

Practical focus on the diagnosis
and treatment of the neuropsychiatric
and neuropsychological aspects of
HIV-infected patients.

Barcelona May 26-27, 2017
www.neuropsychiatry-hiv.com

Risk behavior, effect on HIV-infection and neuropsychiatric consequences of substance use

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CIBERSAM**

HIV and drug use

- significantly impacts HIV medical outcome¹
- accelerates the progression of HIV-disease¹
- is associated with an increases VL and a decrease of CD4 count²
- increases the risk of HIV transmission³

1. Carrico 2011; 2. HIV Surrogate Marker Collaborative Group 2000; 3. Cohen 2011



substances in the context of HIV

- **Methamphetamine**
- **Alcohol**
- **Cocaine**
- **Others: Ecstasy, GHB, Ketamine, Marijuana**

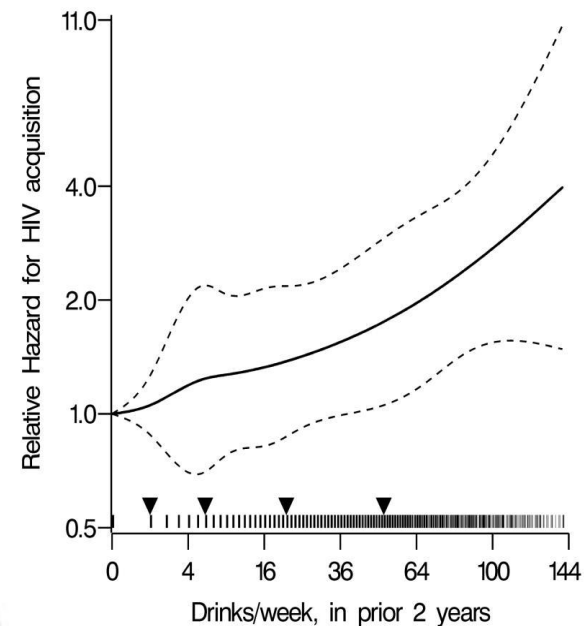
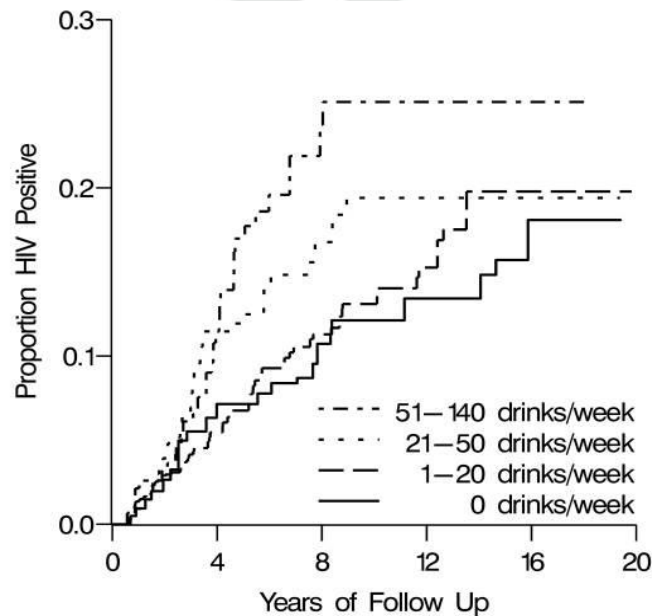
Alcohol and HIV

Alcohol and HIV

- High prevalence of alcohol (Bonacini 2011)
- Alcohol increases the risk of infection (Azar 2010)
- Lower utilization of health services (Zarkin 2004)
- Increases risk behaviors (Justus 2000, Fisher 2007, Ludford 2013)
- It is associated with worse ART compliance (Hendershot 2009)
- Alcohol is associated with a progression of infection

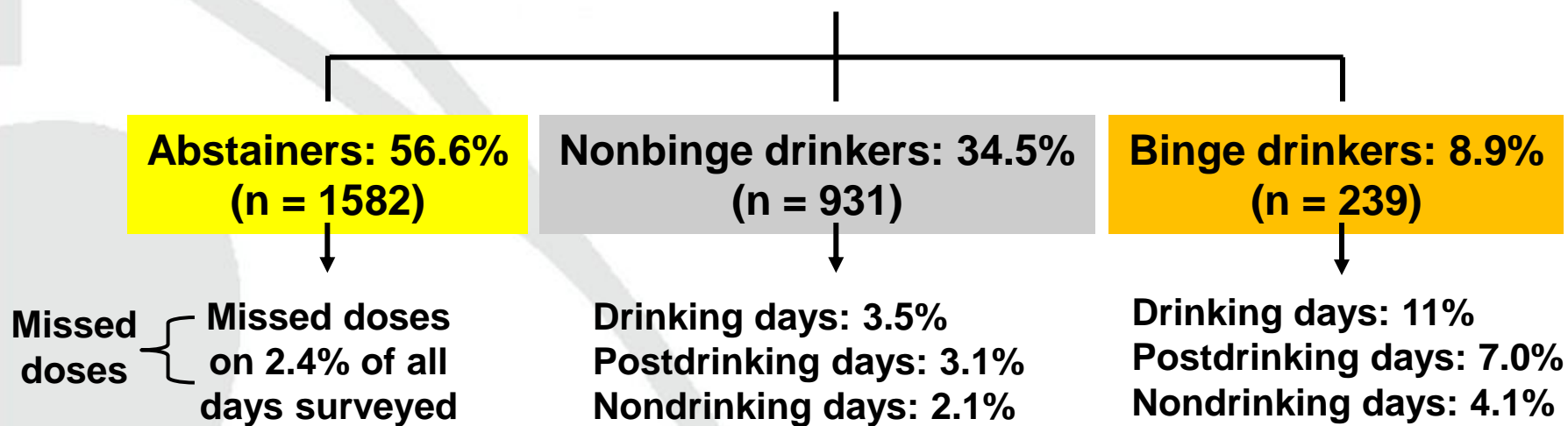
Alcohol Increases the Risk of Infection

(Howe 2011)



