Amy Justice
U24 COMpAAAS Center
SPECIFIC AIMS

The NIAAA-funded Consortium to improve OutcoMes in hiv/Aids, Alcohol, Aging, and multi-Substance use (COMpAAAS) evolved from the Veterans Aging Cohort Study (VACS). The single largest HIV cohort in North America (see also COMpAAAS: Observational Study), VACS is a substantial resource for the study of effects of alcohol among those aging with HIV infection: it encompasses in-depth, longitudinal data, spanning >15 years, on alcohol (63% currently drink, 32% have unhealthy alcohol use (1)), substance use, and health outcomes; it includes uninfected individuals, allowing us to characterize the role of HIV infection in determining alcohol associated outcomes; and supports targeted translational substudies, intervention studies, and operations research. We have developed a rich network of Centers, Cores, and Workgroups with highly complementary domains of expertise and means of effectively coordinating the networks efforts resulting in exceptional productivity. Our group has produced >250 publications, cited >1,700 times in 2014. We have successfully coordinated observational research, operations research (OR) modeling and intervention studies focused on the role of alcohol and multisubstance use in determining modifiable outcomes among HIV+ and uninfected. We are proud of the education, training, and career development support we offer our clinician researchers and methodologists. We have also supported the larger aims of the CHAART Consortia, coordinating two CHAART consortia meetings (a third scheduled February 2016) and closely collaborating with other consortia members. **Our ongoing mission is to build and disseminate the evidence needed to optimize care for HIV+ experiencing medical harm from alcohol and related substance use through coordinated, integrated, and externally validated observational, OR modeling, and intervention studies.** In this application, we propose to build on prior work to: develop unbiased estimates of the effect of polypharmacy, potentially inappropriate medications (PIMs), alcohol use, and treatment for Alcohol Use Disorder (AUD) and hepatitis C (HCV) to inform simplification and prioritization of pharmaceutical treatment (COMpAAAS U01: Observational Study); expand our alcohol intervention studies using contingency management and addressing the interaction between alcohol use and medical conditions (COMpAAAS U01: Intervention Study); and use OR modeling to understand the implications of various approaches to screening for alcohol use prior to HCV treatment (COMpAAAS U01: OR Modeling Study). Drawing on our network of investigators, collaborators, trainees, policy makers and patients, this U24 proposal (COMpAAAS U24: Coordinating Center) will coordinate, support, and inform 3 U01 projects and 2 U24 Resource Centers (COMpAAAS U24: RIB and COMpAAAS U24: CHAMP) with resources, information, technologies, ideas, and expertise to enhance their impact. The prior experience, resources, and momentum of COMpAAAS, uniquely positions us to accomplish the following aims:

Aim 1. Through our network of Centers, Cores, and Workgroups, guide observational, intervention, and OR modeling research to optimize care for HIV+ harmed by alcohol.

A1a. Interim results will be presented to the Steering Committee every 6 months and monthly to Executive and Core Leadership with an emphasis on implications for future work and clinical care.

A1b. Results from observational and intervention studies will be integrated into the operations model with the goal of determining what additional information would have the greatest impact.

Aim 2. Provide support and coordination to our network of Centers, Cores, and Workgroups to facilitate rigorous project review and monitoring to maximize scientific impact.

A2a. Provide administrative support and coordination.

A2b. Use established operating procedures to process concept proposals, monitor their progress, and insure appropriate authorship and acknowledgments on abstracts and publications.

Aim 3. Enhance the impact of our work by further developing functionalities of our Web Based Laboratory, facilitating external validation, and direct communication with policymakers.

A3a. Maintain an updated registry cataloguing data available from cohort collaborations including contact information, proposal forms, and availability of subjects and data for future studies.

A3b. Maintain updated smart phone and email contacts to support future eHealth interventions.

A3c. Ensure that COMpAAAS proposals address plans for external validation.

A3d. Directly communicate our findings to leading regional and national HIV policy makers.

