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Eliminating hepatitis C in a rural Appalachian county: protocol for the Kentucky Viral Hepatitis Treatment Study (KeY Treat), a phase IV, single-arm, open-label trial of sofosbuvir/velpatasvir for the treatment of hepatitis C

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ABSTRACT

Objectives The overall goal of the Kentucky Viral Hepatitis Treatment Study (KeY Treat) is to eliminate hepatitis C transmission from a county in Appalachian Kentucky by removing the barriers to accessing hepatitis C virus (HCV) treatment.

Methods/analysis KeY Treat is a phase IV, open-label, single-arm clinical trial of sofosbuvir/velpatasvir (SOF/VEL) for the treatment of viraemic HCV infections. Those eligible for KeY Treat are at least 18 years of age, viraemic and are residents of the target county. Pregnant women are not eligible. Rapid HCV RNA screening is used to determine eligibility, and those with a quantifiable viral load (VL) consenting to participate initiate SOF/VEL on the same day. All pharmacologic treatment and related medical care is provided free of charge using a non-specialist provider model. Follow-up visits occur at 2, 6 and 12 weeks during treatment to assess medication adherence (measured via VL and self-report), side effects and engagement in risk behaviours. Post-treatment visits occur at 12 weeks (sustained virologic response (SVR12) visit), 6 months and 12 months post-treatment completion to assess re-infection. A control county has also been identified, and prevalence and incidence of chronic HCV infections will be compared with the target community longitudinally. The primary outcome to assess elimination is SVR12. However, several outcomes will be measured to assess the effectiveness of removing the barriers to HCV treatment, including treatment entry, completion and re-infection. Analyses will be conducted via a generalised linear model framework that can incorporate flexible covariate adjustment and multiple outcome types with a compatible link function. Mathematical modelling will be completed assessing the impact and cost-effectiveness of the intervention.

Ethics and dissemination KeY Treat has been approved by the Institutional Review Board at the University of Kentucky. Results from KeY Treat will be presented at conferences and published in peer-reviewed journals.

Trial registration number NCT03949764.

Strengths and limitations of this study

- The results may not be generalisable since the study is being conducted at a single site in rural Kentucky.
- All viraemic residents of the target county aged ≥18 years are eligible for study participation, which will reduce bias and should lead to significant reductions in community viral load and potential elimination of the hepatitis C virus.
- The study is adequately powered to detect subgroup differences in treatment uptake, completion and outcomes of sustained virologic response at 12 weeks . If re-infection rates are low, there is potential for type 2 error.
- Participation in the study is incentivised for completion of research-related questionnaires and response to medication reminders, which may not be replicable in clinical practice.
- The rapid RNA assay allowing for same-day medication initiation may not be available for use outside of research in the USA.

BACKGROUND

Hepatitis C is a serious chronic liver disease that can have fatal consequences, including cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC).[1–3] However, recent advances in the treatment of those infected with the hepatitis C virus (HCV) have raised the possibility of eliminating HCV in the next few decades.[4 5] Previous

ribavirin/pegylated interferon-α-based treatments for HCV were limited by low efficacy, numerous contraindications, high toxicity, lengthy treatment duration and subsequent non-adherence.[6 7] Conversely, newer pharmacologic treatments for HCV, direct-acting antivirals (DAAs), can consistently cure (sustained virologic response (SVR)) upwards of 95% of patients.[8 9] Moreover, significantly increased tolerability has been observed, along with considerably shortened treatment duration.[10] Equally important, interferon-free regimens allow for all-oral drug administration, removing the barrier of regular interferon injections and associated impacts on morbidity and patient compliance.[8 11]

The high rates of SVR as well as ease of treatment for the newer HCV regimens allow targeting of treatment to marginalised groups, such as people who use drugs (PWUD)/people who inject drugs (PWID).[12 13] The advantages of treating PWUD, and PWID in particular, is the potential to not only cure the individual, but to prevent further transmission of the virus to injecting partners, that is, treatment as prevention (TAP).[14 15] The TAP approach is cost-effective,[16 17] even when modelled in rural areas.[18] However, PWUD often cite barriers to accessing HCV treatment, many of which are tied to stigma around drug use and a general lack of resources available to active PWID.[19 20] Reluctance from providers and payors to treat chronic HCV in PWID is also pervasive and only exacerbates the challenges of readily accessing the HCV treatment cascade if one is injecting.[21 22] From a public health perspective, however, PWID represent one of the most important, if not *the* most important, populations that must be treated to achieve elimination by 2030.[14 23]

Access to harm reduction, syringe services programmes (SSPs) and evidence-based treatments for substance use disorder (SUD), in particular, are also an important piece of the elimination puzzle.[24] Evidence suggests that in combination, medication for opioid use disorder (OUD) treatment (eg, methadone and buprenorphine) and SSPs are associated with a 74% reduction in HCV acquisition risk.[25] Modelling data also suggest that scaling-up harm reduction in conjunction with increasing access to HCV treatments will result in the greatest progress towards elimination, especially in rural areas.[24 26]

