Treating Tobacco Use Among People Living with HIV

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Disclosures

- Consultant to Pfizer, GlaxoSmithKline, and Curaleaf
- Received research support (medication and placebo) from Pfizer
CFAR/CIRNA Team
Penn HIV and Tobacco Program

Clinical Trial (R01 DA033681) - Randomized controlled trial of varenicline for smoking cessation

Behavioral Lab Study (Harrison et al., 2017) - HIV+ smokers exhibit worse cognitive performance

Biomarker Study (R01 HL151292) - Determinants & Outcomes of NMR in PLWH

Cognition Trial (R01 DA042682) - Evaluating cognition as unique risk factor for relapse among HIV+ smokers

Botswana Study (R01 DA045604) - RCT of behavioral txs for smoking

Clinical Trial (R01 CA243914) - Optimizing Tobacco Treatment with NMR and Adherence

Cognition and Inflammation (R01 DA044906) - Testing role of tobacco use and targeting cholinergic function on inflammation and cognition
ARTs Have Transformed HIV

HIV Medicines Help People with HIV Live Longer

(AVERAGE YEARS OF LIFE)

- A person without HIV: 79 YEARS
- A person with HIV diagnosed at age 20 taking current HIV medicines: 71 YEARS
- A person with HIV diagnosed at age 20 not taking current HIV medicines: 32 YEARS

Focus Shifted to Health Behaviors

Helleberg 2013 Clinical Infectious Diseases; Humfleet 2013 Nicotine Tob Res; Turner 2001 J Gen Intern Med
PLWH are more likely to smoke

Smoking rates are 3 times higher among people living with HIV than in the general population.
HIV+ smokers are more likely to smoke despite wanting to quit.
Varenicline – gold standard, but not well tested in PLWH

- RCT in France showed small but significant benefit of varenicline (15%) vs placebo (6%) at 1-year
- < 4% of PLWH report using varenicline
- 1 in 5 clinicians report prescribing
- Concerns about psychiatric and cardiovascular side effects linger

Pacek et al 2017 AIDS Care; Sterling et al 2016 J Am Heart Assoc; Mercie et al 2018 Lancet HIV
Randomized controlled trial of varenicline for smoking cessation
Testing the Efficacy of Varenicline in HIV+ Smokers

![Diagram showing the efficacy of Varenicline in HIV+ smokers]

BSL = Baseline (and Intake Session and Randomization); A = Assessment; C = Counseling; TQD = Target Quit Day; * Corresponds to End-of-Treatment and 6-months post-TQD and primary outcomes.
### Varenicline is safe and well-tolerated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=90)</th>
<th>Varenicline (N=89)</th>
<th>Total (N=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with an adverse event</td>
<td>28 (31.1%)</td>
<td>19 (21.3%)</td>
<td>47 (26.3%)</td>
</tr>
<tr>
<td>Participants with a serious adverse event</td>
<td>3 (3.3%)</td>
<td>5 (5.6%)</td>
<td>8 (4.5%)</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td>70</td>
<td>43</td>
<td>113</td>
</tr>
<tr>
<td>Skin swelling</td>
<td>28</td>
<td>19</td>
<td>47</td>
</tr>
<tr>
<td>Depression</td>
<td>16</td>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>Agitation</td>
<td>16</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>Hostility</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Weakness</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Irritability</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Skin redness</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>ER visit</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total number of serious adverse events</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Suicidality</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cancer diagnosis</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cancer metastasis</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Number of high blood pressure recordings</td>
<td>30</td>
<td>17</td>
<td>47</td>
</tr>
</tbody>
</table>
Varenicline had no adverse effects on viral load or ART adherence.
Varenicline is safe and effective but quit rates are lower than general population.

- Week 12: Placebo 12.1%, Varenicline 28.1%, Varenicline Gen Pop 50.3% (OR=4.5, p=.001)
- Week 18: Placebo 11.1%, Varenicline 21.3%, Varenicline Gen Pop 40% (OR=3.1, p=.02)
- Week 24: Placebo 10%, Varenicline 14.6%, Varenicline Gen Pop 33.5% (OR=1.9, p=.20)

Ashare et al., 2019; DAD
Why are treatments less effective?
PLWH may be particularly vulnerable to risk factors for relapse

• Cognition
• Nicotine metabolism rate (NMR)
• Medication adherence
• Negative Affect
Evaluating cognition as unique risk factor for relapse among HIV+ smokers
HIV-related Comorbidities are Barriers to Quitting

- HIV-associated neurocognitive disorder (HAND)
  - 39%-69% exhibit deficits in multiple cognitive domains
  - Associated with functional disabilities
  - Smoking can accelerate the incidence and progression of HAND

Ciesla 2001 Am J Psychiatry; Heaton 2011 J Neurovirol; Schouten 2011 AIDS
HIV-infected (n=103)

• Enrolled in placebo-controlled clinical trial of varenicline for smoking cessation among those with HIV (NCT01710137)

HIV-uninfected (n=70)

• Enrolled in placebo-controlled trial evaluating the effects of galantamine on short-term smoking abstinence (NCT01845961)

