Special Challenges
Clinical Management of the HIV-Infected Drug User

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Learning Objectives

• To describe the complex array of medical and psychiatric morbidities among HIV+ drug users

• To describe how active drug use negatively impacts HIV treatment outcomes

• To describe the types of drugs used and treatments available for substance use disorders

• To describe which evidence-based interventions are effective to promote adherence in HIV-infected drug users
Disclosures

• All disclosures are available in the program book
• There will be no off-label discussion of medications in this presentation
Have you ever prescribed buprenorphine or extended release naltrexone?

1. Yes

2. No, but I would if I had more training

3. No, and I never will

4. I have no idea what those are
Emerging Roles of the HIV Specialist

Secondary HIV Prevention and Adherence Counseling

Pharmacologist

Addiction Treatment Specialist
An estimated\(^a\) 22 million individuals are classified with substance abuse or dependence (9.4% of US population, 2002 data).

**Substance dependence**: associated with impact on health, emotional problems, attempts to cut down on use, tolerance, withdrawal, and other substance-specific symptoms.

**Substance abuse**: not necessarily dependent; associated with problems at work, home and school; problems with family or friends, physical danger, trouble with the law due to substance use.

\(^a\)Estimated from a sample of 68,126 individuals representative of the US population.
HIV in people who use drugs:
“We want to see inappropriately aggressive, state-sponsored hostility to drug users replaced by enlightened, scientifically driven attitudes and more equitable societal responses.”

July 2010; 376(9738):367-87

HIV in people who use drugs 4

Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs

Frederick L Altice, Adeeba Kamarulzaman, Vincent V Soriano, Mauro Schechter, Gerald H Friedland
The Potential Impact of Substance Use Disorders on HIV Patients

• Approximately half of all HIV-infected patents in the United States have a history of substance abuse or dependence.¹

• The coexistence of substance abuse and HIV is associated with: ¹,²
  – Delayed HIV diagnosis and entry into care
  – Overlapping signs and symptoms that complicate care
  – Increased HIV-associated morbidity and mortality
  – Increased non-HIV morbidity and mortality (liver, renal, cardiovascular)
  – Decreased access and adherence to ART
  – Increased HIV transmission risk behaviors

¹. Altice FL et al.  Lancet, 2010
². Azar MM et al.  Drug Alcohol Depend, 2010
Common Complications Among HIV+ Drug Users

Table 3: Complications

<table>
<thead>
<tr>
<th>Organisms or cause</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and soft-tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Group A and other streptococci, <em>Staphylococcus aureus</em></td>
<td>Antistaphylococcal and antistreptococcal agents</td>
</tr>
<tr>
<td>Abscess</td>
<td>Same as for cellulitis</td>
<td>Same as for cellulitis</td>
</tr>
<tr>
<td>Necrotising fascitis</td>
<td>Polymicrobial, clostridial infections</td>
<td>Parenteral antibiotics to cover both gram-positive and gram-negative organisms</td>
</tr>
<tr>
<td>Septic thrombophlebitis</td>
<td><em>S aureus</em></td>
<td>Antistaphylococcal agents</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td><em>S aureus</em>, streptococci, enteric gram-negative rods</td>
<td>Antistaphylococcal agents until cultures grow; treat for 4-6 weeks</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Substance induced; associated with vascular spasm and cocaine and amphetamine-group substance use, increased pro-inflammatory response from HIV CVV potential small increases from ART regimens</td>
<td>Fibrinolytic agents and supportive care; lipid-lowering agents in those with hyperlipidaemia and smoking cessation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug-induced myocardial infarction associated with no evidence of endovascular stenosis on angiogram</td>
</tr>
</tbody>
</table>

- Skin Soft Tissue disorders
- Cardiovascular disorders
- Pulmonary disorders
- Liver disorders
- CNS disorders
- Renal disorders

*Altice, Lancet 2010*
Emerging Co-Morbidity Among HIV+ Drug Users as ART Increases

- AIDS-related mortality decreases
- Non-AIDS-related mortality increases
- Increases in:
  - End-stage liver disease
  - Viral hepatitis
  - Medication-related toxicity
  - Cardiovascular disease
  - Renal disease
  - Non-AIDS cancers
  - Tuberculosis mortality in endemic regions

Altice, Lancet 2010
Depression and Drug Use

Rounsaville, Arch Gen Psychiatry 1991.
Why Get Drug Users Into Drug Treatment?

