A. 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**