• Except for HIV status, trials had similar inclusion criteria
• Completed same cognitive tasks
• Data are from baseline, prior to initiation of treatment

R01 DA033681, K23 DA035295
## Neurocognitive Performance

<table>
<thead>
<tr>
<th>Measure</th>
<th>HIV-uninfected</th>
<th>HIV-infected</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>N-back Discrimination Index</td>
<td>0.72</td>
<td>0.09</td>
<td>0.62</td>
</tr>
<tr>
<td>N-back RT</td>
<td>616.8</td>
<td>111.7</td>
<td>728.2</td>
</tr>
<tr>
<td>N-back CV</td>
<td>0.25</td>
<td>0.05</td>
<td>0.24</td>
</tr>
<tr>
<td>CPT Discrimination Index</td>
<td>0.85</td>
<td>0.15</td>
<td>0.81</td>
</tr>
<tr>
<td>CPT RT</td>
<td>452.8</td>
<td>52.5</td>
<td>488.8</td>
</tr>
<tr>
<td>CPT CV</td>
<td>0.18</td>
<td>0.03</td>
<td>0.21</td>
</tr>
</tbody>
</table>

**Note.** Raw values are depicted for each task. CV = Coefficient of Variation
Cognitive variables predict HIV status

- **Demographic and Smoking Variables**
  - Education: HIV+ < HIV-
  - Nicotine Dependence: HIV+ < HIV-

- **Neurocognitive Performance**
  - Accuracy: HIV+ < HIV-
  - Response time: HIV+ > HIV-
  - Intraindividual variability: HIV+ > HIV-

\[ X^2(1) = 12.8, \ p = 0.0003 \]
Why is cognition important?

• Nicotine withdrawal produces impaired cognition

• Domains of cognitive function impaired during abstinence similar to HAND

• Withdrawal-related cognitive impairment predict relapse

Ashare & Hawk 2012 Psychopharm; Lerman 2002 Drug Alcohol Depend; Loughead 2015 Neuropsychopharmacology; Patterson 2009 Biol Psychiatry; Strong 2009 Nicotine Tob Res
Ongoing Mechanistic Observational Trial

Pre-Quit Lab Phase

Order counterbalanced

Lab 1

Lab 2

Treatment Phase

Counseling + TN
8 weeks

EOT

HIV+ Smokers

HIV- Smokers

R01 DA042682
Possible neurobiological mechanisms

• HIV-1 infection may cause neuronal damage (Lindl et al, 2010)

• Brain regions critical for neurocognitive function are impacted by HAND and smoking (Hakkers et al, 2016; Weiland et al, 2015)

• In the post-ART era, persistent inflammation may contribute to HAND (Hunt et al, 2016; Lederman et al, 2013)

• Tobacco smoking also induces inflammatory markers implicated in HAND (e.g., CRP, IL-6, MCP-1) (Stampfli and Anderson, 2009)
Smoking rate is related to inflammation among HIV+ smokers
Working memory is related to inflammation among HIV+ smokers

HIV+

HIV-

\[ r = -0.65, \ p = 0.001 \]
Targeting cholinergic function to address HIV-related inflammation and cognitive function

GAL: nAChR & AChE
ing

Modulation by Smoking Status

Smoking

Monocyte Activation
Monocyte Gene Expression

T Cell Activation

Neuroinflammation & Neuronal Processing

Neurocognitive Performance

HIV-related Health Outcomes

R01 DA044906
Optimizing Tobacco Treatment with NMR and Adherence
Nicotine metabolism is associated with smoking phenotypes

- Ratio of 3HC:cotinine = NMR
- CYP2A6 mutations alter nicotine metabolism
- Reflects environmental and demographic factors
- Strong test-retest reliability

Smokers with HIV may metabolize nicotine faster

Ashare...Schnoll, *AIDS*, in press
Smokers with HIV metabolize nicotine faster than matched controls

Ashare et al, 2019 AIDS

$p < 0.001$
The Adherence Problem

• 40-50% of those treated with varenicline are adherent (42% in our trial)

• Quit rates among those treated with varenicline who were adherent are significantly higher

• Little understanding of factors associated with non-adherence to varenicline (side effects and negative affect; Quinn et al., 2020)

• No evidence-based interventions (Pacek et al., 2018)
Varenicline Effect Related to Nicotine Metabolism and Varenicline Adherence

OR = 2.22, 95% CI: 1.3-3.9, p < .01

OR = 3.39, 95% CI: 1.6-7.3, p < .01
Nicotine Metabolism and Adherence

• Effects of NMR on abstinence enhanced when considering adherence to varenicline (General Population)

![Figure 2. EOT Abstinence Rates on Varenicline by Adherence and NMR](image)

- OR=1.33, p=.18
- OR=2.00, p=.005
NMR Optimization

• Quit Rates: Varenicline was more efficacious than nicotine patch in fast metabolizers but not in slows

• Side effects: Increased side effects on varenicline for SMs, but not for fast metabolizers