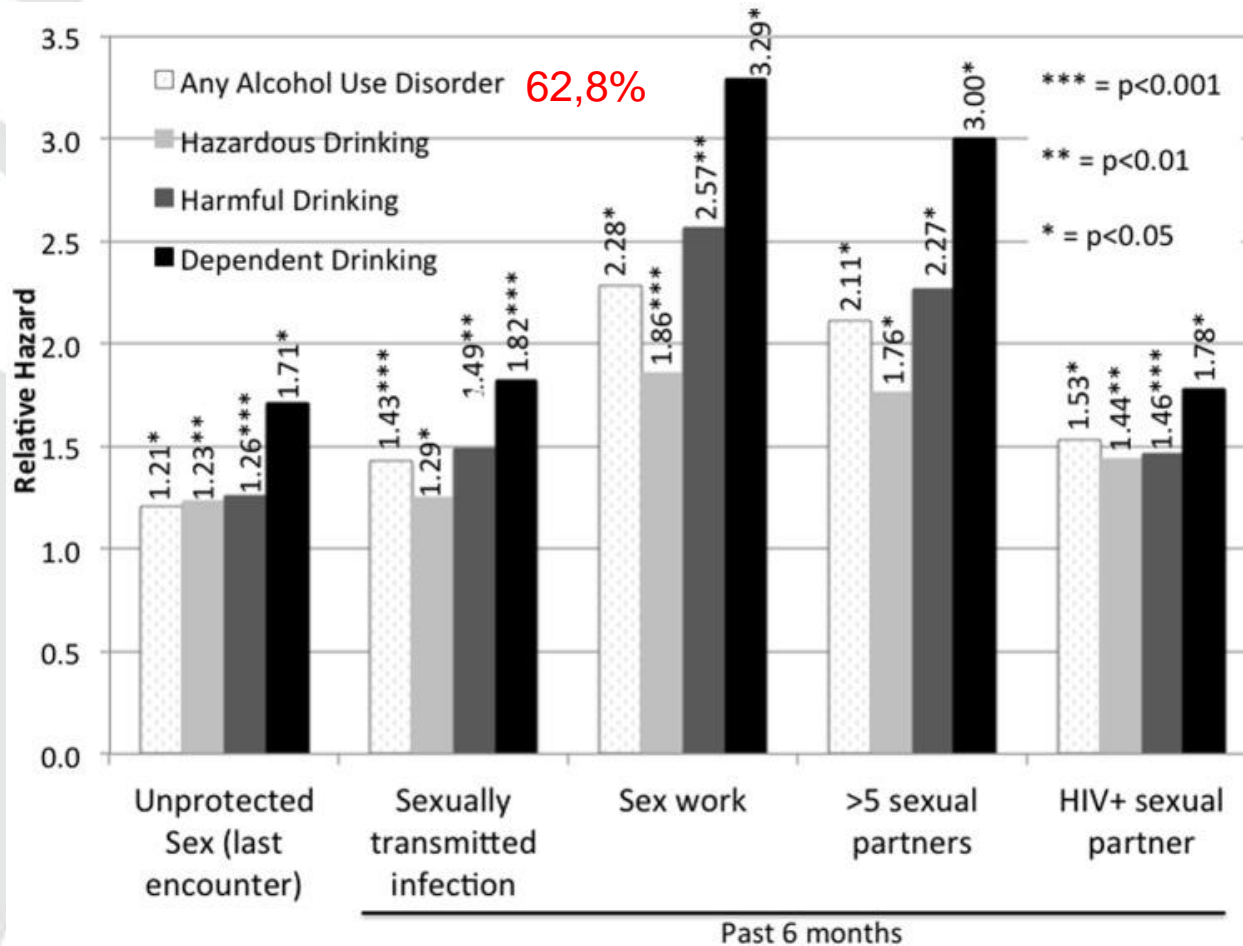
Alcohol Consumption and Adherence

Veterans Aging Cohort Study (N = 2702)



Braithwaite RS, et al. Alcohol Clin Exp Res. 2005;29:1190-1197.

Alcohol and HIV

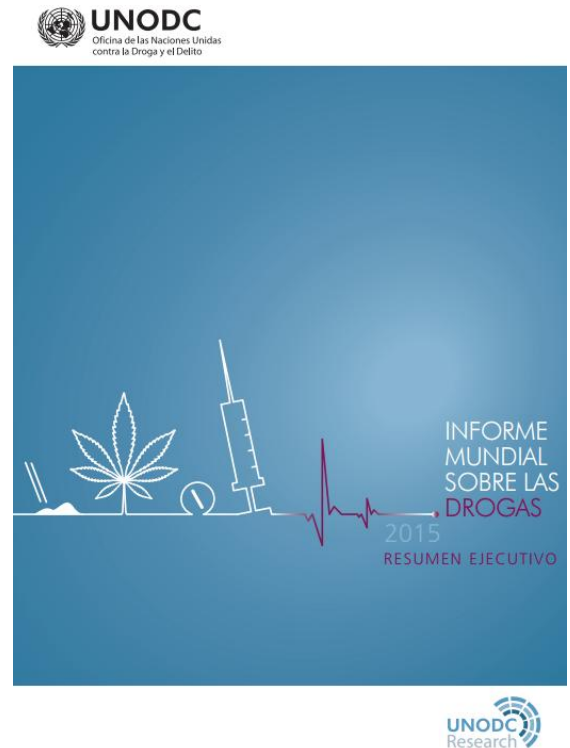


Ludford et al. PLoS One. 2013

Metha-amphetamine

Nations Office on Drugs and Crime

- the world market for synthetic drugs is still dominated by methamphetamine
- increasingly diversified market for methamphetamine in East and South-East Asia
- crystallized methamphetamine consumption is increasing in some regions of North America and Europe





Methamphetamine

- **CNS stimulant: euphoric, stimulating, aphrodisiac**
- **obtained: drugs marketed or clandestine laboratories**
- **white, crystalline, odorless and bitter powder**
- **smoking, inhaling, injecting or taking oral**
- **Inhibits ejaculation**
- **Greater use in MSM**
- **"Crystal", "crystal met", "meth"**





National Institute
on Drug Abuse

The Science of Drug Abuse & Addiction

Methamphetamine

- increases dopamine release
- blocks dopamine reabsorption
- reduces the expression of the cell surface dopamine transporter
- inhibits MAO: increase in dopamine
- increased tyrosin-hydroxylase activity (catalyzes tyrosine to l-dopa)
- fast acting mechanism

Panenka 2013

Symptoms of MA use

- Decreased appetite
- Increased libido
- Increased sense of safety
- Increased mood / dysphoria
- Restlessness, dyskinesia, increased physical activity
- Insomnia, increased alertness
- Anxiety, compulsive behaviors
- psychosis
- tremor
- Increased HR / RR, HBP, hyperthermia

Semple et al 2002; Rajasingham et al 2012



National Institute
on Drug Abuse

The Science of Drug Abuse & Addiction

Meta-anfetamina

- **chronic consumption produces**
 - decreased motor performance
 - impairment of verbal / memory learning
 - emotional disturbances
 - behavioral changes
 - physical changes: meth mouth, etc.



SKIN

Acne appears or worsens. Obsessive skin-picking often causes meth users' faces to be covered in small sores and scarring - the result of a common sensory hallucination of bugs crawling beneath the skin.



FACIAL MUSCULATURE AND FAT

Meth, like other stimulants, suppresses appetite and can lead to undernourishment due to long periods without eating. Over time, the body begins consuming muscle tissue and facial fat, giving users a gaunt, hollowed-out appearance.



