Assessment and Management of Psychiatric Issues in the HIV Positive Patient

Carrie L. Ernst, MD
Assistant Professor of Psychiatry
Icahn School of Medicine at Mount Sinai
March 26, 2014
Disclosure

Author/royalties: American Psychiatric Publishing, Inc
Speaker’s Bureau (spouse): AstraZeneca Pharmaceuticals
Objectives

• Understand the mechanisms and manifestations of HIV infection of the central nervous system
• Describe the clinical presentations and differential diagnoses of HIV associated psychiatric comorbidities
• Understand the central role played by psychiatric issues in the assessment, presentation, and management of individuals with HIV
• Become familiar with special considerations in the use of standard psychiatric treatment modalities in the HIV-infected population
Epidemiology and Overview

Stages of HIV Infection

- **Stage 1**: No AIDS-defining condition + CD4 ≥500 cells/μL or CD4 ≥29%

- **Stage 2**: No AIDS-defining condition + CD4 200–499 cells/μL or CD4 14–28%

- **Stage 3 (AIDS)**: AIDS-defining condition or CD4 <200 cells/μL or CD4 <14%

- **Stage unknown**: No reported information on AIDS-defining conditions & no information available on CD4 count or percentage

CDC. *MMWR* 2008;57(RR-10):1–12.
HIV Prevalence and Incidence, 1980-2010 in US

www.cdc.gov/hiv/statistics
Estimated Number of AIDS Cases, Deaths, and Persons Living with AIDS, 1985-2010: US and Dependent Areas

Source: CDC, 2011
Estimated New HIV Infections in the United States, 2010

www.cdc.gov/hiv/statistics
New Diagnoses of HIV Infection among US Adults and Adolescents by Race/Ethnicity, 2008-2011

Source: CDC, 2011
Estimated Rate of New HIV Infections, 2010

- Male:
  - Black: 103.6
  - Hispanic: 45.5
  - White: 15.8

- Female:
  - Black: 38.1
  - Hispanic: 8.0
  - White: 1.9

Number of infections per 100,000 individuals

www.cdc.gov/hiv/statistics
New Diagnoses of HIV among Adults and Adolescents, by Transmission Category, 2008-2011: US and Dependent Areas

Source: CDC, 2011
Estimated New HIV Infections Among Heterosexuals, 2010, by Gender and Race/Ethnicity

Heterosexuals 12,100

Male 4,100
- B: Black - 2,700
- H: Hispanic - 780
- W: White - 620

Female 8,000
- B: Black - 5,300
- H: Hispanic - 1,200
- W: White - 1,300

B = Black  H = Hispanic  W = White

www.cdc.gov/hiv/statistics
Proportion of New HIV/AIDS Cases among US Adults and Adolescents, by Sex and Transmission Category 2011

Source: CDC, 2011
Percentage of AIDS Classifications among U.S. Adults and Adolescents with HIV Infection, by Race/Ethnicity and Year of Diagnosis, 1985-2011

Source: CDC, 2011
Percentage of AIDS Classifications among U.S. Adults and Adolescents with HIV Infection, by Transmission Category and Year of Diagnosis, 1985-2011

- Male-to-male sexual contact
- Injection drug use (IDU)
- Heterosexual contact
- Male-to-male sexual contact and IDU
- Other
Why HIV Psychiatry?

*Psychiatric issues play a central role in HIV epidemic*

- HIV as multisystem disease
  - CNS infection $\rightarrow$ neuropsychiatric symptoms
- Psychiatric disorders as vectors of HIV transmission
- Psychiatric issues a/w worse outcomes
- HIV as chronic illness
- Neuropsychiatric side effects of treatment
HIV Life Cycle & Drug Targets
HIV Life Cycle & Drug Targets

Source: Nat Med © 2003 Nature Publishing Group
Antiretroviral Therapy: 1987

Zidovudine (AZT)
## Antiretroviral Therapy: 2014

### Nucleoside Reverse Transcriptase Inhibitors
- Abacavir (Ziagen)
- Didanosine (Videx EC)
- Emtricitabine (Emtriva)
- Lamivudine (Epivir)
- Stavudine (Zerit)
- Tenofovir (Viread)
- Tenofovir/Emtricitabine (Truvada)
- Zidovudine (Retrovir, AZT)
- Lamivudine/Zidovudine (Combivir)
- Abacavir/Lamivudine (Epzicom)