Amy Justice
U01 COMpAAAS Observational
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.

David Fiellin
U01 COMpAAAS Intervention
SPECIFIC AIMS

Some HIV-infected patients who consume alcohol experience avoidable premature morbidity, mortality, and adverse HIV outcomes due to their drinking. Unhealthy alcohol use refers to alcohol consumption that spans at-risk drinking and DSM-5 alcohol use disorder (AUD).1,2 In this proposal we expand the definition to include alcohol use among HIV-infected patients with medical conditions that can be adversely impacted by alcohol such as presence of a detectable HIV viral load, tobacco use disorder, liver fibrosis, untreated hepatitis C (HCV) infection, depression and prescription of psychoactive medications that interact with alcohol. Abstinence from alcohol is recommended for patients with AUD, untreated HCV, and liver fibrosis and recent research demonstrates increased mortality risk among HIV-infected patients who consume more than 30 drinks per month.3 Counseling and medications are the mainstay of treatment for unhealthy alcohol use but are rarely offered or accepted in HIV clinical settings. Patients who come to these settings for routine medical care may be identified via screening but are not typically motivated to address their drinking nor are they aware of treatment efficacy. In addition, the effect of these treatments can be modest. In our ongoing **S**tarting **T**reatment for **E**thanol in **P**rimary care (**STEP**) Trials (AA0201795, See Significance and Preliminary Studies section), we have addressed the challenges of motivation and the modest impact of some interventions by integrating treatment into HIV clinics and using stepped care models that adapt the intensity of the intervention based on treatment response.4 We now propose to expand our focus to address patients' limited awareness of the impact of alcohol on medical conditions5,6 and add financial reinforcers for abstinence.

Contingency management (CM) is a behavioral therapy in which tangible rewards are provided to individuals who use substances contingent on achieving goals such as abstinence.7 CM has efficacy in decreasing use of a range of substances such as alcohol in uninfected populations.7-12 It improves linkage to care, retention in care and antiretroviral (ART) adherence in HIV-infected patents.13-17 CM has not been studied for unhealthy alcohol use in HIV-infected patients. Of note, over 50% of patients enrolled in the integrated arm of the **STEP** Trials have met criteria for "stepping up". Thus, for patients who do not respond to CM, it is important to evaluate the impact of "stepping" up treatments to include Addiction Psychiatrist Management (with alcohol pharmacotherapies as indicated) and Motivational Enhancement Therapy to harness internal motivation.

Biomarkers outcomes are useful in alcohol trials.18 Discerning the benefit of alcohol treatment using CD4 count and HIV viral load can be difficult due to the potency of ART.19-22 The VACS Index, which includes data on age, liver (FIB-4), kidney, hematologic function, HCV status, CD4 count and HIV viral load, is a validated biomarker that reflects overall health. It reflects the impact of abstinence among HIV-infected patients receiving addiction treatment, even when they enter such treatment with an undetectable HIV viral load.23 A clinically meaningful difference is 5 points, translating to a 20% change in 5-year mortality risk.24-26 Similarly, phosphatidylethanol (PEth), a biomarker easily collected via finger stick, has a specificity of 95-100% for alcohol exposure in the past 21 days and provides an objective assessment of response to alcohol treatment in HIV clinics.27-29 Building on our integrated care model and evidence of need for stepped care in the **STEP** Trials (See Significance section) we plan to determine the effectiveness of CM plus stepped care for unhealthy alcohol use in HIV-infected patients. Among HIV-infected patients with unhealthy alcohol use enrolled in the **F**inancial **I**ncentives, **R**andomization with **S**tepped **T**reatment (**FIRST)** trial our **specific aims** are:

Aim 1: To compare the efficacy of CM plus stepped care vs. treatment as usual (TAU) on alcohol abstinence as measured using PEth and alcohol consumption using Timeline Followback (TLFB).

Hypothesis 1a: CM plus stepped care will lead to a greater proportion of individuals with PEth documented abstinence.

