Managing Opioid Dependence in HIV Primary Care Settings
Addiction and Pain in a Post-HAART World

Paula J. Lum, M.D., M.P.H.
The Medical Management of HIV/AIDS

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.  
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]
  - 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
  - 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
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


- 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

<table>
<thead>
<tr>
<th>Use in last 12 months</th>
<th>n=185</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any illicit drug</td>
<td>149</td>
<td>81</td>
</tr>
<tr>
<td>Alcohol</td>
<td>73</td>
<td>39</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>71</td>
<td>38</td>
</tr>
<tr>
<td>Heroin or prescription</td>
<td>67</td>
<td>36</td>
</tr>
<tr>
<td>Opioids</td>
<td>64</td>
<td>35</td>
</tr>
<tr>
<td>Cocaine</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>23</td>
<td>12</td>
</tr>
</tbody>
</table>

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 piloerrection; 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


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

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, Arch Intern Med 2000;133:4054

Treating opioid dependence

- Most effective treatment is agonist maintenance therapy with methadone

  – National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction
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


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
• Lower probability of HIV disease progression
  – BMJ 1990, 15;301(6765):1362-5
• Fewer hospitalizations
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 µ-opioid receptor agonist**
- Agonist in the absence of opioids
- Antagonist in the presence of opioids


**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

<table>
<thead>
<tr>
<th>Opioid Effect</th>
<th>Log Dose</th>
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<tbody>
<tr>
<td>Opioid Agonist</td>
<td>Pharmacological Ceiling</td>
</tr>
<tr>
<td>Opioid Partial Agonist</td>
<td>Opioid Antagonist</td>
</tr>
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</table>

*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

BUP AUC (ng-h/L)  

<table>
<thead>
<tr>
<th></th>
<th>Pre-EFV</th>
<th>Post-EFV</th>
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<tbody>
<tr>
<td>BUP AUC (ng-h/L)</td>
<td>48.5</td>
<td>20.6</td>
</tr>
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</table>

P < 0.001

BUP CL (L/h)  

<table>
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<tr>
<th></th>
<th>Pre-EFV</th>
<th>Post-EFV</th>
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</thead>
<tbody>
<tr>
<td>BUP CL (L/h)</td>
<td>485</td>
<td>1033</td>
</tr>
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P = 0.002

- Opioid Withdrawal Scale remained unchanged
- CROI 2005; Abstract 653
CYP3A4 inducers

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Anticonvulsants</th>
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<tr>
<td>efavirenz</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>nevirapine</td>
<td>phenobarbital</td>
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<tr>
<td>rifampin</td>
<td>phenytoin</td>
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<tr>
<td>rifabutin</td>
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**Herbals**

- St. John’s wort

- Pharmacist’s Letter 2003

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Protease inhibitors

<table>
<thead>
<tr>
<th>Perpetrato</th>
<th>Interaction</th>
<th>Impact on BUP</th>
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<tbody>
<tr>
<td>Ritonavir</td>
<td>Inhibition</td>
<td>↑ Concentration</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Inhibition</td>
<td>↑ Concentration</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*(In vitro)*

- *Drug Metab Disp* 1998;26:257-260
Managing Opioid Dependence in HIV
Primary Care Settings

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.
  

CYP 3A4 inhibitors

- Antimicrobial
  - azole antifungals
  - macrolide antibiotics
  - protease inhibitors

- Antidepressants
  - fluvoxamine
  - fluoxetine
  - nefazodone

- Others
  - grapefruit juice
  - diltiazem
  - verapamil

- 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+ 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 ($P = 0.005$)

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.
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 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 > 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