### Non-Nucleoside Reverse Transcriptase Inhibitors
- Delavirdine (Rescriptor)
- Efavirenz (Sustiva)
- Etravirine (Intelence)
- Nevirapine (Viramune)
- Rilpivirine (Edurant)

### Protease Inhibitors
- Atazanavir (Reyataz)
- Darunavir (Prezista)
- Fosamprenavir (Lexiva)
- Amprenavir (Agenerase)
- Indinavir (Crixivan)
- Lopinavir/Ritonavir (Kaletra)
- Nelfinavir (Viracept)
- Ritonavir (Norvir)
- Saquinavir (Invirase)
- Tipranavir (Aptivus)

### Combination Products
- Atripla (efavirenz, emtricitabine, tenofovir)
- Complera (emtricitabine, rilpivirine, tenofovir)
- Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir)

### Fusion Inhibitors
- Enfuvirtide (Fuzeon)

### Entry Inhibitors
- Maraviroc (Selzentry)

### Integrase Inhibitors
- Raltegravir (Isentress)
- Dolutegravir (Tivicay)
- Elvitegravir (part of Stribild)
HIV Infection of the Central Nervous System
HIV Infection of the CNS

- HIV invades CNS within hours to days via infected monocytes (differentiate into macrophages)
- Cell free virus also enters CNS by infecting endothelial cells of blood brain barrier
- Infected macrophages infect other cells in CNS by direct contact
- Neurons are not directly infected
- Get further CNS viral replication in microglia and macrophages
- Direct & indirect neuronal damage occurs
  - Virally infected cells secrete neurotoxic inflammatory substances
  - Viral particles/proteins are directly neurotoxic
- HIV prefers subcortical structures- 1st basal ganglia
- CNS is independent reservoir of HIV replication
Model of HIV-related Neuronal Damage

Neuropsychiatric Syndromes: HIV-Associated Neurocognitive Disorder (HAND)

- **HIV-associated dementia (HAD)**
  - Acquired impairment in ≥2 cognitive domains
  - >2 SD from age-adjusted population norms
  - Caused by HIV
  - Marked impairment in ADLs

- **Mild neurocognitive disorder (MND)**
  - Similar to HAD except ≥1 SD from population norms with *some* impairment in ADLs

- **Asymptomatic neurocognitive impairment (ANI)**
  - Same neurocognitive impairment as MND but no impairment in ADLs
Neuropsychiatric Syndromes: HIV Associated Dementia (HAD)

Motor
- Unsteady gait/loss of balance
- Leg weakness
- Dropping things
- Tremors/poor handwriting
- Poor fine motor skills

Cognitive
- Poor visuospatial memory
- Poor visuomotor coordination
- Poor complex sequencing
- Impaired attention/concentration
- Impaired verbal memory
- Mental slowing

Affective
- Apathy
- Mania, new psychosis
- Irritability
- Risk factor for suicide

Behavioral
- Psychomotor slowing
- Personality change
- Social withdrawal
Epidemiology of HAND

- Pre-HAART: up to 40% prevalence of dementia
- Post-HAART: HAD uncommon but milder neurocognitive impairment common; 20-85% prevalence
- CHARTER Study\(^1\)
  - HAD: 2%
  - MND: 25%
  - Any HAND diagnosis: 50%

1. Heaton et al, Neurology 2010; 75:2087-2096
Risk Factors for HAND

- Low current CD4 count
- Nadir CD4 count
- High plasma or CSF viral load
- Anemia (?)
- Co-infection with Hepatitis C
- Extremes of age
- IVDU
- Metabolic & Cardiovascular factors