Hypothesis 1b: CM plus stepped care will lead to fewer self-reported drinks per week by TLFB.

Aim 2: To compare the efficacy of CM plus stepped care vs. TAU on the VACS Index.

Hypothesis 2: CM plus stepped care will lead to a greater proportion of patients who experience at least a 5- point decrease in the VACS Index.

Aim 3 (Exploratory): Among patients with medical conditions adversely impacted by alcohol, to compare the impact of CM plus stepped care vs. TAU on measures including detectable HIV viral load, cotinine and anabasine (for smoking cessation), FIB-4, detectable HCV, depressive symptoms and use of psychoactive medications that interact with alcohol.

As part of **C**onsortium to improve **O**utcoMes in hiv/**A**ids, **A**lcohol, **A**ging, and multi-**S**ubstance use (COMpAAAS), the **FIRST** trial will provide novel data on the efficacy of CM plus stepped care for unhealthy alcohol use in HIV clinics and inform parallel COMpAAAS Observational and Operations Research projects.

Scott Braithwaite
U01 COMpAAAS Operations Research Modeling
SPECIFIC AIMS

Many persons with HIV have Hepatitis C (HCV) co-infection and consume alcohol.1,2 Now that highly effective and easily tolerated therapies for HCV are available, singular opportunities exist to prevent downstream morbidity and mortality from HCV including liver failure and hepatocellular carcinoma (HCC).3-5 However, alcohol consumption may offset those benefits as it magnifies damage from HCV infection, potentially leading to liver inflammation, increased risk of liver failure, and HCC.6-8 Persons with HIV are at particularly high risk of the adverse effects of alcohol consumption because they already sustain multiple sources of hepatic injury, such as steatosis and hepatotoxic medications.9-11 Moreover, the high cost of HCV therapies ($63,000 to $190,000)12-14 and enormous burden on health expenditures (10% of US prescription drug spending)13 magnifies the importance of employing these treatments successfully and with favorable value.

Accordingly, current recommendations endorse complete abstinence from alcohol for individuals with HCV.15 But it is unclear whether abstinence should be linked to HCV treatment eligibility, and if so, whether by recommendation or requirement. It is also unclear if HIV co-infected persons would merit distinct scrutiny for alcohol cessation prior to HCV treatment, as alcohol impairs cognition and medication adherence at lower consumption levels among HIV infected individuals.16,17 Reflecting these uncertainties, providers have wide variability in their tolerance of alcohol consumption prior to HCV treatment.18 Evidence from the interferon era suggests that in recent drinkers treatment completion rates were worse compared to nondrinkers, but among those who completed the full course of therapy SVR rates were similar.19,20 It is unclear if these relationships will hold in the emerging era of non-interferon direct-acting antivirals. Questions regarding abstinence prior to HCV treatment are becoming even more important because new biomarkers such as phosphatidylethanol (PEth) could objectively evaluate abstinence. While advantages of linking HCV treatment to abstinence are formidable, including the potential for greater HCV and HIV treatment success and mitigating downstream risk of liver failure and HCC, there are possible adverse consequences, in particular reducing access to HCV therapy and increasing HCV reinfection risk. Thus, deciding whether to link abstinence to HCV therapy presents difficult tradeoffs.

In order to weigh these tradeoffs systematically and to inform future HCV treatment guidelines for individuals with HIV, we seek to employ a decision analytic model to compare alternative strategies for linking alcohol consumption criteria to HCV treatment eligibility. The decision analytic model will take the form of a computer microsimulation that can replicate hypothetical populations of co-infected persons with distinct distributions of drinking patterns. Accordingly, our Aims compare alternative scenarios for specifying alcohol guidelines prior to HCV therapy in HIV patients, assessing life expectancy (H1), quality-adjusted life expectancy (QALY) (H2), and value (H3), as indicated by the incremental cost-effectiveness ratio (ICER).

