HIV and Methamphetamine Use: Public Health Issues and Interventions for an “Intertwined epidemic”

Glenn-Milo Santos, PhD, MPH
Senior Research Scientist
Substance Use Research Unit
Center for Public Health Research
San Francisco Department of Public Health

Assistant Professor
Department of Community Health Systems
University of California San Francisco, School of Nursing
Meth/Amphetamine Used Globally

Source: Country level details can be found in Tables 2-10 and (Degenhardt, et al., 2007)
Epidemiology and Cost of Methamphetamine Use

- Worldwide, meth/amphetamine use remains more prevalent than many other drugs, including opioids
  - Fastest rising drug of abuse globally (Degenhardt 2010)
- In the US, 1.4 million past-year users in the U.S. alone in 2016 (SAMHSA National Survey on Drug Use and Health 2017)
  - Meth use prevalence similar among men and women in US
- Annual economic costs associated with methamphetamine use estimated at $23.4 billion ($16.2-$48.3 billion)(Nicosia, 2010)
Meth, the Forgotten Killer, Is Back. And It’s Everywhere.

The fight against methamphetamines was successful, but only to a point. In some states it’s now the leading cause of drug-related deaths.

By FRANCES ROBLES
February 13, 2018

The decades-long effort to fight methamphetamine is a tale with two takeaways. One: The number of domestic meth labs has declined precipitously, and along with it the number of children harmed and police officers sickened by exposure to dangerous chemicals. But also, two: There is more meth on the streets today, more people are using it, and more of them are dying.
Methamphetamine Health Indicators in San Francisco

National Drug Early Warning System (NDEWS) San Francisco Sentinel Community Site Drug Use Patterns and Trends, 2017.
Methamphetamine vs. Cocaine

Dopamine Release: Methamphetamine

![Graph showing dopamine release over time for various substances including Food, Sex, EtOH, Nicotine, Morphine, Cocaine, and Methamphetamine.](https://www.drugabuse.gov/publications/research-reports/methamphetamine/how-methamphetamine-different-other-stimulants-such-cocaine)

Plausible Pathways for relationship with HIV

Altered Mental State
Loss of Muscle Control

Decreased Experience of Pain

Enhanced Sexual Function, Desires, or Confidence

Injection Administration

Reduced Condom Use
Increased Condomless Intercourse

Increased Number of Partners or Duration of Sexual Activity

Increased Tissue Damage or Bleeding
Blood-Blood Contact
Blood-Semen Contact

Increased Risk of STI/HIV Acquisition

Needle Sharing

Increased Risk of STI/HIV Acquisition

Drumright, et al., 2006
Meth use associated with HIV-related risk behaviors among heterosexuals

Meta-Analysis of the Association Between Methamphetamine Use and High-Risk Sexual Behavior Among Heterosexuals

James B. Hittner
College of Charleston

A large body of research has found that nonheterosexual methamphetamine users engage in substantially higher levels of risky sex compared to nonusers. Considerably fewer studies have examined methamphetamine use and high-risk sex among heterosexuals. The present study is a meta-analysis of the empirical literature on methamphetamine use and high-risk sexual behavior among heterosexual individuals. Four risky sex outcomes were examined: unprotected vaginal intercourse, unprotected anal sex, inconsistent condom use, and sex with multiple partners. Analysis of 24 studies (26 independent samples) including 286,781 individuals found that the pooled mean weighted odds ratios ranged from 1.37 (unprotected vaginal intercourse) to 1.72 (inconsistent condom use), indicating that the odds of engaging in risky sex for heterosexual methamphetamine users is, on average, between 37% and 72% greater than for nonmethamphetamine users. Date of publication, percentage of White Caucasian respondents, and sample size were significant moderators of effect size magnitude. Moreover, symmetry plots revealed little direct evidence for publication bias. It is recommended that future research explore additional categorical and continuous variables as potential moderators of effect size strength.
Methamphetamine use and condomless vaginal intercourse

Methamphetamine use and condomless intercourse with multiple partners

Methamphetamine use and HIV among Men Who Have Sex with Men (MSM)
MSM disproportionately impacted by HIV in the US