TEETH AND GUMS

"Meth Mouth" is caused by several factors; tooth enamel is dissolved by the harsh chemicals of the drug, the blood vessels contained in healthy gums and teeth shrink, increasing the rate of decay, the production of saliva diminishes, allowing harmful acids to further damage the mouth, cravings for sugary foods increases with meth use, oral hygiene is typically neglected while high, and heavy tooth-grinding is an additional side effect of the drug.



3 AGE: 25



2 AGE: 25



1 AGE: 23



MSM using MA

A Systematic Review of Behavioral and Treatment
Outcome Studies Among HIV-Infected Men
Who Have Sex with Men Who Abuse
Crystal Methamphetamine

Radiha Rajasingham, M.D.,¹ Matthew J. Mimiaga, Sc.D., M.P.H.,^{2,3,5} Jaclyn M. White, M.P.H.,⁵
Megan M. Pinkston, M.A., Ph.D.,⁴ Rachel P. Baden, M.D.,¹ and Jennifer A. Mitty, M.D., M.P.H.¹

- **Increased risk of**
 - Unprotected anal intercourse
 - Group sex
 - Having multiple sexual partners
 - Contact sexual partners online
 - Sexual relations with UDVP
 - Be intoxicated while keeping rrrsbe
- **Unrelated to the HIV- infection**



HUGE SALE!

BUY CRYSTAL, get HIV FREE!

BONUS SPECIAL

Buy this trendy accessory pipe, get a life-time addiction absolutely **FREE**

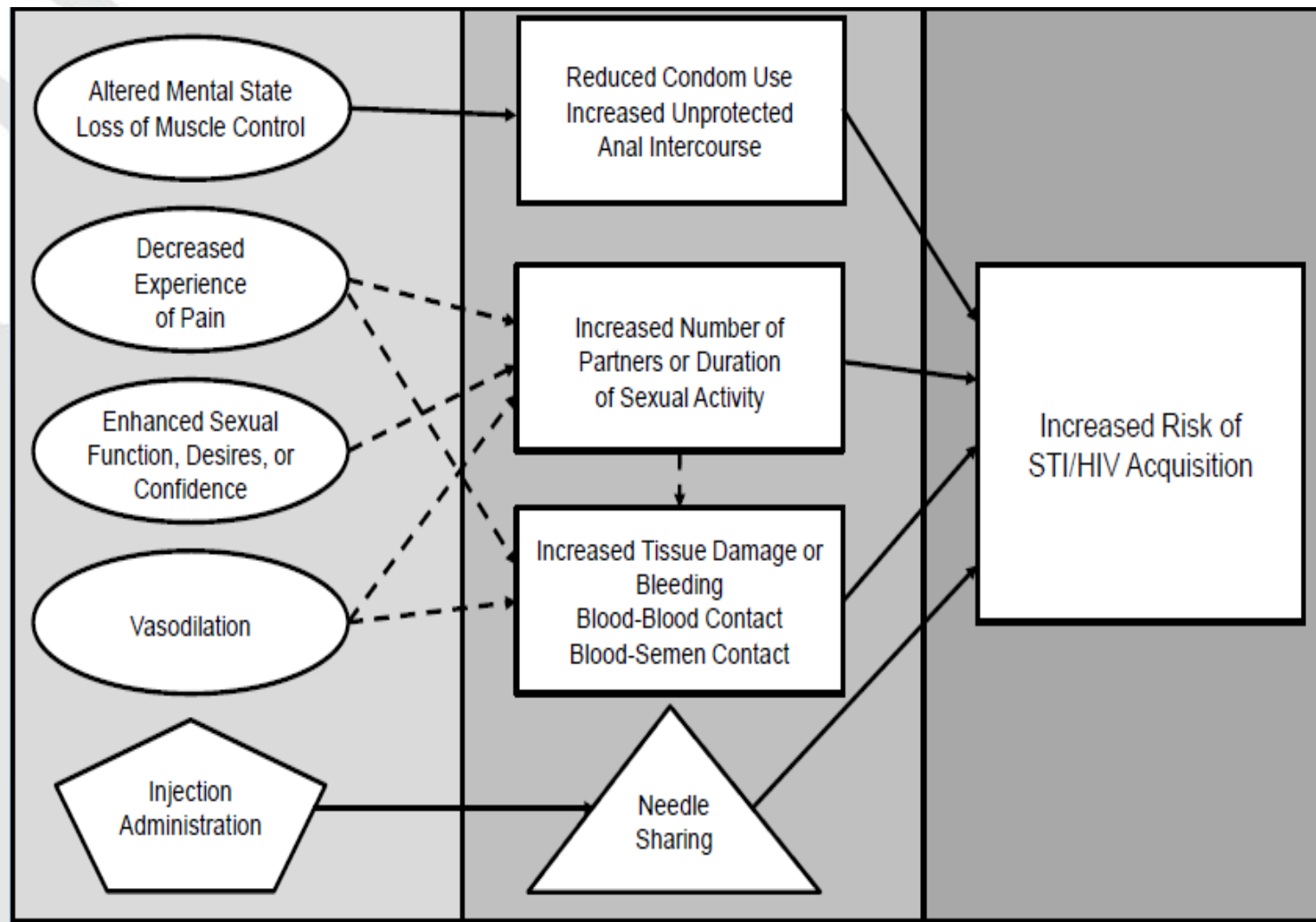
"It's frightening. I've seen a huge increase of newly infected gay men that got HIV from unprotected sex during crystal meth binges. Our community is self-destructing with this drug."
— Howard Grossman, MD
HIV Specialist, St. Luke's-Roosevelt Hospital

Chelsea Phone Booth Ads Paid for by **AIDS MEDS.COM**
Conceived and Designed by Peter Staley and Vincent Gagliostro

This Ad space donated by Gay City News

Why is MA use highly associated to HIV infection?

Modelo conceptual de posibles vías de riesgo de contagio (Drumright 2006)





HIV+ MSM were more likely to use MA for sexual reasons compared to HIV- MSM

- **to enhance sexuality**
 - prolonging sexual encounters
 - enhancing sexual feelings
 - enhancing attitudes toward sex
- **to cope with their HIV diagnosis**
 - by feeling more physically energetic
 - by helping to view own situation in a more positive light
 - by providing an escape from social rejection and depression

Rajasingham et al 2012

Methamphetamine and VIH

- **more consumption (20-30%) in MSM that are HIV + compared to HIV-** (Buchacz et al., 2005, Forrest et al., 2010, Mansergh et al., 2006; Schwarcz et al., 2007).
- **higher VL** (Ellis et al., 2003, Fairbairn et al., 2011, King et al., 2009, Feldman 2015)
- **lower CD4 count** (Shoptaw et al., 2012)
- **accelerates the progression of the disease** (Carrico, 2011).
- **increased risk of transmission** (Cohen 2011)
- **neurotoxic** (Silverstein 2011)
- **changes the BBB** (Northrop 2015)



Studies in animals

(Passaro et al 2015)

- One animal study using transgenic mice indicate that MA potentiates HIV-1 replication
- SIV studies suggest that METH has minimal or no effects on the viral load in the periphery but enhances viral load in the brain
- MA enhances HIV-1 infection in the cultures of astrocytes, dendritic cells and macrophages
- Increases expression of CCR5 co-receptor in macrophages and inhibits IFN-alfa expression (Liang et al. 2008)

MA and the antiretroviral treatment

- MA is metabolized to amphetamine through P450 2D6
- Ritonavir inhibits 2D6 and may cause increases of 3-10 times the concentrations of MA
- Potential increase of MA with cobicistat

Has HIV DX caused a change in MA consumption?