Rackstraw. Psychology, Health & Medicine, 16:5, 548-563, 2011
Screening for HAND

- Assess neurocognitive function early in all HIV patients
- Screen every 6-12 months if higher-risk patients, every 12-24 months in lower-risk patients
- Screen immediately if evidence of clinical deterioration or major change in clinical status
- Many proposed brief screens
- Neuropsychological testing if available or for selected patients
- Use screens with clinical information & risk profiles
- Assess adherence
- Psychosocial history + functional assessment
HIV Dementia Scale

Brief but sensitive screening instrument (sensitivity 80%, specificity 91%, PPD 78%)

Max Score
(6) Psychomotor speed (timed written alphabet)
(4) Memory (recall of 4 words at 5 minutes)
(4) Attention (antisaccadic eye movements)
(2) Construction (timed cube copy)

Score ≤ 10 indicates possible HAD

Work-up for the HIV patient with Neurocognitive Impairment

- Thorough medical and neurological history
- Developmental history
- Substance use- past and present
- Psychiatric assessment (depression, anxiety, PTSD)
- Neurological examination
- Laboratory studies: CD4 cell count, HIV RNA, RPR, HCV Antibody, TSH, testosterone profile, metabolic panel, hepatic function tests, B12, folate
- CSF Analysis
- Brain MRI

Modified from The Mind Exchange Working Group; CID 2013:56
HIV Dementia: Neuroimaging

A: MRI-T2
B: MRI-FLAIR
Management of HAND

- Combination ARV therapy
- Assess and improve adherence to ARVs
- Must decide if brain penetration is a crucial component in the design of future HIV therapy
- Treat co-morbidities (Hepatitis C, cardiovascular risk factors)
- Monitor frequently, especially if higher risk
### Management of HIV Dementia: Antiretrovirals and CNS penetration

<table>
<thead>
<tr>
<th>Increasing CNS Penetration</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>nRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zalcitabine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir/r</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tipranavir/r</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir/r</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management of HAND: Adjunctive Pharmacological Treatment

- Minocycline
- Memantine
- Cholinesterase inhibitors
- Lithium
- Valproic Acid
- SSRIs
- Psychostimulants
- Modafinil
Management of HIV Dementia: Non-pharmacological

- Simplify complex tasks (ex- drug regimens)
- Use pill boxes, diaries, timers
- Repeat information
- Write out instructions
- Educate caregivers and patients
- Maintain orientation cues
- Keep environment familiar
- Structured routines and activities
- Cognitive stimulation
Additional CNS Complications Accompanying HIV Infection

- Infectious: CMV, syphilis, HSV, TB, toxoplasmosis, progressive multifocal leukoencephalopathy (PML), fungal
- Oncological: Lymphoma, metastatic disease
- Endocrine/Nutritional: thyroid, addison’s, B12 deficiency, anemia
- Drug intoxication or withdrawal
- Antiretroviral medications and drug-drug interactions
- Psychiatric
HIV-Associated Psychiatric Comorbidities
HIV and Psychiatric Illness: HIV Cost and Services Utilization Study

- Nationally representative probability sample of HIV-infected adults receiving medical care in US

- Screened for symptoms of MDD, dysthymia, GAD, panic attacks, and illicit drug use and dependence within the past year

- N = 2864

- 77.4% male, 49.2% white, 40.4% heterosexual

Bing et al, Arch Gen Psychiatry 2001; 58:721-728
## HIV Cost and Services Utilization Study: Results

### Table: % Screening Positive (95% CI)

<table>
<thead>
<tr>
<th>Condition</th>
<th>HCSUS (N = 2864)</th>
<th>NHSDA (N = 22,181)</th>
<th>NCS-R (N= 9282)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression</td>
<td>36.0 (33.6-38.3)</td>
<td>7.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>26.5 (23.5-29.5)</td>
<td>...</td>
<td>1.5</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>15.8 (14.0-17.7)</td>
<td>2.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Panic attack</td>
<td>10.5 (8.0-13.0)</td>
<td>2.5</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; HCSUS, HIV [human immunodeficiency virus] Cost and Services Utilization Study; NHSDA, National Household Survey on Drug Abuse; and ellipses, these conditions were not assessed.