Gay, bisexual, and other men who have sex with men (MSM) represent approximately 2% of the United States population, yet are the risk group most impacted by HIV.  

https://aidsvu.org/aidsvu-in-use/msm-population-profile/

- Methamphetamine
- Cocaine

<table>
<thead>
<tr>
<th>Year</th>
<th>Methamphetamine</th>
<th>Cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM1 (2003-05)</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>MSM2 (2008)</td>
<td>13%</td>
<td>25%</td>
</tr>
<tr>
<td>MSM3 (2011)</td>
<td>12%</td>
<td>26%</td>
</tr>
<tr>
<td>MSM4 (2014)</td>
<td>13%</td>
<td>35%</td>
</tr>
</tbody>
</table>
Meth and Sexual Behaviors among MSM

Odds Ratio (95% Confidence Interval)

Methamphetamine Use

Mansergh 2006 [29]
  UA
  URA
  UA
  DUA
  DURA
  DUIA

Chaisson 2007 [31]
  UA Single Partner
  UA Multi Partner

Koblin 2007 [32]
  UA

Ober 2009 [40]
  UA

UA (Respondent HIV+)

UA (Partner HIV+)

Prestage 2009 [41]
  DUA

Colfax 2001 [52]
  DUA

Drumright 2006 [27]
  UA (Within Group)
  UA (Between Group)

Drumright 2009 [38]
  UA
  URA
  UA

Recently HIV+

Rect HIV+ (cntr meth+pprs)

-Vosburgh, AIDS and Behavior 2012
Project ECHO: Frequency of Stimulant use and HIV-related sexual risk behavior (SDUAI) among MSM in San Francisco (N=3,173)

*SDUAI = serodiscordant unprotected anal intercourse

Santos GM et al. JAIDS 2013
Longitudinal patterns of stimulant use in Multicenter AIDS Cohort Study

Lim, et al. AIDS and Beh. 2012
Perspectives of a recovering Methamphetamine user

“New Year’s Eve was when I discovered meth; it was placed in my juice. For the next several months I used meth intermittently. But in short time I had moved from snorting meth to smoking it.”

“I had the ability to get clean for two or three months at a time, but then would slip... my slips would be another three months out. By far the biggest challenge in my life was getting the speed off my back and figuring how to do it because it was so intertwined with sex.

“Within three months I was infected with HIV...”

“...I would get high then in a 24 hour period, I would have multiple partners. It could be either multiple partners at the same time playing or it could be four, five, six, seven, eight, nine, ten, fifteen partner over a 24 hour period, and it might be five, six, seven days that I would be out doing meth and having sex...”

-Colfax, Santos et al, Lancet 2010
Stimulant users were more likely to have sub-optimal PrEP Adherence (TVF-DP concentrations <700 fmol per punch in dried blood spots/less than 4 doses per week) at the 4-week follow-up: aOR 5.04; [95% CI: 1.35 to 18.78]).
Meth/Amphetamine Use and HIV infection among MSM

Amphetamine-type stimulants and HIV infection among men who have sex with men: implications on HIV research and prevention from a systematic review and meta-analysis

Results: Meth/Amphetamine use significantly associated with higher Prevalence, Odds, and Hazard Rates for HIV infection

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Pooled Summary Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-Sectional Studies:</td>
<td>PRR: 1.7 (1.47-1.96)</td>
</tr>
<tr>
<td>Case-Control:</td>
<td>OR: 2.90 (2.04-4.12)</td>
</tr>
<tr>
<td>Longitudinal Studies:</td>
<td>HR: 3.13 (2.05-3.70)</td>
</tr>
</tbody>
</table>
### Meth Use among MSM living with HIV