Kentucky has some of the highest rates of HCV infections in the USA,[27 28] largely attributed to opioid injection in rural areas,[29–31] which has been aptly dubbed the opioid/HCV syndemic.[32 33] In a cohort of 503 people who use opioids to get high recruited in 2008 in rural Perry County, Kentucky, 80% had a history of injection, many of whom injected prescription opioids.[29] The potential for the proliferation of injection-related HCV and HIV in rural areas could not be greater. Indeed, a large-scale HIV outbreak was reported in Austin, Indiana, a rural town just north of Louisville, Kentucky in 2015.[34 35] The majority of those infected with HIV were coinfected with HCV, which was not suprising given that transmission was primarily among PWID[36] where coinfection is common.[37] The subsequent hotspot analysis conducted by the Centers for Disease Control and Prevention (CDC) in the aftermath of the Austin HIV outbreak was a wake-up call for many states, and Kentucky in particular. Of the 220 US counties identified as high-risk for HIV/HCV outbreaks associated with injection drug use, 25% of them were in Kentucky including 12 of the top 15 counties.[38] The target area for this study, Perry County, ranked #4 within the 220 counties identified as high risk.[38] Only after this outbreak was large-scale harm reduction implemented in Kentucky.[39]

HCV infection in Perry County has been well-documented due to an ongoing cohort study among 503 rural PWUD and a risk-reduction intervention among 400 incarcerated women at risk for HIV/HCV. To date, 347 of the 503 participants in the rural PWUD cohort have tested HCV-antibody-positive (69.8% seroprevalence overall),[29] 115 of which represent incident cases occurring in the past 10–12 years, primarily among young PWID; of those, approximately 70% are RNA-positive,[40] and are, therefore, eligible for hepatitis C treatment. However, data suggest low uptake of HCV treatment among PWUD and PWID in this region,[41] a lack of partner notification of HCV status[42] and social networks that facilitate continued transmission of the virus.[43] Among rural women in a local risk-reduction intervention, the prevalence of HCV-antibody-positives was also high at 69% among PWID.[44]

There is a clear need for improving access to HCV treatment in rural Kentucky, with particular attention paid to PWID/PWUD. Treating this vulnerable group as well as those with a history of PWUD not only has great potential to prevent additional infections and significantly lower the community viral load (VL),[26] but also has implications for the potential prevention of the development of advanced liver disease and HCC[45] in a region plagued by marked health disparities.[46]

HYPOTHESIS

The overarching hypothesis of KeY Treat is that removal of barriers to accessing DAAs for the treatment of viraemic HCV infections (substance use, stigma, lack of insurance, evidence of HCV chronicity, strict guidelines for retreatment, prescriber restrictions and/or disease severity restrictions) will increase the number of people achieving cure such that the community VL will be dramatically reduced and elimination potentially achieved.

METHODS

Study design

KeY Treat is a phase IV, single-arm, open-label clinical trial of sofosbuvir/velpatasvir (SOF/VEL) for the treatment of viraemic hepatitis C infection among residents of Perry County, Kentucky. A single-arm study design is used since the course of hepatitis C infection is well understood and the study drug is FDA-approved, well-tolerated and efficacy has been demonstrated. As the goal is HCV

elimination, the study was designed to ensure participants had access to all aspects of the study and ancillary services (treatment for OUD, syringe services and case management).

Approvals

The Institutional Review Board at the University of Kentucky approved the KeY Treat protocol. The protocol is also subject to annual re-reviews and is registered at ClinicalTrials.gov.

Setting

KeY Treat is being conducted in a suite at a medical office park in Hazard (Perry County), Kentucky, USA.

Study team

To increase scalability of the KeY Treat protocol to rural areas, non-specialist provider model is used. The clinical study team consists of two on-site nurse practitioners, a registered nurse, phlebotomist and licensed clinical social worker. An infectious disease (ID) physician housed at the University (approximately 2 hours from the study site) is available for consultation on treatment-related issues and to guide treatment of hepatitis B and/or HIV coinfected individuals. A pharmacist is also available via email to conduct medication reconciliations for new participants. The research team consists of a study director, computer specialist and three interviewers.

Study population and enrolment

Eligibility criteria for the study includes consenting Perry County residents with HCV viraemia. Only Perry County residents are included since the goal is to eliminate the virus in this particular county. As the study drug is not FDA-approved for use in those <18 years of age and during pregnancy, children <18 years of age and pregnant women are excluded from study participation. It is anticipated that upwards of 900 residents will enrol in the study and initiate the medication. Enrolment began in September 2019 and will be completed in June 2023. Participants are recruited via the local SSP, referrals from local physicians and OUD treatment clinics and word -of-mouth from active or former participants. Participants testing positive for antibodies to HCV in an epidemiological study[29] being conducted in the same community are also referred to KeY Treat. The Xpert HCV Viral Load Fingerstick (Cepheid) assay is used to determine study eligibility.