<table>
<thead>
<tr>
<th>NNT</th>
<th>Patch</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMs</td>
<td>10.3</td>
<td>8.1</td>
</tr>
<tr>
<td>FMs</td>
<td>26</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Lerman, Schnoll et al., 2015; Lancet Res Med
Adherence Optimization

- Managed problem solving (MAPS) counseling: brainstorming, planning, implementation, and assessment and modification
- RCT vs. usual care found significant increased adherence (MEMS and viral load)
- MAPS associated with higher adherence (Missing=0%: Odds of being in a higher category of adherence 1.78 (1.07-2.96) for MAPS vs. UC
- MAPS associated with higher odds of UDVL (Missing=0%: Odds of UDVL=1.48 (0.94-2.31) favoring MAPS

Gross et al., 2013; JAMA Internal Med
Optimizing Tobacco Treatment with NMR and MAPS

- NMR-tailored treatment and MAPS counseling to boost cessation
- Aims:
  - Intervention effects on cessation
  - Mediators (e.g., adherence, treatment outcome expectancies, motivation)
  - Moderators (e.g., demographics, smoking, psychiatric)
Faster NMR may be related to ART regimen

CD4+ Count

- Slow
- Fast

% Undetectable Viral Load

% Efavirenz Use

Schnoll...Ashare, *JAIDS*, in press
Determinants and Outcomes of NMR in Smokers with HIV

Aim 1

HIV viremia

Immune dysregulation → CY2A6 induction

Attenuation of viremia effect

ART-induced viral suppression and CD4 recovery

Aim 2

↑ NMR

↑ Dependence

↑ Exposure per puff

Inability to quit

Smoking-related complications (e.g., MI)

Aim 3

Aim 4

Penn Mental Health AIDS Research Center

R01 HL151292
RCT of behavioral intervention for smoking in Botswana
### Smoking and HIV in Botswana

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected ART-exp*</th>
<th>Females</th>
<th>Males</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Category N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-39</td>
<td>167 (46.6)</td>
<td>131 (54.8)</td>
<td>36 (26.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>40-49</td>
<td>135 (37.7)</td>
<td>78 (32.6)</td>
<td>57 (41.9)</td>
<td>.</td>
</tr>
<tr>
<td>50-59</td>
<td>41 (11.5)</td>
<td>14 (5.9)</td>
<td>27 (19.9)</td>
<td>.</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>13 (4.2)</td>
<td>3 (1.2)</td>
<td>12 (8.8)</td>
<td>.</td>
</tr>
<tr>
<td><strong>Current Cigarette Smoking, N(%)</strong></td>
<td>85 (22.7)</td>
<td>15 (6.3)</td>
<td>70 (51.5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Known CVD</strong></td>
<td>2 (0.5)</td>
<td>2 (0.6)</td>
<td>0 (0)</td>
<td>&gt; 0.9</td>
</tr>
<tr>
<td><strong>HIV parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since HIV diagnosis (years) Mean (SD)</td>
<td>8.9 (2.8)</td>
<td>8.7 (2.6)</td>
<td>8.9 (3.0)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Mosepele M, Open AIDS Journal 2017
Smoking and Depression Symptoms

- Smoking 2x higher
- 20% of population but about half of tobacco-related deaths
- Those with SMI express quit motivation
- High rates of depression among PLWH

LeCook et al., 2014; Callaghan et al., 2014; Olfsen et al., 2015; Colton & Manderscheid, 2006; US Dept of VA, 2016
Behavioral Activation for MDD

• Behavioral activation (BA) derived from CBT for depression
• Simpler than CBT; easier to train
• Increases engagement in rewarding activities not associated with smoking (substitute reinforcers) and reduces engagement in activities associated with smoking (complementary reinforcers)
• Small studies showing some efficacy for BA for smoking cessation (e.g., MacPherson et al., 2010)

Hitsman et al., (2013); Goelz et al., 2014; Schnoll et al., 2016
Thotoletso Intervention

- Adapt Behavioral Activation and Merge with Problem Solving from MAPS
Thotloetso Pilot

• Adaptation process
  – English to Setswana and back
  – Iterated until considered equivalent
  – All concepts deemed culturally relevant

• Team (N=5) trained
  – No one had smoking cessation or clinical research experience
  – Enrollment focused on teamwork and non-judgmental attitude

• N=44 enrolled
  – Study completed
Thotloetso Results

• Characteristics
  – 38 male (95%)
  – Median PHQ-8 = 2 (IQR 1-4)

• Quit rate
  – 15/20 at EOT
  – Overall 15/40 (37.5%)

• Exit interviews
  – All endorsed BAPS
  – Would refer others
Thotloetso Trial

- RCT of Behavioral Activation and MAPS vs. standard behavioral smoking cessation counseling

- Large N will provide power for testing mediator and moderator aims (depression symptoms)

- Potential for developing a new paradigm for addressing tobacco use among HIV+ smokers in low-income countries
Acknowledgements

R01 DA033681
R01 DA042682
R01 DA044906
R01 DA045604

R01 HL151292

R01 CA243914

P30 AI045008