Recent efficacy trials in HIV-uninfected patients have identified three medications – varenicline, gabapentin and topiramate – that are used for the treatment of medical conditions such as neuropathic pain and epilepsy, but have also been shown to decrease alcohol consumption. Although these medications have the potential to be used to improve alcohol-related outcomes among HIV-infected patients, they each have a unique side-effect and adverse event profile that may limit their use in these patients who tend to have a higher prevalence of medical and psychiatric comorbidities and take more medications than do uninfected patients. In addition, no efficacy or effectiveness research has been performed using these medications in HIV-infected individuals. Before the widespread implementation of these medications among HIV-infected patients, it is advisable to conduct pharmacopidemiologic and comparative effectiveness research based on existing use of these medications to help establish their relative safety and potential benefit in HIV-infected patients, compared to uninfected individuals. Their benefit may extend to standard alcohol and HIV-related outcomes (AUDIT-C, CD4, viral load) and expanded prognostic biomarkers of HIV disease progression such as the VACS Index. The NIAAA-funded Veterans Aging Cohort-Virtual Cohort (VACS-VC) presents an ideal opportunity for such research as it contains longitudinal data on 44,180 HIV-infected patients and 88,360 uninfected controls including AUDIT-C, administrative codes, pharmacy, laboratory, and health service utilization information.

As part of our research program evaluating interventions for unhealthy alcohol use in HIV-infected patients, it is prudent to evaluate the safety and comparative effectiveness of potential medications that could be widely used to decrease alcohol consumption. Varenicline, used for smoking cessation, decreases alcohol consumption. Varenicline, however, has been associated with depression, suicide and cardiovascular complications. Gabapentin, an anticonvulsant that is commonly used for the treatment of neuropathic pain and epilepsy has demonstrated efficacy in the treatment of alcohol dependence. Gabapentin can cause adverse neurologic effects including dizziness, somnolence and seizures. Topiramate is an anticonvulsant that has demonstrated efficacy in treating alcohol dependence but can cause dizziness, sedation, anorexia and kidney stones. Since these medications have been used for more than 10 years among HIV-infected and uninfected patients for other indications, it is prudent to examine existing “real world” data for evidence of harms and benefits. In particular, it is important to establish if there are specific determinants of adverse clinical outcomes such as HIV status. Due to the relapsing nature of unhealthy alcohol use, we anticipate that long-term use (≥90 days) is more likely to be associated with improved alcohol-related outcomes.

In response to RFA-AA-14-004 and the overall goal “to inform clinical decision-making that will enhance treatment outcomes and reduce harms associated with interventions for HIV+ individuals with alcohol use disorders” and the specific goal to conduct “comparative research on medications for the treatment of alcohol use disorders in “real world” clinical settings” we propose to conduct pharmacoepidemiologic and comparative effectiveness research to support the use of “new” pharmacotherapies for alcohol interventions in HIV-infected patients. The specific aims of the study using “real world” clinical data are as follows:

**Aim 1:** To determine the incidence of adverse clinical outcomes, by HIV status, associated with the use of varenicline, gabapentin and topiramate.

**Hypothesis 1.** Adverse clinical outcomes will be highest among HIV-infected subjects, especially those who are older, are prescribed more medications, and have more comorbidity.

**Approach:** We will conduct propensity score matched analyses, by HIV status, of specific adverse clinical outcomes potentially related to varenicline, gabapentin and topiramate.

**Aim 2:** To compare the individual effectiveness of varenicline, gabapentin and topiramate on AUDIT-C scores in HIV-infected and uninfected patients.

**Hypothesis 2.** Long-term use of varenicline, gabapentin or topiramate will be associated with decreased AUDIT-C scores.

**Approach:** We will conduct propensity score matched analyses, by HIV status, of AUDIT-C scores 12 months before and up to 24 months following medication initiation.

**Aim 3:** To compare the individual effectiveness of varenicline, gabapentin and topiramate on CD4, viral load and the VACS-Index in HIV-infected patients.

**Hypothesis 3.** Improvements in CD4, viral load and the VACS-Index among those receiving varenicline, gabapentin or topiramate will be mediated by changes in alcohol use as assessed using AUDIT-C scores.

**Approach:** We will conduct propensity score matched analyses of changes in CD4, viral load and VACS-Index, and mediation analyses to determine if observed changes are mediated by changes in AUDIT-C.