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colfax</td>
<td>2007</td>
<td>Frequent meth use (at least weekly) was associated with <strong>NNRTI resistance</strong> (OR 3.5; 95% CI 1.2–10.8), but not with protease inhibitor resistance or NRTI resistance</td>
</tr>
<tr>
<td>Gorbach</td>
<td>2008</td>
<td>Meth use during sexual activity associated with 4 times greater odds of phenotypic drug resistance (aOR 4.0; 95% CI 1.19–13.38)</td>
</tr>
<tr>
<td>Hinkin</td>
<td>2007</td>
<td>Stimulant users (cocaine or meth) were associated with 7 times greater risk of poor ART adherence (OR=7.0; 95% CI=1.8–9.3).</td>
</tr>
<tr>
<td>Marquez</td>
<td>2009</td>
<td>Meth use in prior 4 weeks was associated with poor ART adherence (27% vs. 13%, p&lt;0.05). Meth users in the prior 12 months were less likely to be on ART (RR=0.7, 95% CI: 0.6–0.9)</td>
</tr>
<tr>
<td>Horvath</td>
<td>2013</td>
<td>Stimulant use was significantly associated with not attending any HIV medical appointments adjusting for demographic (RRR = 3.16, 95% CI=1.13-8.84) and psychosocial (RRR = 3.44, 95% CI=1.17-10.15) factors. Stimulant-using men rated HIV medical care a high priority less frequently than non-stimulant users (57% versus 85%; P &lt; 0.01).</td>
</tr>
<tr>
<td>Carrico</td>
<td>2014</td>
<td>Stimulant use at 50% or more of study visits was associated with a 1.5-fold increase in the odds of progression to AIDS or all-cause mortality (aOR= 1.54; 95%CI=1.02-2.33).</td>
</tr>
<tr>
<td>Reback</td>
<td>2003</td>
<td>Qualitative data: Unplanned nonadherence while using meth</td>
</tr>
</tbody>
</table>

**NNRTI resistance** refers to resistance to non-nucleoside reverse transcriptase inhibitors.
MSM would doubly benefit from effective meth interventions

- Meth use intertwined with
  - HIV-related sexual risk behaviors
  - Less optimal ART and PrEP adherence
- Hence, meth interventions may prevent new HIV infections and improve HIV health outcomes
- Imperative to develop NEW meth and HIV prevention interventions for MSM
Interventions for Methamphetamine Use

- Given morbidity and harms of methamphetamine, combination of multi-level interventions needed
- Structural and policy
  - Precursor regulation:
    - Limited evidence of effectiveness
  - Prohibition and “War on Drugs”
    - Evidence of failure
  - Social marketing
    - Some well received, efficacy unproved
- Behavioral Interventions
- Pharmacotherapy
  - Great need
  - No medication approved for treatment
# Methamphetamine vs. Cocaine

<table>
<thead>
<tr>
<th>Methamphetamine</th>
<th>Cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulant</td>
<td>Stimulant and local anesthetic</td>
</tr>
<tr>
<td><strong>Synthetic</strong></td>
<td>Plant-derived</td>
</tr>
<tr>
<td>Smoking produces a long-lasting high</td>
<td>Smoking produces a brief high</td>
</tr>
<tr>
<td>50% of the drug is removed from the body in 12 hours</td>
<td>50% of the drug is removed from the body in 1 hour</td>
</tr>
<tr>
<td>Increases dopamine release and blocks dopamine re-uptake</td>
<td>Blocks dopamine re-uptake</td>
</tr>
<tr>
<td>Limited medical use for ADHD, narcolepsy, and weight loss</td>
<td>Limited medical use as a local anesthetic in some surgical procedures</td>
</tr>
</tbody>
</table>

[https://www.drugabuse.gov/publications/research-reports/methamphetamine/how-methamphetamine-different-other-stimulants-such-cocaine](https://www.drugabuse.gov/publications/research-reports/methamphetamine/how-methamphetamine-different-other-stimulants-such-cocaine)
Precursors of methamphetamine, amphetamine

Figure 1: Chemical structure of amphetamine, methamphetamine, and their precursors. Structures sourced from the PubChem Project.