Aim 1: Evaluate the impact of recommending abstinence from alcohol on HCV treatment criteria

H1.1: Recommending abstinence from alcohol prior to HCV treatment improves life-years
H1.2: Recommending abstinence from alcohol prior to HCV treatment improves QALYs
H1.3: Recommending abstinence from alcohol prior to HCV treatment improves the ICER of HCV treatment

Aim 2: Evaluate the impact of requiring abstinence from alcohol before HCV treatment and using AUDIT as a confirmatory test, exploring different cutoffs (here denoted as "X")

H2.1 Requiring AUDIT score < X will improve life-years
H2.2 Requiring AUDIT score < X will improve QALYs
H3.3 Requiring AUDIT score < X will improve the ICER of HCV treatment

Aim 3: Evaluate the impact of requiring abstinence from alcohol before HCV treatment and using PEth as a confirmatory test, exploring different cutoffs (here denoted as "Y")

H3.1 Requiring PEth < Y will improve life-years
H3.2 Requiring PEth < Y will improve QALYs
H3.3 Requiring PEth < Y will improve the ICER of HCV treatment

Exploratory Aims:

a. Identify performance characteristics and costs that would enable an improved alcohol biomarker to have a favorable incremental cost-effectiveness ratio
b. Identify amount of monetary incentive for alcohol cessation at which incentive costs are offset by reductions in future treatment costs

Janet Tate-Cynthia Brandt

U24 COMpAAAS Resource for Informatics and Biostatistics (RIB)

SPECIFIC AIMS

The overall aim of the **Consortium to improve OutcoMes in hiv/Aids, Alcohol, Aging, & multi-Substance use (COMpAAAS)** is to build and disseminate the evidence needed to optimize care for HIV+ experiencing medical harm from alcohol and related substance use, through coordinated, integrated, and externally validated observational, operations research modeling, and intervention studies. Combining and integrating the complimentary expertise of informatics, biostatistics and epidemiology, we propose a U24 **Resource for Informatics and Biostatistics (RIB)** fully integrated with and supportive of all other COMpAAAS components:

COMpAAAS U24: **Coordinating Center**

COMpAAAS U01: **Observation** (Optimizing Treatment in HIV and HCV: ART, Alcohol and Polypharmacy)

COMpAAAS U01: **Intervention** (The FIRST Trial)

COMpAAAS U01: **Operations Research (OR) Modeling** (Simulation to inform intervention design for alcohol-using HIV+ persons)

COMpAAAS U24: **CHAMP** (Consortium on HIV/Alcohol research in Minority Populations)

This resource will address the complex challenges required to maximize power and minimize bias in analyses addressing consortium-wide questions. Advanced informatics methods supported include natural language processing (NLP), ontologies, database and clinical decision support, and application of vital data management tools for secure data collection, storage, annotation, retrieval, and integration. Advanced epidemiological and statistical methods include time-updated exposure techniques, multiple imputation, propensity score techniques, regression correction, and competing risks regression. Routine, but essential, statistical methods include Cox proportional hazards, logistic and linear regression, goodness of fit diagnostics, and agreement/accuracy metrics (kappa, sensitivity, specificity, etc.). The RIB will further leverage the observational and interventional studies, simulation models, and well-coordinated network of cores and workgroups of COMpAAAS with advanced informatics and biostatistical techniques tailored to the particular challenges of large scale, longitudinal data from multiple sources including electronic health records (EHR), clinical interventions, patient self-report, and tissue repositories. For example, the Observational study will build on previous work developed by the Biostatistics Core such as improved alcohol measures and techniques to adjust for confounding; plus data collection and data management tools including Snap and REDCap applied and/or supported by the Informatics Core.

Drawing on our network of investigators, collaborators, trainees, policy makers and patients, we propose to continue to support, and inform the U01 and other U24 projects with information, technologies and expertise to multiply their impact. Because of the prior experience, resources, and momentum of COMpAAAS, the RIB is uniquely positioned to accomplish its mission through the following aims:

Aim 1. Provide statistical expertise for COMpAAAS to maximize scientific impact.

