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








Center for AIDS Research
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Children's Hospital of Philadelphia
Wistar Institute

Penn
University of Pennsylvania

CIRNA | Center for Interdisciplinary Research on Nicotine Addiction

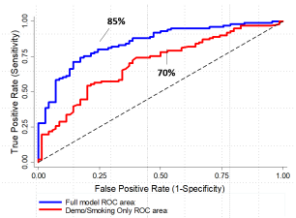
Penn HIV and Tobacco Program

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

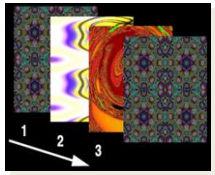


Biomarker Study (R01 HL151292)

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

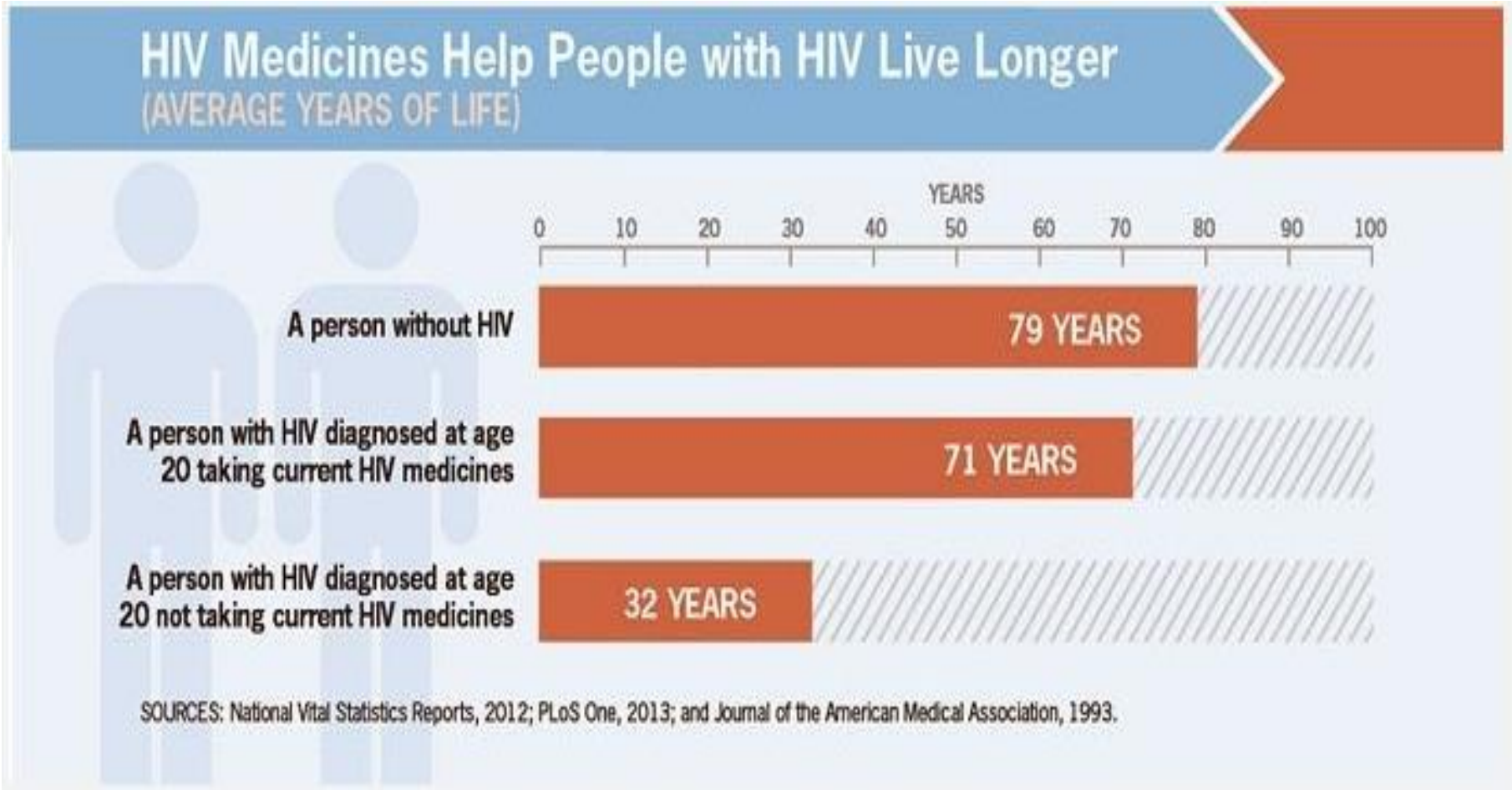
Clinical Trial (R01 CA243914)

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

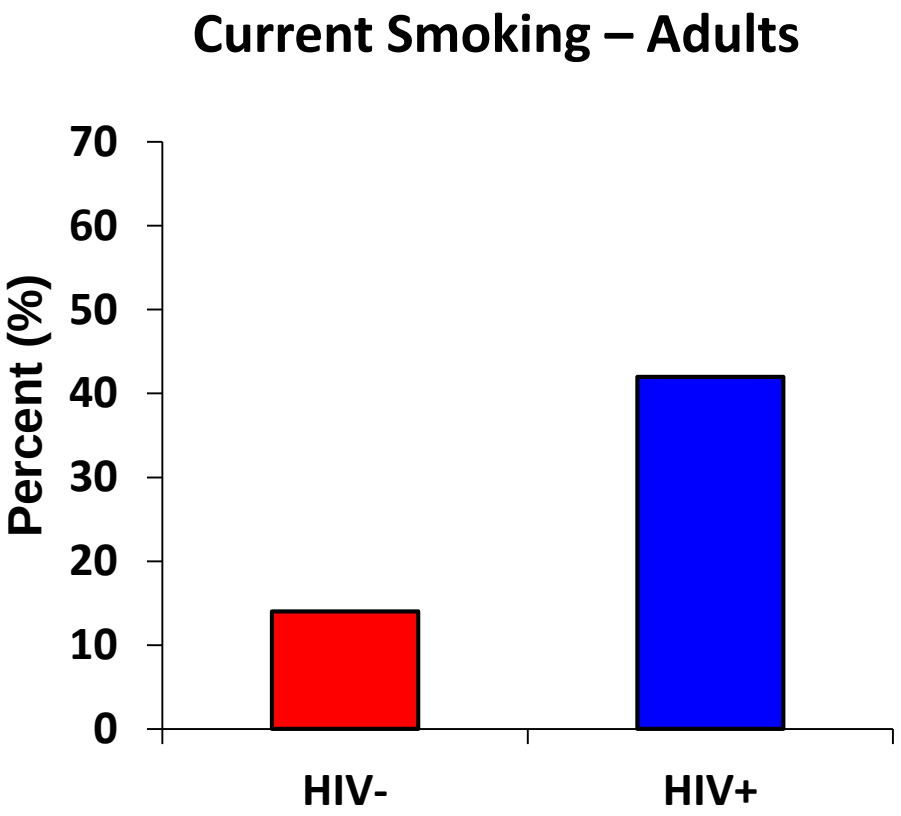
ARTs Have Transformed HIV



Focus Shifted to Health Behaviors

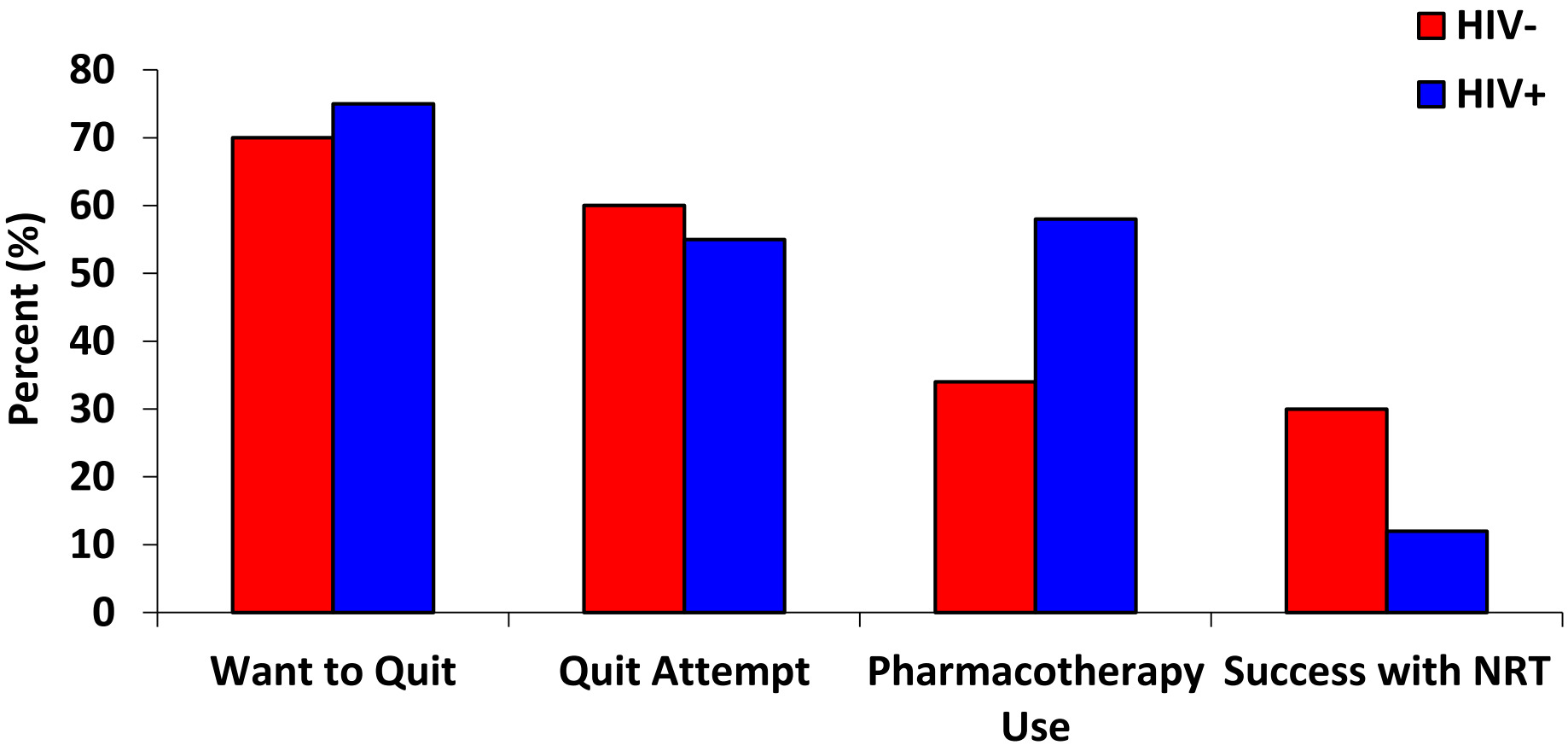
Helleberg 2013 Clinical Infectious Diseases; Humfleet 2013 Nicotine Tob Res; Turner 2001 J Gen Intern Med

PLWH are more likely to smoke



Smoking rates are <u>3 times higher</u> among people living with HIV than in the general population

