

# Managing Opioid Dependence in HIV Primary Care Settings

Addiction and Pain  
in a Post-HAART World

Paula J. Lum, M.D., M.P.H.  
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## Goals of Talk

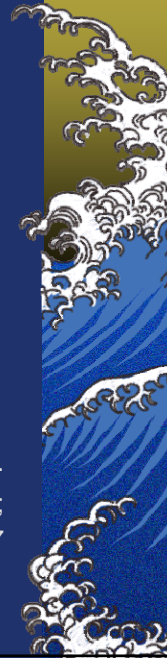
1. Epidemiology of injecting drug use in HIV/AIDS
2. HIV treatment issues for IDU
3. Treating opioid dependence
4. Drug-drug interactions
5. Managing pain in HIV+ drug users

## Injecting drug use & AIDS

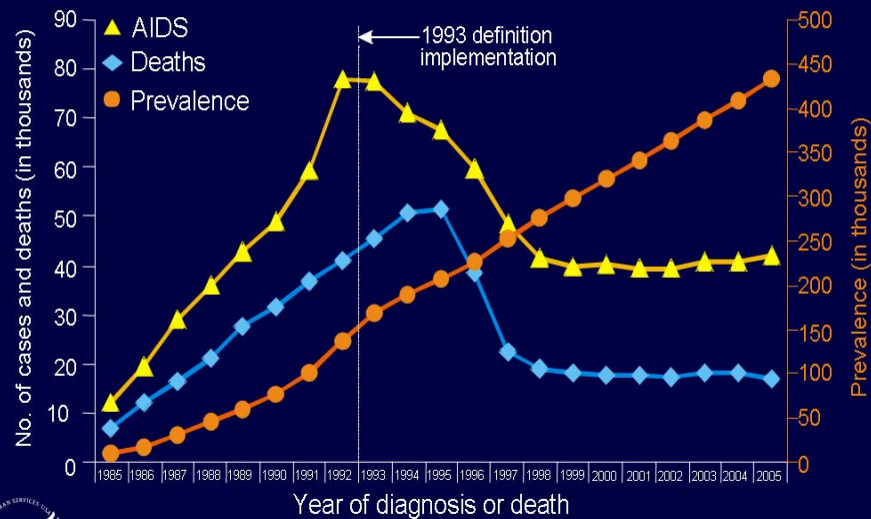
984,155 cumulative cases of AIDS reported in US through 2005

- Males = 22% IDU, 9% MSM-IDU
- Females = 40% IDU

Centers for Disease Control and Prevention.  
HIV/AIDS Surveillance Report, 2005. Vol. 17. Rev ed.;  
2007



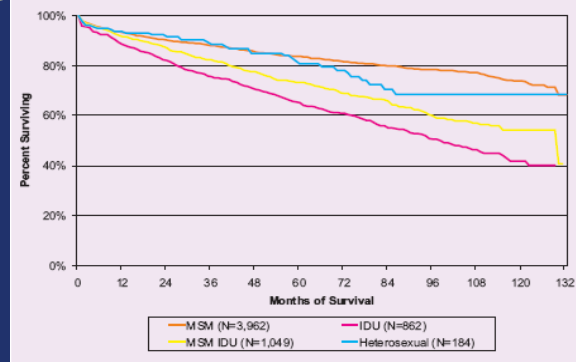
### AIDS Cases, Deaths, and Persons Living with AIDS, 1985–2005—United States and Dependent Areas



Note. Data have been adjusted for reporting delays.



## Survival by exposure category, 1996-2006 San Francisco



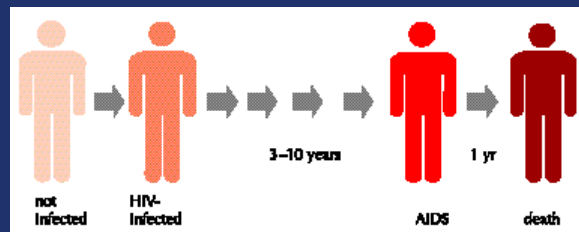
- 5-year survival after AIDS diagnosis: MSM 84%, heterosexuals 81%, MSM-IDU 73%, heterosexual IDU 65%

