SUMMARY EVALUATION REPORT TEMPLATE

Study Title: "Gabapentin to Reduce Alcohol and Improve Viral Load Suppression (GRAIL)– Promoting Treatment as Prevention"
NDA CTA Number: 0244

Protocol No. NCT05443555

Version No. 1.4 **Date:** June 1,2023

National Principal Investigator (NPI): Dr. Winnie Muyindike

Institution /Trial Site:

1. ISS Clinic in Mbarara Regional Referral Hospital
2. Mbarara City Council Health Centre.

Sponsor: Jeffrey Samet (Sponsor representative)

REC of Record: Mbarara university of health sciences & Technology Research Ethics Committee **REC Reference number:** MUST-2022-668

UNCST Reference Number: HS2622ES

NDA date of Approval: 3rd August 2023

Study background and Rationale

Ending the HIV epidemic requires achieving HIV viral load (HVL) suppression (i.e., undetectable viral load) for key populations. Unhealthy alcohol use by people with HIV (PWH) is a barrier to reaching HVL suppression at multiple stages of the HIV care cascade. Alcohol use is common among PWH and results in lower antiretroviral therapy (ART) adherence and HVL suppression, mitigating the effectiveness of Treatment as Prevention (TasP), a key strategy for preventing HIV transmission. Treating alcohol use is therefore a mechanism to support PWH with unhealthy alcohol use along the HIV care cascade (e.g., ART initiation, retention in care, medication adherence, and HVL suppression).
Gabapentin is an anti-convulsant and acts against pathologic neuro-transmission by inhibiting the release of excitatory neurotransmitters (e.g., neuropathic pain, seizure disorders). It is efficacious for reducing alcohol consumption and preventing relapse. The investigators propose the Gabapentin to Reduce Alcohol and Improve Viral Load Suppression (GRAIL) trial to test the efficacy of gabapentin vs. placebo on achieving viral load suppression among PWH. The study population will be heavy drinkers with a detectable viral load at least 6 months after their HIV diagnosis. The rationale for this trial is that effective pharmacological alcohol treatment will help PWH with heavy alcohol use who have a known HIV diagnosis for at least 6 months to successfully engage in HIV care. The overarching strategy to achieve TasP is that gabapentin will

reduce heavy alcohol use, thereby increasing HIV care engagement, ART use and adherence while decreasing pain, all of which ultimately promote viral load suppression. GRAIL is a randomized, double-blinded, placebo-controlled clinical trial that will evaluate the efficacy of gabapentin in promoting HVL suppression via reducing alcohol use among PWH but not virally suppressed (i.e., The study population will be heavy drinkers with a detectable viral load for 6 months or more after their HIV diagnosis). Participants will be randomized 1:1 to receive either gabapentin (1800mg/day target dose) or placebo for 3 months; both arms will employ a brief intervention to reduce alcohol use.

Rationale

GRAIL is significant as it employs a Treatment as Prevention (TasP) approach to prevent transmission of HIV by targeting alcohol use and consequently improving progression along the care cascade, thus achieving HVL suppression among PWH. If shown to be effective, this highly generalizable pragmatic approach can be added to the HIV prevention toolkit and implemented within existing medical infrastructure.12 If demonstrated effective in improving rates of HVL suppression in this population, gabapentin could be rapidly deployed, given its relatively low cost and availability in both the US and Uganda.

We hypothesize that: Participants randomized to the intervention group will have improved HVL suppression as compared to the control group; and Participants in the intervention group will have less heavy alcohol use, less pain, greater ART adherence, and greater engagement in HIV care compared to the control group.

Potential study risks and side effects of gabapentin

• Psychological stress from sensitive questions
• Loss of confidentiality
• Phlebotomy associated risks
• Adverse effects from gabapentin
• Common side effects of gabapentin are: lack of coordination, feeling tired, viral infection, fever, feeling drowsy, jerky movements, nausea and vomiting, difficulty with coordination, difficulty with speaking, double vision, tremor, unusual eye movement, and swelling (usually of legs and feet)

Prior clinical trial report summaries that establish probable safety and efficacy in humans Ending the HIV epidemic requires achieving HIV viral load (HVL) suppression for key populations. Unhealthy alcohol use by people with HIV (PWH) is a barrier to reaching HVL suppression at multiple stages of the HIV care cascade. Alcohol use is common among PWH and results in lower antiretroviral therapy (ART) adherence and HVL suppression. Treating alcohol use is therefore a mechanism to support PWH with unhealthy alcohol use along the HIV care cascade. Most pharmacological alcohol interventions in PWH involved naltrexone, but inconclusive about the effects on HVL suppression. Gabapentin is an anti-convulsant and acts against pathologic neuro-transmission by inhibiting the release of excitatory neurotransmitters (e.g., neuropathic pain, seizure disorders). It is efficacious for reducing alcohol consumption

and preventing relapse. By targeting alcohol consumption in PWH, we aim to improve ART medication adherence, improve HVL suppression, and therefore, reduce HIV incidence.