HIV+ smokers are more likely to smoke despite *wanting* to quit



Pacek 2015 Curr HIV/AIDS Rep

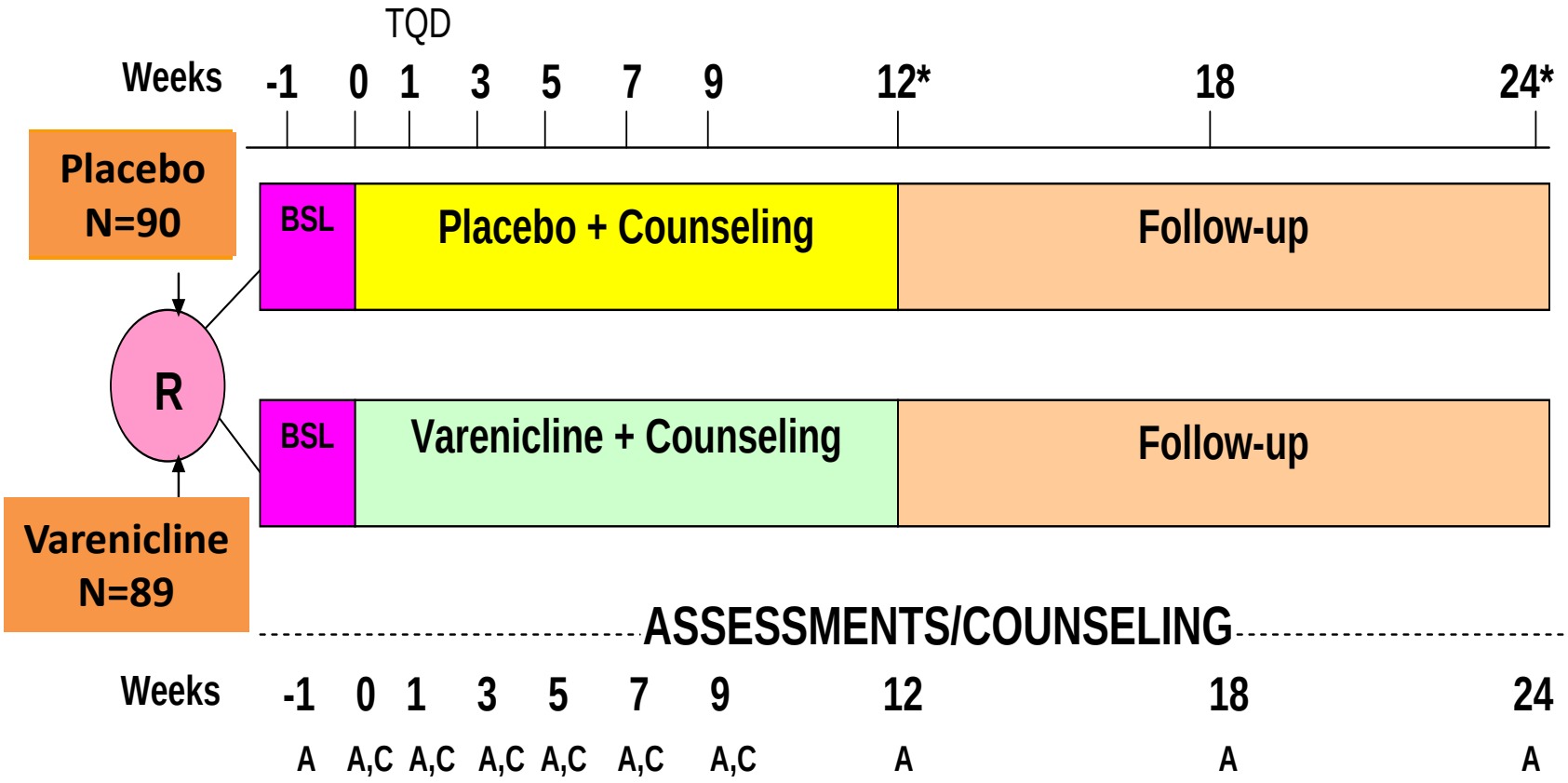
Varenicline – gold standard, but not well tested in PLWH

- 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



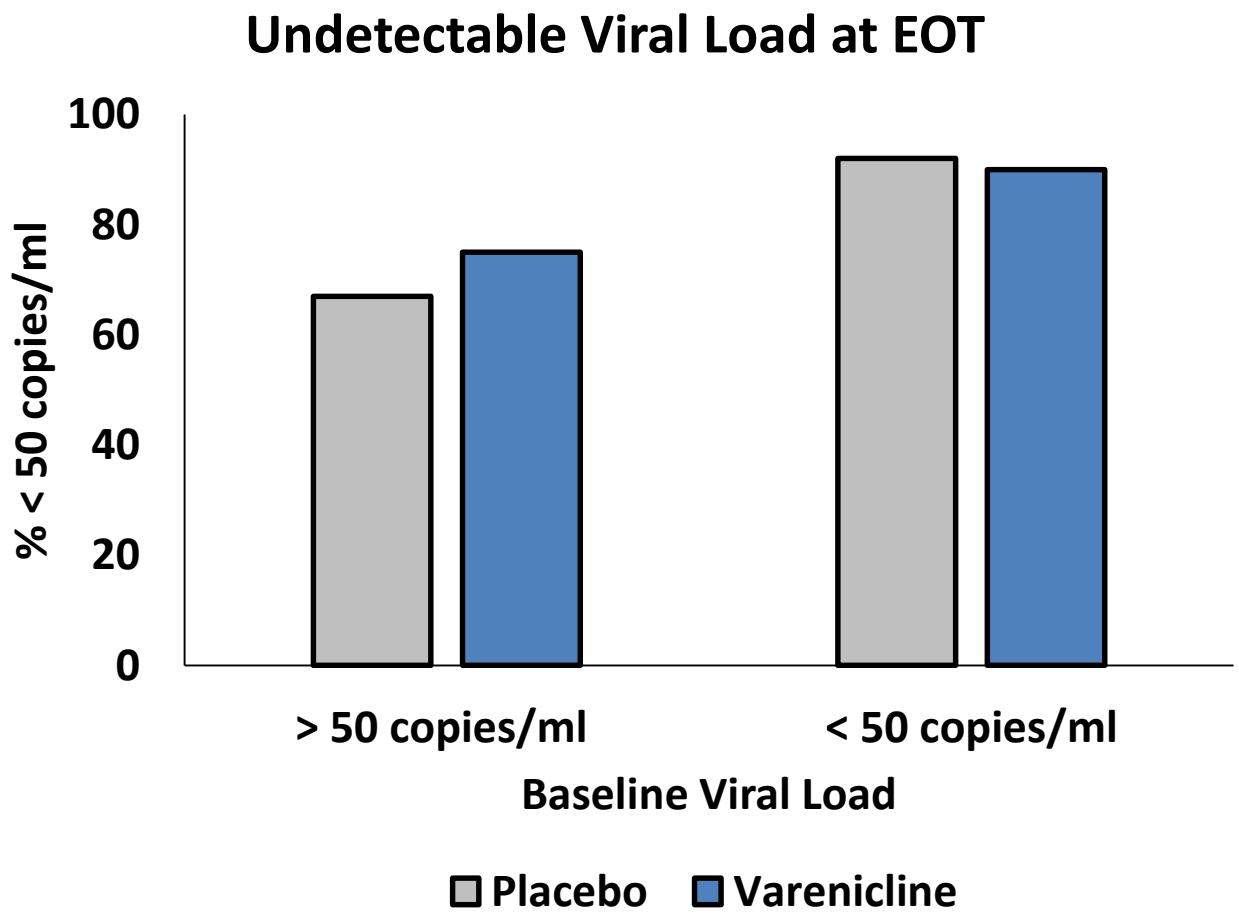
BSL = Baseline (and Intake Session and Randomization); A = Assessment; C = Counseling; TQD = Target Quit Day; * Corresponds to End-of-Treatment and 6-months post-TQD and primary outcomes.

R01 DA033681

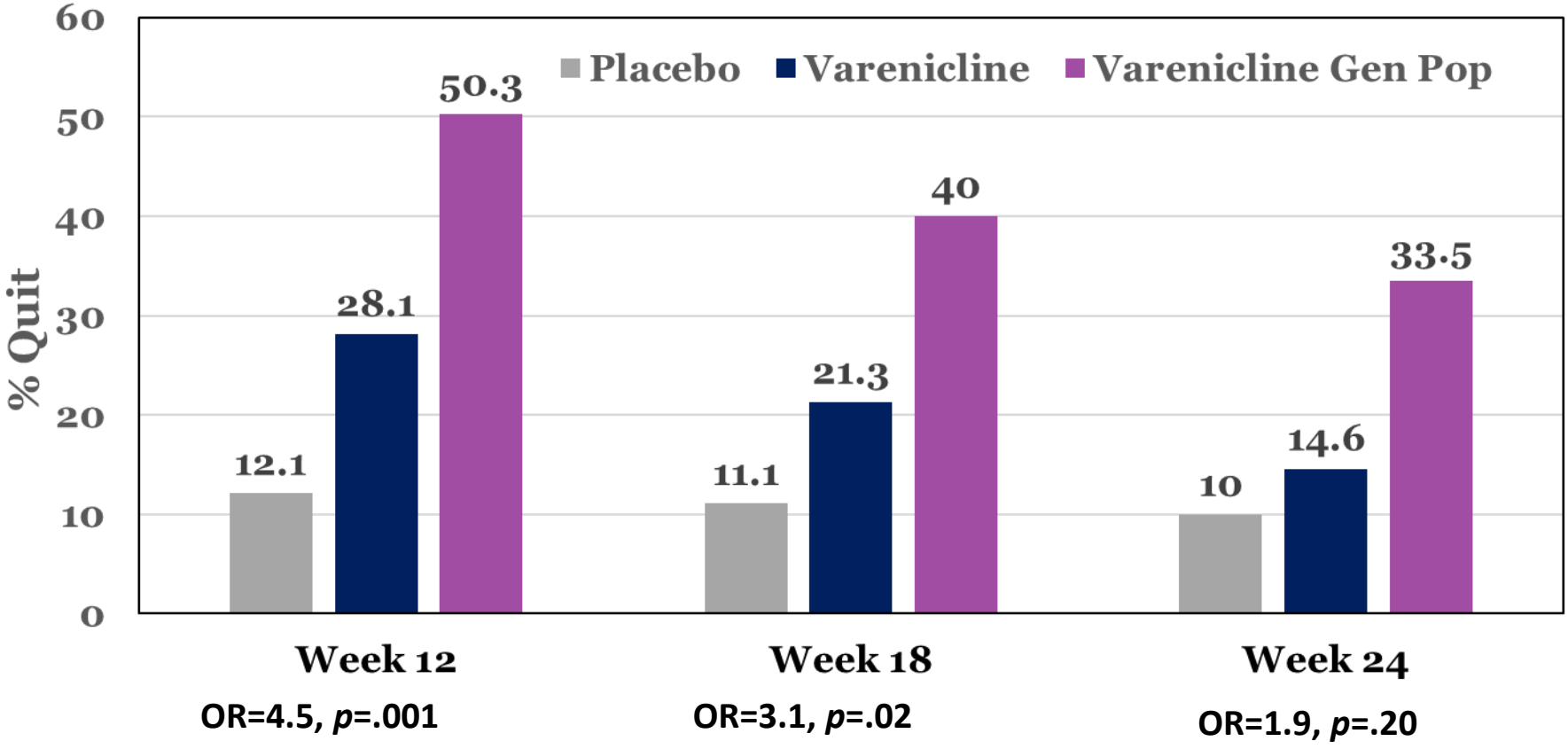
Varenicline is safe and well-tolerated

Variable	Placebo (N=90)	Varenicline (N=89)	Total (N=179)
Participants with an Adverse Event	28 (31.1%)	19 (21.3%)	47 (26.3%)
Participants with a Serious Adverse Event	3 (3.3%)	5 (5.6%)	8 (4.5%)
Total Number of Adverse Events	70	43	113
Skin swelling	28	19	47
Depression	16	7	23
Agitation	16	8	24
Hostility	5	2	7
Weakness	0	1	1
Irritability	2	0	2
Skin redness	1	1	2
Dizziness	0	1	1
Headache	1	3	4
Abdominal pain	1	1	2
ER visit	2	0	2
Total Number of Serious Adverse Events	8	8	16
Suicidality	1	1	2
Cancer diagnosis	1	1	2
Cancer metastasis	0	1	1
Hospitalization	3	5	8
Death	1	0	1
Number of High Blood Pressure Recordings[a]	30	17	47