## AIDS deaths in NYC, 1999-2004

- IDU significantly increased risk for death compared to MSM due to
  - HIV-related causes: hazard ratio, 1.59 [95% CI, 1.49 to 1.70]
  - and**
  - Non-HIV-related causes (overdose, liver disease, other infections): hazard ratio, 2.54 [95% CI, 2.24 to 2.87]

Sackoff, Ann Intern Med. 2006;145:397-406

## Does illicit drug use promote HIV disease progression?



## Direct or indirect biologic effects

Opioid exposure *in vitro* associated with

- Increased replication of HIV-1

AIDS 1990;4:869-73

- Impaired lymphocyte function

AIDS 1991;5:35-41

## Impaired adherence

- Subjugation of health concerns to the needs of addiction
- Competing medical conditions
- Unstable living conditions
- Alienation from family and social support structures
- Mistrust of the medical system

## Impaired access to care

- Suboptimal access to ARV/OI regimens despite mixed evidence on adherence
  - Celentano, JAMA 1998, 280:544–546
  - Strathdee, JAMA 1998, 280:547–9
  - Bassetti, JAIDS 1999, 21:114–119
  - Loughlin, AIDS Care 2004, 16:485–500
- No difference in ARV resistance between IDU and non-IDU
  - Wood, AIDS 2005, 19:1189–1195

## Physician attitudes toward IDU

“Treating IV drug users seems futile”

or

“When given a choice, I would not treat  
intravenous drug users with HIV infection”

Strength of agreement and ARV initiation

- Negative score: IDU (13.5%) vs. non-IDU (36%)
- Positive score: IDU (32.3%) vs. non-IDU (34.4%)

HCSUS Cohort. Arch Intern Med. 2005;165:618-623

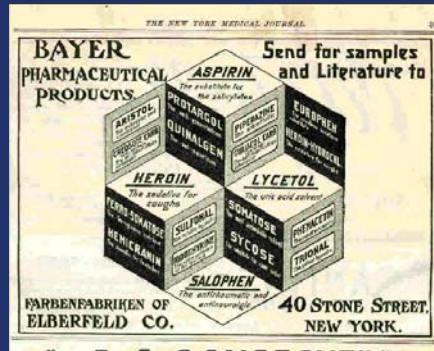
## Training, assessment, intervention & satisfaction

- 8 of 126 medical schools required a course in addiction medicine, 1991-92. - Academic Med 1994, 69:362-369
- Most primary care providers inadequately screen for or intervene in diagnosed cases of substance abuse. - Substance Use & Misuse 2005, 40:1071-1084
- Professional satisfaction
  - Positive attitudes toward substance use treatment
  - Confidence in assessment and intervention
  - Perceived responsibility for addressing substance use problems

## Opiates & opioids



*Papaver somniferum L.*



diacetylmorphine

## Heroin (diacetylmorphine)



- 3.5 million tried heroin at least once in 2005, compared with 2.9 million in 1996
- 91,000 used heroin for the first time in past 12 months in 2006
- 136,000 current (past month) heroin users in 2005 → 338,000 in 2006

- National Survey on Drug Use and Health, 2005 & 2006

## Prescription opioids



- In 2005, 31.8 million used narcotic pain relievers for non-medical purposes at some time in their lives.
- First time users of oxycodone (455,000) and hydrocodone (1.3 million) in 2005
- 5.2 million current (past month) non-medical users of prescription pain relievers in 2006

- National Surveys on Drug Use and Health, 2005 & 2006

## Prescription opioids



In 2003, 1.7 million persons were users of both oxycodone and heroin

## Waiting room survey, 2007 SFGH Positive Health Program

Use in last 12 months	n=185	%
Any illicit drug	149	81
Alcohol	73	39
Methamphetamine	71	38
Heroin or prescription opioids	67	36
Crack	64	35
Cocaine	43	23
Benzodiazepine	23	12

## Case - DW

- 33-year old white female, new HIV diagnosis
- Anti-HCV+, multiple soft tissue infections, femoral pseudoaneurysm, PID, depression
- Onset heroin age 17; smokes pot, tobacco
- Methadone detoxification x 4
- “Clean & sober” x 60 d in jail before court mandated to residential treatment program
- Daily heroin cravings, nervous, insomnia

## Physical exam

- Thin, alert, anxious female
- Normal vital signs
- No jaundice, rash, or piloerection; old track marks and surgical scars
- Reactive pupils 3 mm, no lacrimation or rhinorrhea
- Normal lung, heart, abdominal exam
- No tremor

## Question

What is DW's problem?