Study medication

The study medication for KeY Treat is SOF 400 mg/VEL 100 mg, an all-oral, once-per-day pill that is FDA-approved in the USA and has a favourable side effect profile. Participants are initially provided with a 14-day supply of SOF/VEL. If they are adherent (measured by HCV VL and self-report) they are given a 28-day supply, and 42 days of medication for the final 6 weeks of treatment, for a total of 12 weeks of medication. Study clinicians are allowed flexibility to bring participants in every 2 weeks if they are non-adherent. Those participants are also referred to the social worker to determine whether referral to additional resources may improve adherence. Participants are not removed from the study if they are non-adherent; however, removal is by request of the participant or if the participant becomes pregnant during the medication phase. If the participant is using opioids and indicates interest in treatment, they are referred to OUD treatment at a local opioid treatment programme. Participants who are re-infected after achieving SVR are offered additional treatment with either SOF/VEL or sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg (SOF/VEL/VOX) at the discretion of the study clinicians.

Participants with medications that are contraindicated for use with SOF/VEL are asked to work with their primary care providers to change medications (if possible), and SOF/VEL is initiated once a letter from the provider noting the medication change has been secured. Those with known hepatitis B virus (HBV) infection are required to meet with the study ID physician via telemedicine or at the university clinic (transportation is provided or reimbursed) prior to initiating SOF/VEL. Those screening positive for HBV infection as a result of the initial blood draw who have already initiated treatment with SOF/VEL continue on the medication, but are scheduled for immediate consultation with the study ID physician either in-person or via telehealth. All study medications and related medical care is provided free of charge to participants. HIV/HCV coinfected participants will be treated for both infections concurrently, if they are not already engaged in HIV care.

Study visits

Potential participants are initially screened by phone. If they are a resident of Perry County, at least 18 years of age and suspect they have been exposed to HCV, an appointment is scheduled for in-person screening, usually within 2–3 days of the call. Phase I of in-person screening involves consenting to the screening, rapid antibody testing for HCV and HIV, and a pregnancy test for women of childbearing age. If HCV antibody-positive, an additional fingerstick is conducted at the same visit to collect a small blood specimen for rapid RNA testing (Xpert HCV Viral Load Fingerstick assay; Cepheid). Participants with a detectable VL are invited to participate in KeY Treat. Anti-HCV-positive, RNA-negative individuals are invited to return at regular intervals for RNA testing. Pregnant women are encouraged to return once they are no longer pregnant. A second consent is presented to participants for the full study to initiate phase II of the baseline visit. If signed, the phlebotomist conducts a full blood draw, clinical staff conduct the history and physical (H&P), medications are reconciled for potential interactions with SOF/VEL, research questionnaires are completed, medication reminders are established and a 14-day supply of SOF/VEL is dispensed to each participant. The majority of eligible participants are screened, enrolled and initiated on SOF/VEL within 4 days. A minimum of two

additional visits are conducted during treatment (2 and 6 weeks post-treatment initiation), one visit at the conclusion of the 12 weeks, and at 12 weeks, 6 months and 1 year post-medication completion for a total of seven visits over approximately 18 months. Clinicians are given flexibility to schedule additional visits during the medication phase for participants who are non-adherent to SOF/VEL. Participants are remunerated for completion of the research questionnaires (US$50 at baseline and US$25 at each follow-up) and response to medication reminders (US$1 per day during the medication phase).

Patient consent

A two-stage consent process is used for screening and enrolment. All potential participants who screen in-person first consent to screening for HCV and HIV antibody testing, urine pregnancy screen and HCV VL testing. Participants who are eligible for study participation complete a second form, consenting to KeY Treat participation. Separate consent forms are also provided to those who are interested in receiving hepatitis A and/or hepatitis B vaccines. Consents are administered by trained research staff. All consent forms were approved by the Institutional Review Board at the University of Kentucky in August of 2019. The study protocol and consents are reviewed on an annual basis.

Medication adherence

SOF/VEL requires once-per-day dosing. Medication timing is discussed with each participant; the study clinician reviews potential side effects and strategies to mitigate side effects (ie, take medication with a meal or at bedtime). A daily medication reminder is set up with participants based on their chosen time, and the reminder arrives 30 min prior to that time. These reminders can occur via SMS text message using an automated system, via Facebook or phone call for those who do not have access to a cell phone. Response to medication reminders is incentivised at US$1 per response/per day to encourage responses to the reminders.

Adherence is measured in two ways. The first is via VL. RNA testing is completed at each visit during treatment. If adherent to SOF/VEL, the VL should decrease or be undetectable at the subsequent visit. Both clinicians and the research staff also ask about self-reported medication adherence. Participants who are found to be non-adherent meet with the social worker to determine whether referrals to additional services may assist in improving adherence, but are not removed from the study. Medication adherence, dichotomised as undetected VL/detected VL, will be an important predictor of the primary study outcome, SVR.

