Assessment and Management of Psychiatric Issues in the HIV Positive Patient

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## Disclosure

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# **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**

Source: Centers for Disease Control and Prevention. *HIV Surveillance Report, 2011; vol. 23. http://www.cdc.gov/hiv/topics/surveillance/resources/rep orts/. Published February 2013.* 



# **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%</li>
- 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



#### Estimated Number of AIDS Cases, Deaths, and Persons Living with AIDS, 1985-2010: US and Dependent Areas



# Estimated New HIV Infections in the United States, 2010



#### **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



#### New Diagnoses of HIV among Adults and Adolescents, by Transmission Category, 2008-2011: US and Dependent Areas



### Estimated New HIV Infections Among Heterosexuals, 2010, by Gender and Race/Ethnicity





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



# Why HIV Psychiatry?

Psychiatric issues play a central role in HIV epidemic

- HIV as multisystem disease
  CNS infection → 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**



# **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/Emtrictabine (Truvada) Zidovudine (Retrovir, AZT)

Lamivudine/Zidovudine (Combivir)

Abacavir/Lamivudine (Epzicom)

#### **Entry Inhibitors**

Maraviroc (Selzentry)

#### *Non- Nucleoside Reverse Transcriptase Inhibitors*

Delavirdine (Rescriptor) Efavirenz (Sustiva) Etravirine (Intelence) Nevirapine (Viramune) Rilpivirine (Edurant)

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

**Fusion Inhibitors** 

Enfuvirtide (Fuzeon)

#### **Protease Inhibitors**

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

#### 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- 1<sup>st</sup> basal ganglia
- CNS is independent reservoir of HIV replication



# **Model of HIV-related Neuronal** Damage



Kaul et al, Nature 410: 988-994, 2001

### Neuropsychiatric Syndromes: HIV-Associated Neurocognitive Disorder (HAND)

- HIV-associated dementa (HAD)
  - Acquired impairment in  $\geq$ 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

### Affective

Apathy Mania, new psychosis Irritability Risk factor for suicide

# Cognitive

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

# 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<sup>1</sup>
  - 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

Power et al. J AIDS 1995; 8:273-278.





#### 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





#### **HIV Dementia: Neuroimaging**





MRI-T2

#### **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

Increasing CNS Penetration			
	0	0.5	1
nRTIs	Didanosine	Emtricitabine	Abacavir
	Tenofovir	Lamivudine	Zidovudine
	Adefovir	Stavudine	
	Zalcitabine		
NNRTIs		Efavirenz	Delavirdine
			Nevirapine
Pls	Nelfinavir	Atazanavir	Amprenavir/r
	Ritonavir	Fosamprenavir	Fosamprenavir/r
	Saquinavir	Indinavir	Indinavir/r
	Saquinavir/r	Atazanavir/r	Lopinavir/r
	Tipranavir/r		Darunavir
Other	Enfuvirtide	Raltegravir	Maraviroc
		Elvitegravir	

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Adapted from Smurzynski et al AIDS. 2011 January 28; 25(3): 357–365.

### 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 HIVinfected 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

	is buildening it		
Condition	HCSUS (N = 2864)	NHSDA (N = 22 181)	NCS-R <sup>2</sup> (N= 9282)
Major depression	36.0 (33.6-38.3)	7.6	6.7
Dysthymia	26.5 (23.5-29.5)	(4.8.6.)	1.5
Generalized anxiety disorder	15.8 (14.0-17.7)	2.1	3.1
Panic attack	10.5 (8.0-13.0)	2.5	2.7

"Cl 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%



### **Depression and HIV**

- Most common psychiatric manifestation associated with HIV Infection
- Prevalence: 18-81%
- HCSUS: 36% MDD, 26.5% dysthymia<sup>1</sup>
- HCSUS re-estimation of data: 22% MDD, 5% dysthymia<sup>2</sup>
- Meta-analysis: 2x increased risk MDD in HIV pts<sup>3</sup>
- 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
- 2. Orlando et al, Int J Methods Psychiatr Res 2002; 11: 75-82
- 3. Ciesla and Roberts, Am J Psychiatry 2001; 158: 725-730



