

## SPECIFIC AIMS

In the aging literature, potentially inappropriate medications (PIMs) are those which likely cause more harm than benefit due to drug interactions and adverse reactions. PIMs increase with age and the number of medications used(1-3). Most people on 5+ (polypharmacy), and nearly everyone on 10+ medications, are taking at least one PIM and experiencing adverse effects(1-3). From 2000-2012, the rate of polypharmacy nearly doubled in the US from 8.2% to 15%(4). Among those with HIV infection (HIV+) on antiretroviral therapy (ART) polypharmacy is 3 fold more common, occurs 10 years earlier(5-8), and, likely due to greater physiologic frailty(9, 10), is associated with greater mortality(11). While criteria for PIMS among 65+ year olds (Aging PIMs) are established(1, 15), they have not been validated among HIV+ individuals. ART and alcohol use increase PIMs(5-8, 12-14): 48% of uninfected drinkers are prescribed alcohol interactive medications (Alcohol PIMS)(12) and 71% Of HIV+ individuals on ART take at least one ART interactive medication (ART PIMS)(8). Thus, we do not know which co medications are helpful and which are inappropriate among HIV+ who drink.

Conversely, HIV and alcohol use can prove a barrier to receipt of helpful co medications. In the face of limited evidence, providers may be reluctant to treat Alcohol Use Disorder (AUD) with medications among HIV+ individuals due to safety concerns. Further, despite the fact that HIV+ individuals co infected with HCV (HIV+/HCV+) progress more rapidly to cirrhosis(16-18) and alcohol accelerates this process(19), alcohol use is a relative contraindication for HCV treatment(20-22). As a result, drinkers may choose to under report use to gain access to direct acting agents (DAAs) but may experience more harm and less benefit. We need to quantify the impact of PIMs (Aging, ART and Alcohol) and of pharmacotherapies for AUD and HCV on patient salient outcomes (PSOs) including mortality, hospitalization, falls, bacterial pneumonia, and delirium to inform prioritization of medications and to limit harm from polypharmacy among HIV+ individuals who drink.

Our study is timely, innovative, and impactful. Among HIV+ individuals on ART, polypharmacy is the norm, AUD is under treated, and DAAs for HCV have only recently become available. While others have quantified PIMs, we will measure their impact on PSOs and characterize the benefit from pharmacotherapy for AUD and HCV among HIV+ and uninfected individuals who drink. These studies will be instrumental in the design of eHealth interventions facilitating personalized care and simplification of co medications among HIV+ individuals who drink (see U24s CHAMP & RIB). Methodological innovations (see U24 RIB) include: 1) text processing to capture PSOs; 2) propensity score techniques to account for confounding by indication; 3) electronically assisted medication reconciliation; 4) near real time data analyses; 5) trajectories of alcohol exposure (averaging 10 AUDIT-C measures); and 6) correction for systematic bias using Phosphatidylethanol (PEth) and telephone medication reconciliation(23, 24). These activities also inform other U01 projects (see Intervention and OR Modeling) and will enhance collaborations (see U24 Coordinating Center). Aims include:

### **Aim 1: Among those with Alcohol Use Disorder (AUD), characterize AUD pharmacotherapies used and estimate their effects on PSOs, by HIV status, using propensity score methods.**

- A1H1: AUD will be associated with PSOs; risk will be greater among HIV+ than uninfected.
- A1H2: HIV+ individuals will be less likely to receive AUD pharmacotherapy than uninfected individuals.
- A1H3: Receipt of AUD pharmacotherapy will decrease risk of PSOs more for HIV+ than uninfected individuals.

### **Aim 2: Fully characterize impact of polypharmacy and alcohol on PSOs by HIV status.**

- A2H1: Excess polypharmacy will increase PSOs, risk will be greater among HIV+ and current drinkers.
- A2H2: Controlling for polypharmacy, drinkers taking Alcohol PIMs will have greater risk of PSOs compared with drinkers unexposed to Alcohol PIMs and risk will be greater among HIV+ individuals.
- A2H3: Controlling for polypharmacy, HIV+ on ART also taking ART PIMs will have greater risk of PSOs, compared with HIV+ on ART not exposed to ART PIMs.
- A2H4: Polypharmacy and PIMs (Aging, Alcohol, and ART) will be associated with ART discontinuity.
- A2H5: All Aim 2 associations will increase when full medication reconciliation and PEth data are included.

### **Aim 3: Compare self report (AUDIT-C) vs. biomarker (PEth) estimate as measures of alcohol exposure in determining DAA treatment and response among HIV+/HCV+ and HCV+ individuals.**

- A3H1: Self-report will be a greater barrier to DAA initiation than equivalent biomarker levels.
- A3H2: Biomarker estimates will be a greater barrier to virologic response (SVR) than equivalent self report.
- A3H3: HIV infection will enhance associations between alcohol use and poorer access/response to DAAs.