St PETER HIV: Studying Partial-agonists for Ethanol and Tobacco Elimination in Russians with HIV

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Russia ARCH and ZINC Status Update

• Recruitment completed as of June 2015
  • Russia ARCH Cohort (N=351)
    • Zinc for HIV Disease among Alcohol Users - An RCT in the Russia ARCH Cohort (N=254)
    • Follow up is ongoing

• Russia ARCH progress 9/2011-12/2015 (including ZINC and HERMITAGE)
  • 25 abstract submissions
  • 15 published manuscripts
  • 4 manuscripts under review
  • 16 manuscripts in process

• Mentoring highlights
  • Kaku So-Armah, PhD – NIAAA Diversity Supplement (awarded)
  • Karsten Lunze, DrPH, MD, MPH – NIDA K00/R99 (pending)
  • Bulat Idrisov, MD, MSc – 2016-2017 NIDA INVEST Fellow (awarded)
St PETER HIV – Building on Russia ARCH
St PETER HIV Study Investigators

St. Petersburg
- Evgeny Krupitsky - site PI
- Elena Blokhina
- Dmitry Lioznov
- Edwin Zvartau

Boston
- Jeffrey Samet - PI
- Chris Chaisson
- Debbie Cheng
- Natalia Gnatienko

Nashville
- Hilary Tindle – PI
- Matt Freiberg – PI
- April Shaffer

Providence
- Michael Stein
HIV+ people with heavy drinking and smoking are at high risk for future HIV-associated non-AIDS diseases such as coronary heart disease (CHD).\textsuperscript{1}

Heavy alcohol consumption and smoking are also common pro-inflammatory conditions.\textsuperscript{2,3}

Varenicline and cytisine are nicotinic partial agonists shown to be effective for smoking cessation.


Recent RCTs, particularly Litten et al., suggest that varenicline also has efficacy for reducing alcohol consumption and alcohol craving among heavy drinkers.4

In murine models, cytisine reduces alcohol consumption, nicotine-induced alcohol consumption, and self-administration of alcohol.5-7

The comparative effects of varenicline and cytisine to reduce alcohol consumption and smoking—and, by extension, inflammation, CHD, and mortality—in humans have not been tested.

Neither partial agonist has been tested for smoking against nicotine replacement therapy (NRT) in HIV+ people who are heavy drinkers and current daily smokers.

• FDA warnings exist for varenicline
  • Concern about neuropsychiatric side effects
  • Concern about interaction with alcohol
• Cytisine not FDA approved in the US, but used extensively in Eastern Europe
  • Cytisine is not associated with neuropsychiatric side effects
To compare effects of varenicline, cytisine, and NRT at 3 months in Russia ARCH on:

1. % heavy drinking* days in past month (self-report, primary outcome) and alcohol craving (self-report)
2. Cigarettes smoked per day (past week, self-report); 7-day point prevalence abstinence (biochemically verified)
3. Inflammation (hsCRP, IL-6), CHD risk (Reynolds risk score), and mortality risk (VACS index)

*We define heavy drinking as per NIAAA risky drinking criteria: > 4 standard drinks in a day (or > 14 standard drinks/week) for men and > 3/day (or > 7/week) for women.
St PETER HIV Hypotheses

1. Varenicline will have greater effects than NRT for reducing:
   - Alcohol consumption
   - Alcohol craving
   - Smoking
   - Inflammation
   - CHD risk
   - Mortality risk

2. Cytisine will have greater effects than NRT for the same outcomes

3. Varenicline will have greater effects than cytisine for the same outcomes
St PETER HIV Study Design

• Double-Blind Randomized Controlled Trial
• Target enrollment = 400
• Randomized to one of four groups:
  1) Varenicline + NRT placebo
  2) Varenicline placebo + NRT
  3) Cytisine + NRT placebo
  4) Cytisine placebo + NRT
• Randomization stratified on:
  1) alcohol consumption (≥ 3 vs. < 3 heavy drinking days in the past week)
  2) average daily cigarettes (< 1 vs. >1 pack per day)
  3) ART use (yes vs. no)
• Four assessments with lab work (0, 1-, 3-, 6-months)
• Weekly check-in/adherence calls
• Additional in-person assessment at 12-months
<table>
<thead>
<tr>
<th><strong>Inclusion Criteria</strong></th>
<th><strong>Exclusion Criteria</strong></th>
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<tbody>
<tr>
<td>18-70 years old</td>
<td>Not fluent in Russian</td>
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<td>HIV-infected</td>
<td>Cognitive impairment</td>
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<tr>
<td>≥5 heavy drinking days in the past 30 days [i.e., NIAAA at-risk drinking levels]</td>
<td>Pregnant or planning to become pregnant in next 3 months</td>
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<td>Current daily smoker</td>
<td>Breastfeeding</td>
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<td>Provision of contact information for 2 contacts to assist with follow-up</td>
<td>Serious psychiatric illness (e.g., hallucinations)</td>
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<td>Stable address within 100 kilometers</td>
<td>History of pheochromocytoma</td>
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<td>Possession of a telephone (home or cell)</td>
<td>Taking smoking cessation medications</td>
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<td>Interest in cutting down/ quitting alcohol or tobacco</td>
<td>Systolic BP &gt; 180 mm Hg or diastolic BP &gt; 100 mm Hg</td>
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<td>Able and willing to comply with all study protocols and procedures</td>
<td>Acute coronary syndrome in past month</td>
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<td>History of seizures</td>
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St PETER HIV Study Design

**Screening, Enrollment, & Baseline Assessment**

**Randomization 1:1:1:1 N=400**
- Counseling for Alcohol & Tobacco Use

| Arm 1 N=100: | Arm 2 N=100: | Arm 3 N=100: | Arm 4 N=100: |
| Varenicline + NRT placebo | Varenicline placebo + NRT | Cytisine + NRT placebo | Cytisine placebo + NRT |

**Follow Up Visits and Phone Calls**

- **Phone Calls**: Weeks 1, 3, 5, 6, 7, 8, 9, 10, 11
- **In-Person Visits**: Week 2; Months 1, 3, 6, 12

**Trial Endpoints at 3 months**: Heavy Drinking Days, Alcohol Craving, Cigarettes Per Day, Smoking Abstinence, HsCRP, IL-6, Reynolds Risk Score, VACS Index
Trial endpoints are at 3 mo & assess % heavy drinking days in past month (primary study endpoint, Aim 1) & alcohol craving (secondary outcome, Aim 1); cigarettes/day (past week) & 7-day point prevalence abstinence verified by expired CO (primary & secondary outcomes, respectively, Aim 2); hsCRP+IL-6 (primary outcome, Aim 3), Reynolds score, VACS index (both secondary outcomes, Aim 3). Self-reported alcohol & tobacco-related outcomes (Aims 1 & 2) are also assessed at 1, 6, & 12 mo.
Questions?
## St PETER HIV Study Activities

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<tr>
<th>Study Activity</th>
<th>0</th>
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*Includes questions on substance use, demographics, ART use and adherence, co-morbidities
± Also assessed weekly while on study medication

~ Reynolds Risk Score
*Biomarker of Inflammation
¥ Safety Measures

± VACS Index