1. Bing et al, Arch Gen Psychiatry 2001; 58:721-728
2. Kessler et al, Arch Gen Psychiatry 2005; 62:617-627
HIV Cost and Services Utilization Study: Results

Risk factors associated with screening positive for a psychiatric disorder:

• Age < 35 years
• Caucasian
• Living alone or with non-partner
• Unemployed or disabled
• Greater # of HIV-related symptoms
• Illicit drug use or dependence (excluding marijuana)
• Heavy alcohol use

Bing et al, Arch Gen Psychiatry 2001; 58:721-728
AIDS Healthcare Foundation
Retrospective Cohort Study

• N = 7834 HIV-positive patients receiving treatment in ambulatory care clinics in California

• Any psychiatric condition: 53%
• Any mood-related disorder: 23%
• Any anxiety-related disorder: 16%
• Any substance-related disorder: 19%

Parhami et al, AIDS Behav 2012
Depression and HIV

• Most common psychiatric manifestation associated with HIV Infection
• Prevalence: 18-81%
• HCSUS: 36% MDD, 26.5% dysthymia¹
• HCSUS re-estimation of data: 22% MDD, 5% dysthymia²
• Meta-analysis: 2x increased risk MDD in HIV pts³
• HIV+ women > men
• ↑ risk if advanced disease, hx MDD, psychosocial stressors
• Atypical features
• Associated with poor ARV adherence and worse outcomes

1. Bing et al, Arch Gen Psychiatry 2001; 58: 721-7281
Depression and HIV

Depression

Demoralization, Stigma, Isolation
Debility, disability
Substance Abuse
Cognitive Impairment
Direct cortical & subcortical injury
Pro-inflammatory cytokines

Risk Behaviors
Substance Abuse
Cognitive Impairment
Poor Adherence
↑ Mortality
↑ Cortisol
Faster disease progression
↓ # and activity of NK & CD4 cells

↑ Mortality
↑ Cortisol
Faster disease progression
↓ # and activity of NK & CD4 cells

HIV/AIDS
HIV-Related Mortality in Depressed Women

HIV Epidemiology Research Study (n= 765)

8% mortality
16% mortality
23% mortality

Ickovics et al, JAMA 2001; 285:1466-1474

(log-rank test: \( P < .001 \))
Mania and HIV

- **Prevalence:** 1-2% in HIV, 4-8% in AIDS

- Associated with CD4+ < 100, HAD, MCMD

- **Unique Features of HIV-associated mania:**
  - Irritability > Euphoria
  - Chronic > Episodic
  - Later age of onset
  - Increased talkativeness
  - No history mood disorder
  - Higher rates of HAD
  - No family history
Mania and HIV

- Impulsivity/Risk Behaviors
- Substance Abuse
- Cognitive Impairment
- Poor Adherence
- ↑ Cortisol

Mania

Poor adherence
Increased stress
Hypothyroidism
Direct CNS effects (cytokines, caudate)

HIV/AIDS
Anxiety Disorders & HIV

- Prevalence: 10-72%
  - HCSUS: 15.8% GAD, 10.5% panic disorder
- Increase with illness progression
- Pre-existing anxiety disorders exacerbated
- Associated with: ↓ Adherence, ↑ Risk behaviors and ↑ Substance abuse
- May affect immune function
  - PTSD a/w ↓CD4+, CD4+/CD8+, & NK cells
  - ↑ Cortisol → ↓ immune function
  - PTSD a/w disturbed regulation of HPA axis & sympathoadrenomedullary system
Illness Milestones

- HIV Testing
- News of HIV positive status
- Appearance of 1st illness symptoms
- Onset AIDS-defining illness
- Disclosure of HIV status
- Initiation of ARVs
- ↓ CD4 counts/↑viral load
- ↓ Cognition
- Functional disability
- Bereavement
- Death/Dying preparation
Psychotic Disorders and HIV

• Can be primary or secondary
• HIV prevalence among people with serious mental illness is greater than that of the general population
  • 2001 data: 3.1% prevalence (8x greater than general population)\textsuperscript{1}
• Schizophrenia is a risk factor for HIV
• Poor adherence
• Many barriers to medical care
• Longer medical hospitalizations
• ↑ suicidality
• May decompensate upon diagnosis
• More sensitive to extrapyramidal side effects of antipsychotics