Varenicline had no adverse effects on viral load or ART adherence



Varenicline is safe and effective but quit rates are lower than general population



OR=4.5, *p*=.001

OR=3.1, *p*=.02

OR=1.9, *p*=.20

Ashare et al., 2019; DAD

R01 DA033681

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

J. Neurovirol.
DOI 10.1007/s13365-017-0526-z

The nature and consequences of cognitive deficits among tobacco smokers with HIV: a comparison to tobacco smokers without HIV

Joseph D. Harrison[1] · Jessica A. Dochney[1] · Sonja Blazekovic[1] · Frank Leone[2] · David Metzger[1] · Ian Frank[3] · Robert Gross[3,4] · Anita Hole[1] · Karam Mounzer[5] · Steven Siegel[6] · Robert A. Schnoll[7] · Rebecca L. Ashare[1]

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

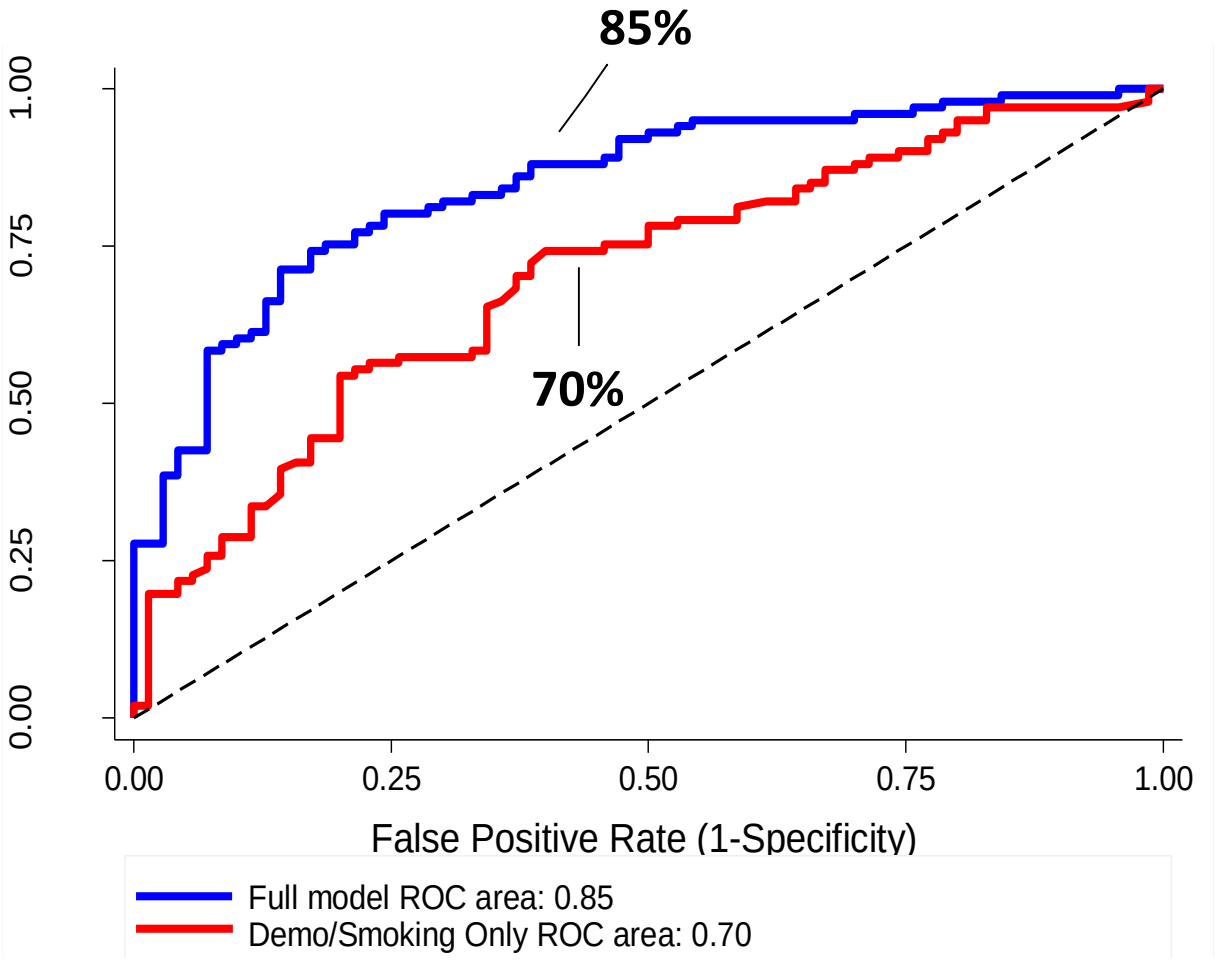
Neurocognitive Performance

Measure	HIV-uninfected		HIV-infected	
	Mean	SD	Mean	SD
N-back Discrimination Index	0.72	0.09	0.62	0.14
N-back RT	616.8	111.7	728.2	174.5
N-back CV	0.25	0.05	0.24	0.07
CPT Discrimination Index	0.85	0.15	0.81	0.12
CPT RT	452.8	52.5	488.8	49.6
CPT CV	0.18	0.03	0.21	0.03

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-



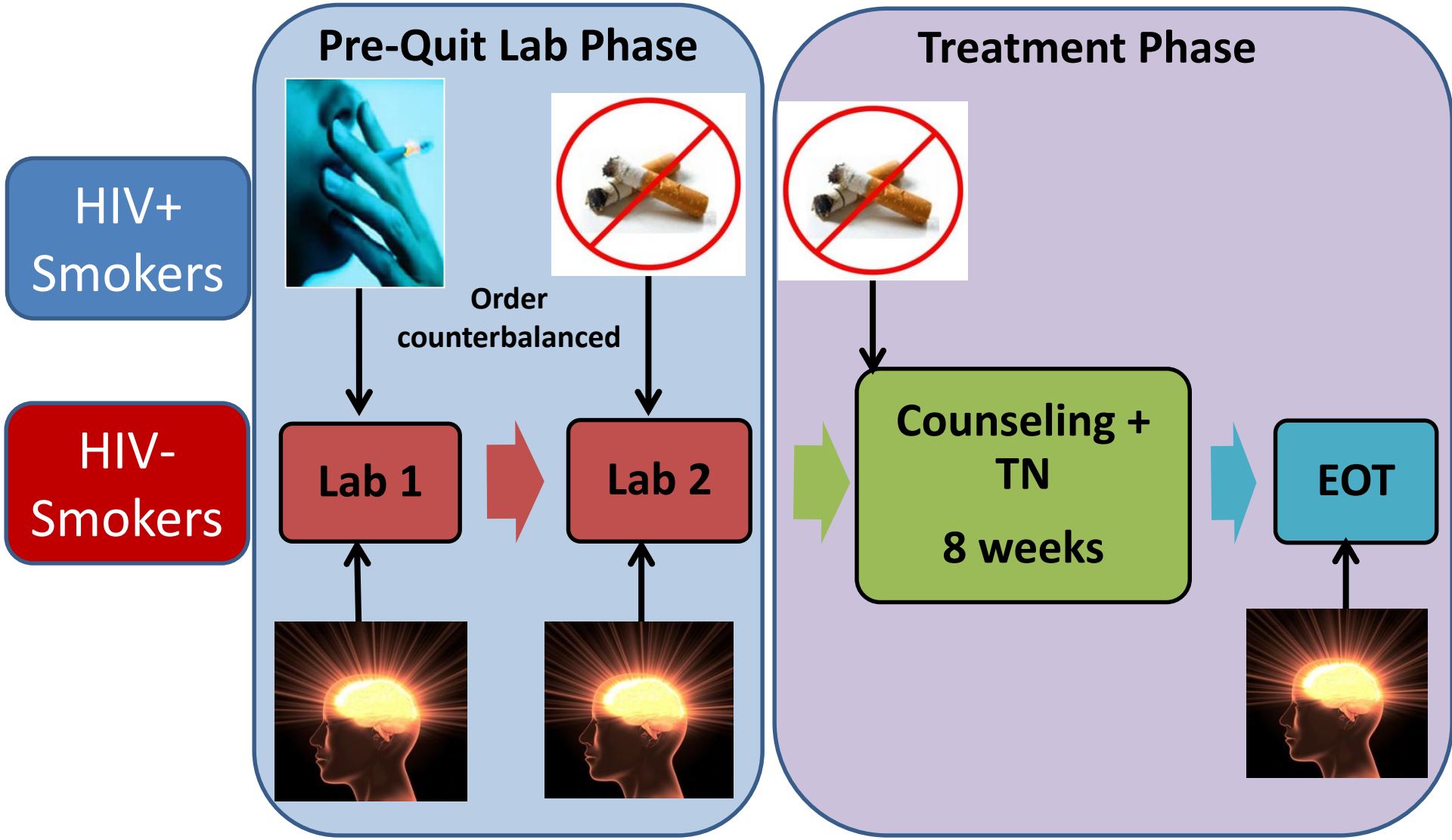
$X^2(1) = 12.8, p = 0.0003$

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

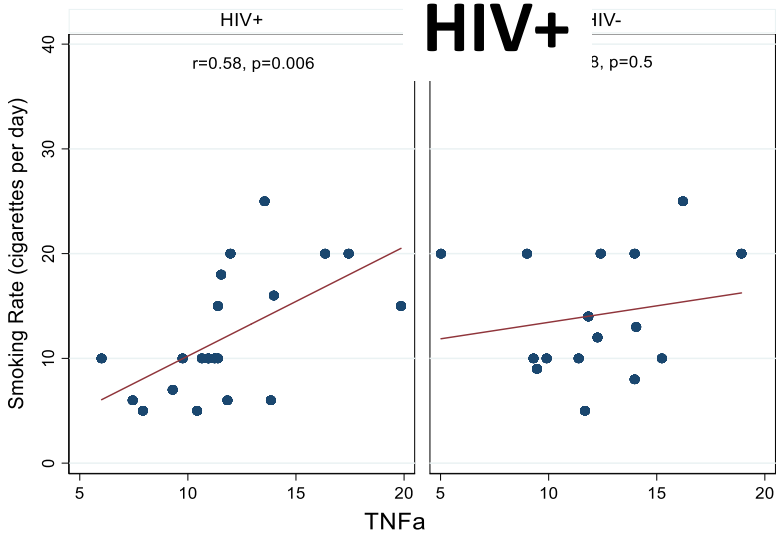


R01 DA042682

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)

