality and reduce the likelihood of study-related harm(s).

*Clinical follow up data:* Quantitative data will be collected regarding follow up on referrals to clinical and addiction treatment services to capture the "cascade of care" outcomes. We will also be accessing the NMDoH Immunization registry to assess levels of vaccination for HBV and to record new vaccinations. All participants will be asked to sign medical release form for the study to access medical information.

*Qualitative data:* We anticipate that three interviews will be conducted among participants who are identified with HCV reinfection following HCV treatment. Interviews will be saved into electronic files using Tablet PCs, with options for wireless or cabled data transfers .

All survey data, results of on-site laboratory testing for HIV, HBV and HCV, and any other study forms (for instance receipts for compensation for study time) and administrative forms will be identified by a coded Study ID number that is linked to each

participants biometric identifier. All electronic data files will exclude personal identifying information. Data files will be maintained, updated, backed up regularly (daily and monthly) on site on the local area network. Only authorized study staff will have access to paper or electronic study records. Monthly back up records will be stored off site in a secure location. All data will be maintained on-site for a minimum of five years after completion of the trial.

No names or individual identifiers will be used in any reports of publications resulting from this study. All process steps which involve data being converted from physical form to electronic form (e.g., scanning) will be digitally signed by the person performing the process, using protocols and techniques developed to meet the standards outlined in 49CFR11.

## 16) Withdrawal of Subjects

Subjects are free to withdraw from study participation at any time during this clinical study. The Investigator may withdraw a subject if continued participation is not in the interest of the subject's health and welfare, for noncompliance with protocol-specified procedures, or because of a protocol violation. This will be evaluated on a case-by-case basis by the Investigator. Overall, because this is an observational study with a low risk to participants, no other stopping rules apply.

The primary reason for discontinuation or withdrawal will be documented as one of the following:

- AE
- Noncompliance
- Protocol violation
- Consent withdrawn

## 17) Risks to Subjects

There is a risk of loss of confidentiality, however, the research team will ensure they reduce this possibility through data management and security measures. Being tested for HCV and HIV may cause anxiety regarding test results, whether they are positive or negative. Risks relating to blood draws include: bruising, discomfort and possible infection.

## 18) Potential Benefits to Subjects

Information gained from this study will help researchers in the future better treat and prevent the spread of HCV and HIV. Participants may benefit from learning their HBV, HCV and HIV status, as well as having the opportunity for risk reduction counselling and referrals for and linkage to care.

## 19) Vulnerable Populations

N/A

## 20) Multi-Site Research

This study will take place in a mobile clinical research van where two "health regions" of NMDoH harm reduction sites exist. The PI will have regular communication with the locations to confirm all research staff are competent, properly trained; they will have the most current version of the protocol, consent documents, and HIPAA authorization; any modifications will be communicated to sites and implemented only after IRB approval; they will safeguard all research data; any non-compliance with the study protocol or applicable requirements will be reported immediately to the PI; all adverse events, interim results and study closure determinations will be communicated via email and/or teleconference between the PI and study staff.

## 21) Community-Based Participatory Research/Field Research

See attached Letters of Support from NMDoH, United Blood Services and Dr. Cox of Johns Hopkins University.

## 22) Sharing of Results with Subjects/Incidental Findings

Subjects will be informed of any new study findings that become available during the course of the study, in addition to their blood results as indicated above.

## 23) Resources Available

This study is based on the collective experience, expertise and infrastructure put together by a respected team of researchers, community and clinical experts from the state of New Mexico, home to a burgeoning HCV epidemic in non-urban young adult PWID. This collaborative team, from the University of New Mexico (UNM) Health Sciences Center (HSC) and the New Mexico Department of Health NMDoH) combine expertise in HCV epidemiology, clinical care, and community-based prevention. The team at UNM will include **Dr. Kimberly Page (PI),** an infectious disease epidemiologist with 20 years of experience conduct HCV research in young adult PWID, and extensive knowledge and expertise in comprehensive strategies of recruiting and enrolling young PWID into research studies, collecting epidemiological information, testing for HCV infection, provide linkage to primary care services and prevention-based education. Dr. Page will provide leadership for the study as a whole and working closely the collaborative group from Project ECHO and the NMDoH. **Drs. Sanjeev Arora, Karla Thornton, and Miriam Komaromy** from Project ECHO (Extension for Community Healthcare Outcomes) at UNM-HSC. The Project ECHO team will bring expertise and leadership in enhanced community-based treatment for HCV, especially in non-urban settings. **Dr. Thornton** is an Associate Director of Project ECHO and has experience managing the expansion of the Project ECHO HCV program in the community and in the New Mexico Department of Corrections. **Dr. Komaromy** is an Associate Professor of Medicine and an Associate Director of Project ECHO as well as Medical Director for the Project ECHO Addiction Treatment Program, which aims to engage and support primary care medical clinicians in treating addiction.