\textsuperscript{1} Rosenberg et al. Am J Public Health 2001; 91:31-37
Substance Abuse and HIV

- Substance abuse ↑ risk for HIV transmission
- HIV Cost & Service Utilization Study: 50% of HIV+ individuals reported drug use in past 12 mo

**Table 2. Percentage of People Screening Positive for Conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>HCSUS (N = 2864)</th>
<th>NHSDA (N = 22,181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drug use</td>
<td>49.9</td>
<td>89.7</td>
</tr>
<tr>
<td>Marijuana use only/no dependence</td>
<td>12.1</td>
<td>...</td>
</tr>
<tr>
<td>Other drug use/no dependence</td>
<td>25.6 (22.1-29.1)</td>
<td>...</td>
</tr>
<tr>
<td>Drug dependence</td>
<td>12.5 (10.2-14.8)</td>
<td>...</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; HCSUS, HIV [human immunodeficiency virus] Cost and Services Utilization Study; NHSDA, National Household Survey on Drug Abuse; and ellipses, these conditions were not assessed.

Bing et al, Arch Gen Psychiatry 2001; 58:721-728
Substance Abuse and HIV

- Poor adherence
- Less likely to access HAART
- Diagnosed at more advanced stage
- More opportunistic Infections
- High risk sexual and injection behaviors
- Interactions with HAART
- ↑ risk cognitive impairment/dementia
Substance Abuse & HIV: Effects on Immune Function

- **Cocaine**: augments HIV replication, ↑ permeability of BBB to HIV
- **Alcohol**: immunosuppressive; enhances HIV infection of lymphocytes
- **Opioids**: ↑ ability of HIV to infect target cells; Morphine inhibits CD8+ T-cell-mediated anti-HIV activity in latently infected immune cells
- **Methamphetamine**: may ↑ viral replication and mutation rates
Additional Psychiatric Issues Associated with HIV

- Insomnia (30-40%)
- Suicide
- Fatigue (30-65%)
- Bereavement
- Adjustment Disorders
- Psycho-dynamic Themes
Psychodynamic Themes

- Suffering as sign of weakness in face of adversity
- Guilt over getting HIV
- Guilt over infecting others
- Anger at source of disease, oneself, God
- Precipitous revelation of hidden sexual or drug abuse behavior → shame and self loathing
- Stigma leading to rejection or abandonment by others, feel like lepers
- Some become hopeless and nihilistic and refuse tx
How Would You Differentiate Between Primary and Secondary Psychiatric Disorders?

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Personal history of similar episodes</td>
<td>• No personal or family psych hx</td>
</tr>
<tr>
<td>• Family psychiatric history</td>
<td>• More chronic</td>
</tr>
<tr>
<td>• Episodic</td>
<td>• Neuro-cognitive deficits</td>
</tr>
<tr>
<td>• Neuro-cognitive symptoms rare</td>
<td>• Fluctuating consciousness</td>
</tr>
<tr>
<td>• Typical features</td>
<td>• Evidence of organ dysfunction</td>
</tr>
<tr>
<td>• Uniquely psychiatric symptoms (ex- hopelessness, helplessness, worthlessness, apathy)</td>
<td>• Prominent neurovegetative symptoms</td>
</tr>
<tr>
<td></td>
<td>• Personality change</td>
</tr>
<tr>
<td></td>
<td>• Temporal association</td>
</tr>
<tr>
<td></td>
<td>• Atypical Features</td>
</tr>
<tr>
<td></td>
<td>• Age of onset &gt;40</td>
</tr>
<tr>
<td></td>
<td>• Abnormal vital signs</td>
</tr>
<tr>
<td></td>
<td>• Lower CD4 counts &amp; higher VLs</td>
</tr>
</tbody>
</table>
Differential Diagnosis of Psychiatric Symptoms in HIV Patients

• Direct CNS manifestation of HIV
• CNS infections & malignancies
• Endocrine/Metabolic disturbances
• HAND
• Vitamin Deficiencies
• Drug intoxication or withdrawal
• Cardiovascular or pulmonary disease
• Medications
Neuropsychiatric Side Effects of ARVs