• Improves access to and retention in HIV care, access to ART and ART adherence.
• Reduces the transmission of HIV and viral hepatitis
  – Primary and secondary prevention
• Reduces bacterial infections from injection-related behaviors
  – Skin & soft tissue infections, endovascular infections
• Reduces hospitalization and ED visits
• Improves poverty, employment and social functioning

Bruce et al, ID Clinics NA, 2007; Altice et al, Lancet 2010
Screening, Brief Intervention and Referral to Treatment (SBIRT)

• An evidence-based approach to reduce the negative consequences of alcohol or drug abuse
• Has effectively been used in primary care, ER and drug treatment programs
• Can be done by treating clinicians, nurses & case managers
• Is both efficacious and cost-effective
• Can be used as a computer module

Sources: Madras, DAD, 2009; Bohman, J Addict Med, 2008; Vaca, Subst Abuse, 2011
Substance Abuse Assessment Algorithm

Have you ever used (tried) ………. ?

- Alcohol or drug abuse suspected
  - Verbal screening (CAGE, 4-question tool)
    - Brief Verbal Screening (e.g. CAGE)
      - 0 Yes responses
        - Substance abuse/dependence unlikely
          - Continue periodic assessments
      - ≥1 Yes responses
        - Brief intervention (FRAMES, 6-step approach)
          - Self or family report of problematic alcohol or drug use, clinical markers (e.g., positive toxicology screen), or physical symptomatology during exam
CAGE Questionnaire

1. Have you ever felt you should **cut** down on your *drinking*? 
2. Have people **annoyed** you by criticizing your *drinking*? 
3. Have you ever felt bad or **guilty** about your *drinking*? 
4. Have you ever had *a drink* first thing in the morning to steady your nerves or get rid of a hangover (*Eye-opener*)?

<table>
<thead>
<tr>
<th>CAGE Score</th>
<th>Probability of Abuse or Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7%</td>
</tr>
<tr>
<td>1</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>72%</td>
</tr>
<tr>
<td>3</td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td>98%</td>
</tr>
</tbody>
</table>

Feedback: Address concerns about use: I’m concerned about how alcohol is affecting your liver” (your work, relationships, mood, behavior)

Responsibility: Emphasize that change is up to patient. “Only you can decide to make your life better. There are programs that can help you.”

Advice: Give your specific goals for the patient: “I believe it would be helpful for you to be evaluated at a treatment center.”

Menu: Offer alternatives to advice: “There are effective medications to treat your problems.” or “You could go to an AA (or NA) meeting or consider medications for treatment.”

Empathy: Listen with empathy: “I imagine talking about this is difficult.”

Self-efficacy: Encourage responses that support patient’s confidence: “Change can happen, but it takes time and commitment by you.”

Source: Hester & Miller, Handbook of Alcoholism Treatment Approaches. 2 ed. 1995
Evidence-Based Treatment for Substance Use Disorders

• Opioid Dependence
  – Methadone (pure opioid agonist) *
  – Buprenorphine (partial opioid agonist) *
  – Naltrexone (pure opioid antagonist)

• Alcohol Use Disorders
  – Naltrexone (oral, extended release)
  – Acamprosate (thrice daily)
  – Disulfuram (aversion therapy)

• Nicotine Dependence
  – Nicotine replacement (patches, gum, vaporized)
  – Varenicline

Altice et al, Lancet, 2010
## Club Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical effect</th>
<th>Route</th>
<th>Effect on HIV</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methamphetamine (rINN and amphetamine group substances)</td>
<td>CNS stimulation; increased alertness and energy; high doses induce euphoria, enhance self-esteem, and increase sexual pleasure; physiologically causes increased heart rate and blood pressure, vasoconstriction (including cerebrovascular events), bronchodilation, and hyperglycaemia; neurotoxic resulting in permanent brain damage</td>
<td>Injection; inhalation; per rectum</td>
<td>Decreases access to and use of care, decreased prescription of ART, decreased adherence to ART</td>
<td>None</td>
</tr>
<tr>
<td>MDMA</td>
<td>With overdose: serotonin syndrome, stimulant psychosis, and/or hypertensive crisis, cognitive and memory impairment, acute delirium, cardiac arrhythmias or infarction, coma; profound depression several days after use</td>
<td>Oral (tablet)</td>
<td>Decreased adherence to ART on days of MDMA use</td>
<td>None</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Hypertension, cardiac arrhythmias, cognitive impairment</td>
<td>Injection; inhalation (sniffed or smoked)</td>
<td>Not known</td>
<td>None</td>
</tr>
<tr>
<td>Gamma-hydroxybutyrate</td>
<td>Oversedation, coma, death, seizures, hypotension and shock, psychosis and agitation</td>
<td>Oral (liquid)</td>
<td>Not known, but likely similar to alcohol</td>
<td>None</td>
</tr>
<tr>
<td>“G”</td>
<td></td>
<td>Inhalation (liquid)</td>
<td>Associated with increased HIV risk behaviours</td>
<td>None</td>
</tr>
<tr>
<td>Nitrates/nitrates (poppers)</td>
<td>Methaemoglobinemia, haemolytic anaemia (especially in those with G6PD deficiency), hypotension, cardiac arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Altice FL, Lancet, 2010**