- **UCLA 2011**
 - 1/3 (193) of MSM with primary infection who consumed, continued to do so in the year after DX
 - anal sex was reduced with HIV- or HIV + people, but after 9 months it increased again

Gorbach et al. JAIDS 2011

Treatment of MA use disorder

- **Psychopharmacological treatment**
 - antidepressants
 - Mirtazapine
 - Bupropion (facilitates dopamine / norepinephrine reuptake)
 - Mixed results; Probably better for males with mild to moderate MA
 - antipsychotics
 - Aripiprazole (mixed results)
 - replacement
 - Amphetamine, methylphenidate
- **Non-pharmacological therapies**
 - motivational interview
 - contingency management
 - cognitive behavioral therapy

Conclusiones

- **MA está asociada a un mayor riesgo de contraer el VIH o de reinfectarse**
- **En las personas VIH+: mayor riesgo de progresión de la enfermedad**
- **el tratamiento de la adicción a la MA debe incluir asumir prácticas sexuales seguras y detectar adicción al sexo**
- **los estudios de tratamiento no demostraron un impacto sostenido en la disminución de consumo de metanfetamina en HSH VIH +**
- **Es necesario insistir en la prevención en consumidores de MA**

Summary

- **MA is associated with an increased risk of contracting HIV or reinfecting itself**
- **In HIV + people: increased risk of disease progression**
- **The treatment of addiction to MA should include taking safe sex and detecting sex addiction**
- **The treatment studies did not demonstrate a sustained impact in the decrease of methamphetamine consumption in HIV +**
- **It is necessary to insist on prevention in MA consumers**

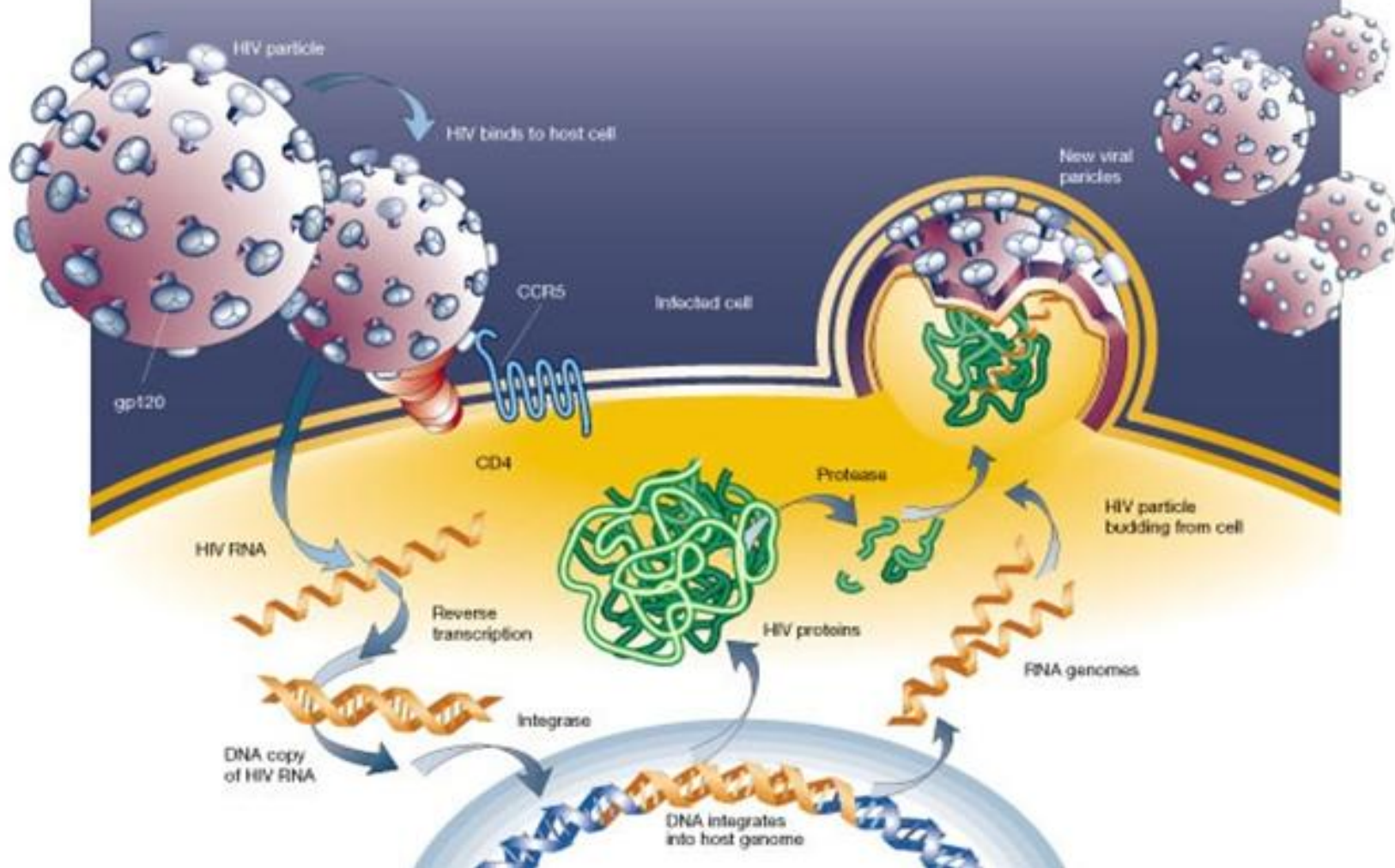


Gràcies!