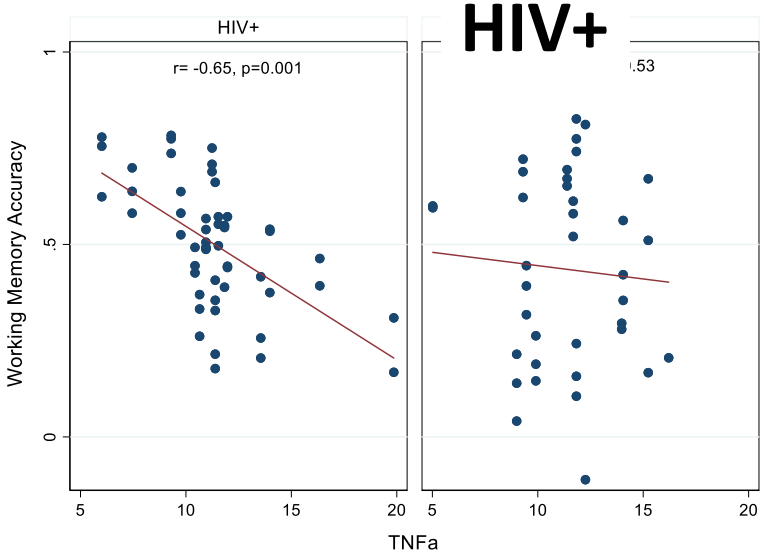
Smoking rate is related to inflammation among HIV+ smokers



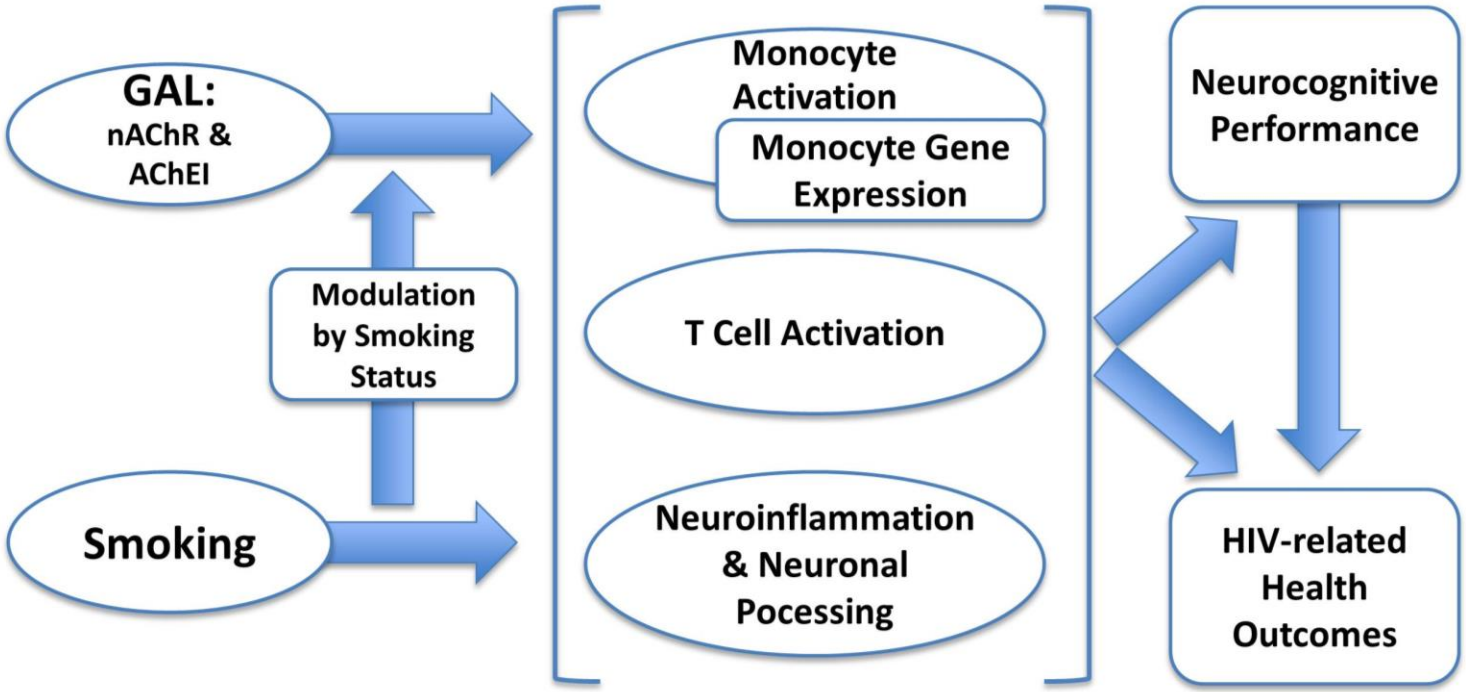
HIV+

HIV-

Working memory is related to inflammation among HIV+ smokers



Targeting cholinergic function to address HIV-related inflammation and cognitive function



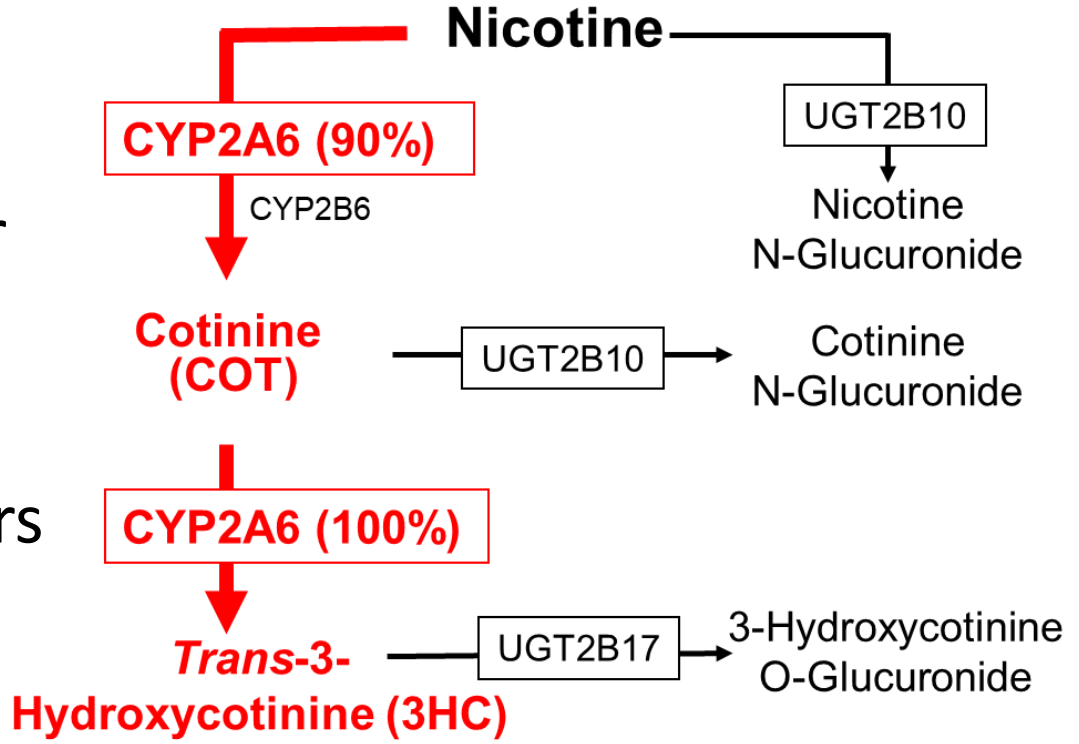
R01 DA044906

Optimizing Tobacco Treatment with NMR and Adherence

R01 CA243914

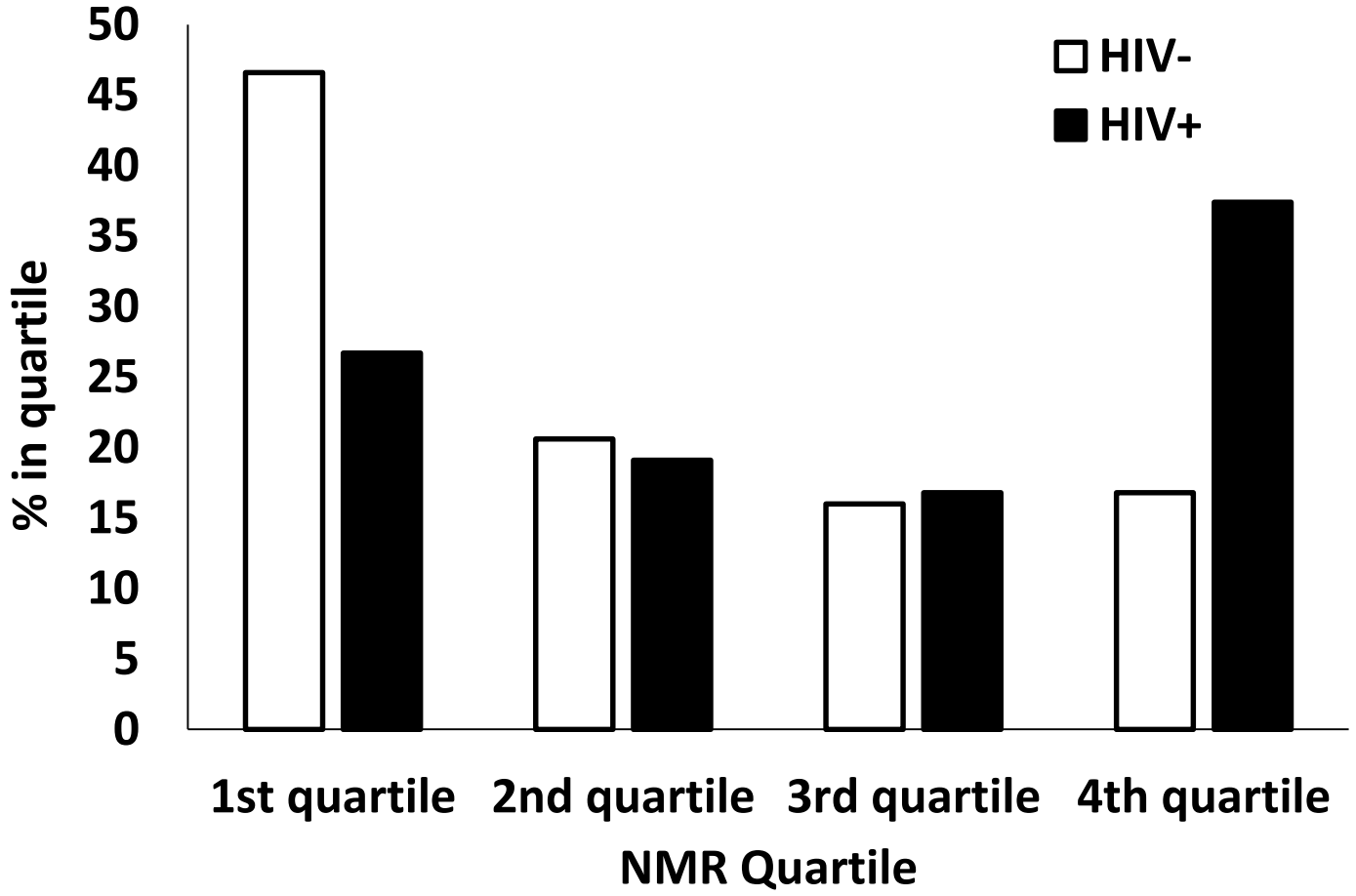
Nicotine metabolism is associated with smoking phenotypes