Participants who are jailed during treatment are provided with medication that is dispensed by the medical provider at the jail. Daily checks of the jail census are conducted and/or participants call to inform study staff that they incarcerated. Those who drop-out during treatment are eligible to restart the medication after consultation with the on-site providers and ID physician.

Additional services

All participants meet with the study social worker at the initial visit, if they are non-adherent to the study medications, or if the participants request a meeting. The social worker continuously compiles a list of resources and potential referral mechanisms. In addition, the social worker will aid in securing identification, post office boxes (for services requiring a physical address) and, if necessary, medical insurance. KeY Treat has contracted with a local opioid treatment programme to provide subsidised OUD treatment (buprenorphine or methadone) for any participant who is interested. The study will pay for medication treatment of OUD while actively enrolled in KeY Treat, regardless of insurance status (~18 months). KeY Treat also provides funding to the local SSP so that clean syringes and other works are available to those enrolled in the study. Hepatitis A and B vaccinations are offered free of charge to all participants without laboratory-demonstrated immunity.

Outcomes

To determine whether the community VL is has been impacted by KeY Treat, the primary outcome is SVR. Three additional outcomes for this novel protocol—treatment uptake, completion and re-infection, are also important to determine whether removing the barriers to accessing treatment was effective. Treatment uptake is measured as the proportion of those screened eligible in-person who consent to treatment. Treatment completion is measured as the proportion of participants who complete 12 weeks of medication after starting treatment. SVR is determined at 12 weeks post-treatment completion (SVR12) and is measured using VL results from the rapid RNA test. Participants with undetectable RNA at this visit have achieved SVR and are considered cured. Finally, re-infection is measured using VL results at 6 and 12 months post-treatment completion. Those with detectable RNA after achieving SVR will be considered re-infected. To differentiate re-infection from rebound infection, any participant presenting with a detectable VL after achieving SVR will undergo a blood draw to determine HCV genotype, which will be compared with the baseline genotype. In addition, the post-SVR visits measure engagement in risk behaviours that would also allow for a determination of the possibility of re-infection versus rebound infection. An additional outcome compares the incidence and prevalence of HCV viraemia in the target county and a control county, prior to and over the course of the KeY Treat study, using data reported to the Kentucky State Department for Public Health. The control county has a similar level of services (physicians actively treating HCV, SSP and access to medication treatment for OUD). It is hypothesised that significant declines in incidence and prevalence will be observed in the intervention compared with the control county (table 1).

Table 1 Visit schedule, measures and outcomes for KeY Treat

Visit	Timing	Activities	Measures	Outcome
1	BL	► Screening ► Lab work ► Medication initiation ► Research questionnaires	HCV/HIV ab, HCV VL, CBC, CMP, HBV and HAV testing, fibrosis stage, HCV genotype, urine pregnancy, H&P, PREP-C, HCV tx and medication hx, demographics, drug use, injection risk behaviours, MH disorders, social networks, SUD tx, QoL	Medication uptake
2	2 weeks post BL	► Med refill ► Lab work ► Research questionnaires	HCV VL, urine pregnancy, adherence, SOF/VEL side effects, drug use, injection risk behaviours, SUD tx, QoL	
3	6 weeks post BL	► Med refill ► Lab work ► Research questionnaires	HCV VL, urine pregnancy, adherence, SOF/VEL side effects, drug use, injection risk behaviours, SUD tx, QoL	
4	12 weeks post BL	► Research questionnaires ► Lab work	HCV VL, adherence, CBC, CMP, SOF/VEL side effects, drug use, injection risk behaviours, SUD tx, QoL	Medication completion
5	24 weeks post BL (12 weeks post-med completion)	► Research questionnaires ► Lab work	HCV VL, drug use, injection risk behaviours, patient satisfaction, social networks, SUD tx, QoL	SVR12
6	6 months post-med completion	► Research questionnaires ► Lab work	HCV VL, drug use, injection risk behaviours, patient satisfaction, social networks, SUD tx, QoL, chronic dx hx, QoL	Re-infection
7	12 months post-med completion	► Research questionnaires ► Lab work	HCV VL, drug use, injection risk behaviours, patient satisfaction, social networks, SUD tx, QoL, chronic dx hx, QoL	Re-infection

BL, baseline; CBC, complete blood count; CMP, comprehensive metabolic panel; HAV, hepatitis A virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; H&P, history and physical; hx, history; KeY Treat, Kentucky Viral Hepatitis Treatment Study; MH, mental health; PREP-C, Preparation for Hepatitis C Treatment; QoL, quality of life; SOF, sofosbuvir; SUD, substance use disorder; SVR, sustained virologic response; tx, treatment; VEL, velpatasvir; VL, viral load.