1a. Support appropriate design and execution of data analyses in VACS and cross cohort collaborations.

1b. Provide advanced statistical methods including time-updated exposure techniques, multiple imputation, propensity score techniques, measurement error correction and competing risks regression.

1c. Enhance design, recruitment, and follow-up of intervention studies (COMpAAAS U01: Intervention) with VACS data.

1d. Provide estimates of alcohol patterns for COMpAAAS U01: OR Modeling and identify sexual/gender minority populations (COMpAAAS U24: CHAMP) from VACS survey data.

Aim 2. Provide informatics expertise for COMpAAAS to maximize scientific impact.

2a. Continue to improve and maintain the Consortium Web-Based Laboratory (WBL Portal) to support ongoing research design, data collection and management, development and testing of interventions and facilitate external validation and dissemination of our findings.

2b. Provide advanced informatics research to the Consortium including clinical decision support and eHealth tool design.

2c. Provide advanced informatics research to the Consortium including development and validation of information extraction tools for textual data. Use cases include NLP for falls, pneumonia, delirium (COMpAAAS U01: Observation); patterns of alcohol use (COMpAAAS U01: OR Modeling), and documentation of sexual and gender minority populations (COMpAAAS U24: CHAMP).

David Fiellin-Janet Tate
R01 Comparative Effectiveness
SPECIFIC AIMS

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.[1-3] 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.[4-6] 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,[7,8] decreases alcohol consumption.[9-11] Varenicline, however, has been associated with depression, suicide and cardiovascular complications.[12] Gabapentin, an anticonvulsant that is commonly used for the treatment of neuropathic pain and epilepsy has demonstrated efficacy in the treatment of alcohol dependence.[13] Gabapentin can cause adverse neurologic effects including dizziness, somnolence and seizures.[14] Topiramate is an anticonvulsant that has demonstrated efficacy in treating alcohol dependence but can cause dizziness, sedation, anorexia and kidney stones.[13,15] 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 ($\geq$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.

Matthew Freiberg
R01 Proteomics
SPECIFIC AIMS:

More than 1 million people in the US are HIV infected (HIV+).[1] With the success of antiretroviral therapy (ART) and improving long-term survival, diseases of aging, including cardiovascular disease (CVD), are now critical health problems facing HIV+ people.[2, 3] HIV+ people have a 50% higher risk of acute myocardial infarction (AMI) compared to uninfected people.[3] Among HIV+ people, traditional Framingham risk factors as well as ART, anemia, hepatitis C co-infection, metabolic abnormalities, and renal disease are all CVD risk factors.[3-6] However, these risk factors do not fully explain the excess risk of CVD among HIV+ people nor, when incorporated into risk prediction models, acceptably predict CVD risk in this population.

Current approaches designed to elucidate the underlying mechanism for the excess risk of CVD and mortality among HIV+ people while also identifying those HIV+ people at greatest risk for CVD are limited in two major ways: 1) the majority of prior studies focused on a small number or even a single specific biomarker to explain what is likely a very complicated mechanism and **2)** such studies typically only assessed whether the incorporation of one specific biomarker would substantially improve CVD risk prediction.

While prior research examining a single protein biomarker (e.g., hsCRP) has provided some insights into the association between inflammation and CVD, hsCRP alone does not fully explain the association between inflammation and CVD nor does its inclusion substantially improve existing CVD risk prediction models.[7]