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



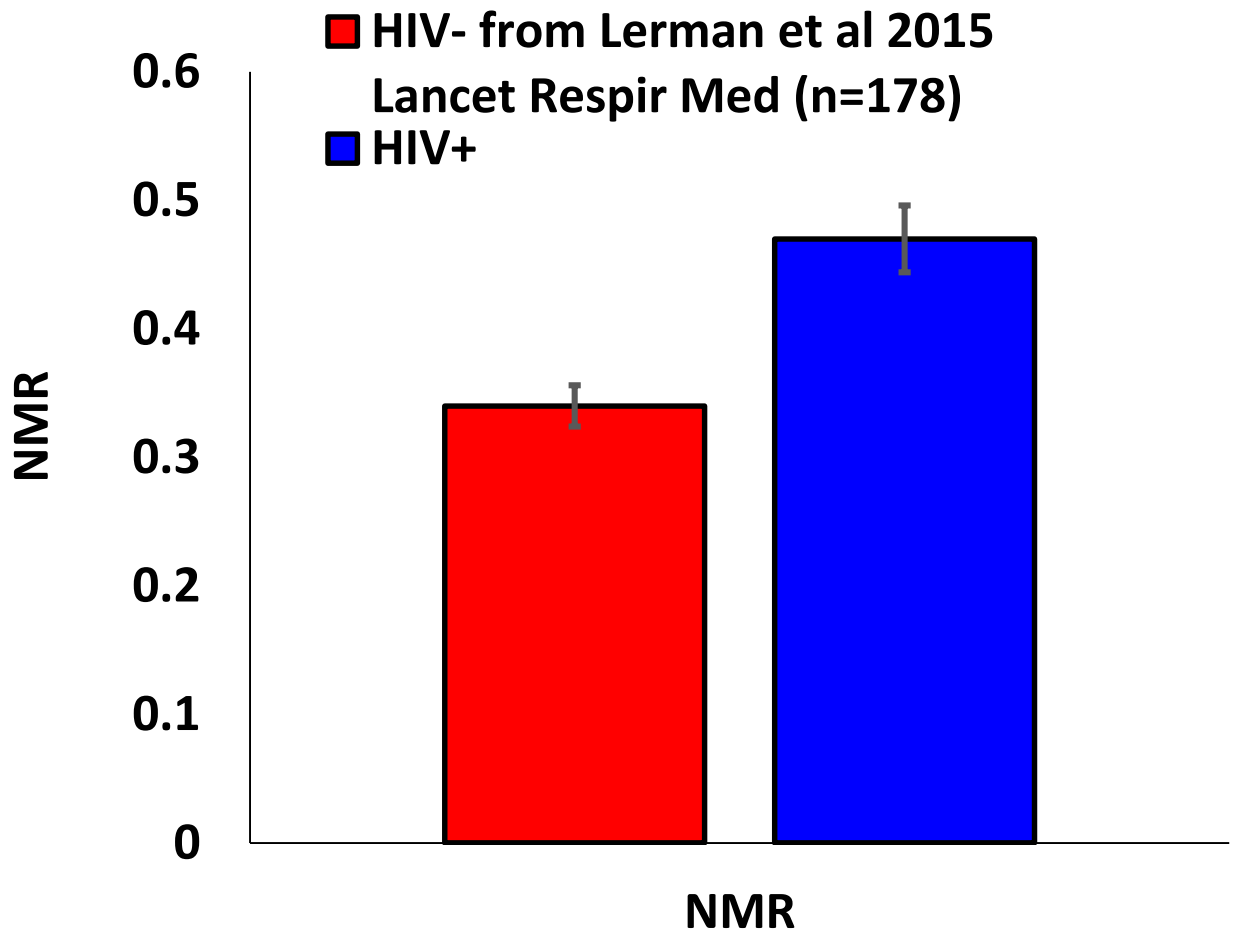
Clin Pharmacol Ther, 2006, 2008, 2010; *Pharmacol Biochem Behav*, 2009; Hamilton et al *Nicotine Tob Res 2015*

