Title: Evaluating values-based motivational interviewing to increase treatment completion with fixed dose combination MK-5172/MK-8742 among Veterans with active substance use disorders and treatment-naïve genotype 1 chronic hepatitis C

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1. Objective and hypotheses.

Primary Objective: Implement a values-based motivational interviewing (VBMI) intervention to promote treatment completion with fixed dose combination (FDC) MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™) x 12 weeks among treatment-naïve Veterans with substance use disorder (SUD) and genotype 1 chronic hepatitis C virus (HCV) infection.

Primary Hypothesis: Veterans with SUD and genotype 1 chronic HCV infection who receive the VBMI intervention will complete the full course of treatment in 90% of cases.

Secondary Objectives:

1) Utilize VBMI to promote self-efficacy in taking FDC MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™)among Veterans with active SUD and chronic HCV infection.

2) Demonstrate the feasibility of FDC MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™) for obtaining sustained virologic response (SVR) in treatment-naïve genotype 1 chronic HCV infection among Veterans with active SUD.

3) Measure the prevalence of baseline NS5a resistance mutations in Veterans with active SUD and genotype 1a chronic HCV infection. NS5a is a nonstructural HCV protein.

Secondary Hypotheses:

1) Veterans with SUD enrolled in this study will demonstrate a trend towards clinically significant increases in HCV treatment adherence self-efficacy scores between baseline and week 4 of treatment.
2) FDC MK-5172/MK-8742(elbasvir/grazoprevir, Zepatier™) will be well-tolerated by Veterans with SUD.

2. Study procedures

2.1Background: The advent of direct acting antivirals (DAAs) for chronic HCV infection has increased the tolerability and effectiveness of curative HCV treatment. Disorders which can affect adherence to HCV treatment, including SUD, can reduce effectiveness of DAAs. During the pegylated interferon era, the VA HCV 001 study group demonstrated an association

between recent alcohol use and early treatment discontinuation, resulting in decreased treatment efficacy[1]. The authors concluded that patients with alcohol use should be provided additional support to assist with treatment completion.

Motivational interviewing (MI) was initially developed to promote abstinence in those with alcohol use disorders[2]. In recent years, the core of MI techniques has been applied to other behavioral areas, including medication adherence[3]. Prior investigations have determined that MI can promote increased medication adherence among patients with HIV infection[3-4], but less is known about the effect of MI on adherence to HCV medications. One prior study has associated self-efficacy, an idea conceptually linked to MI, with reduced risk of missed HCV medication doses[5].

Acceptance and Commitment Therapy (ACT) encourages the patient to use mindfulness to promote dedication to behavioral change[6]. The patients accept the difficulties inherent to making the change and develop techniques to manage these difficulties. One major component of ACT is identifying values that make a life worth living and then mindfully moving towards such values. This approach has shown promise with tobacco use disorders[7] and has been used to promote psychotherapy attendance among substance use disorders[8].

We hypothesize an intervention which uses VBMI would increase rates of HCV treatment completion with FDC MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™)among treatment naïve Veterans with HCV genotype 1 and SUD. MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™) is a fixed dose combination once daily oral medication for chronic HCV. In clinical trials, treatment-naïve patients with genotype 1 HCV who received 12 weeks of MK-5172 and MK-8742 had sustained virologic response rates of 98%[9].

Approximately 1 in 4 Veterans with chronic HCV have an active SUD requiring hospitalization or residential treatment[10]. As patients with active SUD are often excluded from clinical trial participation, examining the feasibility of using emerging DAAs in this population is warranted.

2.2We will conduct a prospective study of **20** Veterans with treatment-naive genotype 1 chronic hepatitis C infection admitted to the Substance Abuse Residential Rehabilitation Treatment Program (SARRTP) and/or diagnosed with SUD with ICD-10 CM code for in past 6 months. at the G.V. (Sonny) Montgomery VA Medical Center. Institutional Review Board approval will be obtained prior to the conduction of the study.

2.3.1 Study Population

The G.V. (Sonny) Montgomery VAMC is an urban, academically-affiliated medical center in the Southeastern United States. . The center provides care to approximately 39,000 unique Veterans annually in rural and urban areas of Mississippi and surrounding states. The hepatitis clinics in the facility meet 3 ½ days weekly and, to date, have provided DAAs to over 600 Veterans with chronic HCV. As part of a pilot treatment program, 4 Veterans initiated HCV treatment while in residential treatment for SUD. Of these, 3 completed all 12 weeks of treatment while 1 relapsed into alcohol abuse and was lost to follow up.

