COMpAAAS Consortium – Operations Research and Modeling

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Work Accomplished Under the Prior CoMPAAAS Grant

• Objectives:
  • Using VACS data, characterize temporal patterns of alcohol misuse, smoking, and depression among veterans in care to determine whether conditions vary concordantly or sequentially.

  • Numerous and pervasive temporally concordant patterns between depression, smoking, unhealthy alcohol use, and other substances.
  • Implications for screening and treatment.

Figure from Ruggles, et al. (under review)
Proposed Specific Aims

Aim 1: Evaluate *recommending* abstinence before HCV tx
- H1.1: Recommending abstinence from alcohol improves Life-years
- H1.2: Recommending abstinence from alcohol improves Quality-Adjusted Life-Years
- H1.3: Recommending abstinence from alcohol improves Cost-effectiveness

Aim 2: Evaluate *requiring* abstinence before HCV tx using **AUDIT** as confirmatory test
- H2.1 Requiring AUDIT score < X will improve Life-years
- H2.2 Requiring AUDIT score < X will improve Quality-Adjusted Life-Years
- H3.3 Requiring AUDIT score < X will improve Cost-effectiveness

Aim 3: Evaluate *requiring* abstinence before HCV tx using **PEth** as confirmatory test
- H3.1 Requiring PEth < Y will improve Life-years
- H3.2 Requiring PEth < Y will improve Quality-Adjusted Life-Years
- H3.3 Requiring PEth < Y will improve Cost-effectiveness
**Significance: More Stringent Requirements for Alcohol Consumption**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>• Prioritize patients “most likely to benefit.”</td>
<td>• Against current Int’l recommendations to treat all, including those who drink alcohol.</td>
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<td>• Alcohol use may offset the benefits of HCV treatment: Continued liver injury and an independent risk factor for liver failure and HCC</td>
<td>• DAAs are efficacious and can potentially reduce much of the liver failure in HIV/HCV patients</td>
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<td>• Can potentially promote a greater likelihood of abstinence (at least for the short term)</td>
<td>• Delays access to treatment, continued accelerated progression of HCV, cirrhosis, and HCC.</td>
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Approach: 3 Steps

1) Build Operations Research Co-Infection and Alcohol Simulator (ORCAS)
2) Estimate best inputs
3) Analyses to address Specific Aims
Step 1: Build ORCAS

- **HCV simulation** (preliminary version developed – progression only)
- **HCV simulation** (progression and transmission). Include alcohol pathways
- **HIV simulation** (already developed) – progression and transmission. Includes alcohol pathways

Drinking pattern “generator” including relapse/remit and tx

**HIV/HCV simulation:**
- HIV progression
- HIV transmission
- HCV progression
- HCV transmission

**Guidelines** for HIV/HCV co-infected persons with varying levels of alcohol consumption

Recommend cessation (Aim 1)

Require cessation AUDIT (Aim 2)

Require cessation PEth (Aim 3)
HIV/HCV Simulation

Existing HIV Progression and Transmission Simulation

HCV uninfected Individual
- Age
- Sexual Orientation
- Condom Use
- Active IDU
- HCV Viral Load

HCV infected but not detected

HCV infected, detected, not in care

HCV infected, detected, in care

No SVR after HCV treatment

HCV in care receiving HCV treatment

SVR after HCV treatment
**HCV treatment is possible in all stages of disease progression with the exception of late stage HCC**

**HCV reinfection is possible in every cycle**

HCC = Hepatocellular cancer  
HCV = Hepatitis C virus  
HIV = Human immunodeficiency infection  
TACE = Trans arterial chemotherapy
Building the Drinking Generator

• Use VACS data to create individual drinking patterns that represent a diverse spectrum of alcohol use
• Individual patterns are dynamic and change over time
• Develop a similar polypharmacy generator also using VACS data: simulate number of simultaneous medications changes with age, stoppage due to ineffective, side effects, or drug interactions

**Age 14**
- Started drinking
- 3 drinks per weekday
- 7 weekends

**Age 22**
- 12 drinks per day

**Age 25**
- Enter alcohol treatment
- 4 drinks per day

**Age 26**
- Stop drinking

**Age 32**
- Relapse
Verification, Calibration, and Validation

- Standard suite of evaluations:
  - **Verification**: Debugging, make sure the model performs consistently with expectations
  - **Calibration**: Minimize differences between simulated and observed outcomes:
    - Life expectancy and QALY
    - HIV-related and liver-related mortality
    - HIV and HCV incidence
  - **Validation**: Test agreement of simulated and observed outcomes
Step 2: Estimate inputs for simulation

• **Data Sources**
  - VACS and STEPS Data
  - Systematic Literature Review and Meta Analysis

• **Input Categories**
  - Alcohol consumption patterns
  - Alcohol pharmacotherapies (efficacy, adherence)
  - Alcohol confirmatory tests (sensitivity, specificity, adherence)
  - HCV transmission/risk behaviors
  - HCV disease progression rates
  - HCV treatment pathway (alcohol test, eligibility, adherence, efficacy)
  - Costs and Utilities
Step 3: Conduct Analysis

• Perspectives: Societal and payer
• Target Population: HIV/HCV co-infected individuals and their risk partners
• Estimate results for cohorts with different distributions of: Age, sex, CD4 count, IDU status, and levels of polypharmacy

Aim 1: Evaluate **recommending** abstinence before HCV tx
Aim 2: Evaluate **requiring** abstinence before HCV tx using **AUDIT** as confirmatory test
Aim 3: Evaluate **requiring** abstinence before HCV tx using **PEth** as confirmatory test
Address Aims

- Run analyses for each Aim by setting inputs to reflect:
  - Recommendation for abstinence
  - Requiring an AUDIT score of varying cutoffs
  - Requiring a PeTH score of varying cutoffs
- Quantify the effect of each strategy on
  - Health outcomes:
    - Life expectancy
    - HIV-related and liver-related mortality
    - HIV and HCV incidence
  - Value outcomes:
    - Incremental cost per life year
    - Incremental cost per QALY
Pre-specified Subgroup Analysis

• Different levels of
  • HIV progression (CD4 count)
  • HIV treatment success
  • HCV progression (Fib 4)
  • Risk behavior (leading to different re-infection rates)
  • Alcohol treatment effectiveness

• Different assumptions regarding
  • Cost of HCV treatment regimens
  • Cost of alcohol treatments

• Different comorbidity burdens
Sensitivity Analysis

- **One-way sensitivity analysis** varying each input across its plausible range to see if results are sensitive to plausible variations.
- Sensitivity analysis also makes the uncertainty over an input transparent.
- **Probabilistic sensitivity analysis**: All inputs are varied simultaneously across their plausible ranges. PSA provides insight into the level of confidence surrounding the results.
Collaboration

VACS Study

VACS Data

Simulation

Simulation Output

Future Iteration of Trial Design

VACS=Veterans Aging Cohort Study