Smokers with HIV may metabolize nicotine faster



Ashare…Schnoll, *AIDS*, in press

Smokers with HIV metabolize nicotine faster than matched controls



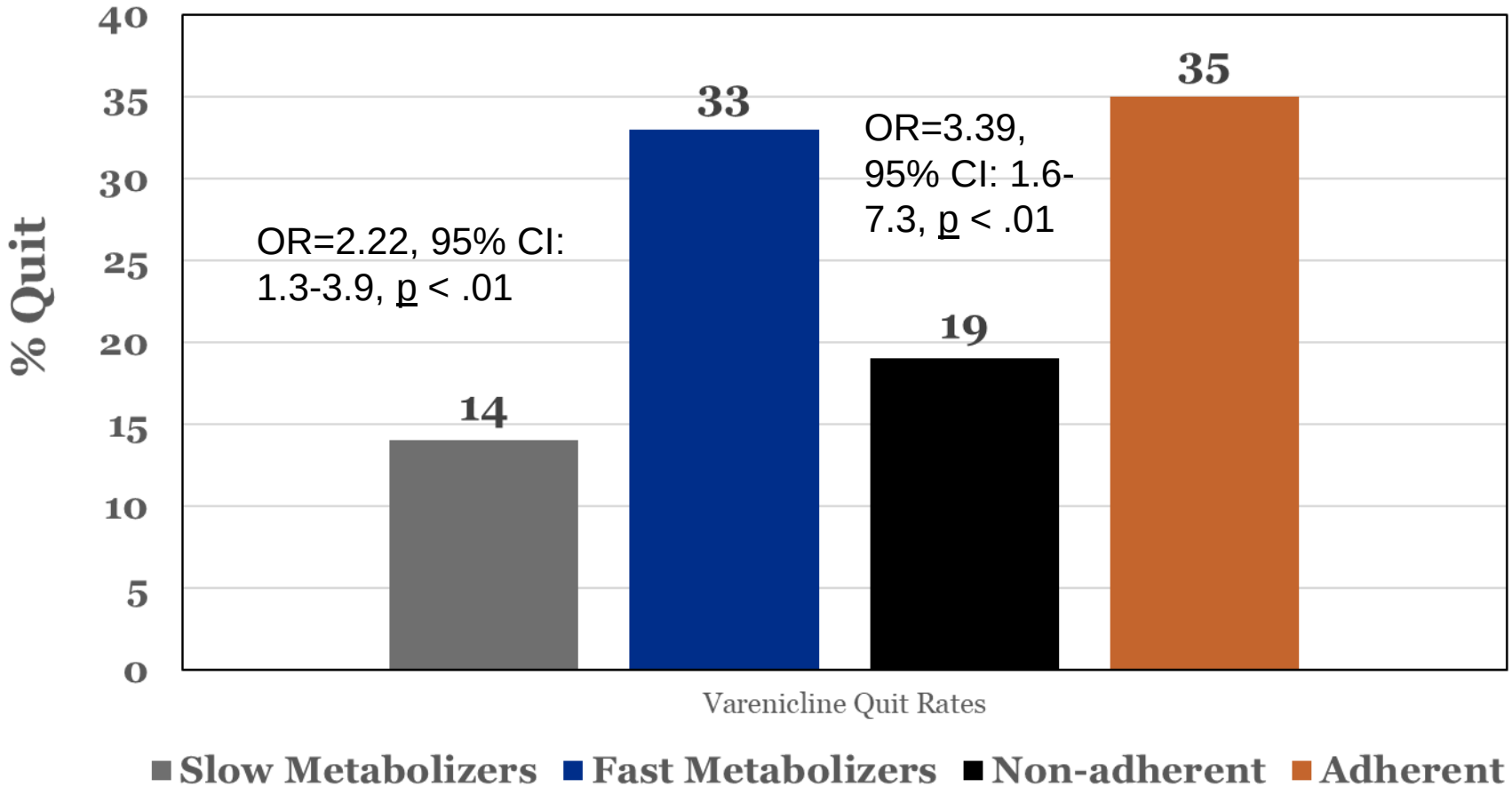
$p < 0.001$

Ashare et al, 2019 AIDS

The Adherence Problem

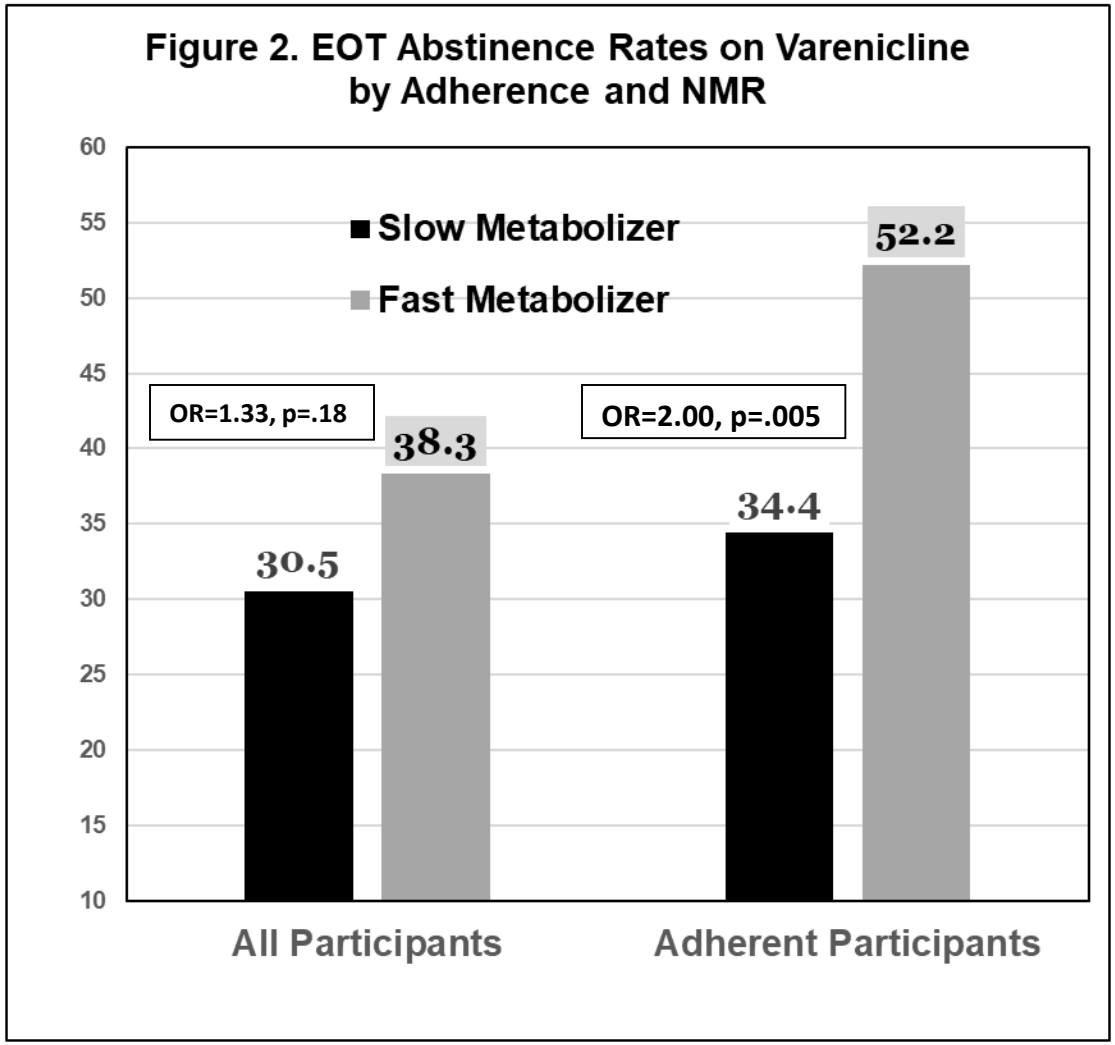
- 40-50% of those treated with varenicline are adherent (42% in our trial)
- Quit rates among those treated with varenicline who were adherent are significantly higher
- Little understanding of factors associated with non-adherence to varenicline (side effects and negative affect; Quinn et al., 2020)
- No evidence-based interventions (Pacek et al., 2018)

Varenicline Effect Related to Nicotine Metabolism and Varenicline Adherence



Nicotine Metabolism and Adherence

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

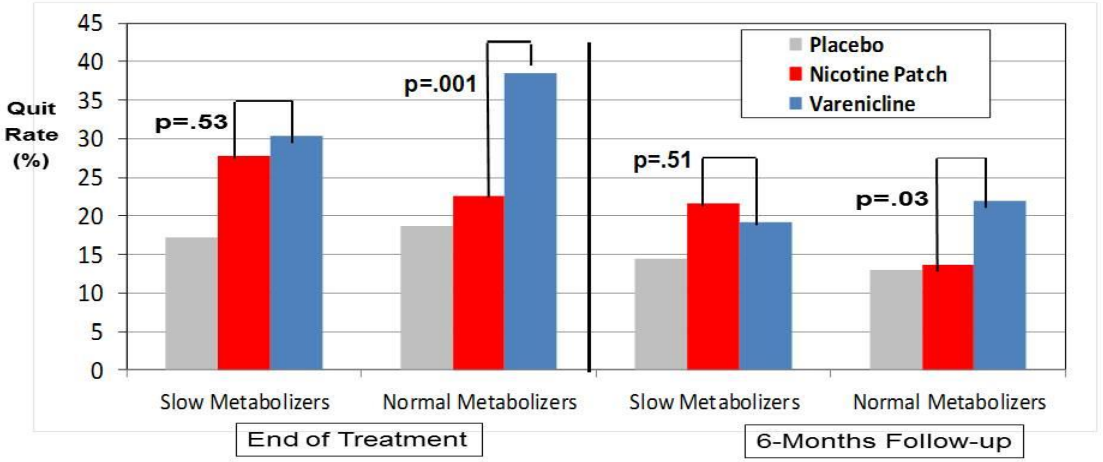


NMR Optimization

- 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

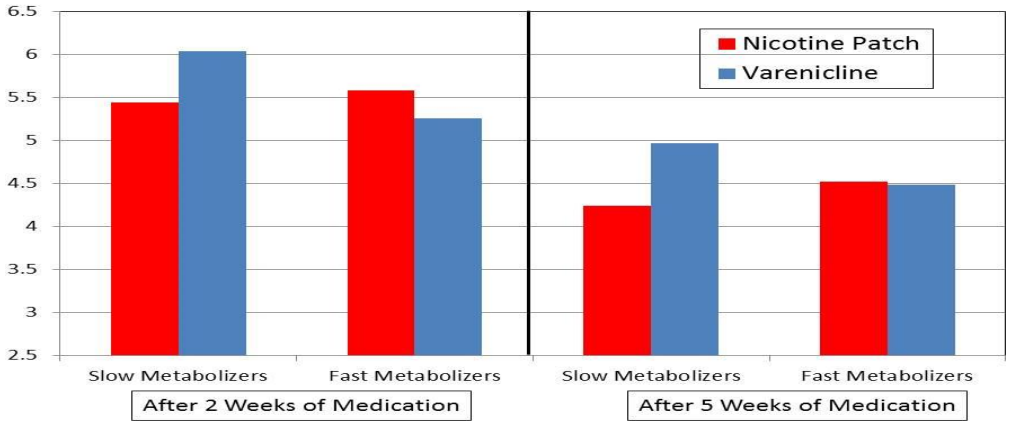
NNT	Patch	Varenicline
SMs	10.3	8.1
FMs	26	4.9

Figure 3. Abstinence Rates Across Treatment Arms and NMR Groups (N = 1246)