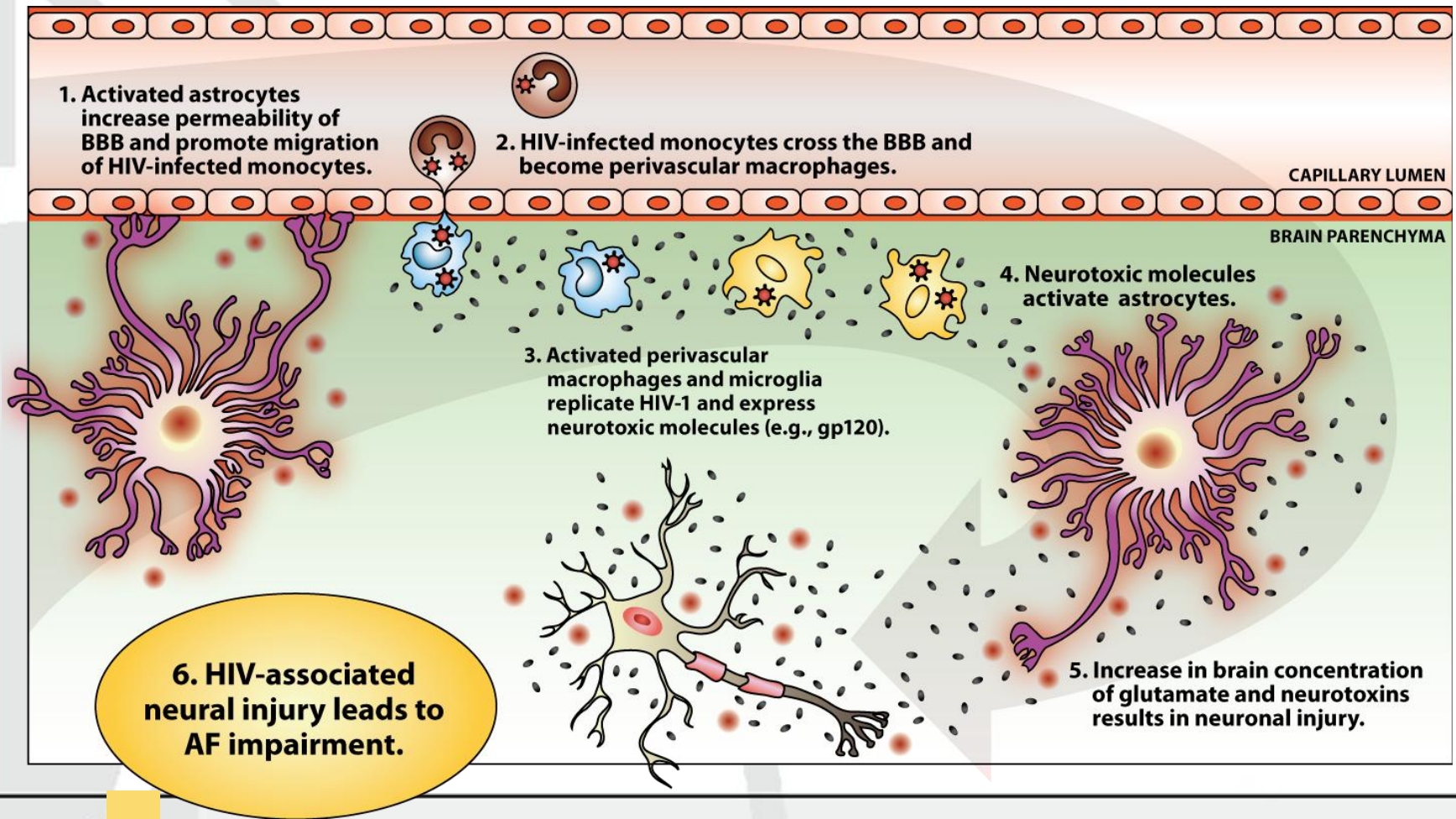
jblanch@clinic.cat



Weiss, EMBO reports 2003; 4, S1, S10–S14

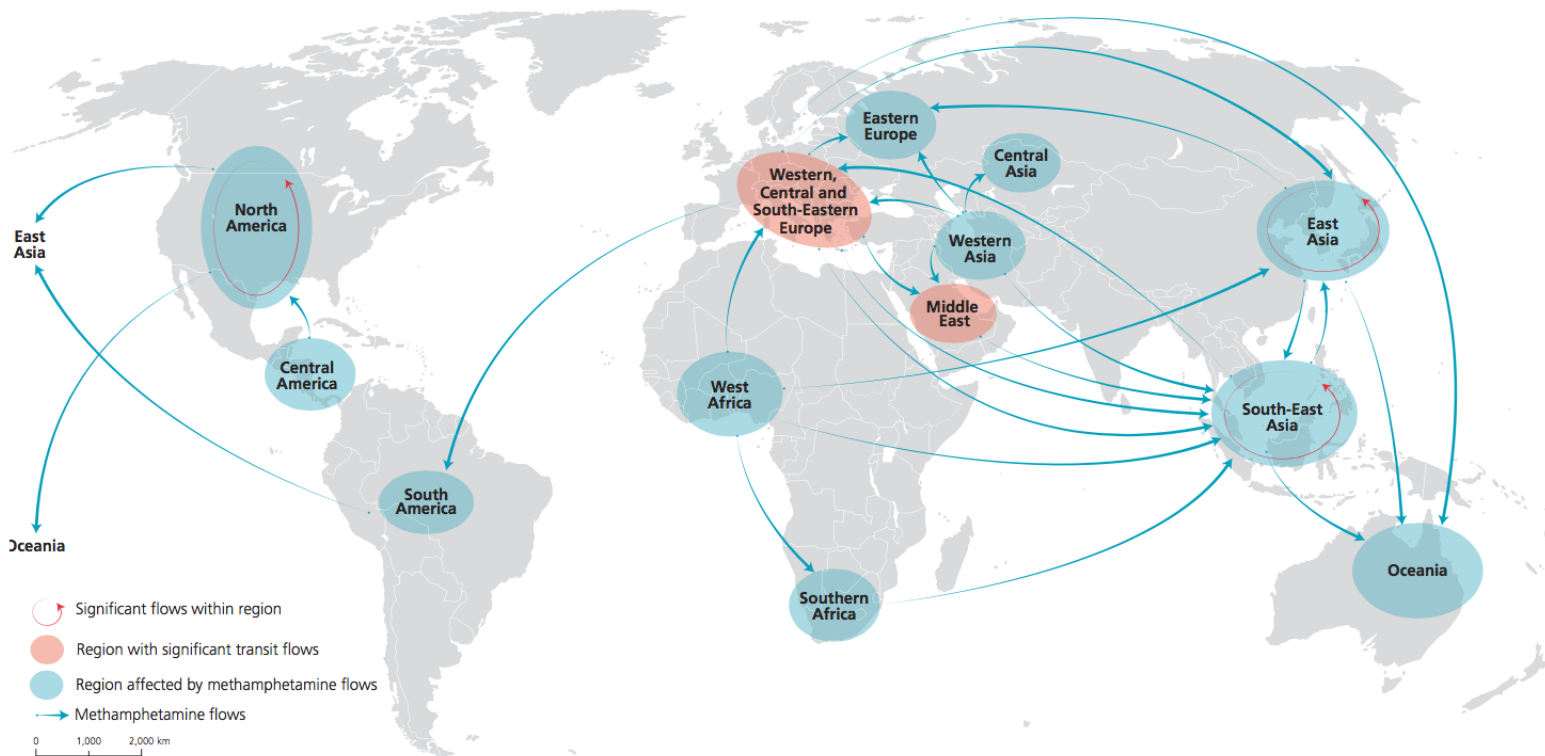


Deterioro cognitivo



Global Distribution of Methamphetamine

MAP 2 | Interregional trafficking flows of methamphetamine, 2011-2014



Spain's crystal-meth problem may be about to get worse (Business Insider 17 Nov 2016)