**Colfax G, Lancet, 2010**
Prevalence of Club-Drug Use Among MSM

Source: MMWR, 2006

* Methamphetamine, ketamine, GHB, MDMA, poppers
Club Drugs and HIV Risk

Non-injection substance use is associated with:

- ↑ Sex partners
- ↑ Unprotected sex
- ↑ Risk of STDs
- ↑ Risk of HIV infection

...data most consistently show these associations with methamphetamine and popper use...

Colfax, CID, 2006
Methadone Maintenance

• Widely adopted in many communities
• Associated with reductions in opioid use, HIV risk behaviors and many improved secondary outcomes
• Highly regulated, specialized licensing and may provide an array of services
• Often not linked to onsite medical care (lack of integration or coordination)
• Patients often discharged from program
• Does not encourage patient autonomy

Amato, Cochrane Database Syst Rev, 2011
Methadone Interactions

- Drug interactions known
  - Increases ZDV levels (41%)
  - No effect on TDF, ABC, DDI-EC, D4T, 3TC, FTC
  - Drugs associated with decreases in methadone levels (may precipitate withdrawal) – induce \( \text{P}_{450} \)
    - NNRTIs: NVP, EFV, ETR
    - PIs: LPV/r,* NFV,* TPV, DRV
  - No effect with ATV, IDV, RTV
  - Not studied in f-APV, SQV, MRV, RTG, RLP

Altice, Lancet, 2010
Opiate Withdrawal and Increasing Methadone Dose

McCance-Katz, Am J Addiction, 2004
Management of Suspected Methadone Drug Interactions

• Withdrawal symptoms in methadone maintenance patients started on new ARV agent
  – Warn methadone patient before starting ARV
  – Raise doses in 10 mg increments every 2–3 days (20 mg with severe withdrawal)
    or
  – Change ARV agent

– Consider obtaining trough methadone levels

• Consider reducing methadone dose for excessive drowsiness

Bruce, JAIDS, 2006
Buprenorphine

- Partial opioid agonist/antagonist
- Avoid if significant pain syndrome requiring opioids
- Long half-life (daily or every other day)
- Often co-administered sublingually with naloxone
- Not associated with significant diversion or abuse
- May be prescribed by the primary physician if 8 hour course completed: limited patients 30 → 100
- Efficacy similar to methadone
- Metabolized by CYP 3A4 but not 2D6

Altice, CID, 2006; Mattick, Cochrane Review, 2008
Clinical Considerations for BPN Treatment in HIV+ Patients

- BPN administered sublingually QD or TIW
  - new SL strips
- May be provided in HIV clinical settings
- Allows for the coordination of medical and drug treatment care
- Switch to methadone or formulation without naloxone in pregnant patients
- Drug interactions not fully evaluated, but few expected
  - No significant withdrawal noted from EFV, LPV/r, TPV/r, yet marked decrease in BPN levels with EFV
  - May need to decrease dose with ATV/r

Bruce et al, JAIDS, 2006; Altice, Lancet, 2010
• Specific to those with substance use disorders
  – Integration of health services
  – Use of medication-assisted therapy (Methadone and Buprenorphine if opioid dependent)
  – Directly administered antiretroviral therapy (DAART)
  – DAART integrated into methadone treatment
Models for Integrating Buprenorphine Therapy into the Primary HIV Care Setting

Sanjay Basu, Duncan Smith-Rohrberg, R. Douglas Bruce, and Frederick L. Altice
AIDS Program, Section of Infectious Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

Policy analysis
Integration and co-location of HIV/AIDS, tuberculosis and drug treatment services

Laurie Sylla\textsuperscript{a}, R. Douglas Bruce\textsuperscript{a}, Adeeba Kamarulzaman\textsuperscript{b}, Frederick L. Altice\textsuperscript{a,*}


Clinical Infectious Diseases, 2006

International J Drug Policy, 2007
Steps in Organizational Change Toward Healthcare Integration

- Separate Sites
- Co-Located Services
- Partial Integration
- Complete Integration
HIV Treatment Outcomes Among HIV-Infected, Opioid-Dependent Patients Receiving Buprenorphine/Naloxone Treatment and HIV Care Settings: Results From a Multisite Study