-Colfax, Santos, et al. Lancet 2010
Limitations of precursor regulation


Sources: INCB, *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances (2009 and previous years)*, Individual Drug Seizures Database and other government sources

Notable ephedrine & pseudoephedrine trafficking route cases
- Routes identified in 2006-2007
- ← Routes common throughout 2006-2009
→ Routes identified in 2008-2009

Other government sources include: ACC (2009), DEA-ODC (2008), INSCR (2010), NDIB (2009), RCMP (2009 and previous years) and WCO (2009 and previous years)

Note: The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the United Nations. Lines represent origin and intended destination, not necessarily exact route, and include completed or stopped trafficking attempts. Modes of transit include by air, sea, overland, or any combination thereof.

-UNODC, 2010
War on Drugs
Behavioral treatment for meth-dependence and sexual risk behaviors among MSM

Fig. 1. Reported number of times participants had unprotected receptive anal intercourse (URAI) with someone other than a primary partner in the previous 30 days by treatment condition: standard cognitive behavioral therapy (CBT), contingency management (CM), combined cognitive behavioral therapy and contingency management (CBT + CM), and culturally tailored, GBM-specific cognitive behavioral therapy (GCBT).

-Shoptaw 2004
Behavioral Interventions Meta-analysis

“Are behavioral interventions among amphetamine-group substance users efficacious at reducing amphetamine-group substance use and/or sexual risk behaviors compared to control conditions?”

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Controls</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amphetamine-group substance users</td>
<td>• Behavioral Interventions</td>
<td>• Passive tx</td>
<td>• Amphetamine-group substance use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Active tx</td>
<td>• Sexual risk behaviors</td>
</tr>
</tbody>
</table>

Colfax, Santos, et al., Lancet, 2010 © Elsevier
Results: High-intensity Behavioral Interventions vs Active Controls

![Graph showing standardised mean difference (95% CI) for various studies.]

- Shoptaw et al (2005)\textsuperscript{111*}: 0.51 (0.06 to 0.95)
- Shoptaw et al (2005)\textsuperscript{111†}: 0.42 (−0.02 to 0.86)
- Shoptaw et al (2006)\textsuperscript{138}: 0.15 (−0.23 to 0.53)
- Roll et al (2006)\textsuperscript{136}: 0.48 (0.10 to 0.85)
- Peirce et al (2006)\textsuperscript{137}: −0.05 (−0.80 to 0.70)
- Shoptaw et al (2008)\textsuperscript{135}: 0.53 (0.13 to 0.94)
- Sherman et al (2009)\textsuperscript{123}: −0.03 (−0.34 to 0.28)

Overall (fixed-effects model): 0.28 (0.13 to 0.44)
Overall (random-effects model): 0.30 (0.11 to 0.49)

Colfax, Santos et al., Lancet, 2010 © Elsevier
Pharmacologic treatments are needed for meth-using MSM

- Current treatment approaches for meth use for MSM are therapy, substance use treatment programs, contingency management, off-label use of pharmacotherapy
- Most substance-using MSM do not access drug treatment
- Behavioral interventions alone have limited efficacy and may benefit from adjuvant pharmacologic agents
- There are no FDA-approved medications for meth use disorders
- Need to develop and test medication-assisted treatment strategies for MSM
  - Open to other treatment goals, including reduction in use and harm
Can we find a drug to treat methamphetamine dependence?

- NIH-funded clinical trials of potential drugs at SFDPH
  - Bupropion (Pilot Study) - completed
  - Mirtazapine - completed
  - Aripiprazole - completed
  - Naltrexone IM – completed
  - Naltrexone PO – completed
  - Mirtazapine 2 – (analysis)
- All study participants receive HIV and substance use counseling
- Community support and input through community consultant group
Mirtazapine Study

• RCT, double-blind, placebo-controlled
• 1:1 randomization
• N = 60 MSM
  ▫ Male
  ▫ Age 18-60
  ▫ Reports anal sex with another man while using methamphetamine in prior 3 months
  ▫ Methamphetamine dependent
• Main outcome: meth in urine
• Secondary outcomes: sexual risk behavior
Mirtazapine for Methamphetamine Dependence