ORR (Biomarker-by-treatment)=1.96; CI=(1.11, 3.46); p=0.02

Figure 4. Mean Side Effect Severity Index by Treatment Arm and NMR

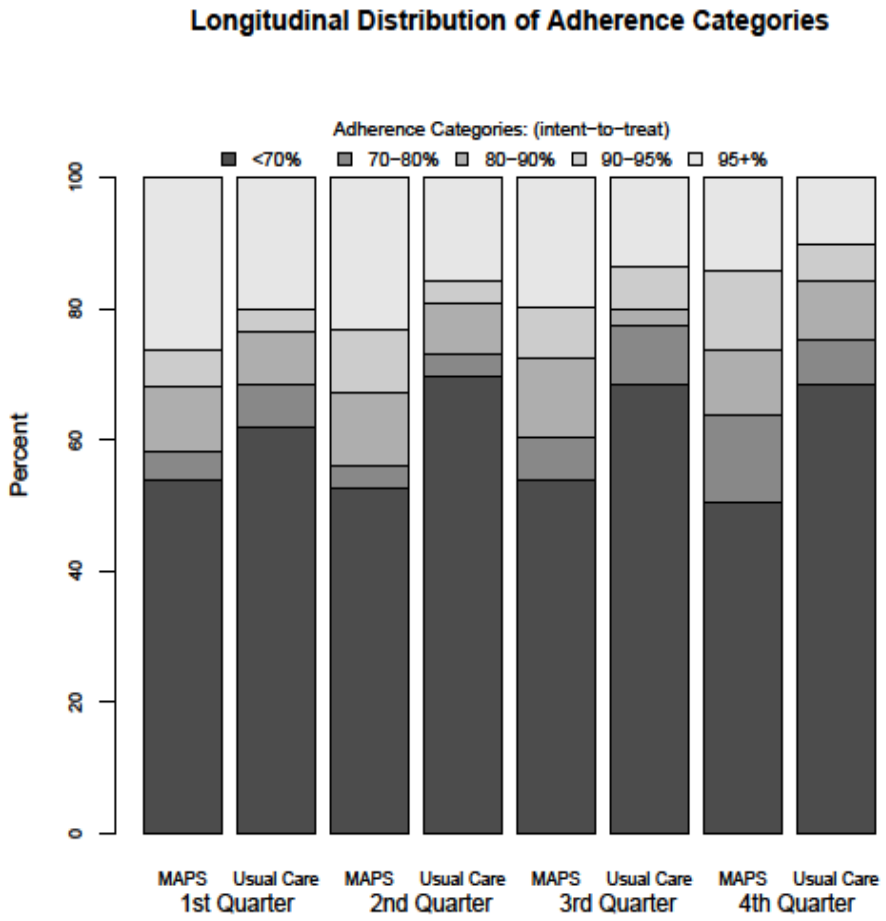


β (Biomarker-by-treatment)= -1.06; CI=(-2.08, -0.03); p=0.044

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

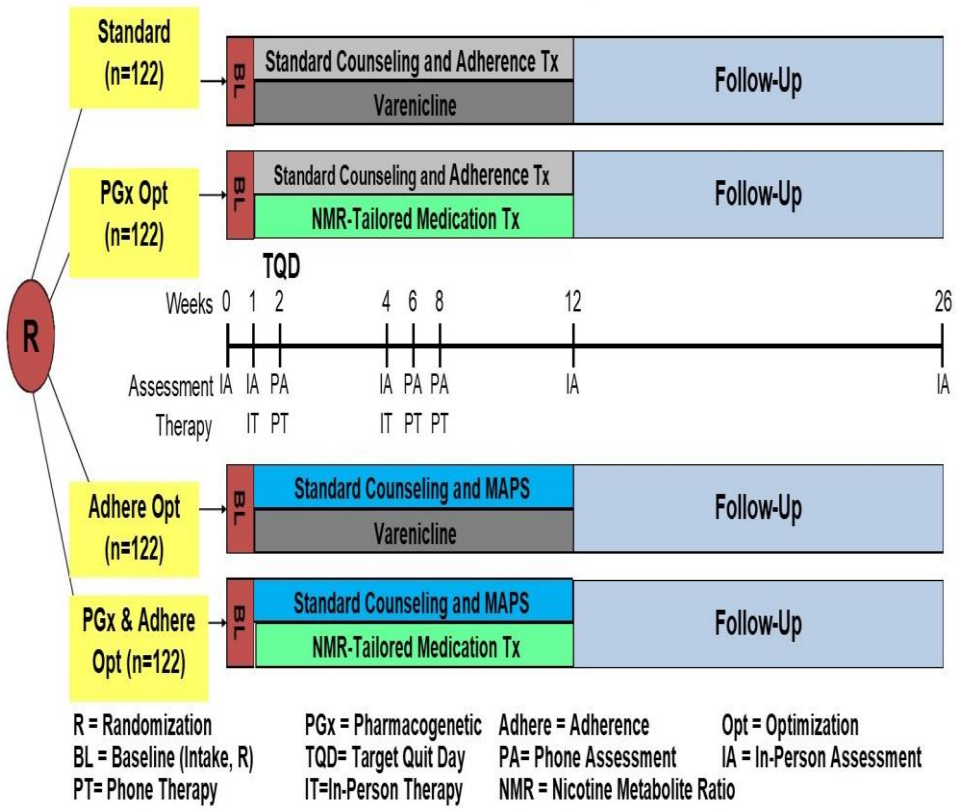


Gross et al., 2013; JAMA Internal Med

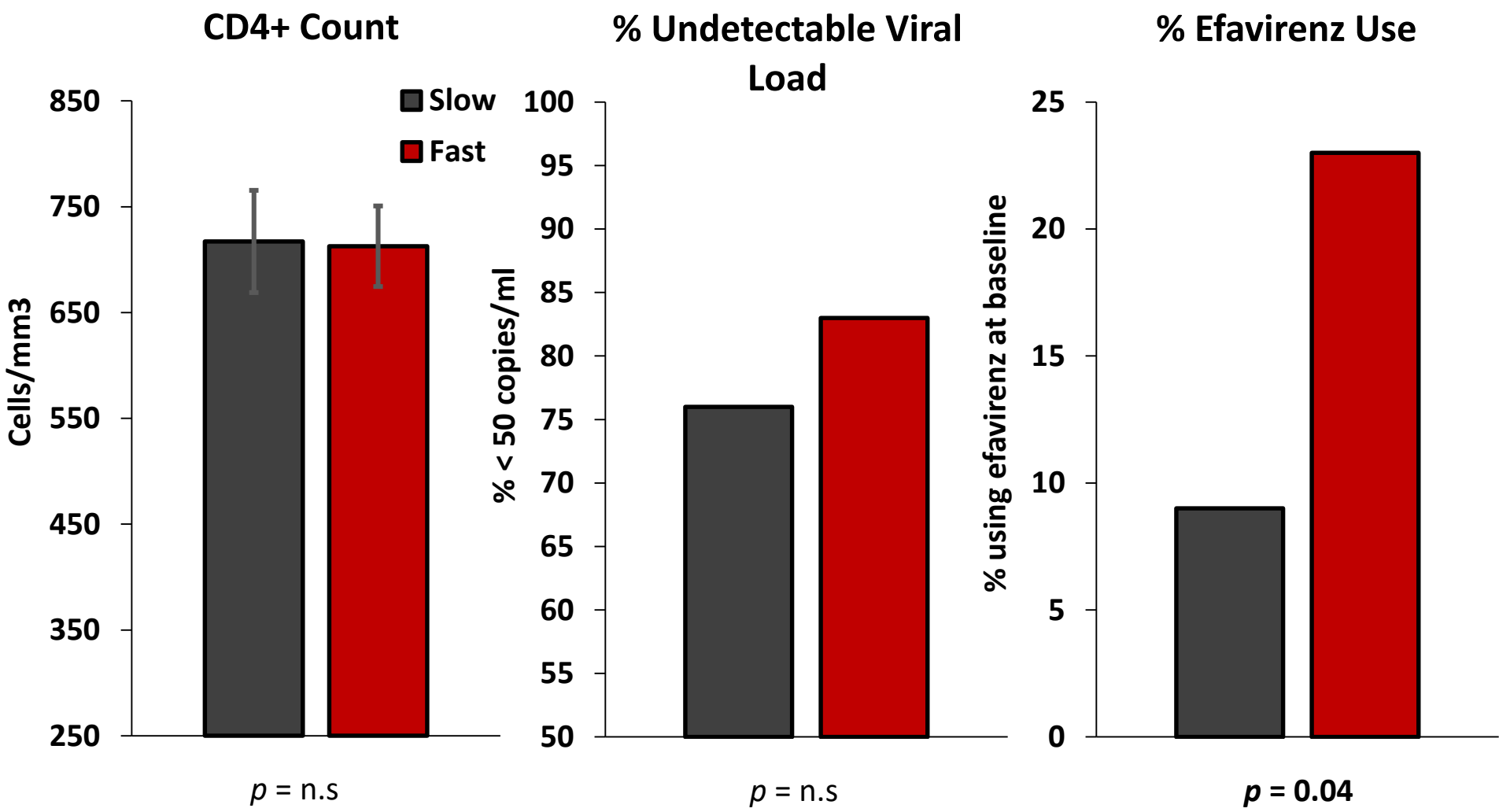
Optimizing Tobacco Treatment with NMR and MAPS

- 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)

Figure 3. Study Design

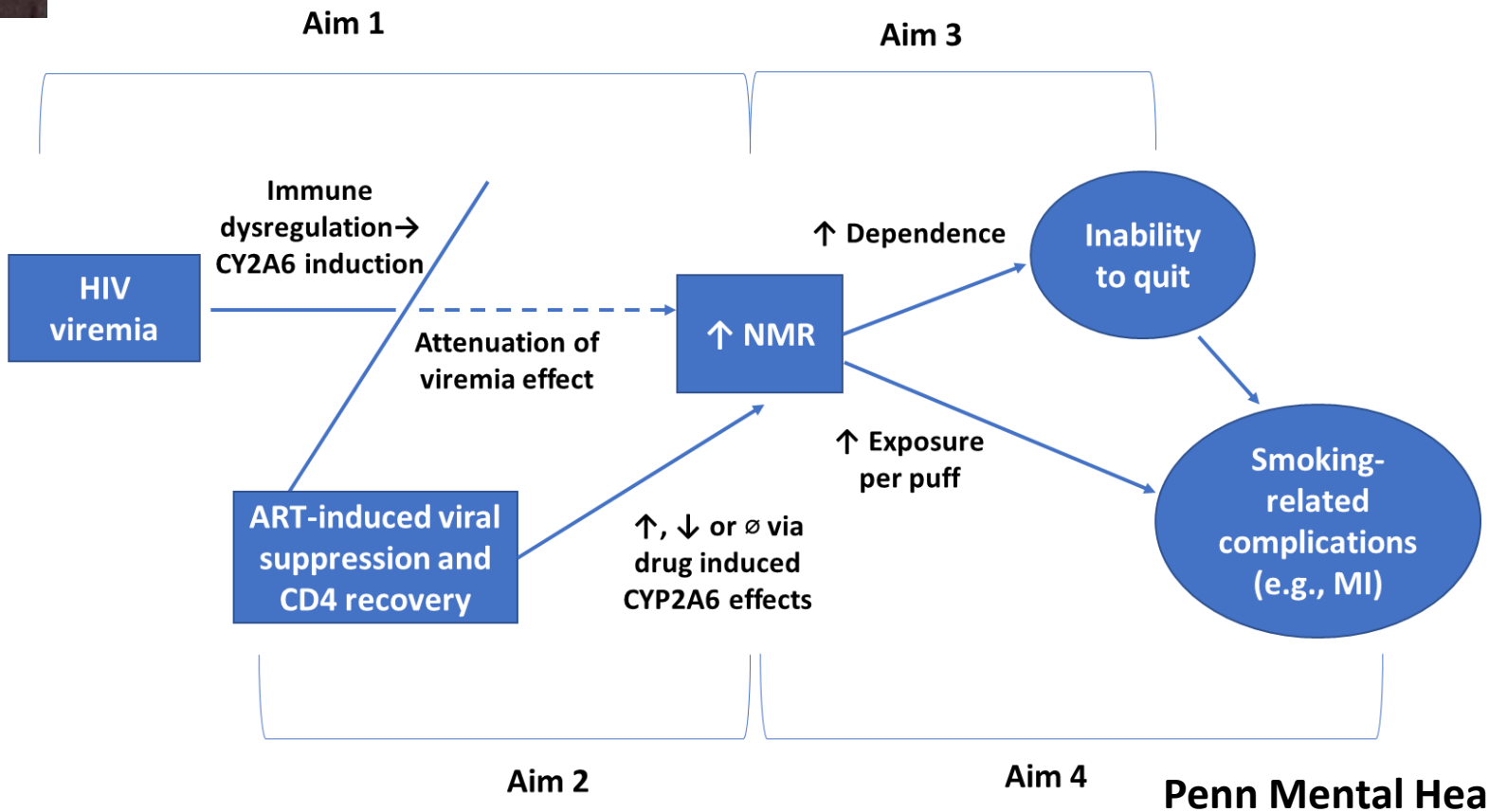


Faster NMR may be related to ART regimen



Schnoll…Ashare, *JAIDS*, in press

Determinants and Outcomes of NMR in Smokers with HIV



CNICS CFAR Network Of Integrated Clinical Systems

MACS MULTICENTER AIDS COHORT STUDY

WIHS Women's Interagency HIV Study

Penn Mental Health AIDS Research Center

CFAR CENTER FOR AIDS RESEARCH

R01 HL151292

RCT of behavioral intervention for smoking in Botswana

R01 DA045604

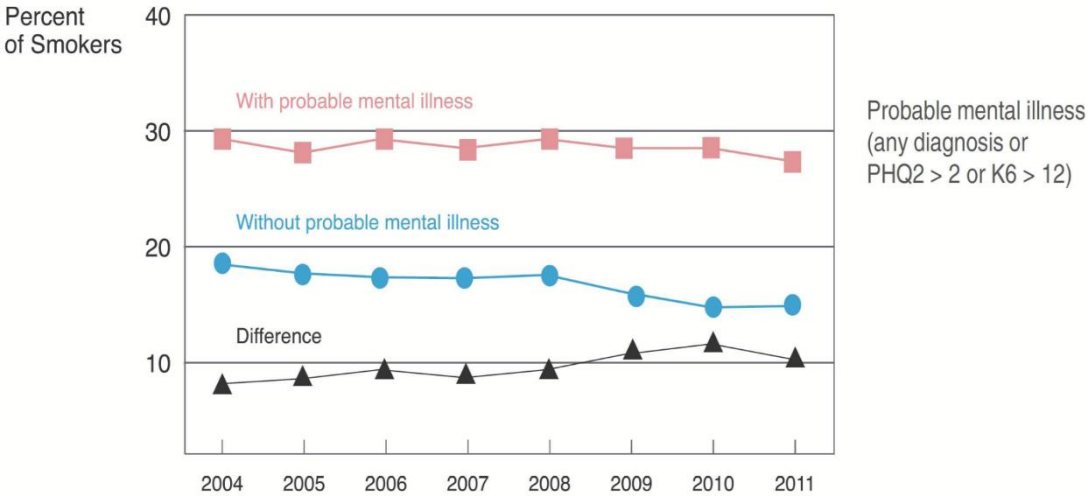
Smoking and HIV in Botswana

	HIV-infected ART-exp*	Females	Males	#P-value
N (%)	375	239 (63.7)	136 (26.3)	
Demographics				
Age Category N (%)				
21-39	167 (46.6)	131 (54.8)	36 (26.4)	< 0.01
40-49	135 (37.7)	78 (32.6)	57 (41.9)	.
50-59	41(11.5)	14 (5.9)	27 (19.9)	.
> 60	15 (4.2)	3 (1.3)	12 (8.8)	.
Current Cigarette Smoking, N(%)	85 (22.7)	15 (6.3)	70 (51.5)	< 0.01
Known CVD** (%)	2 (0.5)	2 (0.8)	0 (0)	> 0.9
HIV parameters				
Time since HIV diagnosis (years) Mean (SD)	8.9 (2.8)	8.7 (2.6)	8.9 (3.0)	0.68

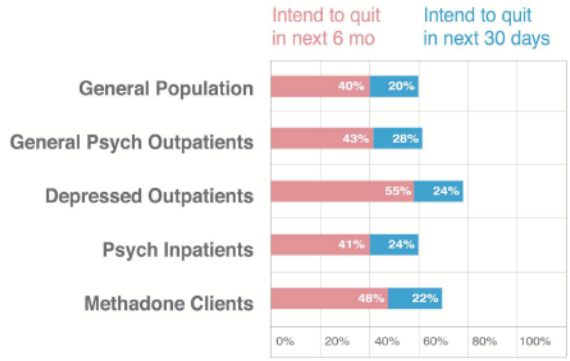
Mosepele M, Open AIDS Journal 2017

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



Smokers with mental illness or addictive disorders are just as ready to quit smoking as the general population of smokers.