Clinical measures

A thorough H&P is conducted with every participant at the initial visit, which includes a list of current medications (participants are asked to bring current medications to the visit) and HCV treatment history (if any). During the screening visit, anti-HCV and anti-HIV tests are conducted using the OraQuick *HCV* Rapid Antibody Test and OraQuick *ADVANCE* Rapid HIV-1/2 Antibody Test (OraSure, Bethlehem, PA, USA). In-house rapid RNA testing is conducted using the GeneXpert HCV VL test (Cepheid). Participants undergo VL testing at the initial visit and all subsequent visits. Urine pregnancy screening is conducted among women of childbearing age at every visit.

Laboratory tests include standard blood panels—complete blood count and comprehensive metabolic panel. Specific to hepatitis C, laboratory-based fibrosis testing (FibroSure), genotyping and quantitative RNA testing are conducted. Testing is also completed to determine exposure, coinfection and/or immunity to hepatitis A and B. Side effects/adverse events and medication adherence are queried at each visit by both clinical and research staff. Participant satisfaction is assessed at the SVR visit. Recent substance use and treatment for SUD are measured at each visit.

Epidemiological/behavioural measures

In addition to the data collected by clinical staff, research questionnaires are completed at each visit. At intake, participants undergo the Psychosocial Readiness Evaluation and Preparation for Hepatitis C Treatment (PREP–C; prepc.org). PREP-C is an online structured interview examining nine areas of psychosocial functioning that may affect HCV treatment uptake and adherence, including motivation, self-efficacy, drug use, psychiatric functioning and cognitive functioning. Demographic indicators are also collected at baseline. These include age, race, gender, education, employment, marital status, transportation, income, housing, child care, insurance and criminal history/incarceration. The EuroQol EQ-5D-5L[47] tool is used to collect quality of life data from participants before, during and after receiving HCV treatment to estimate the benefits in terms of Quality Adjusted Life Years for cost-effectiveness modelling.

The drug use section of the Addiction Severity Index-Lite (ASI-Lite)[48] is collected at baseline and all follow-up

visits. For non-PWUD, the questionnaire has skip patterns embedded that allow the interviewer to query changes in drug use and, if no use is reported, all questions related to substance use are skipped. In addition to drug use, the ASI-Lite includes measures of treatment utilisation for SUD. Injection questions from the Risk Behaviour Assessment[49] determine engagement in injection-risk behaviours among PWID. In addition, PWID are queried about SSP and substance abuse disorder treatment utilisation over the course of the study.

Data collection and management

Research and clinical data are collected using Research Electronic Data Capture (REDCap) hosted at the University of Kentucky. Briefly, the questionnaires are programmed, loaded onto touchscreen laptops and delivered to the participants in a similar manner as a paper and pencil survey. Responses are entered directly into REDCap by the interviewer/clinician, eliminating the need for data entry. As those entering the data move from one page to the next, data are automatically encrypted, ensuring data security if laptops are lost/stolen. Data are downloaded weekly to a secure server where data are compiled, cleaned and stored in password-protected databases on a university server.

Follow-up

Every effort will be made to continue follow-up for participants who are unable to be contacted and a detailed contact form will be completed at baseline that includes multiple contact points for each participant. Participants requesting to be discontinued from the study will not be followed; however, they will be told that they may be assessed for re-enrolment at any time.

Statistical analyses

Analyses will be conducted using a generalised linear model (GLM) framework that can incorporate flexible covariate adjustment and multiple outcome types (eg, binary, quantitative, Poisson and time-to-event) with a compatible link function. This modelling flexibility provides robust investigation into the various research questions of interest. Given that there are four outcomes, a Bonferroni correction will be applied, and an α level of 0.0125 (0.05/4 outcomes) will be considered statistically significant. General analyses are described below based on the distribution of the dependent (outcome) variable. Data will not be imputed for those that are lost to follow-up, and only those with complete data will be used to assess each outcome described below. The principal investigator will have access of the final dataset and permit analyses by outside investigators on a case-by-case basis.

Outcomes 1–3: treatment uptake, completion and SVR

Treatment uptake is measured as the proportion of those screened eligible in-person who consent to treatment. Treatment completion is measured as the proportion of participants who complete 12 weeks of medication after starting treatment. SVR is determined at SVR12 and is measured using VL results from the rapid RNA test. These dependent variables are all dichotomous, and therefore GLM with a binary outcome specified is proposed to examine the predictors of treatment uptake, completion and SVR.

Outcome 4: re-infection

Although the dependent variable is dichotomous, time-to-event analyses will be used. Given that the exact date of re-infection is unknown, the outcome will be modelled using discrete time survival analysis, whereby time is represented in two separate blocks (0–6 months post-treatment completion and 6–12 months post-treatment completion).

Outcome 5: reductions in HCV incidence and prevalence across counties

Changes in prevalence and incidence over time will be modelled using GLM with a Poisson distribution specified.