• **Efavirenz**: 50% develop neuropsychiatric sx
  Dizziness, headache, ↓concentration, confusion, insomnia, nightmares, anxiety, amnesia, depersonalization, euphoria, depression, hallucinations, SI

• **NRTIs**:
  - **Didanosine**: anxiety, insomnia, seizures, confusion
  - **Lamivudine**: insomnia, mania
  - **Stavudine**: h/a, malaise, depression, mania, insomnia, seizures
  - **Zidovudine**: h/a, malaise, insomnia, vivid dreams, AH agitation, mania, confusion, depression
Management of Psychiatric Disorders in HIV patients
Effects of Mental Health Interventions for HIV Patients

• Improved ARV adherence
• Increased CD4 cell count
• Decreased risky sexual behaviors
• Decreased suicidality
• Improved quality of life
• Decreased medical complications
• Improved prognosis (?)

Springer et al. AIDS Care 2009; 21:976-983
Pharmacological Considerations for HIV Patients

• Psychotropic-ARV interactions
  • PIs
    • Substrates, inducers, inhibitors of multiple CYP450 isoenzymes
    • Ritonavir is CYP3A4 & CYP2D6 inhibitor
  • NNRTIs
    • CYP3A4 substrates & inducers
    • CYP2C9 & 2C19 inhibitors
    • Most psychotropics: CYP 2D6 & 3A4 substrates and/or inhibitors
• Increased or atypical adverse effects
• Neuropsychiatric side effects of ARVs
• Adherence (pill burden, cognitive deficits)

## Treatment of MDD Associated with HIV: Antidepressant Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo &lt;33%</th>
<th>Placebo &gt;33%</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markowitz 1998 TCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabkin 1994 TCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zisook 1998 SSRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elliot 1998 SSRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elliot 1998 TCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardised mean difference (95% CI)</td>
<td>0.44 (-0.12, 1.00)</td>
<td>0.04 (-0.97, 0.88)</td>
<td>0.57 (0.28, 0.85)</td>
</tr>
<tr>
<td>% Weight</td>
<td>13.1</td>
<td>7.0</td>
<td>100.0</td>
</tr>
<tr>
<td>(Imipramine)</td>
<td>(Fluoxetine)</td>
<td>(Fluoxetine)</td>
<td></td>
</tr>
<tr>
<td>(Fluoxetine)</td>
<td>(Paroxetine vs Imipramine)</td>
<td>(Fluoxetine)</td>
<td></td>
</tr>
</tbody>
</table>

Himelhoch and Medoff, AIDS Patient Care STDS, 2005; 19: 813-822
<table>
<thead>
<tr>
<th></th>
<th>SSRIs</th>
<th>TCAs</th>
<th>Other Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs</strong></td>
<td>Fluoxetine and fluvoxamine may ↑ NNRTIs (3A4, 2D6)</td>
<td></td>
<td>Efavirenz may ↑ bupropion</td>
</tr>
<tr>
<td></td>
<td>Nevirapine may ↓ fluoxetine (3A4)</td>
<td></td>
<td>St. John’s Wort may ↓ NNRTIs (3A4)</td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td>Most SSRIs may ↑ PIs (2D6, 3A4)</td>
<td>PIs ↑ most TCAs (2D6)</td>
<td>PIs may ↑ trazodone, duloxetine, venlafaxine, mirtazapine, modafinil, &amp; stimulants (3A4, 2D6)</td>
</tr>
<tr>
<td></td>
<td>PIs may ↑ most SSRIs (2D6)</td>
<td></td>
<td>Ritonavir may ↑ bupropion</td>
</tr>
<tr>
<td></td>
<td><em>Potential for serotonin syndrome</em></td>
<td></td>
<td>St. John’s Wort ↓ PIs (3A4)</td>
</tr>
</tbody>
</table>
Novel Antidepressants