The HCV treatment clinics meet 3 ½ days weekly to provide DAA treatment for HCV. Veterans with co-existing MH conditions are frequently seen in clinic, including active SUD. Active SUD is not a contraindication for treatment provided the Veteran demonstrates he/she can adhere to medications and follow up visits. Patients with active SUD who begin DAA treatment as an outpatient are followed every 2 weeks.

Inclusion criteria:

1) Identified as having treatment-naïve genotype 1 chronic HCV infection; Veterans who are genotype 1a must have baseline NS5a resistance testing
2) Current resident of the SARRTP program and/or ICD-10 CM code for SUD (F10-F19) within the past 6 months
3) Willing to initiate treatment with FDC MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™)

Exclusion criteria:

1) Contraindications for therapy with FDC MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™
2) Unable to provide written informed consent
3) Hepatocellular carcinoma or other medical condition precluding HCV treatment
4) Acute HCV infection
5) Prior treatment for chronic HCV
6) History of decompensated cirrhosis
7) Platelet count < 75 K/cmm and/or albumin < 3 grams/dL
8) Females and male sex partners of females who are pregnant, nursing and/or unwilling to use contraception
9) Patients infected with genotype 1a who have not undergone baseline NS5a resistance testing

See attached flow chart.

2.5.1Participant Recruitment and Enrollment: Veterans with active SUD are regularly screened for chronic HCV infection. All patients with chronic HCV are subsequently referred to the HCV treatment clinic for treatment evaluation. When evaluating a patient for HCV treatment, current diagnoses including SUD (ICD10 CM F10-F19) are routinely noted. It is standard of care for patients who are infected with HCV genotype 1a to undergo baseline resistance testing before initiation with MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™). Patients meeting inclusion criteria will be offered study participation at their clinic visit. Basic demographic data (age-if less than 89 years, race, gender) will be recorded on all patients who are asked to participate in the study to allow investigators to assess for enrollment bias. Patients who agree to participate will give their written informed consent. Patients will be assigned a unique study number that does not contain personal identifiers after signing informed consent. Each patient will have only one number for the duration of the study. Study records will be labeled with this unique study number and will not contain PHI. Treatment will be prescribed in accordance with US labeling as described in the package insert.
Genotype 1b: 12 weeks MK-5172/MK-8742(elbasvir/grazoprevir, Zepatier™)
Genotype 1a without NS5a RAVs: 12 weeks MK-5172/MK-8742(elbasvir/grazoprevir, Zepatier™)
Genotype 1a with NS5a RAVS: 16 weeks MK-5172-MK-8742 (elbasvir/grazoprevir, Zepatier™) with weight based ribavirin

2.5.2 Baseline visit: Patients will complete a survey of demographic (age, gender, race/ethnicity, income level, marital status, education level, distance from medical center) and medical information. Drug Abuse Screening Test(DAST) and AUDIT will be completed to assess severity of SUD. We will also assess health related quality of life (Rand-36 item Health Survey [Short Form-36]), social support (Medical Outcomes Study Social Support Survey [MOS-SSS]), depressive symptoms (Patient Health Questionnaire [PHQ-9]), and treatment adherence self-efficacy (HCV Treatment Self Efficacy-A [HCV TSE-A]).

2.5.3. Description of the VBMI intervention

Patients enrolled will receive 60-minute sessions at Weeks 0 and 2 and four 15-minute sessions at Weeks 4, 6, 8, and 10. The sessions at Weeks 0 and 2 will focus on identifying values and creating short-term goals within those values, consistent with an ACT framework[6]. Specifically, during these first two sessions values directly (e.g., "My health is important to me.") and indirectly (e.g., "My family is important to me, and I need to be healthy to have time for my family.") related to health behaviors and medication adherence will be elicited. Veterans will discuss how well they are living in accordance with their stated values and identify specific goals and objectives for increasing valued living through the use of goal-setting exercises. The sessions in Weeks 4, 6, 8, and 10 will predominately be brief "check-in" meetings that will focus on helping the participant problem solve barriers to moving towards their values. For a more comprehensive description of the intervention, see Appendix F. The therapeutic approach of all sessions will be founded in MI techniques and specifically utilize the four core processes of *engaging* the Veteran to establish rapport, *focusing* the conversation on unhealthy behaviors and/or targets for change, *evoking* change-oriented talk and increased self-confidence, and *planning* specific practical steps for making change. All sessions will be conducted by a licensed psychologist who has extensive knowledge in ACT and MI or by a trained post-doctoral fellow under the supervision of a licensed psychologist. The sessions will be recorded (audio only) for the purposes of monitoring adherence of the psychologist to the VBMI protocol.