Power calculations

Calculations of power and sample size were generated from both the entire proposed sample as well as subsamples to demonstrate adequate power to conduct key subgroup analyses within the dataset. For all power calculations, the most conservative estimate of the outcome and primary independent variable of interest is used and a two-sided, 5% significance level test is assumed. A sample power calculation is as follows for an outcome that would have the least power (ie, dichotomous). For the primary outcome of treatment uptake, assuming recruitment of 900 participants and a probability of no or low-grade fibrosis (fibrosis score=0, 1 or 2) of 70%, we have 80% power to detect a change from 70% probability of treatment uptake to 80% comparing low fibrosis score to high. We use a standard large sample approximation[50] to compute this in the logistic regression setting adjusting for multiple other potential confounding variables that are potentially collinear with the fibrosis predictor of interest. It is assumed that 20% of the variability in fibrosis score is explained by other predictors in the GLM.

Mathematical modelling plan for guiding and evaluating KeY Treat

In addition to the analyses described above addressing the primary outcomes, the intervention will be evaluated for its impact and cost-effectiveness using mathematical modelling.

As partly done for Perry County,[26] modelling will initially be used to gain a better understanding of the state and likely course of the epidemic and produce projections for the potential impact of different scenarios for how HCV treatment, SSP services and medication for OUD (MOUD) treatment may scale-up during Key Treat. This is important for setting coverage targets for HCV treatment, SSP components and MOUD treatment of KeY Treat to ensure the intervention achieves sufficient impact on incidence. The modelling will test different

intervention and timing options to help study planners decide what is most feasible and then give milestones for what is required at different time points of KeY Treat.

During the KeY Treat study, the model will be updated as new data become available (on treatment, SVR12 or re-infection rates from initial participants) to evaluate the impact of what has been achieved so far (interim impact evaluation once 300 and 600 participants have been enrolled, respectively) and, through projecting forward, will assess whether current strategies are adequate or need adapting to ensure KeY Treat achieves sufficient impact. Sufficient impact meaning scale-up of treatment and reductions in HCV incidence consistent with WHO elimination goals (80% treated and an 80% reduction in incidence).[14] For instance, in the first half of the intervention, data may suggest that more HCV treatment has occurred than was initially planned, but less scale-up of OUD treatment and SSP. Modelling can assess whether this change to the initial strategy is still likely to achieve the planned final outcome on HCV prevalence and/or incidence, and if not, then what change to this intervention strategy is needed to maximise the chances of still achieving sufficient impact (ie, significant reductions in incidence and prevalence over time in the target county).

At the end of the KeY Treat project period, modelling will be used to help evaluate the impact of the intervention, disentangling its impact from the possible effect of natural epidemic dynamics or changes in other interventions or factors that may affect transmission (eg, changes in drug use patterns or incarceration patterns). Subgroup analyses will be conducted for PWUD/non-PWUD and those engaged in treatment for OUD. These data would be linked to the observed outcomes from the control county to assess the impact of the study on epidemiological outcomes (decreases in prevalence or incidence). Additionally, modelling will be used to estimate the intervention's impact on additional outcomes (morbidity and mortality) and evaluate the impact of each intervention component (eg, case-finding in different venues, SSP and OUD treatment). Through this and linking with intervention cost data collected from the project, the cost-effectiveness of KeY Treat and its components will also be estimated. Lessons learnt from KeY Treat will be used to improve intervention strategies for increasing HCV treatment access in other rural areas.

DISCUSSION

KeY Treat is one of the first microelimination trials in the USA and is uniquely targeting high-risk rural PWUD/PWID and former PWUD for HCV treatment. Results from this study will inform treatment efforts in rural regions adversely affected by the opioid/HCV/methamphetamine syndemic as well as the 2030 HCV elimination goals set forth by the WHO.

Ethics and dissemination

This study ClinicalTrials.gov and informed consent documents indicate that clinical trial information will be posted at ClinicalTrials.gov per internal and National Institutes of Health policies. Once the study is completed, the results (ie, summary statistics and graphical/tabular representation of the data) from this study will be presented at local, regional, national and/or international conferences. Subsequently, manuscripts describing the results will be prepared for submission to peer-reviewed journals, and the final, accepted version of the manuscripts will be submitted to PubMed Central. All data will be made available through ClinicalTrials.gov. The rights and privacy of individuals who participate will be protected at all times, and at no time will identifiers be included that would permit linkages to the individual participants and variables that could lead to deductive disclosure of the identity of participants. Informed consent documents for the project will include a specific statement relating to the posting of clinical trial information at ClinicalTrials.gov. The University of Kentucky Office of Research has an internal policy in place to ensure that clinical trial registration and results reporting occur in compliance with policy requirements. The Institutional Review Board at the University of the Kentucky approved the protocol and a Data Safety and Monitoring Board (DSMB) was not required given the study drug is FDA-approved.