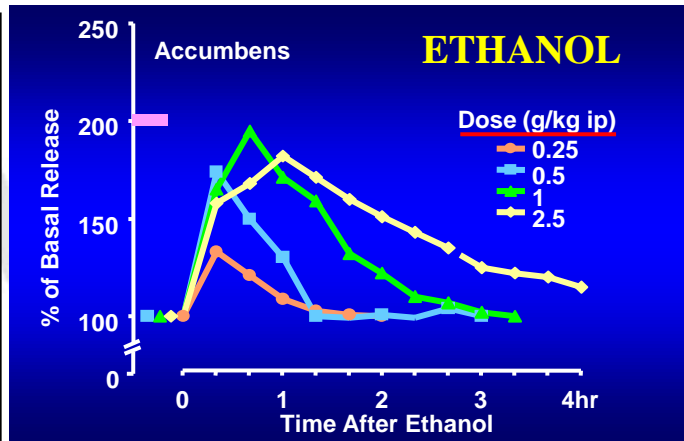
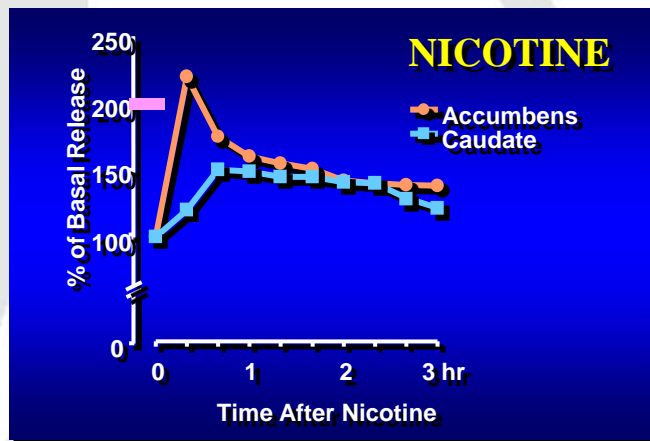
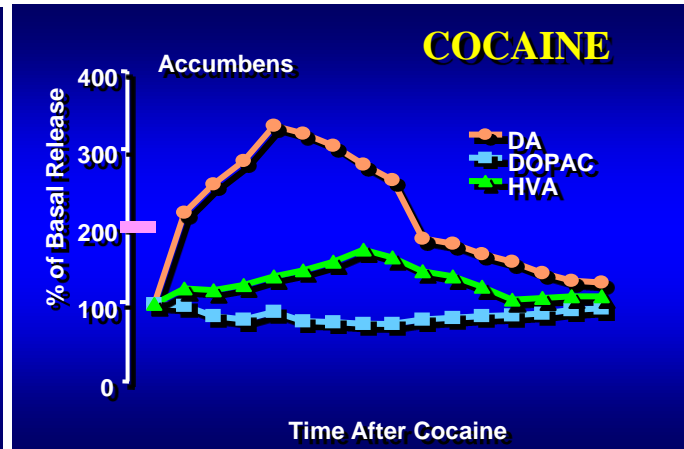
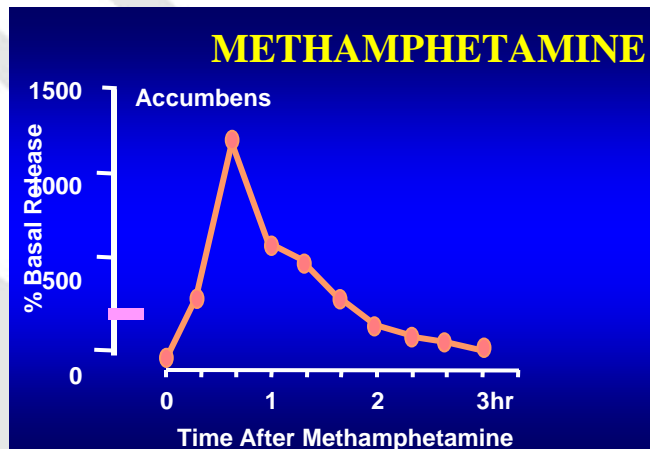


Spanish police broke up a drug ring smuggling methamphetamine using packages of chocolates, December 2014



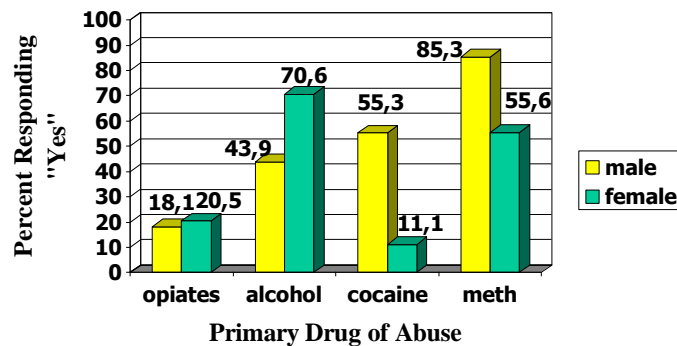
Lab equipment allegedly used to produce synthetic drugs recovered by Spanish police, September 2016

Effects of Drugs on Dopamine Release



Source: Shoblock and Sullivan; Di Chiara and Imperato

My sexual drive is *increased* by the use of ...