2.5.4 Description of instruments:

The **Rand-36 item Health Survey (SF-36)** is a validated instrument which evaluates physical and mental health. The 36 questions cover 8 domains: physical function, role function as limited by physical health, bodily pain, social functioning, mental health, role function as limited by emotional health, vitality and general health perception. The survey was developed by Rand Corporation as part of the Medical Outcomes Study and has been previously used in Veterans with hepatitis C.

The **Medical Outcomes Study Social Support Survey (MOS-SSS)** has also been widely used and validated among persons with chronic medical illness, including Veterans with chronic hepatitis C. This 19-item survey assesses the patients' perceptions of their existing emotional support, tangible support, affectionate support, and social interactions.

The **Patient Health Questionnaire(PHQ-9)** is a validated survey of depressive symptoms. Higher scores indicate a greater likelihood of clinical depression. This survey is currently used to screen for depression annually in Veterans in care at VA Medical Centers.

The HCV-Treatment Self Efficacy (HCV-TSE) is a standardized survey which assesses self-belief that a patient can complete his/her treatment regimen of pegylated interferon and ribavirin. The patient rates their confidence in their ability to take medications on a scale of 0 to 10, where 0 indicates no confidence and 10 indicates full confidence. The answers to the four individual questions are averaged to a score of 0 to 10. We have adapted 4 questions from the original scale regarding medication adherence **(HCV-TSE-A)** to assess a patient's perceptions of his/her ability to adhere to DAAs.

2.5.5 Follow-up visits:
The study will last 12 weeks, with follow up visits at Weeks 2, 4, 6, 8, 10 and 12, which will be coordinated to occur on the same date as Veterans' substance abuse aftercare visits. Side effects of medications and tolerance of medications will be monitored at each visit using a single question about side effects experienced and response options including the most common side effects and a response of "other" and a description of that side effect. A single question will also be used to assess for any substance use since the last visit, with quantity and frequency being recorded if the response is positive.
Adherence will be assessed at each follow up visit using the Visual Analog Scale and pill counts. Routine laboratory monitoring will include a CBC, CHEM 14, HCV RNA and a urine sample analyzed for cocaine, marijuana, opioid, and amphetamine use (all tests are standard of care). The HCV-TSE-A will be repeated at week 4. Assessments of depressive symptoms (PHQ-9) and health-related quality of life (SF-36) will be repeated at weeks 4 and 12.
If a patient fails to complete the study, a lost to follow up form will be completed,
As part of standard of care for HCV treatment, HCV RNA is measured 12 weeks after treatment completion to assess for sustained virologic response (SVR). Although there will not be a study visit 12 weeks post treatment, this data will be collected and listed in the informed consent.
Although blood is only drawn as part of labs measured for standard of care and is not part of the study activities per se, the amount of blood drawn will not exceed 15 cc per visit.

2.5.6 Measures of adherence:
Visual Analog Scale (VAS): VAS is a self-report adherence measurement tool that is well-validated in HIV populations[1]. The VAS is a 100 mm line which is anchored by word descriptions at either end.
The patient will first name his medication and the prescribed dosing intervals. The interviewer will demonstrate the equivalence of 0%, 50% and 100% adherence on the scale. The patient will then mark their level of adherence with each medication over the two-week interval. The VAS is scored by measuring the distance in mm between 0 and the patient's mark, which is recorded as % adherence. This % will be recorded at Weeks 2, 4, 6, 8, 10, and 12 for FDC MK-5172/MK-8742(elbasvir/grazoprevir, Zepatier) .