- A. Acute opiate withdrawal
- B. Protracted abstinence syndrome
- C. Brain-related disorder
- D. Lack of will power
- E. Post-traumatic stress disorder

## Opioid dependence

- Brain-related medical disorder with inherited and environmental causative factors
- Cluster of cognitive, behavioral, and physiological symptoms in which opiate use continues despite significant opiate-induced problems

- NIH Consensus Development Panel. JAMA 1998, 280:1936-1943

## Diagnosing dependence > 3 criteria over 12 months

### Physiologic symptoms

- Tolerance
- Withdrawal

### Behavior

- Taking larger amounts or over a longer period
- Inability to control use
- More time spent to obtain, use, or recover
- Social and other activities given up or reduced
- Continued use despite adverse consequences

## Treating opioid dependence

1. Detoxification: relieve acute withdrawal symptoms while adjusting to a drug-free state
2. Long-term or maintenance treatment: prevent relapse



## Treating opioid withdrawal

### Detoxification

- Supportive measures: safe environment, adequate nutrition, careful monitoring
- Pharmacologic therapies to alleviate withdrawal symptoms:
  - Opioids – methadone, buprenorphine
  - Non-opioids – clonidine
  - Rapid or ultrarapid – naloxone or naltrexone plus clonidine, sedation, and general anesthesia

O'Connor, et al. Ann Intern Med. 2000;133:40-54.

## Treating opioid dependence

- After detoxification, long-term treatment is designed to prevent relapse to illicit drug use
  - Behavioral therapies: CBT, contingency mgmt
  - Opioid antagonists (naltrexone) block opioid effects, diminish reinforcing effects
  - Opioid agonist therapy prevents withdrawal, stabilizes brain receptor neurochemistry

O'Connor, et al. Ann Intern Med. 2000;132:40-54

## Treating opioid dependence

- Most effective treatment is agonist maintenance therapy with methadone

– National Consensus Development Panel  
on Effective Medical Treatment of Opiate Addiction  
JAMA 1998, 280:1936-1943

## Methadone maintenance therapy

- Reduced illicit opiate and non-opiate use
- Reduced HIV-related risk behavior
- Reduced crime
- Enhanced social functioning
- 3-fold decreased mortality
- 10-fold more cost effective

- JAMA 1998, 280:1936-1943

## Opioid agonists in HIV+ patients

- Decreased HIV seroconversion
  - Moss, AIDS 1994, 8:223–231
- Receipt of optimal ART
  - Med Care 2002, 40(10):976-95
- Adherence to ART
  - Manif 2000 Study Group, AIDS 2000, 14(2):151-5
- Lower probability of HIV disease progression
  - BMJ 1990, 15:301(6765):1362-5
- Fewer hospitalizations
  - JAMA 2001, 285(18):2355-62

## Treatment gap

- In the U.S., only 14% opioid-dependent persons have access to MMT

Arch Intern Med. 2004;164:277-288

- In San Francisco, ~2700 MMT slots funded through public, federal, and private sources
  - 15,000 to 17,000 active heroin users
  - Over 500 patients cycle through detox programs yearly, hoping to get into MMT
  - maybe 15% actually do get a MMT slot

Personal communication, D. Hersh,  
SFDPH, Community Behavioral Health Services

## Drug Addiction Treatment Act (DATA) 2000

- Allows for office-based opiate treatment with Schedule III, IV or V medications
- Buprenorphine is the only approved medication