We hypothesize that large-scale proteomics will identify important new CVD biomarkers/mediators and biological pathways in HIV. Aptamer proteomics (SOMAscan, SomaLogic, Boulder CO) allows for rapid quantification of over 1100 proteins in a small volume of blood, making this proteomic technology ideal for large cohort studies.[8] We have already utilized SOMAscan in the Heart and Soul and HUNT3 cohorts of over 2000 subjects with stable coronary heart disease to identify 200 protein biomarkers prognostic of cardiovascular and mortality events (Preliminary Data). We have applied bioinformatic approaches to these proteins to derive and externally validate a 9-protein cardiovascular risk model which is superior to risk models derived from traditional risk factors. In this application, we hypothesize that by using large-scale proteomics, we can identify novel protein biomarkers that (1) will be associated with incident CVD and mortality events in

HIV, (2) will generate new information about biological pathways unique to HIV-associated CVD, and (3) can be used to improve CVD risk prediction in HIV+ people. Importantly, results from this study may identify novel proteins that could potentially serve as new targets for pharmacologic therapies to treat CVD in HIV.

We will leverage the existing Veterans Aging Cohort Study Biomarker Cohort (VACS BC), a longitudinal, prospective observational cohort of 1525 HIV+ and 853 uninfected veterans. All participants have stored plasma, existing data on biomarkers of inflammation, measures of immune function (T cell, B cell, and monocyte subsets), and adjudicated CVD outcomes from 2005 to 2020. Using the existing infrastructure from

R01HL095136 (PIs, Freiberg and Justice), Drs. Hsue, Ganz, and Freiberg (Co-PIs on this proposal) will link these biospecimens and biomarker data to (1) longitudinal survey data; (2) VA electronic medical record (EMR) data, including all pharmacy, laboratory, radiology, pathology, clinical measurements, and clinical notes; (3) Medicare, Medicaid, VA fee for service, mortality, and national death index data; and (4) adjudicated CVD events within and outside the VA health care system.

We propose to collect the following new data: measurements of 1130 plasma proteins using SOMAscan technology on previously collected plasma specimens from 2005-2006 on all 2,378 VACS BC participants. By linking these new data with existing VACS data, we will complete the following aims:

Aim 1: To discover a broad range of protein biomarkers predictive of CVD and mortality events in HIV.

1a) To discover novel proteins associated with CVD/mortality events, not recognized by candidate approaches in HIV using a large scale proteomics approach. Hypothesis: Proteins associated with incident CVD events/mortality will differ between HIV+ and uninfected veterans.

1b) To elucidate biological pathways of CVD in HIV by applying pathway analysis to the prognostic proteins discovered in Aim 1a. Hypothesis: Pathway analyses, focused on atherosclerotic and thrombotic pathways, will allow us to identify proteins that have a plausible biological relationship with CVD and death outcomes in HIV.

Aim 2: To identify a small (parsimonious) multi-protein panel of biomarkers among HIV+ people that predicts CVD outcomes and mortality events. Hypothesis: A multi-protein cardiovascular risk model will be identified that delivers excellent performance in HIV.

Aim 3: To evaluate the relative prognostic utility of a proteomics risk prediction model compared to traditional, Framingham based clinical risk models in subjects with HIV. Hypothesis: Risk assessment based on the multi-protein panel identified in Aim 2 will be superior to traditional risk factors and common laboratory tests for predicting CVD and mortality events in HIV-infected individuals.

If we are successful, we will identify new protein biomarkers/mediators of CVD and mortality in HIV+ people while also deriving new biological insights into the excess risk of CVD in HIV.

Kevin Kraemer

R01 Comparative Effectiveness

SPECIFIC AIMS

Alcohol and substance use disorders (ASUD) are common in HIV-infected patients and adversely affect HIV-related outcomes. Although behavioral treatment and pharmacotherapy for ASUD are highly effective in the HIV uninfected, less is known about their efficacy and comparative effectiveness in HIV-infected populations. Moreover, because few HIV-infected individuals with ASUD receive high quality ASUD treatment of any type, understanding the factors associated with initiating, engaging, and remaining in ASUD treatment is at least as important as comparing specific types of treatment. This is especially important now, in the context of the Affordable Care Act of 2010 (ACA), and its potential to give HIV-infected patients with ASUD more options.