Meth-dependent sexually active MSM

Pharmacotherapy (Mirtazapine) + Substance Use Counseling + HIV risk reduction counseling

Placebo + Substance Use Counseling + HIV risk reduction counseling

43% risk reduction in methamphetamine urine-positivity in treatment arm

Colfax G, SantosGM, et al., Arch Gen Psych, 2011
**Meth-reductions**

Parallel Reductions in Sexual Risk Behaviors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incident Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Substance Use</strong></td>
<td></td>
</tr>
<tr>
<td>Methamphetamine urine positivity</td>
<td>0.57 (0.35, 0.93)</td>
</tr>
<tr>
<td><strong>Sexual Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Number of male partners</td>
<td>0.20 (0.04, 0.93)</td>
</tr>
<tr>
<td>Number of male partners w/ whom meth was used</td>
<td>0.45 (0.24, 0.82)</td>
</tr>
<tr>
<td>Anal sex w/ serodiscordanant partners</td>
<td>0.31 (0.14, 0.66)</td>
</tr>
<tr>
<td>Unprotected anal sex with serodiscordanant partners</td>
<td>0.34 (0.17, 0.70)</td>
</tr>
<tr>
<td>Unprotected insertive anal sex with serodiscordanant partners</td>
<td>0.29 (0.14, 0.58)</td>
</tr>
<tr>
<td>Unprotected receptive anal sex with serodiscordanant partners</td>
<td>0.27 (0.05, 1.57)</td>
</tr>
</tbody>
</table>

Colfax G, SantosGM, et al., *Arch Gen Psych*, 2011
Project ECHO: Frequency of Stimulant use and HIV-related sexual risk behavior (SDUAI)

Adjusted Log Odds

- Meth: Episodic 3.31, At least weekly 5.46
- Cocaine: Episodic 1.86, At least weekly 3.13

*SDUAI = serodiscordant unprotected anal intercourse

Santos GM et al. JAIDS 2013
Behavioral + Biomedical Intervention

IN b4 u go out!
Use alcohol + meth? Interested in cutting down or quitting?

IN b4 the party
are you a gay or bi man who uses meth and alcohol? Interested in cutting down?
we are studying a medication to be taken on an as-needed basis that may help.

$24-53 per study visit

www.sfhiv.org/studies/project-IN
project.IN@sfdph.org 415.554.4233

a research study with UCSF and the SF Department of Public Health | UCSF CHA Approval 12-09809
## Sample Characteristics (n=30)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean = 43</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td>Latino = 17%</td>
</tr>
<tr>
<td></td>
<td>Asian = 7%</td>
</tr>
<tr>
<td></td>
<td>Black = 30%</td>
</tr>
<tr>
<td></td>
<td>White = 40%</td>
</tr>
<tr>
<td></td>
<td>Mixed = 3%</td>
</tr>
<tr>
<td></td>
<td>Other = 3%</td>
</tr>
<tr>
<td><strong>HIV-status</strong></td>
<td>Positive = 40%</td>
</tr>
<tr>
<td></td>
<td>Negative = 60%</td>
</tr>
</tbody>
</table>
Intermittent “as needed” dosing:

- Preemptive dosing, prior to risk
  - before meth:
    - *when* craving meth/use is expected

- No dosing required if:
  - no risk of use is expected
  - and no craving
Study Population Considerations for Intermittent use

- Pattern of stimulant use for non-dependent
  - episodic, non-daily
  - target chemoprophylaxis according to pattern of use
  - risk-benefit ratio: more tolerable with intermittent use
  - cost-effective, efficient

- Daily adherence not always feasible
  - Lower patient burden

- Some element of planning with substance use and sex
  - “iN before you go out”

### Efficacy of intermittent naltrexone on meth use and sexual risk behaviors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment effect IRR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meth use</td>
<td>0.82 (0.60-1.12)</td>
</tr>
<tr>
<td>Number of meth use days*</td>
<td>0.78 (0.62-0.99)§</td>
</tr>
<tr>
<td>Serodiscordant receptive anal intercourse events</td>
<td>0.15 (0.05-0.42)§</td>
</tr>
<tr>
<td>Serodiscordant condomless receptive anal intercourse events</td>
<td>0.11 (0.03-0.37)§</td>
</tr>
</tbody>
</table>