## Buprenorphine hydrochloride

Long-acting, partial  $\mu$ -opioid receptor agonist

- Agonist in the absence of opioids
- Antagonist in the presence of opioids

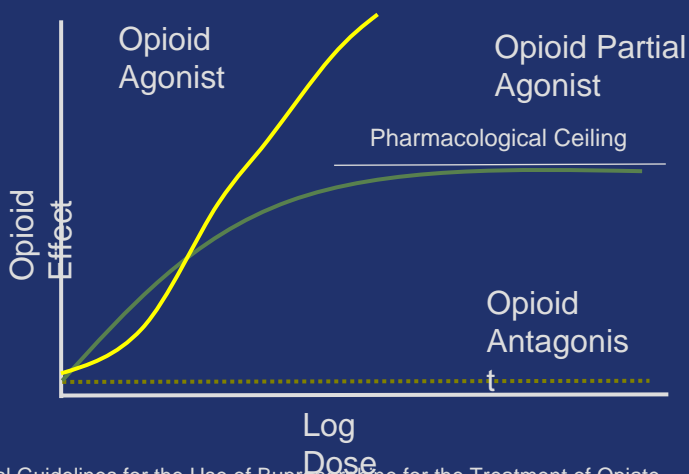
J Clin Psychopharmacol 1996;16:58-67

Equivalent efficacy to methadone

- Reductions in positive urine toxicology screens
- Retention in drug treatment programs

Cochrane Database Syst Rev 2003;(2):CD002207

## Spectrum of opioid activity



Clinical Guidelines for the Use of Buprenorphine for the Treatment of Opiate Addiction 2004

## Buprenorphine pharmacokinetics

- Poor oral bioavailability
  - Sublingual formulation mixed 4:1 with naloxone
  - Naloxone (full antagonist) activated only if tablet is crushed and injected
- Rapidly distributed to brain
- High receptor affinity, slow dissociation
- Average duration of action 72-96 h
- Cytochrome P450 3A4

- Drug and Alcohol Dependence 2003;S39-S47

## Buprenorphine toxicity is rare

- Higher degree of safety than methadone
  - Poor bioavailability if swallowed by small children
  - Ceiling effect on degree of CNS depression
- Ameliorated withdrawal syndrome
  - Slow dissociation associated with gentler detoxification
- Monitor for LFT elevations
- Few deaths reported when injected with benzodiazepines or alcohol in France

## Buprenorphine treatment

### 1. Induction

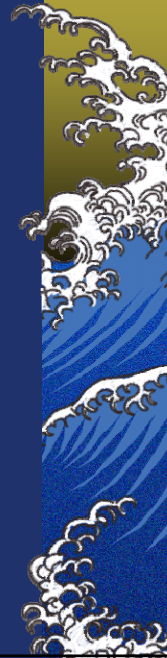
- Opioid-free state for 12-24 hours prior
- Rapid titration over 3-7 days, slower if methadone transfer

### 2. Stabilization

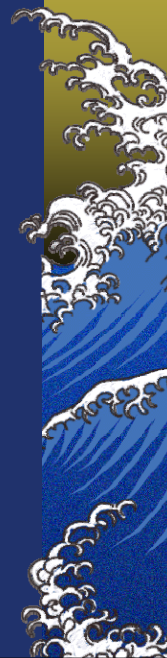
- Adjust dose until other drug use stopped or reduced and no reports symptoms of opiate cravings or withdrawal or opioid excess (max dose 36 mg)

### 3. Maintenance

- Monitor at stable dose, typically monthly
- Option for thrice weekly dosing



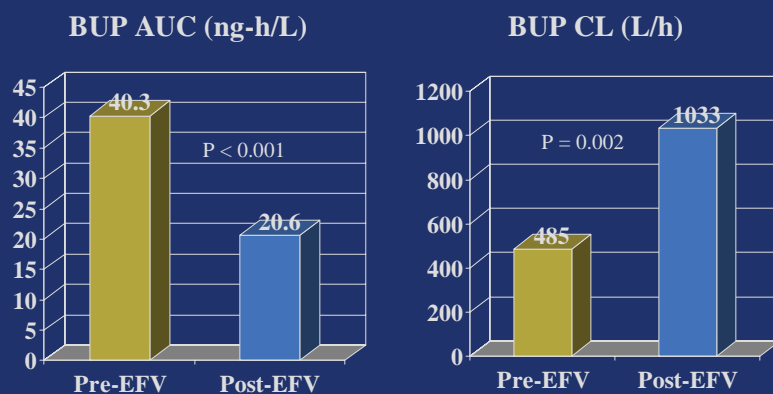
## Potential drug interactions



## Question

- AK is on stable dose of buprenorphine and wishes to restart ARVs. Which of the below are contraindicated with BUP/NX?
  - a) Efavirenz
  - b) Stavudine
  - c) Ritonavir
  - d) Saquinavir
  - e) None of the above