Frederick L. Altice, MD, MA,* R. Douglas Bruce, MD, MA, MSc,* Gregory M. Lucas, MD, PhD,† Paula J. Lum, MD, MPH,‡ P. Todd Korthuis, MD, MPH,§ Tim P. Flanigan, MD,‖ Chinazo O. Cunningham, MD, MPH,¶ Lynn E. Sullivan, MD,* Pamela Vergara-Rodriguez, MD,** David A. Fiellin, MD,* Adan Cajina, MPH,†† Michael Botsko, MSW, MPhil,††† Vijay Nandi, MPH,§§ Marc Gourevitch, MD, MPH,¶¶¶ Ruth Finkelstein, ScD,§§ and the BHIVES Collaborative¶¶¶
Integration of BPN into HIV Clinical Care Settings (BHIVES Study)

- Prospective, cohort study of 295 HIV+ patients initiated BPN at 10 diverse HIV clinical care settings
- Subjects on ART (N=176, 60%) were more likely than those not on ART (N=119) to be older, heterosexual, have lower alcohol addiction severity scores and lower VL; they were less likely to be homeless and report sexual risk behaviors.
- Initiating BPN was associated with increased likelihood of receiving ART and increases in CD4 count (but not VL suppression) in a sample where 60% were on ART at baseline; longer retention on BPN was most effective in those not on ART at baseline

*Altice, JAIDS, 2011*
Compared to baseline: (*) p<0.05 for all quarters for being on antiretroviral therapy; (+) p=ns for all quarters for HIV-1 RNA<400 copies/mL

Altice, JAIDS, 2011
P<0.05 for all comparisons between subjects on BPN/NX < 3 Quarters and those on longer duration. Using GEE and incorporating being on BPN/NX 3 or 4 Quarters, β=1.34 95% CI: (1.18, 1.53).

P<0.5 for all comparisons between subjects on BPN/NX < 3 Quarters and those on longer duration and for comparisons from baseline. Using GEE and incorporating being on BPN/NX 3 or 4 Quarters, β=1.25 95% CI: (1.10, 1.42).
Naltrexone

• Complete opioid antagonist and effective for treatment of alcohol & opioid dependence
• Must be without chronic pain syndromes and abstinent from opiates before treatment
• Administered orally (QD or TIW) and through monthly depot injection (4cc)
• Has not been studied in HIV+ patients receiving ART, though no anticipated drug interactions

Altice et al, Lancet, 2010
Krupitzky, APA, 2009
Lobmaier, Cochrane Reviews, 2008
Summary of DAART

- New adherence guidelines from the International Association of Physicians in AIDS Care (IAPAC)
- DAART is recommended for individuals with substance use disorders based on 5 RCTs, but not recommended for general use\(^1\)
- Post-intervention outcomes in DAART trials remain problematic with regression to the mean; one trial documented clinical deterioration after DAART cessation\(^2,3\)
- Likely needed are transitional interventions

\(^1\textit{Thompson, Ann Int Med, 2012}; \ ^2\textit{Maru, JAIDS, 2008}; \ ^3\textit{Gross, Achive Int Med, 2010}\)
Randomized Controlled Trial of DAART Among HIV+ Drug Users in Community Settings

VL Response

CD4 Response

Altice, CID, 2007
DAART RCT: Released Prisoners

Altice, CROI, 2011
Summary

- HIV+ drug users have markedly increased medical, psychiatric and substance use co-morbidity, each of which can be effectively managed.
- Considerable challenges remain in the management of the HIV-infected drug user.
- Drug dependence and abuse is not going away!
- Necessity is the mother of invention!
- Despite these challenges, innovative strategies to integrate care and promote adherence and persistence are becoming increasingly available to optimize patient management.
Which of the following is **NOT** a recommended adherence intervention according to IAPAC guidelines specific for substance use disorders?

1. Directly administered antiretroviral therapy (DAART)
2. Medication-assisted therapy using methadone or buprenorphine
3. Beepers and reminders
4. Integrating DAART into methadone maintenance
5. Integrating health services
Which of the following is most likely to have a clinically significant pharmacokinetic interaction with NNRTIs?

1. Acamprosate
2. Naltexone
3. Methadone
4. Buprenorphine
5. None of the above
In a patient receiving methadone 120 mg per day and experiences diarrhea, diaphoresis, chills (no fevers or rash) and myalgias 5 days after starting a new ART regimen, which of the following are correct?

1. Tell them to stop their new medications secondary to hypersensitivity reaction
2. Check for signs of opioid withdrawal
3. Tell them it is the flu and to drink lots of fluids and that it will go away soon
4. Call the methadone program and ask the staff to increase methadone in 5-10 mg per day increments until symptoms resolve