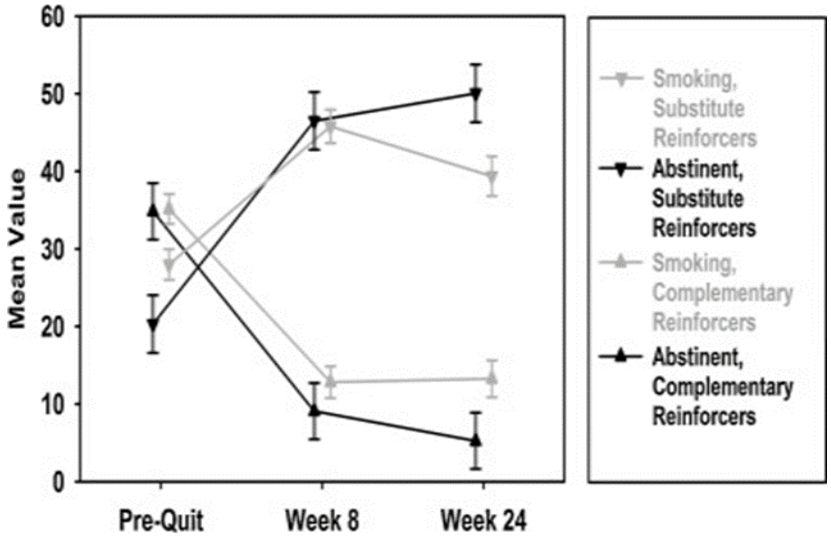


* No relationship between psychiatric symptom severity and readiness to quit

LeCook et al., 2014; Callaghen et al., 2014; Olfsen et al., 2015; Colton & Manderscheid, 2006; US Dept of VA, 2016

Behavioral Activation for MDD

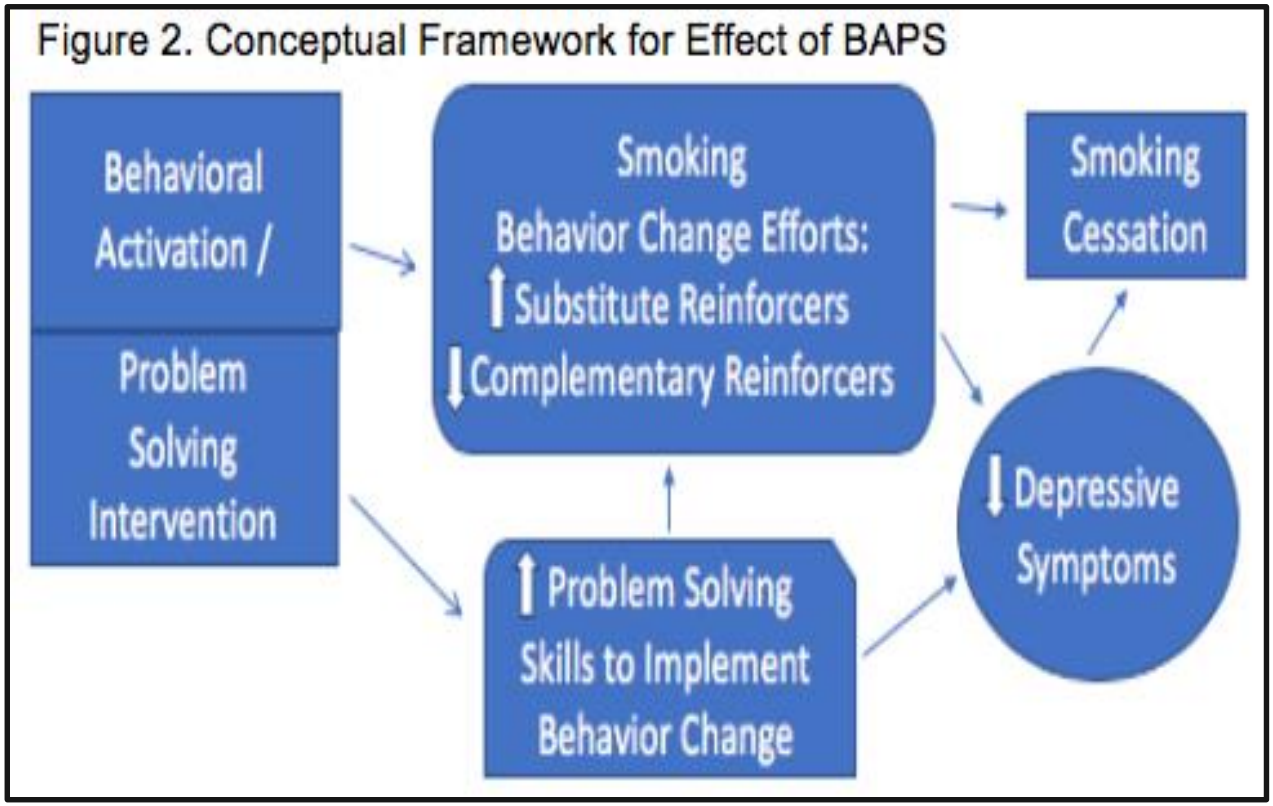
- Behavioral activation (BA) derived from CBT for depression
- Simpler than CBT; easier to train
- Increases engagement in rewarding activities **not** associated with smoking (substitute reinforcers) and reduces engagement in activities associated with smoking (complementary reinforcers)
- Small studies 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

Thotloetso Intervention

- **Adapt Behavioral Activation and Merge with Problem Solving from MAPS**

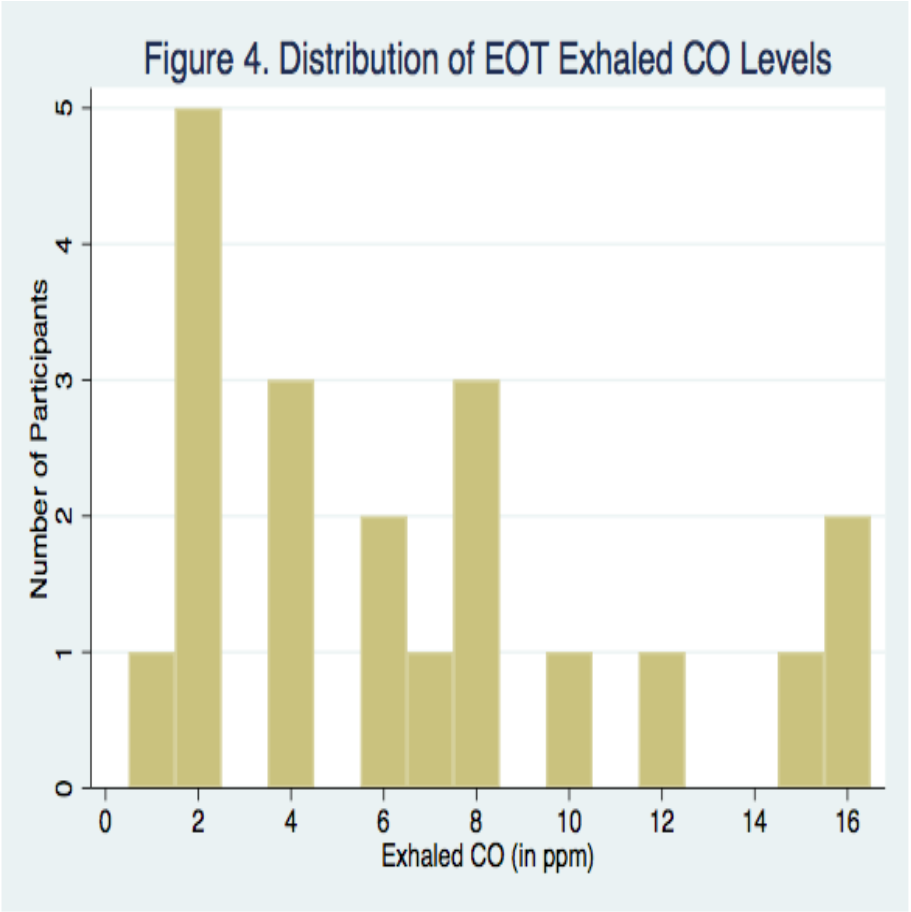


Thotloetso Pilot

- 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

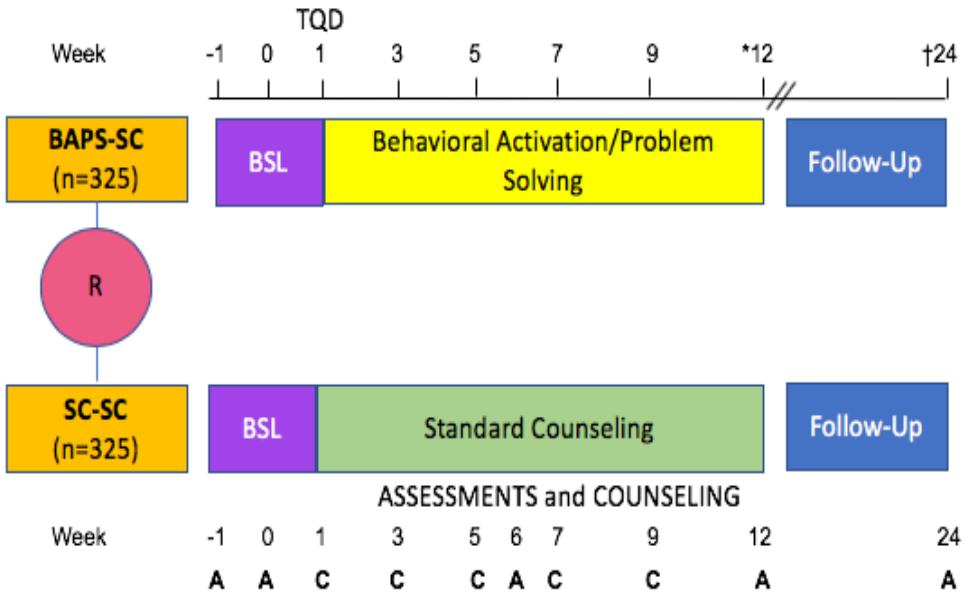
- Characteristics
  - 38 male (95%)
  - Median PHQ-8 = 2 (IQR 1-4)
- Quit rate
  - 15/20 at EOT
  - Overall 15/40 (37.5%)
- Exit interviews
  - All endorsed BAPS
  - Would refer others



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

Figure 5. Thotloetso Trial Schema



BSL=Baseline (and Intake Session and Randomization (R)); A=Assessment; C=Counseling
TDQ=Target Quit Day; *End-of-Treatment; †6 months post-TQD

Acknowledgements

R01 DA033681
R01 DA042682
R01 DA044906
R01 DA045604

R01 CA243914

R01 HL151292

P30 AI045008