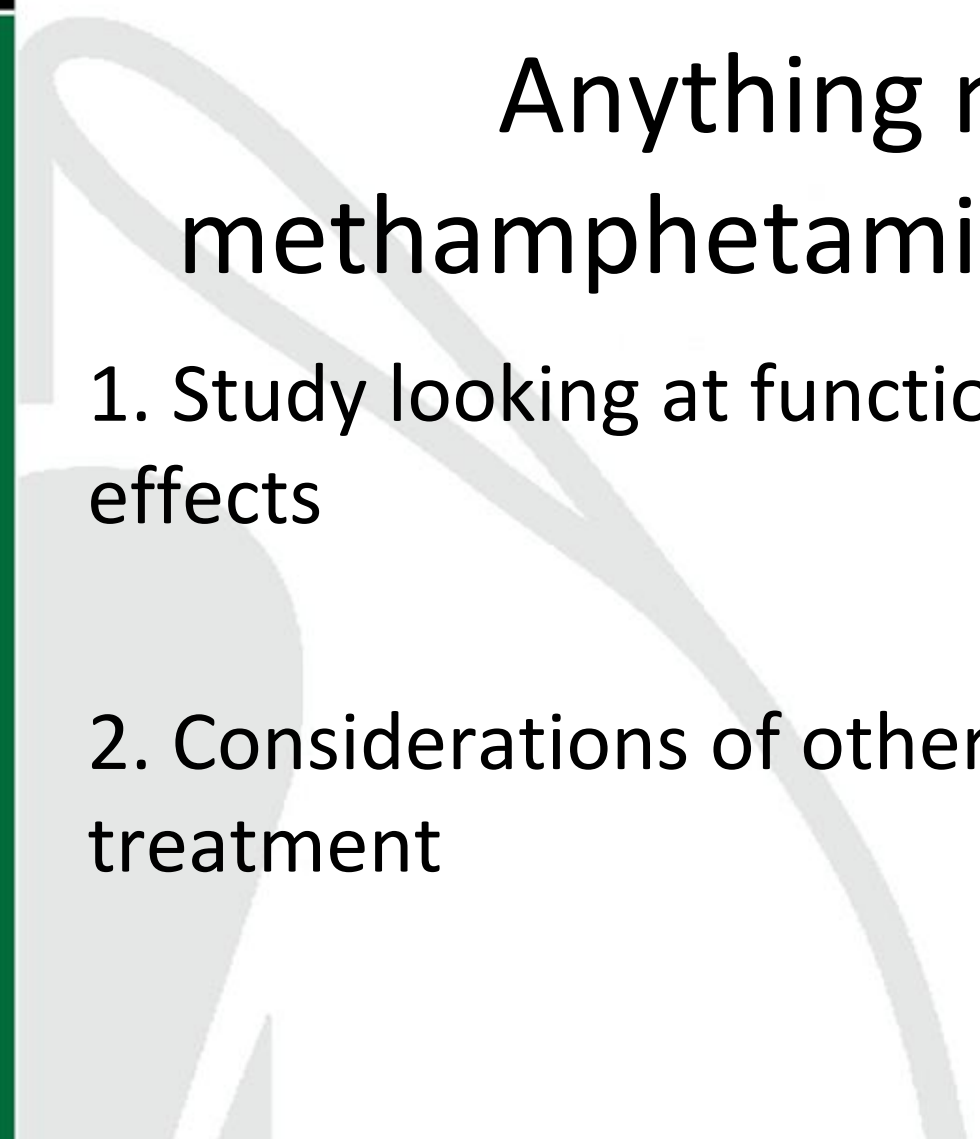


Rawson RA, Washton AM, Domier, CP, Reiber, C.
Drugs and sexual effects: Role of drug type and
gender. *Journal of Substance Abuse Treatment*, 22,
103-108, 2002

Treatment of methamphetamine use disorder

- Medications that have found limited success include bupropion, naltrexone, mirtazapine
 - Treat symptoms: depression, psychosis
- Contingency management
 - Reward patients who are able to abstain
 - Combined with medications it can be more effective

- Cognitive behavioral therapy, Matrix Model



Anything new in methamphetamine research?

1. Study looking at functional and structural effects
2. Considerations of other adjuncts in treatment

Chronic Methamphetamine Effects on Brain Structure and Function in Rats (Thanos, Volkow et al 2016)



- Rats were randomly split into three distinct treatment groups and treated daily for four months, via i.p. injection, with saline (controls), or low dose (LDMA) meth (4mg/kg), or high dose (HDMA) meth (8mg/kg)
- Structural findings
 - When compared with controls, chronic HDMA-treated rats had enlarged striatal volume

The dorsal striatum = caudate nucleus and the putamen. The ventral striatum = nucleus accumbens and olfactory tubercle


(subcortical part of the forebrain and a critical component of the reward system)

- Functional Findings

The differential effects of alprazolam and oxazepam on
methamphetamine self-administration in rats (Spence et al
2016)



- Rats were pretreated with oxazepam, alprazolam, or vehicle prior to methamphetamine self-administration.
 - Oxazepam significantly reduced methamphetamine self-administration.
 - In contrast, alprazolam significantly enhanced methamphetamine self-administration.
- The GABA-A receptor is responsible for the alprazolam-induced enhancement of TSPO (translocator protein) formerly called PBR (peripheral benzodiazepine receptor) methamphetamine self-administration,



The Effect of Buprenorphine on Methamphetamine Cravings (Salehi et al 2015)

- Study conducted in Iran, where methamphetamine has become a significant problem



A huddle of drug addicts use crystal meth beside a fire in a suburb of Tehran.

IMAGE: EBRAHIM NOROOZI/ASSOCIATED PRESS

- Buprenorphine is a partial agonist of the μ receptor with antagonistic effects on opioid receptors δ and κ that enhances dopamine release in the nucleus accumbens in cocaine-treated mice and decreases the propensity for cocaine consumption.
- This study investigated the efficacy of adding buprenorphine in reducing METH cravings during treatment with the Matrix program
- Randomized, double-blind, controlled

- The intervention group received buprenorphine in its sublingual form, beginning at a dose of 2 mg/d and increased to 6 mg within 7 days (3 sublingual tablets).
- Buprenorphine augmentation, in comparison with the placebo, significantly reduced the craving to use METH during treatment. Significantly fewer positive urine toxicology screens in treatment group.



Conclusions: Methamphetamine

- Methamphetamine is a drug with deleterious CNS effects
- MSM who use methamphetamine are at an increased risk of acquiring HIV
- Although methamphetamine may seem to provide some immediate benefits, those benefits are outweighed by the risks and consequences
- Treating methamphetamine addiction should include addressing safer sex practices and screening for sex addiction, body issues, eating disorders
- Overall treatment studies (until Dec 2010) had failed to show a sustained impact in decreasing crystal meth use in HIV+ MSM. (Rajasingham et al. AIDS Patient Care and STDS. 2012). Thus, prevention needs to be a major public health consideration.



Cocaine and HAND (Cai et al. 2016)

- Cocaine has been extensively studied for its ability to exacerbate the neuropathogenesis of HAND.
 - Cocaine not only facilitates viral replication in macrophages and microglia, but also inflicts deleterious effects on various other cells of the CNS, thereby contributing to the potentiation of HAND.
 - Cocaine has been shown to enhance the permeability of the blood-brain barrier (BBB) through various mechanisms
 - Cocaine enhances viral replication in CNS astrocytes and promotes astrogliosis via astrocyte activation and proliferation.
 - Cocaine exacerbates neuroinflammatory responses by mediating microglial activation and migration.
 - Cocaine directly affects the brain reward system by disrupting the homeostasis of neurotransmitters such as dopamine and acetylcholine and works synergistically with viral proteins such as tat and gp120 to promote neuronal injury.