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Contributors All authors provided editorial support for the manuscript. JH obtained funding, wrote the study protocol and developed study materials, and drafted the manuscript. TS, AH and ML provided clinical support for KeY Treat related to hepatitis and substance use disorders. TS is the study physician and contributed to developing the laboratory procedures. TS and ML also provided substantive clinical expertise to the study protocol. HF and PV drafted the modelling portion of the manuscript. MS, AY and SLW were integral in obtaining funding, drafting of the protocol and development of the study questionnaires and other outcome measures.

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Competing interests None declared.

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REFERENCES

1 Davis GL, Albright JE, Cook SF, *et al*. Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl* 2003;9:331–8.
2 Rosen HR. Clinical practice. chronic hepatitis C infection. *N Engl J Med* 2011;364:2429–38.
3 Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nat Rev Gastroenterol Hepatol* 2013;10:553–62.
4 Applegate TL, Fajardo E, Sacks JA. Hepatitis C virus diagnosis and the Holy Grail. *Infect Dis Clin North Am* 2018;32:425–45.
5 Spengler U. Direct antiviral agents (DAAs) - A new age in the treatment of hepatitis C virus infection. *Pharmacol Ther* 2018;183:118–26.
6 Ascione A, De Luca M, Tartaglione MT, *et al*. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. *Gastroenterology* 2010;138:116–22.
7 Cornberg M, Wedemeyer H, Manns MP. Treatment of chronic hepatitis C with pegylated interferon and ribavirin. *Curr Gastroenterol Rep* 2002;4:23–30.
8 Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, *et al*. Oral direct-acting agent therapy for hepatitis C virus infection: a systematic review. *Ann Intern Med* 2017;166:637–48.
9 Baumert TF, Berg T, Lim JK, *et al*. Status of direct-acting antiviral therapy for hepatitis C virus infection and remaining challenges. *Gastroenterology* 2019;156:431–45.
10 Jones CR, Flower BF, Barber E, *et al*. Treatment optimisation for hepatitis C in the era of combination direct-acting antiviral therapy: a systematic review and meta-analysis. *Wellcome Open Res* 2019;4:132.
11 Marcellin F, Roux P, Protopopescu C, *et al*. Patient-Reported outcomes with direct-acting antivirals for the treatment of chronic hepatitis C: current knowledge and outstanding issues. *Expert Rev Gastroenterol Hepatol* 2017;11:259–68.
12 Latham NH, Doyle JS, Palmer AY, *et al*. Staying hepatitis C negative: a systematic review and meta-analysis of cure and reinfection in people who inject drugs. *Liver Int* 2019;39:2244–60.
13 Day E, Hellard M, Treloar C, *et al*. Hepatitis C elimination among people who inject drugs: challenges and recommendations for action within a health systems framework. *Liver Int* 2019;39:20–30.
14 Grebely J, Dore GJ, Morin S, *et al*. Elimination of HCV as a public health concern among people who inject drugs by 2030 - What will it take to get there? *J Int AIDS Soc* 2017;20:22146.
15 Hajarizadeh B, Grebely J, Martinello M, *et al*. Hepatitis C treatment as prevention: evidence, feasibility, and challenges. *Lancet Gastroenterol Hepatol* 2016;1:317–27.
16 Martin NK, Vickerman P, Grebely J, *et al*. Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology* 2013;58:1598–609.
17 Martin NK, Vickerman P, Dore GJ, *et al*. Prioritization of HCV treatment in the direct-acting antiviral era: an economic evaluation. *J Hepatol* 2016;65:17–25.
18 Barbosa C, Fraser H, Hoerger TJ, *et al*. Cost-Effectiveness of scaling-up HCV prevention and treatment in the United States for people who inject drugs. *Addiction* 2019;114:2267–78.
19 Morris MD, Mirzazadeh A, Evans JL, *et al*. Treatment cascade for hepatitis C virus in young adult people who inject drugs in San Francisco: low number treated. *Drug Alcohol Depend* 2019;198:133–5.
20 Wolfe D, Luhmann N, Harris M, *et al*. Human rights and access to hepatitis C treatment for people who inject drugs. *Int J Drug Policy* 2015;26:1072–80.
21 Litwin AH, Drolet M, Nwankwo C, *et al*. Perceived barriers related to testing, management and treatment of HCV infection among physicians prescribing opioid agonist therapy: the C-SCOPE study. *J Viral Hepat* 2019;26:1094–104.
22 Pedlar A, Sandhu Prabjot (Jodie), Sandhu PJ. Promoting treatment for hepatitis C in people who inject drugs: a review of the barriers and opportunities. *J Am Assoc Nurse Pract* 2020;32:563–8.
23 Trickey A, Fraser H, Lim AG, *et al*. The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. *Lancet Gastroenterol Hepatol* 2019;4:435–44.