- **Psychostimulants**: may help depression + fatigue
- **Testosterone**: potential benefits for depressive symptoms and fatigue in hypogonadal patients with AIDS wasting
- **DHEA**: may help milder forms of depression
- **Modafanil/Armodafinil**: Open-label & RCT data for fatigue in HIV patients
Additional Effects of Antidepressants in HIV patients

- Improved pain control (SNRIs)
- Improved sleep (mirtazapine)
- Improved appetite/weight (mirtazapine, stimulants)
- Improved energy (stimulants, modafinil, bupropion)
- Decreased nausea (mirtazapine)
Psychotherapy for Depression in HIV patients

- Interpersonal psychotherapy
- Cognitive behavioral therapy
- Cognitive behavioral stress management group
- Brief supportive psychotherapy
Use of Antipsychotics in HIV Patients

• Appear to be efficacious but not well studied
• More sensitive to extrapyramidal side effects
• PIs may ↑ typical antipsychotics, aripiprazole, quetiapine, risperidone, ziprasidone (3A4, 2D6)
  • Pimozide contraindicated with PIs (cardiac)
• PIs may ↓ olanzapine (1A2)
• In late stage infection, start low, go slow
• Overlapping metabolic effects
• Bone marrow toxicity with Clozapine and Zidovudine
Use of Mood Stabilizers in HIV Patients

- Additive renal toxicity from lithium + tenofovir
- Lithium may improve neuropsychological function
- Data suggesting valproate increases HIV replication in vitro (but not found in vivo)
- Hepatotoxicity from valproate
- Lamotrigine effective in HIV-associated neuropathic pain
- Avoid Carbamazepine
## Psychotropic-HAART Interactions: Mood Stabilizers

<table>
<thead>
<tr>
<th></th>
<th>Valproate</th>
<th>Carbamazepine Oxcarbazepine</th>
<th>Other AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTIs</td>
<td></td>
<td>CBZ may ↓ NNRTIs</td>
<td></td>
</tr>
<tr>
<td>NRTIs</td>
<td>Valproate may ↑ zidovudine (gluc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td>PIs may ↓ valproate (gluc)</td>
<td>CBZ ↓ PIs (3A4) PIs ↑ CBZ (3A4)</td>
<td>PIs may ↓ lamotrigine (gluc)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>CBZ ↓ maraviroc</td>
<td></td>
</tr>
</tbody>
</table>
Use of Sedative/hypnotics in HIV Patients

- HIV patients more sensitive to side effects
- Limited data examining benzodiazepine efficacy for anxiety treatment in HIV
- Most sedative/hypnotics have extensive CYP3A4 metabolism
- Decreased benzodiazepine and non-benzodiazepine hypnotic clearance when administered with PI
- Midazolam & triazolam contraindicated with PI or efavirenz
- Lorazepam, clonazepam preferable
Helpful Resources for Drug-Drug Interactions

Micromedex
Epocrates Rx
http://www.drug-interactions.com
http://www.hiv-druginteractions.org
http://hivinsite.ucsf.edu
Other Aspects of Psychiatric Care for HIV Patients

- Therapeutic relationship
- Care coordination
- Treatment adherence
- Health education
- Prevention of high risk behaviors
- Coping with disability and chronic illness
- Work with families, friends and partners
- Integration of religion and/or spirituality
- Expanding support network
Conclusions

- Among new HIV/AIDS cases, an increasing percentage comes from unprotected heterosexual activity and higher-risk demographic groups.
- Common neuropsychiatric syndromes associated with HIV include cognitive dysfunction, depression, psychosis, substance abuse and suicidality.
- All HIV patients should be screened for cognitive dysfunction, regardless of virologic control.
- Sexual and drug use histories should be incorporated into routine psychiatric evaluations and HIV testing should be considered as appropriate.
Conclusions (continued)

- Traditional psychotropic medications are effective but require closer monitoring due to higher risk for adverse effects and drug-drug interactions.
- Antiretrovirals carry risk of neuropsychiatric side effects and risk/benefit analyses are important.
- Medical, psychiatric and substance use treatment services should be integrated with efforts directed at improving access to care.
- Skill-based risk reduction strategies designed for the seriously mentally ill and cognitive impaired should be considered.