* Subgroup analysis § p-value <0.05

-Santos GM, JAIDS 2016
Motivations for joining the pharmacologic study

1. Stop meth use
2. I want to help my community/public health
3. I want to try the medication
4. Reduce but not stop meth use
5. Incentive/Money
6. Other treatment approaches have not worked

-Santos GM, JAIDS 2016
Summary

- Meth use remains prevalent worldwide and US, associated with range of medical and economic consequences
- Meth use intertwined with HIV risk and less optimal HIV care outcomes, particularly among key pops. like MSM
- Key pops. like MSM may doubly benefit from effective meth use interventions (behavioral & pharmacologic)
- Medication-assisted treatments shown to reduce meth use and sexual risk behaviors among MSM in trials
  - Reductions in meth use associated with parallel reductions in sexual behaviors (consistent w/ cohort data)
- Some MSM may have different treatment goals
- Continue to develop treatment options to reduce meth use and harms, including HIV
Thank you!
Feasibility and acceptability of a phase II randomized pharmacologic intervention for methamphetamine dependence in high-risk men who have sex with men

Moupali Das\textsuperscript{a, b}, Deirdre Santos\textsuperscript{a}, Tim Matheson\textsuperscript{a}, Glenn-Milo Santos\textsuperscript{a}, Priscilla Chu\textsuperscript{a}, Eric Vittinghoff\textsuperscript{b}, Steve Shoptaw\textsuperscript{c} and Grant N. Colfax\textsuperscript{a, b}

Objective: To determine whether actively using, methamphetamine (meth)-dependent men who have sex with men (MSM) could be enrolled and retained in a pharmacologic intervention trial, and the degree to which participants would adhere to study procedures, including medication adherence.

Study design: Phase II randomized, double-blind trial of bupropion vs. placebo.

Methods: Thirty meth-dependent, sexually active MSM were randomized to receive daily bupropion XL 300mg or placebo for 12 weeks. Participants received weekly substance use counselling, provided weekly urine specimens, and completed monthly audio-computer assisted self-interview (ACASI) behavioral risk assessments. Adherence was measured by medication event monitoring systems (MEMS) caps (the number of distinct MEMS cap openings divided by the number of expected doses) and self-report.

Results: Ninety percent completed the trial; 89% of monthly ACASIs were completed, 81% of study visits were attended, and 81% of urine samples were collected. Adherence by MEMS cap was 60% and by self-report was 81% and did not differ significantly by treatment assignment. The median number of positive urine samples was 5.5 out of a possible 11 (50%). Participants in both arms reported similar declines in the median number of sex partners ($P = 0.52$). No serious adverse events occurred and there were no significant differences in adverse events by treatment assignment ($P = 0.11$).

Conclusions: It is feasible to enroll and retain actively using, meth-dependent MSM in a pharmacologic intervention. Bupropion was well tolerated. Study participation and retention rates were high, however, study drug medication adherence was only moderate. Findings support a larger trial with improved adherence support to evaluate the efficacy of bupropion and other pharmacologic interventions for meth dependence in this population.

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AIDS 2010, 24:991–1000

Keywords: bupropion, HIV prevention, men who have sex with men, methamphetamine
Treatment Considerations: Dopamine Dysfunction

Homeostatic Dopaminergic Tone

↑ DA

Euphoria
Paranoia

↑ DA

↓ DA

↓ DA

Dopamine Replacement

Courtesy of James Gasper
Conclusions of Bupropion Trial

• Bupropion was safe and well-tolerated
• It was feasible to enroll and retain a significant majority of **actively-using, non-treatment-seeking** meth-dependent MSM in a pharmacologic intervention
• Compared to prior studies, retention rates were high, but study drug medication adherence was only moderate
• Further studies should include more intensive adherence support measures such as more intensive counseling or MEMS feedback to evaluate whether bupropion is effective in this population