24 Fraser H, Zibbell J, Hoerger T, *et al*. Scaling-up HCV prevention and treatment interventions in rural United States-model projections for tackling an increasing epidemic. *Addiction* 2018;113:173–82.
25 Platt L, Minozzi S, Reed J, *et al*. Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a cochrane review and meta-analysis. *Addiction* 2018;113:545–63.
26 Fraser H, Vellozzi C, Hoerger TJ, *et al*. Scaling up hepatitis C prevention and treatment interventions for achieving elimination in the United States: a rural and urban comparison. *Am J Epidemiol* 2019;188:1539–51.
27 Zibbell JE, Iqbal K, Patel RC, *et al*. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. *MMWR Morb Mortal Wkly Rep* 2015;64:453–8.
28 Rosenberg ES, Rosenthal EM, Hall EW, *et al*. Prevalence of hepatitis C virus infection in US states and the district of Columbia, 2013 to 2016. *JAMA Netw Open* 2018;1:e186371.
29 Havens JR, Lofwall MR, Frost SDW, *et al*. Individual and network factors associated with prevalent hepatitis C infection among rural Appalachian injection drug users. *Am J Public Health* 2013;103:e44–52.
30 Schalkoff CA, Lancaster KE, Gaynes BN, *et al*. The opioid and related drug epidemics in rural Appalachia: a systematic review of populations affected, risk factors, and infectious diseases. *Subst Abus* 2020;41:35–69.
31 Valdiserri R, Khalsa J, Dan C, *et al*. Confronting the emerging epidemic of HCV infection among young injection drug users. *Am J Public Health* 2014;104:816–21.
32 Zibbell JE, Asher AK, Patel RC, *et al*. Increases in acute hepatitis C virus infection related to a growing opioid epidemic and associated injection drug use, United States, 2004 to 2014. *Am J Public Health* 2018;108:175–81.
33 Perlman DC, Jordan AE. The Syndemic of opioid misuse, overdose, HCV, and HIV: Structural-Level causes and interventions. *Curr HIV/AIDS Rep* 2018;15:96–112.
34 Conrad C, Bradley HM, Broz D, *et al*. Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone--Indiana, 2015. *MMWR Morb Mortal Wkly Rep* 2015;64:443–4.
35 Peters PJ, Pontones P, Hoover KW, *et al*. Hiv infection linked to injection use of oxymorphone in Indiana, 2014-2015. *N Engl J Med* 2016;375:229–39.
36 Ramachandran S, Thai H, Forbi JC, *et al*. A large HCV transmission network enabled a fast-growing HIV outbreak in rural Indiana, 2015. *EBioMedicine* 2018;37:374–81.
37 Platt L, Easterbrook P, Gower E, *et al*. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis* 2016;16:797–808.
38 Van Handel MM, Rose CE, Hallisey EJ, *et al*. County-Level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States. *J Acquir Immune Defic Syndr* 2016;73:323–31.
39 Bixler D, Corby-Lee G, Proescholdbell S, *et al*. Access to syringe services programs - Kentucky, North Carolina, and West Virginia, 2013-2017. *MMWR Morb Mortal Wkly Rep* 2018;67:529–32.
40 Young AM, Crosby RA, Oser CB, *et al*. Hepatitis C viremia and genotype distribution among a sample of nonmedical prescription drug users exposed to HCV in rural Appalachia. *J Med Virol* 2012;84:1376–87.
41 Stephens DB, Young AM, Havens JR. Healthcare contact and treatment uptake following hepatitis C virus screening and counseling among rural Appalachian people who use drugs. *Int J Drug Policy* 2017;47:86–94.
42 Hofmeister MG, Havens JR, Young AM. Silence surrounding hepatitis C status in risk relationships among rural people who use drugs. *J Prim Prev* 2017;38:481–94.
43 Young AM, Jonas AB, Mullins UL, *et al*. Network structure and the risk for HIV transmission among rural drug users. *AIDS Behav* 2013;17:2341–51.
44 Strickland JC, Staton M, Leukefeld CG, *et al*. Hepatitis C antibody reactivity among high-risk rural women: opportunities for services and treatment in the criminal justice system. *Int J Prison Health* 2018;14:89–100.

45 Chhatwal J, Wang X, Ayer T, *et al*. Hepatitis C disease burden in the United States in the era of oral direct-acting antivirals. *Hepatology* 2016;64:1442–50.
46 Rodriguez SD, Vanderford NL, Huang B, *et al*. A Social-Ecological review of cancer disparities in Kentucky. *South Med J* 2018;111:213–9.
47 Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
48 Cacciola JS, Alterman AI, McLellan AT, *et al*. Initial evidence for the reliability and validity of a "Lite" version of the Addiction Severity Index. *Drug Alcohol Depend* 2007;87:297–302.
49 Needle R, Fisher DG, Weatherby N, *et al*. Reliability of self-reported HIV risk behaviors of drug users. *Psychology of Addictive Behaviors* 1995;9:242–50.
50 Demidenko E. Sample size determination for logistic regression revisited. *Stat Med* 2007;26:3385–97.