HIV and Alcohol Research center focused on Polypharmacy (HARP) Pilot 1

ClinicalTrials.gov ID NCT05560932

Sponsor Yale University

Information provided by Yale University (Responsible Party)

Study Protocol
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PROJECT DESCRIPTION

1. Principal Investigator:
Dr. Amy C. Justice

2. Purpose:

This pilot intervention will consist of a brief intervention for patients with HIV who take 5 or more medications and currently (within the past month) consume alcohol. The focus of this pilot will be on bothersome symptoms and the impact of alcohol use and medications on these symptoms. The rationale is that any alcohol use may interact with medications in serious ways leading to adverse outcomes, including bothersome symptoms.

3. Background:

Introduction
Unhealthy alcohol use[1] is a major preventable public health problem resulting in over 100,000 deaths each year[2] and costing society over 185 billion dollars annually.[3] The effects of unhealthy alcohol use have far-reaching implications not only for the individual who consumes alcohol, but also for the family, workplace, community, and the health care system. Polypharmacy -- being on five or more medications at one time -- is also a growing problem, especially for people aging with HIV (PAH)[4-6]. Due to physiologic frailty, polypharmacy starting at early ages, and continued alcohol use, PAH experience substantial excess harm from alcohol and polypharmacy [5]. Yet, risk of harm from alcohol and polypharmacy (AP risks) are rarely tackled together.

Alcohol Impact in PAH
Among patients with HIV, alcohol use is associated with poor adherence to ART medications in a dose-dependent fashion[7-12]. While ART adherence in this population ranges from 60% to 70%[13,14], estimates for adherence in individuals with at-risk alcohol use with HIV is significantly lower (42%).[15] The risk for non-adherence has been shown to increase with increasing levels of alcohol consumption. One study revealed a 2.7 times increase in non-adherence in individuals with frequent heavy drinking (defined below)[16]. A Veteran's Aging Cohort Study (VACS) analysis found that medication adherence was lower on days when patients drank heavily, and on the following day. Alcohol consumption was the most significant predictor of ART medication adherence. Heavy drinking in patients with HIV is also associated with poor treatment response as evidenced by lower CD4 lymphocyte counts and higher HIV RNA.[10,11] In turn, it has been shown that individuals who have stopped drinking have an improved response to HIV therapy.[10]

Spectrum of Alcohol Use/Terminology
PAH represent the entire spectrum of unhealthy alcohol use as described in scientific guidelines from the National Institute of Alcohol Abuse and Alcoholism (NIAAA). This includes individuals with at-risk alcohol use who are at risk for injury and illness because they drink any alcohol all the way up to AUD. For individuals taking 5 or more medications, any alcohol use can be problematic given risk of medication-alcohol interactions and potential increased risk of adverse health outcomes. The HARP Pilot Interventions that you will provide focus on individuals currently consuming alcohol (but not currently meeting criteria for moderate to severe AUD) and taking at least 5 medications. Study participants not eligible for this pilot who meet criteria for moderate to severe AUD may be enrolled in a separate pilot study that includes provision of a medication to address AUD. If a study participant qualifies for a diagnosis of AUD, you will also need to notify their HIV clinician to help facilitate appropriate care.

Impact of Alcohol Combined with Polypharmacy in PAH
We have found that patients and clinicians have limited awareness of alcohol exposure and its associated risk.[17,18] But both patients and clinicians are concerned about polypharmacy.[19] Our guiding hypothesis is that patients will be more receptive to and we can more effectively intervene on medical harms from

alcohol among PAH by addressing the combined risks of alcohol and polypharmacy because alcohol interacts with a long list of medications.

Once ART has been initiated, many non-ART medications are prescribed to address symptoms and to treat or prevent comorbid disease. An estimated 15% to 39% of PAH are exposed to polypharmacy,[20-25] with higher rates among older individuals.[26] Polypharmacy is often measured as a threshold (e.g., concurrent receipt of five or more medications) but medication count must also be considered as each additional medication contributes risk. A conceptual model of harm from polypharmacy for PAH includes independent and interacting effects of physiologic frailty, medication burden, the prescription of potentially inappropriate medications and omission of indicated medications, and a host of known and unknown medication interactions. PAH are exposed to polypharmacy a decade earlier than the general population and it presents unique management issues in this population [27-29]. ART interacts with many non-ART medications[30] and PAH may be more susceptible to side effects due to increased physiologic frailty. Polypharmacy itself may decrease ART adherence, threatening the patient's ability to maintain viral suppression. Increasing polypharmacy adds to medication burden and increases the probability of significant two-way and higher order interactions as well as medication-gene and medication-alcohol use interactions. Physiologic frailty reflects the degree to which organ system reserve capacity is lost, allowing a relatively minor injury to result in disproportionate harm.[31] Increasing physiologic frailty is associated with increasing polypharmacy and vice-versa. These mechanisms contribute to a host of adverse health events.