We propose to study the comparative effectiveness of ASUD treatments and their delivery in HIV-infected Veterans. ASUD and HIV infection are high priority conditions among US military Veterans. The Department of Veterans Affairs (VA) cares for nearly a half million Veterans with current ASUD, a greater number with past ASUD, and is the single largest provider of HIV care in the US. In prior work, we have shown that the quality of HIV care in Veterans is decreased in the presence of ASUD and is associated with decreased survival. Unfortunately, despite the potential benefit of ASUD treatment, only a minority of Veterans with active ASUD initiate (16%) and engage (15%) in treatment. Implementation of the ACA on HIV-infected Veterans with ASUD is uncertain; it will likely improve ASUD and HIV care for many Veterans but may have unintended consequence in others.

Our proposed project will be based within the Veterans Aging Cohort Study (VACS), a large, multisite, national study with 2 main components: 1) a **"Virtual" Cohort** of 44,180 HIV-infected Veterans and 88,360 uninfected comparators on which we have access to administrative (e.g. ICD-9 codes), health factors, pharmacy, laboratory, pathology, health service utilization, and linked Medicaid/Medicare data; and 2) **VACS 8**, a prospective cohort of 3631 HIV-infected and 3693 matched HIV-uninfected Veterans that adds semi-annual self-report survey information to data available in the Virtual Cohort. Our **specific aims** are to:

Aim 1. *Compare the effectiveness of initiation, engagement, and retention in different types of ASUD treatment on quality of HIV care, virologic suppression, and costs in HIV-infected Veterans with ASUD.*

Hypothesis 1a. Initiation, engagement, and retention in ASUD treatment will be associated with higher quality of HIV care, virologic suppression, and lower ASUD-related, HIV-related, and total costs.

Hypothesis 1b. ASUD treatment that includes behavioral therapy and pharmacotherapy will be associated with higher quality of HIV care, virologic suppression, and lower ASUD-related, HIV-related, and total costs than ASUD treatment that includes only behavioral therapy, only pharmacotherapy, or neither.

Approach: Using a quasi-experimental design, we will conduct propensity score adjusted, difference-in-differences analyses of outcomes during the 12 months before and after each new ASUD treatment episode among the 44,180 HIV-infected VACS Virtual Cohort participants.

Aim 2. *Identify predictors of initiation, engagement, and retention in ASUD treatment in HIV-infected Veterans.*

Hypothesis 2. Minority race and decreased accessibility (rural residence, greater distance) and availability of services will be associated with decreased initiation, engagement, and retention in ASUD treatment.

Approach: We will conduct time-updated, generalized estimating equations logistic regression analyses to identify independent predisposing, enabling, and need predictors of initiation, engagement, and retention in ASUD treatment among HIV-infected VACS Virtual Cohort participants.

Aim 3. *Assess effects of ACA insurance expansion on initiation, engagement, and retention in ASUD treatment for HIV-infected Veterans.*

Hypothesis 3a. African American, men who have sex with men (MSM), and homeless HIV-infected Veterans who gain insurance coverage will have increased initiation, engagement and retention in ASUD treatment.

Hypothesis 3b. HIV-infected Veterans in low accessibility and availability areas who gain insurance coverage will have increased initiation, engagement, and retention in ASUD treatment in non-VA facilities.

Approach: We will use a mixed-methods approach to prospectively assess HIV-infected VACS 8 participants with ASUD over several years as the ACA insurance expansion occurs.

These Aims are responsive to 2 of RFA-AA-13-003's directives: 1) to assess alternative strategies for alcohol interventions to reduce HIV disease transmission and progression; and 2) to "understand factors related to alcohol reduction and patient engagement in appropriate alcohol and HIV care leading to long-term retention in treatment." Achieving these aims will provide "real world" estimates of which ASUD strategies are associated with the best outcomes in a national sample of often vulnerable HIV-infected Veterans and identify factors associated with increased engagement and retention in treatment as health care reform is implemented.