The UNM team will be collaborating with the NMDoH, including Mr **Andrew Gans,** MPH, Section Manager for HIV, STD and Hepatitis, Harm Reduction Program Manager, **Dominick Zurlo,** M.A. and Viral Hepatitis Coordinator, **Laine Snow**. The NMDoH leads and contracts with organizations to offer one of the most extensive syringe service programs (SSPs) in the country, in operation since 1998, and has experience conducting integrative prevention programs and surveillance. The Harm Reduction Program will serve as the primary point of contact and recruitment for the population of young adult PWID. This program was one of the first such statewide efforts in the nation and remains one of the largest, serving several thousand unduplicated PWID each year and distributing and collecting well over 3 million syringes through this effort. This positions New Mexico better than almost any other state to recruit this hard-to-reach population quickly and effectively. Collectively, this team including both academic and clinical health leaders from UNM with the NMDoH has the potential to generate real and sustainable impact in this high-risk population.

## 24) Prior Approvals/Attachments Requiring Signatures

Departmental Review and Approval

## 25) Confidentiality

Only IRB approved study team members will be able to view and have access to research related data. All study documents will be stored on a password protected computer in the Division of Epidemiology, Biostatistics and Preventive Medicine.

## 26) Provisions to Protect the Privacy of Subjects

Subjects will be consented and seen for research related procedures in a private clinic room for each visit.

## 27) Compensation for Research-Related Injury

If the subject becomes sick or injured as a direct result from the study, they may receive emergency treatment, however, there is no commitment by the UNM HSC to cover the costs related to research related injuries. The subject and/or their third party payer will be charged in the usual way.

## 28) Economic Burden to Subjects

| Research Procedures | Number of Samples/Procedures | Responsible Party | |
|---|---|---|---|
| | | Study | 3rd Party Payer or Participant |
| HCV, HIV, HBV testing | One | X | |
| HBV Vaccine | All | X | |
| _____ | _____ | | |
| _____ | _____ | | |
| _____ | _____ | | |
| _____ | _____ | | |
| _____ | _____ | | |
| _____ | _____ | | |
| **Standard of Care Procedures** | **Number of Samples/Procedures** | **Responsible Party** | |
| | | **Study** | **3rd Party Payer or Participant** |
| HCV evaluation | All | | X |
| 12 or 24 weeks of treatment based on genotype | All | | X |
| Interferon (if applicable) | All | | X |
| Consultations and education | All | X | X |
| _____ | _____ | | |
| _____ | _____ | | |
| _____ | _____ | | |
| _____ | _____ | | |

The subject will be responsible for the treatment of any adverse events.

## 29) Consent Process (including waiver request for HIPAA, waiver of HIPAA for recruitment only, Waiver of Informed Consent, and Alteration of Informed Consent)

### Consent

In a private location in the closed clinic room within the van, the research staff will review all elements of the study: provide an overview of the study, explain its purpose, procedures, risks and benefits, alternatives, research-

related procedures, etc. The patient is allowed adequate time to review the consent in order to make a decision as to whether to participate, preferably taking the consent form home to discuss it with their primary care physician, family members, and/or friends. All research staff have been adequately trained and the patients will be reminded during the informed consent and throughout the study that their participation is strictly voluntary and that they may withdraw for any reason and at any time without penalty. No claims will be made to the patient as to the efficacy or the experimental treatment.

**Waiver or Alteration of Informed Consent: Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)"in the Click IRB Library to ensure you have provided sufficient information for the HRRC to make these determinations.**

N/A

**Waiver of Written Documentation of Consent: Review the "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" in the Click IRB library to ensure you have provided sufficient information for the IRB to make these determinations.**

N/A

**HIPAA Authorization**

- the history and diagnosis;
- specific information about the treatments, including previous treatment(s;
- information about other medical conditions that may affect treatment;
- medical data, including laboratory test results, radiology and pathology results;
- information on side effects (adverse events), and how these were treated;
- long-term information about general health status and the status of disease;
- data that may be related to tissue and/or blood samples that may be collected;

and numbers or codes that identifiable, such as medical record number.

**Waiver of HIPAA authorization: Review the "CHECKLIST: HIPAA Waiver of Authorization (HRP-441)" in the Click IRB library to ensure you have provided sufficient information for the IRB to make these determinations.**

N/A

**Non-English Speaking Subjects**

This study may enroll participants who are mono-lingual Spanish speakers. Study materials will be available in Spanish. Study personnel will include Spanish speakers.

### Planned Emergency Research Consents

N/A

### Cognitively Impaired Adults/ Adults Unable to Consent/ Use of a Legally Authorized Representative (LAR)

N/A

## 30) Drugs or Devices

N/A

### Drugs: Please respond to all questions in this section and include a completed and signed Drug Attachment form.

N/A

### Medical Devices: Please respond to all questions in this section.

N/A