Many commonly used medications have the potential to interact with alcohol (A-PIMS). These interactions may alter metabolism (pharmacokinetics) or effects (pharmacodynamics) of alcohol and/or the medication.[32] Some interactions can occur with ANY alcohol consumption, whereas others follow a dose-response pattern[33] and still others are genetically determined.[34] When an older adult combines medications with alcohol, they experience an increased risk of medical complications including hypoglycemia, hypotension, sedation/confusion, gastrointestinal bleeding, and liver damage.[32,35-37] These concerns are heightened for PAH as they have greater physiologic frailty, [22] making them more liable to injury. Further, several ART medications directly (e.g. ritonavir and efavirenz) interact with alcohol.[38-40]

Brief Interventions can successfully decrease alcohol consumption

There is compelling evidence in the literature that brief interventions are efficacious in reducing alcohol consumption and associated consequences.[41] Multiple studies have demonstrated the efficacy of brief interventions in a variety of settings, including general populations, primary care, emergency departments and in-patient trauma care units. In addition, a prior meta-analysis including seven studies on the efficacy of non-physician brief interventions in primary care settings in 2633 patients[42] found that patients who participated in non-physician interventions consumed one- and one-half fewer drinks per week compared to patients who did not receive such an intervention. While some PWH do respond to interventions to decrease their alcohol use, many do not.[43,44] Further, to our knowledge, there is a current lack of brief counseling interventions to address alcohol use for PWH that: 1) focus specifically on the subset of PWH receiving polypharmacy, 2) are designed to be delivered by clinical pharmacists, and 3) integrate highly personalized risk messages based on alcohol-polypharmacy associated risks.

References are included at the end of the document.

4. Significance:

Multiple studies have demonstrated the efficacy of brief interventions in a variety of settings, including general populations, primary care, emergency departments and in-patient trauma care units. In addition, a prior meta-analysis including seven studies on the efficacy of non-physician brief interventions in primary care settings in 2633 patients42 found that patients who participated in non-physician interventions consumed one- and one-half fewer drinks per week compared to patients who did not receive such an intervention. While some PWH do respond to interventions to decrease their alcohol use, many do not.43,44 Further, to our knowledge, there is a current lack of brief counseling interventions to address alcohol use for PWH that: 1) focus specifically on the subset of PWH receiving polypharmacy, 2) are designed to be delivered by clinical pharmacists, and 3) integrate highly personalized risk messages based on alcohol-polypharmacy associated risks.

A key focus of these pilots is learning how best to communicate complex information about risk to patients. This information will help us communicate with VA providers to help improve how we communicate about risk with our VA patients.

5. Recruitment Strategy:

. The Veterans Aging Cohort Study (VACS) survey protocol enrolled 4,502 participants from October 2012 to October 2020 and the Medications, Alcohol, Substance Use in HIV Study (MASH) protocol, which is nested within VACS, has enrolled over 550 veteran participants. All Veterans who will be contacted for the current pilot study are participants in both VACS and MASH.

Based on data already available in VACS and MASH (including EHR data, prior biomarker analyses, and survey data), we will identify patients who are prescribed five or more medications AND who either have a positive PEth value (8+) or a self-reported AUDIT-C value consistent with current alcohol use (score >0). Because patients diagnosed with active moderate to severe AUD may require medication in addition to counseling, those with an AUD diagnosis in the past 12 months or who test positive for AUD on the Alcohol Symptom Checklist for moderate or severe AUD (score of 4 or more) will be excluded. The Alcohol Symptom Checklist will be administered as a screen during the first contact by the coordinator or the clinical pharmacist with the participant.

VA clinical pharmacists will be responsible for recruitment, obtaining consent, and administering the intervention. MASH participants will be familiar with these clinical pharmacists as they spoke with them as part of the MASH study.

Patients will be contacted by phone by the clinical pharmacist who will administer the Alcohol Symptom Checklist and obtain verbal consent from them for the study and verify their contact information. The clinical pharmacist will request that a home test kit for PEth and the initial survey be sent to the participant from the West Haven Coordinating Center. The clinical pharmacist will ask about the participant's comfort with self-administering the blood spot test for PEth and offer video or audio support to facilitate this test if needed. If needed, the clinical pharmacist will schedule a separate, pre-intervention, session to support the participant completing the blood spot and survey. Once completed, the participant will be asked to put the questionnaire in the self-addressed, stamped envelope and mail it back to the West Haven Coordinating Center. A separate envelope will be provided to send the blood spot directly to the analytic lab (USTDL) for rapid analysis.