## Efavirenz



Opioid Withdrawal Scale remained unchanged

- CROI 2005; Abstract 653

## CYP3A4 inducers

### Antimicrobials

efavirenz  
nevirapine  
rifampin  
rifabutin

### Anticonvulsants

carbamazepine  
phenobarbital  
phenytoin

### Herbals

St. John's wort

- Pharmacist's Letter 2003

## Protease inhibitors

<u>Perpetrator</u>	<u>Interaction</u>	<u>Impact on BUP</u>
Ritonavir	Inhibition	↑ Concentration
Indinavir	Inhibition	↑ Concentration
Saquinavir	None	None

(In vitro)

- Drug Metab Disp 1998;26:257-260

## Boosted PIs

- 3 case reports of a clinical interaction with BUP and boosted atazanavir (ATVr): daytime somnolence, decreased mental function; “doped up”; dizzy, “high”, hypersomnolence  
*Bruce, et al. AIDS 2006, 20:783–793*
- With ATV and ATV/r respectively concentrations of BUP ( $p < 0.001$ ,  $p < 0.001$ ) and BUP metabolites increased. BUP treatment did not significantly alter ATV or rit concentrations, but 3 BUP/NX pts reported increased sedation with ATV/r.

*McCance-Katz et al. Drug and Alcohol Dependence 2007, 91:269–278*

## CYP 3A4 inhibitors

### Antimicrobial

azole antifungals  
macrolide antibiotics  
protease inhibitors

### Others

grapefruit juice  
diltiazem  
verapamil

### Antidepressants

fluvoxamine  
fluoxetine  
nefazodone

- *Pharmacist's Letter 2003*

## Case - MP

- MP is on TDF/FTC + LOP/r. Her methadone dose is 100 mg daily. She was recently started on furosemide for bilateral leg swelling.
- On a routine visit, her serum K<sup>+</sup> is 3.0 and an ECG shows prolonged QT interval.

## QT prolongation

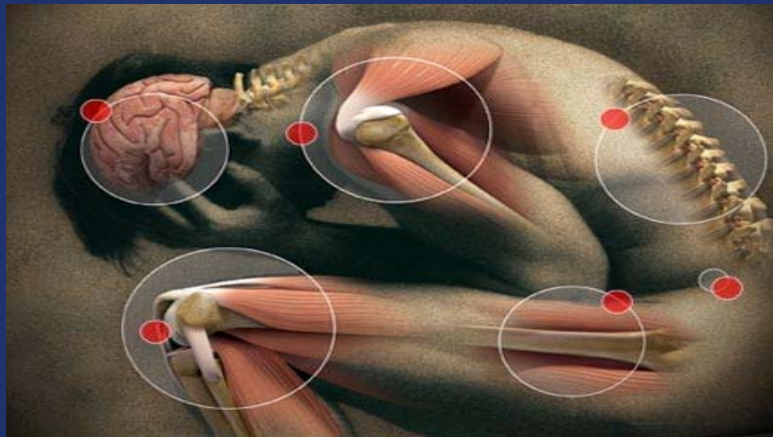
- Concern with methadone and LAAM
- Prospective, open-label study of BUP/NX alone and in combination with EFV, NFV, DLV, RIT, LOP/r
  - BUP/NX alone did not significantly alter the QT interval ( $P = 0.612$ )
  - BUP/NX in combination with ARVs, caused a statistical but not clinically significant increase in QT interval ( $P = 0.005$ )

Baker, et al. *Ann Pharmacother* 2006, 40:392–396

## Take home message

- Patients on buprenorphine can obtain an appropriate clinical response to their ARV medications.
- Pharmacokinetic interactions with some ARVs can affect buprenorphine serum concentration and QT intervals but may not produce clinically significant effects.

## Pain



## Case - HT

- 40-year old male on daily dose of 16 mg BUP/NX and scheduled for tooth extraction.
- How will you treat his acute pain?