Pill Count: The number of each dispensed medications will be recorded at weeks 0, 2, 4, 6, 8, and 10. Patients will bring their pill bottles to each follow up visit where the remaining pills will be counted and recorded. Adherence will be calculated as:
% Adherence = $\frac{\text{number dispensed- number remaining}}{}$ x 100

Number dispensed
3. Data Management: Patients will be assigned a unique study number which does not contain PHI. This number will be used on all data collected for the purposes of this study. A master list of subjects which links the study number and patient identifiers will be maintained on an encrypted VA server. The data for this study will be entered into Microsoft Excel 2010. The investigator(s) and their research personnel are responsible for maintaining the study database, which will be kept on an encrypted VA server. No data will be stored on a hard drive of a PC. Only key personnel for this study will have access to the research data and access to this data will be terminated if/when the personnel are removed from the study. Research data will be maintained according the VA records schedule. Data containing PHI will not leave the VA premises A contract biostatistician will be used to analyze de-identified study data. Variables/Time Points of Interest The primary outcome of interest is the percentage of patients completing 12 weeks of treatment with FDC MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™). Treatment completion will be defined as attendance at the last treatment visit (i.e.,Week 12). Adherence will be categorized into <90% adherence and ≥ 90% adherence, based on an observed relationship between ribavirin adherence and early virologic response[11]. Statistical Methods Binary logistic regression analysis will be used to report adjusted odds ratios. Differences in the distribution of HSV-TSE-A scores across categorical visits (baseline vs. Week 4) will be accessed using Wilcoxon rank sum test. In addition, parametric models (linear regression) will be explored to estimate the differences. Power/Sample Size: In our pilot program of 4 Veterans, we found that 75%) completed 12 weeks of treatment. Estimating a 90% (18/20) completion rate in the VBMI arm, we anticipate that a sample size of 20 patients will demonstrate a trend towards higher completion rates with the VBMI intervention. We also anticipate the study will demonstrates a high rate of medication adherence. It is our intention to use data from this study to develop larger protocols with more robust sample sizes. Limitations: 1) Enrollment bias may select for a different population of SUD patients than those who do not participate. We have requested approval to record demographic information from patients who do not enroll, to allow comparison for significant differences between groups in terms of age, race, gender. 2)Patients with NS5a mutations conferring resistance to elbasvir will require the addition of weight-based ribavirin and treatment extension to 16 weeks. Based on our current observations of patients with HCV infection and SUD, we anticipate that 47% are infected with genotype 1a . Estimating that 11% of patients with genotype 1a will have baseline NS5a resistance, we estimate that 2 patients will require 16 weeks of treatment. We will not assess

adherence beyond 12 weeks of treatment and we will not assess adherence to ribavirin in this protocol.

Adverse event reporting:
Serious and unexpected adverse events to FDC MK-5172/MK-8742 (elbasvir/grazoprevir, Zepatier™) will be reported to the IRB and Research Compliance Officer, Merck at 1-877-888-4231 immediately upon notification and/or the FDA (1-800-FDA-1088) or www.fda.gov/medwatch.
For events regarding data loss/theft/unauthorized access, the ISO, IRB chair, PO and RCO will be notified immediately upon notification of event.

Role of pharmacy:
The research pharmacist will store and dispense MK-5172/MK-8742 . (elbasvir/grazoprevir, Zepatier™).

If a patient fails to complete the study, a lost to follow up form will be completed.

References

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Ammendment:

Microbiome analysis

Stool samples from patients with HCV who are on DAA therapy have been collected with their informed consent at baseline, week 4 and 12 of treatment. Stool samples are stored in -80 degree freezer, identified only by study number with no patient PHI.

16s ribosomal Bacterial DNA will be extracted from the stool samples using the *QIAamp Fast DNA Stool Mini Kit* (Qiagen) and placed into microcentrifuge tubes labeled with the study number. Bacterial DNA extraction will take place in R 403 and R 405.

The stool samples will be returned to the -80 degree freezer and will not leave the VA premises, maintaining the chain of custody.

The extracted bacterial DNA will be sent to the University of Mississippi Medical Center Molecular and Genomics Core for analysis. The bacterial DNA samples will be labeled with the study number (no PHI). The report the Core generates will also not contain PHI.

We will analyze the changes in the gut microbiome during treatment for hepatitis C. We will be able to compare baseline alpha diversity of the microbiome at week 4 and week 12 of treatment in each patient.