Alcohol and HIV (Probst et al 2017)

- Current drinkers of low SES in S Africa had elevated risk of HIV infections
- Consider when allocating scarce resources

Alcohol and HIV

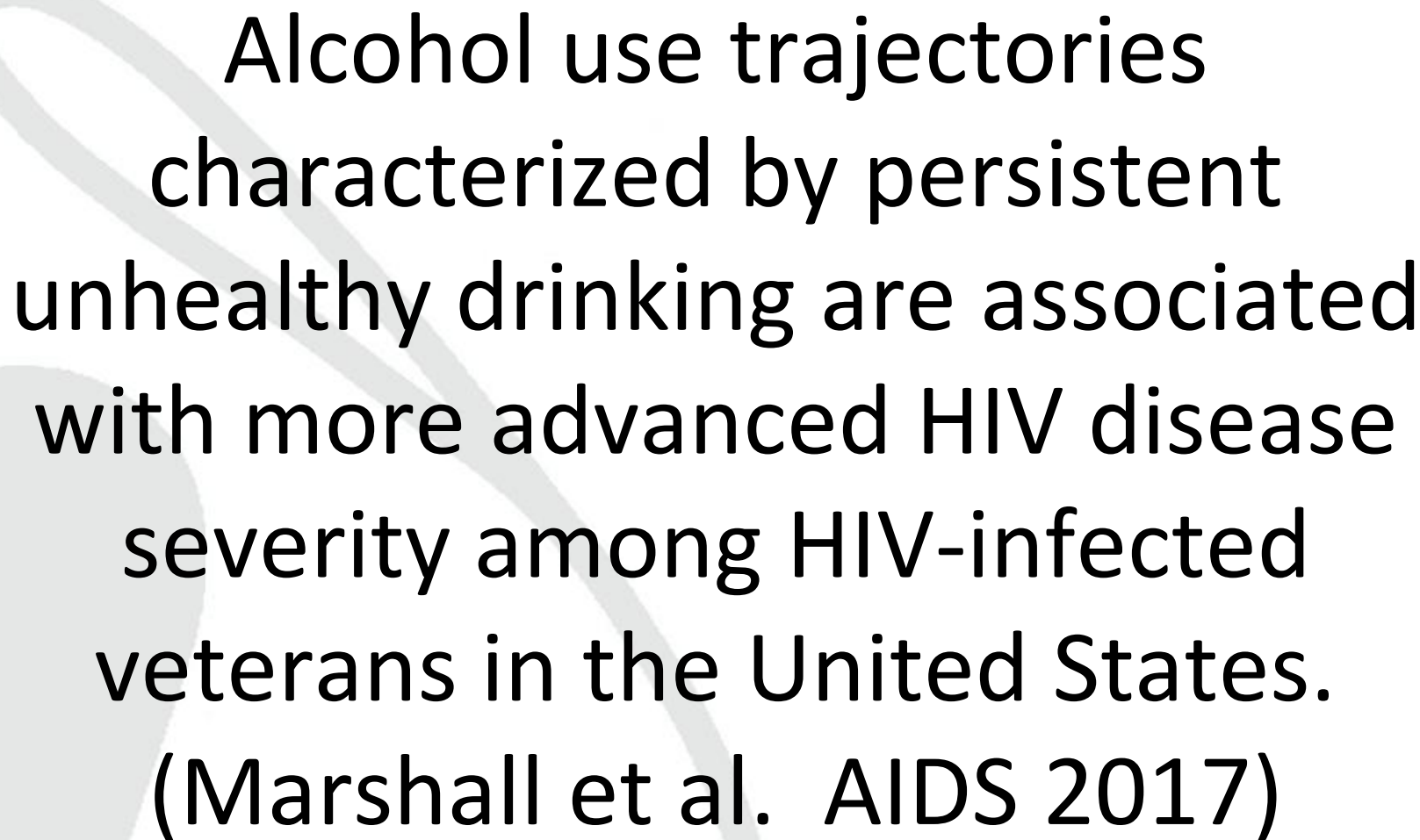
- PLWH are nearly twice as likely to use alcohol as people who do not have HIV
- An estimated 50% of PLWH have histories of alcohol problems ([National Institute on Alcohol Abuse and Alcoholism, 2010](#)).
- Alcohol directly impacts HIV treatment through several mechanisms:

– (a) altered liver function diminished ART metabolism,

(b) immune activation results in accelerated

Alcohol and HIV health

- [Samet and colleagues \(2007\)](#) demonstrated the link between alcohol use and accelerated decline in health in PLWH.
- Participants who were not on ART and continues to drink heavily had lower CD4+ T cell counts than participants who were not on ART but abstained from drinking.
- Alcohol use is also directly related to higher viral loads and decreased ability to achieve and sustain viral suppression (Azar et al)



Alcohol use trajectories
characterized by persistent
unhealthy drinking are associated
with more advanced HIV disease
severity among HIV-infected
veterans in the United States.
(Marshall et al. AIDS 2017)



Poppers and HIV (CROI 2004)

Information was collected from 4,697 high-risk HIV-negative men who have sex with men, who were enrolled at 56 clinical-trial sites in the U.S. for the 36-month trial

Users of amphetamines ("crystal"), hallucinogens, or inhaled nitrites ("poppers") had higher rates of HIV infection than non-users

Overall 2.8 HIV infections per 100 person years

Meth: 4.5 infections

Poppers: 3.6 HIV infections

Poppers and cancer (Dutta et al 2017)

Objectives: Nitrite inhalants (poppers) are commonly used recreational drugs among MSM and were previously associated with elevated rates of high-risk sexual behavior, HIV and human herpesvirus type 8 (HHV-8) seroconversion, and transient immunosuppressive effects in experimental models. Whether long-term popper use is associated with cancer risk among MSM in the HAART era is unclear.

Design: Prospective cohort study of cancer risk in 3223 HIV-infected and uninfected MSM in the Multicenter AIDS Cohort Study from 1996–2010.

Methods: Poisson regression models were used to examine the association between heavy popper use (defined as daily or weekly use for at least 1 year) and risk of individual cancers or composite category of virus-associated cancers.

Poppers and cancer (Dutta et al 2017)

- Results: Among all participants, heavy popper use was not associated with increased risk of any individual cancers.
- Among HIV-uninfected men aged 50–70, heavy popper use was associated with increased risk of virus-associated cancer with causes linked to human papillomavirus, HHV-8, and Epstein–Barr and hepatitis B

and C viruses



Other ingredients and HIV (DeRyck et al 2012)

- Studies have shown more erectile dysfunction (ED) in men living with HIV (MLHIV), relative to age matched HIV-negative men.
- Erection enhancing medication (EEM) is more frequently used by HIV-positive men than in the general male population.
- Increased sexually transmitted infection has been described in HIV-positive men with ED using EEM. This study investigated the use

Club drugs, age, sex in HIV+ MSM (Pappas et al 2011)

- This study examined club drug use (i.e., cocaine, ecstasy, ketamine, gamma-hydroxybutyrate [GHB], and methamphetamine) and unprotected anal intercourse (UAI) in an ethnically and racially diverse sample of 166 New York City-based seropositive, club drug-using, gay and bisexual men, ages 19–61

- Multivariate logistic regression modeling indicated older participants (30s and 40 +)

Summary

- Substances are not uncommonly seen as vehicles for pleasure in the MSM/HIV community
- Drugs present risks. Individuals must also consider their medications, sexual practices, and health status
- Medical providers can become resources for the patient/client who wants more information about the risks (and benefits)