## Acute pain & buprenorphine

Mild - moderate pain (e.g., dental extraction)

- Continue buprenorphine
- Use single dose of short-acting opioid analgesic if timed correctly

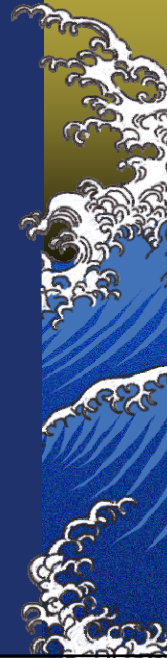
Moderate - severe pain (e.g., renal stone)

- Discontinue buprenorphine
- Treat with opioid analgesics until pain resolves
- Re-induce with buprenorphine

## Acute pain & buprenorphine

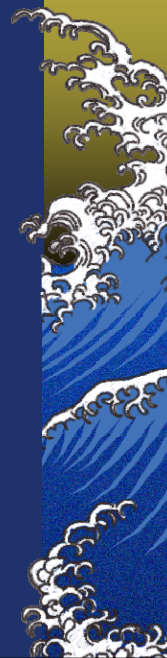
Moderate - severe pain (e.g., surgery, trauma)

- Discontinue buprenorphine
- Begin methadone maintenance therapy
- Use opioid analgesics until pain resolves
- Taper methadone  $\leq 30$  mg
- Re-induce with buprenorphine



## Case - TH

- 59 year old male, CD4 400, no ARVs, reports painful numbness in feet and legs, worse over last 6 months, can't sleep, losing weight.
- History of HCV, depression, heroin dependence; treated 8 years on MMT 90 mg daily; concurrent tobacco and crack use
- "Doc, I need some Oxycontin. I tried a friend's OCs and they really helped."



## Chronic pain & methadone maintenance treatment

- Chronic pain  $\geq$  3 months duration
- Continue MMT and treat with other long-acting opioid analgesics
- Take advantage of 6-8 hours of analgesia from MMT dose
- Work with methadone clinic to split daily methadone dose to TID regimen

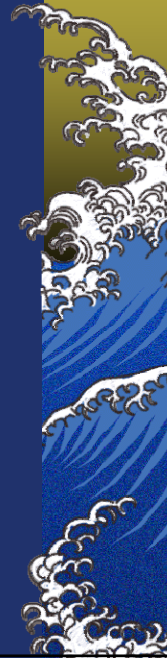
## Universal precautions

- Pain agreements or care plans
- Prescribe in small quantities, schedule frequent visits
- Use a single pharmacy
- Establish cross coverage prescription policy
- Pill counts
- Address (pain versus) suffering
- Encourage/require attendance in drug treatment program
- Conduct regular drug screening to assess therapeutic adherence and non-use of other drugs

Gourlay DL, Heit HA. Pain Medicine 2005

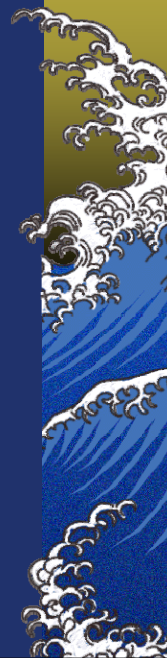
## General principles

- Both pain and addiction must be treated simultaneously
- Pain will not improve with untreated addiction
- Addiction will not improve with untreated pain



## Summary

- Injecting drug use is a major risk factor for HIV acquisition.
- Substance abuse disorders are highly prevalent in HIV+ infected individuals.
- Multiple co-morbidities challenge both patients and providers – creating obstacles to life-extending ARV therapy.



## Summary

- Opioid agonist therapy can help opioid dependent persons with HIV/AIDS to engage and adhere to ARVs
- HIV clinicians should be familiar with the identification and diagnosis of opioid dependence in their patients and be able to initiate treatment both directly and by referral.

## Summary

- Buprenorphine is the newest addition to the array of medications now available for treating dependence on heroin and other opiates.
- Buprenorphine is safer than methadone, equally effective, and can be prescribed in the privacy of a doctor's office.
- Health care models that integrate office-based treatment for opioid dependence in HIV primary care settings represent a new standard of care.



References resource

Lum PJ, Tulsy JP: The medical management of opioid dependence in HIV primary care settings. *Current HIV/AIDS Reports*, 2006;3(4):195-204.