Data will be stored on secure VA servers behind VA firewalls.

6. Research Plan:

There are 9 major steps in the research plan, which are detailed below.

1. Initial surveys will include:
    a. Pre-Intervention Baseline Data (5 minutes): AUDIT-C, lifetime drinking history (LDHx), and the HIV symptom index.
    b. Pre-Intervention IMB-MI assessment (10 minutes)**:** A series of 5-point Likert scale items will assess participants' pre-intervention levels of information, motivation, behavioral skills, readiness to change, as well as behavioral intentions with respect to changing behavior. (Please see the copy of the survey included in this packet). As an indicator of participants' current readiness to change their drinking and polypharmacy behaviors, we will measure "How important is it for them to decrease their (unhealthy alcohol or polypharmacy use)," and "How confident they are that they can decrease their use," each on 10-point scales.
2. Participants will be sent a $25 gift card for a completed survey and a $25 gift card once the results for the PEth are back confirming an adequate sample. Participants who return the survey but do not have an adequate PEth sample will be recontacted and offered a second sampling kit with additional instruction.
3. Once PEth results are available (approximately 1 week after the blood spot is mailed to USTDL), the Coordinating Center will update the participant's medications from the EHR and provide the clinical pharmacist with the participant's personalized feedback form that will be shared with the participant during the intervention. The clinical pharmacist will call the participant and schedule the intervention

and the West Haven Coordinating Center will send the immediate post intervention assessment materials to the participant. In addition, participants will receive text/phone reminders from the clinical pharmacist 1 day before and the morning of the scheduled intervention. If text reminders are sent, they will be HIPAA compliant and will include the following: "In order to protect your privacy, we cannot discuss anything via text and are not able to reply to text messages."

4. The HARP pilot intervention will be conducted by clinical pharmacists trained in IMB-MI procedures, following a manualized approach, and trained to criterion standard. The intervention will be digitally recorded to allow us to monitor fidelity. These recordings will be stored on our servers behind the VA firewall. Only those who are monitoring intervention fidelity will have access to these recordings. The intervention will include the following components:

    a. *Brief review and verification of medications (5 minutes).* Routine for clinical pharmacists.

    b. *Presentation of the behavior change intervention (25 minutes).* This pilot intervention will be delivered by the clinical pharmacist employing the IMB model and motivational interviewing (MI) techniques. This intervention will be informed by the clinical pharmacists' deep knowledge of medication side effects. The clinical pharmacist will employ MI in informational, participant-centered discussions in which the clinical pharmacist and the participant collaboratively discuss the harms of drinking and polypharmacy (specifically alcohol interactive medications), symptoms associated with alcohol and with specific medications, and how to mitigate these harms. Motivational elements will include messages highlighting the participant's personal risk of bothersome symptoms from their use of alcohol and level of polypharmacy, attitude change elements to improve attitudes toward the intended behavior change, social normative support for the intended behavior change including identification of people who can support the participant in this process, and a menu of options for referrals for skill building (e.g. Social Work, meeting with the clinical pharmacist at their clinic, follow-up with the HIV clinician, alcohol-reduction programs, based on what is locally available as part of VA-based care). The clinical pharmacist and participant will jointly develop a plan for the participant to change alcohol and polypharmacy use, review the concept of self-monitoring and how to use a worksheet to self-monitor alcohol use behavior, medications of concern, and symptoms, and obtain any additional resources needed. If the clinical pharmacist identifies a medication that is contraindicated because of concurrent alcohol use but the patient requires treatment of the condition for which the medication was prescribed, the clinical pharmacist will make recommendations for substitutions to the HIV clinician. Otherwise, the goal of this intervention is to help patients stop medications whenever it is safe to do so, not to substitute one medication for another.

    c. *Reassessment:* Once the intervention is complete, the clinical pharmacist will then remind the participant to complete the immediate post intervention survey (information, motivation, behavioral skills, importance, and confidence, and behavioral intentions ~5 minutes) and to return it in the enclosed postage paid envelope immediately after their call. The clinical pharmacist will emphasize that they will not see the results of the survey. The participant is to mail the survey back to the West Haven Coordinating Center in the self-addressed, stamped envelope provided.

    d. *Documentation*: Immediately after completing the interview, the clinical pharmacist will complete, record, and mail to the participant their final personalized feedback form, a summary of what was discussed, and the agreed-upon plan to address alcohol use and polypharmacy. If the participant and clinical pharmacist agree that a medication should be discontinued, the clinical pharmacist will ask the participant's VA HIV clinician to consider this discontinuation via a note in Microsoft Teams documenting their discussion and the rationale for discontinuation. While responses from the clinicians will be analyzed as part of the study; no clinician identifying information will be included.