General objective / Study aims

NA	

Primary Objectives and Outcome Measures

Aim 1: To test the efficacy of gabapentin versus placebo to achieve undetectable HVL (Primary Outcome at 3 months; Secondary Outcome at 6 & 12 months). Aim 2: To assess the impact of gabapentin compared to placebo on: a) alcohol consumption; b) pain severity; c) ART adherence; and d) engagement in HIV care, in order to explore potential mechanisms by which gabapentin may lead to HVL suppression. **Outcome measures** Aim 1. The primary outcome for Aim 1 is defined as an undetectable HVL at 3 months post randomization, assessed by study test. Secondary outcomes are undetectable HVL at 6 and 12 months. Aim 2. Additional outcomes to be examined in order to explore the mechanism by which gabapentin may lead to HVL suppression are the following: number of heavy drinking days in the past month (assessed by self-report using the Timeline Follow back [TLFB] method) and heavy alcohol consumption defined as PEth ≥50 ng/mL (assessed by study test); adherence to ART (defined as taking ≥80% of prescribed medication via Visual Analog Scale); percentage of ART pills taken (assessed by self-report); change in pain severity from baseline to follow-up (assessed by Brief Pain Inventory); and engagement in HIV care (defined as ≥ 1 HIV visit in the past 3 months assessed by medical record review). These outcomes will be evaluated at 3, 6, and 12 months.

Secondary Objectives and Outcome Measures

NA

Study Design

Phase 2
Randomized, double-blinded, placebo-controlled clinical trial.

Study Population

Adults 18 years or older with detectable HIV viral load at least 6 months after HIV diagnosis

Eligibility Criteria

Inclusion Criteria:

1. 18 years or older
2. Having an HIV diagnosis for at least 6 months (assessed via medical charts)
3. Detectable HIV viral load at least 6 months after HIV diagnosis (assessed via medical charts)
4. Positive Ethyl glucuronide EtG urine test (for detection of recent unhealthy alcohol use
5. Able and willing to comply with all study protocols and procedures
6. Provision of contact information for 2 contacts to assist with follow-up
7. Living within 2 hours travel time of the study site

Exclusion criteria:

1. Not fluent in English or Runyankole – the study forms are either in English or Runyankole.
2. Cognitive impairment resulting in inability to provide informed consent based on research assistant (RA) assessment – we need to make sure participants understand the study procedures and the potential risks.
3. Pregnancy, planning to become pregnant in next 3 months, or breast feeding (pregnancy assessed via study test)

While gabapentin exposure during early pregnancy has not been found to be associated with major malformations, there is evidence for the association of gabapentin use later in pregnancy and higher risks of preterm birth, small for gestational age, and neonatal intensive care unit admission. To mitigate this risk, pregnant and breastfeeding women will not be eligible for this study.

4. Taking gabapentin/pregablin in past 30 days (self-report)

We are testing the efficacy of gabapentin; therefore, we will need to exclude participants who have used gabapentin or pregablin in the past.

5. Taking any medication for Alcohol use disorder (AUD) (self-report)
We are testing the efficacy of a medication for alcohol use disorder, therefore, we will need to exclude participants who have used any medication for alcohol use disorder in the past.
6. Known hypersensitivity to gabapentin (self-report)
We need to ensure participant does not have any reaction or allergy to gabapentin.
7. Enrolled in another HIV research study seeking viral load suppression (self-report)
This would affect the integrity of our study.
8. Unstable psychiatric illness (i.e., answered yes to any of the following: past three-month active hallucinations; mental health symptoms prompting a visit to the ED or hospital; mental healthmedication changes due to worsening symptoms; presence of suicidal ideations) Given this is a medication trial, we will need to exclude participants with unstable psychiatric illness.

Study Duration

5 years

Investigational Medicinal Product

Gabapentin 300mg (Conventin 300mg) 300 participants

Study Arms

Eligible participants will be randomly assigned into one of two study arms: 1) gabapentin (1800mg/day target dose) for 3 months vs. 2) placebo for 3 months. All participants will receive evidence-based counseling for alcohol and either an active medication or placebo.

Sample size

300 participants

Evaluator's Risk/Benefit Assessment:

The current information provided on the investigational product is sufficient to justify the proposed clinical trial. The potential benefits of conducting the trial are considered to outweigh the risks involved, provided that the study is carried out in accordance with the approved protocol, applicable local regulatory standards, ethical standards derived from the Declaration of Helsinki and the principles of Good Clinical Practice