5. *After Receipt of the Immediate Post Intervention Assessment*: a $25 gift card will be sent to the participant.

6. *30 Day Post Intervention Follow-up and Measurement*: 30 days after the interview, participants will be sent a second PEth home test kit to measure changes in alcohol consumption with return envelope and recontacted by phone by the clinical pharmacist to discuss any changes in alcohol consumption

or use of medication. They will also be asked to complete a paper survey reporting any changes in their alcohol or prescription drug use. We will also check VA EHR pharmacy data.

7. *Upon Receipt of the 2nd PEth test and survey, participants will be sent a payment of $50*. Participants who fail to return an adequate PEth sample will be recontacted and offered an additional test kit and additional instruction. If they are unable to provide a PEth test, they will receive $25.
8. *After Completion of the Intervention Study--Qualitative, semi-structured interview* (25 minutes). Finally, we will recontact a subset of participants for qualitative interviews that will elicit their feedback on the intervention. This information includes but is not limited to asking how difficult they found self-administering the PEth test, assessing whether their personalized risk estimate influenced their thinking on their alcohol or medication use, their views on how clearly the clinical pharmacists were able to communicate risk information, how well they liked receiving the intervention from a clinical pharmacist, and the usefulness of the intervention provided to reduce alcohol and other substance use. These interviews will be targeted to occur within one week after the 30-day follow-up, but we will allow up to 1 month. We will conduct these interviews by telephone or Microsoft Teams. These conversations will be recorded.
9. *Patients participating in the semi-structured interview will receive an additional $50.*

7. Data Safety Monitoring Board (DSMB):

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Monitoring for data integrity and safety will be the responsibility of the investigators (Drs. Edelman, Fiellin and Justice), the Institutional Review Boards, and a Data Safety Monitoring Board (DSMB). The project leads will have overall and ultimate responsibility for monitoring the data, assuring protocol compliance, conducting the safety reviews, and the specified frequency of the reviews at a minimum of every 6 months (including when re-approval of the protocol is sought). During the review process, the project leads will evaluate whether the study leads or the DSMB or the IRB have the authority to stop or suspend the study or require modifications.

Consistent with our prior experiences, the DSMB will include three members that bring together complementary expertise in addressing alcohol use in PAH with medication and counseling-based interventions and conducting clinical trials.

Twice annually the DSMB will review the progress of the study and frequency of serious adverse events. Based on our prior work, the risks associated with the proposed pilot studies are minimal. We view the risks associated with the proposed interventions to be minimal.

Although we have assessed all aspects of the proposed study as one of minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study. We will use the HIV Symptom Index, a 20-item validated tool that assess symptom burden, to facilitate monitoring of adverse events; any new or worsening symptoms will be reported to the site-PI and study leads immediately.

Attribution of Adverse Events
Adverse events will be monitored for each participant participating in the study and attributed to the study procedures by Dr. Edelman according to the following categories:

1. Definite: Adverse event is clearly related to investigational agent.
2. Probable: Adverse event is likely related to investigational agent.
3. Possible: Adverse event may be related to investigational agent.
4. Unlikely: Adverse event is likely not to be related to the investigational agent.
5. Unrelated: Adverse event is clearly not related to investigational agent.

Plan for Grading Adverse Events

The following scale will be used in grading the severity of adverse events noted during the study:
1. Mild adverse event
2. Moderate adverse event
3. Severe unanticipated adverse event resulting inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
4. Life-threatening adverse event
5. Fatal adverse event

Plan for reporting serious AND unanticipated AND related adverse events and anticipated adverse events occurring at a greater frequency than expected to the IRB.

The investigators will report the following types of adverse events to the IRB: a) serious AND unanticipated AND possibly, probably or definitely related events; and b) anticipated adverse events occurring with a greater frequency than expected. These adverse events will be reported to the IRBs of record within 48 hours of it becoming known to the investigator per protocols. Adverse events will be deemed serious in nature if graded as 3 or higher according to the scale in item #4 above.

Plan for Reporting Adverse Events to Co-Investigators

For this study, the following individuals, funding, and/or regulatory agencies will be notified: all co-Investigators listed on the protocol, the IRB, and the National Institutes of Health. The project leads will conduct a review of all adverse events upon completion of every study participant. The project leads will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

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