### **Depression and HIV**

Depression

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

**HIV/AIDS** 

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

### HIV-Related Mortality in Depressed Women

HIV Epidemiology Research Study (n= 765)



### Mania and HIV

- *Prevalence:* 1-2% in HIV, 4-8% in AIDS
- Associated with CD4+ < 100, HAD, MCMD</li>
- Unique Features of HIV-associated mania: Irritability > Euphoria Chronic > Episodic Later age of onset Increased talkativeness

   Unique Features of HIV-associated mania: No history mood disorder Higher rates of HAD No family history



### Mania and HIV

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

**HIV/AIDS** 

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

Mania



### **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
  - $\uparrow$  Cortisol  $\rightarrow \downarrow$  immune function
  - PTSD a/w disturbed regulation of HPA axis & sympathoadrenomedullary system





### **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)<sup>1</sup>
- 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



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\*

Condition	% Screening Positive (95% CI)		
	HCSUS (N = 2864)	NHSDA (N = 22 181)	
No drug use	49.9 (46.0-53.71)	89.7	
Marijuana use only/ no dependence	12.1 (10.2-14.8)	4.4.4	
Other drug use/ no dependence	25.6 (22.1-29.1)	4.314	
Drug dependence	12.5 (10.2-14.8)	(15576)	

\*Cl 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



### Substance Abuse & HIV: Effects on Immune Function

- Cocaine: augments HIV replication,<sup>↑</sup>
   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





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### **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?

#### Primary

- Personal history of similar episodes
- Family psychiatric history
- Episodic
- Neuro-cognitive symptoms rare
- Typical features
- Uniquely psychiatric symptoms (ex- hopelessness, helplessess, worthlessness, apathy)

#### Secondary

- No personal or family psych hx
- More chronic
- Neuro-cognitive deficits
- Fluctuating consciousness
- Evidence of organ dysfunction
- Prominent neurovegetative symptoms
- Personality change
- Temporal association
- Atypical Features
- Age of onset >40
- Abnormal vital signs
- Lower CD4 counts & higher VLs

## 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 (?)





### Pharmacological Considerations for HIV Patients

- Psychotropic-ARV interactions
  - Pls
    - 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)



Reviewed by Gallego et al, AIDS Rev 2012; 14:101-11

# **Treatment of MDD Associated with HIV: Antidepressant Efficacy**



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Himelhoch and Medoff, AIDS Patient Care STDS, 2005; 19: 813-822

### **Psychotropic-HAART Interactions: Antidepressants**

	SSRIs	TCAs	Other Agents
NNRTIS F	Fluoxetine and		Efavirenz may ↑ buproprion
	NNRTIS (3A4, 2D6)		St. John's Wort may ↓ NNRTIs (3A4)
	Nevirapine may ↓ fluoxetine (3A4)		
Pls	Most SSRIs may ↑ PIs (2D6, 3A4)	Pls ↑ most TCAs (2D6)	Pls may ↑ trazodone, duloxetine, venlafaxine,
	PIs may ↑ most SSRIs (2D6)		mirtazapine, modafinil, & stimulants (3A4, 2D6)
	Potential for serotonin syndrome		Ritonavir may ↑ buproprion
			St. John's Wort ↓ PIs (3A4)

### **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, buproprion)
- 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)
- Hepatoxicity from valproate
- Lamotrigine effective in HIV-associated neuropathic pain
- Avoid Carbamazepine



### **Psychotropic-HAART Interactions: Mood Stabilizers**

	Valproate	Carbamazepine Oxcarbazepine	Other AEDs
NNRTIS		CBZ may ↓ NNRTIs	
NRTIs	Valproate may ↑ zidovudine (gluc)		
Pls	PIs may ↓ valproate (gluc)	CBZ ↓ PIs (3A4) PIs ↑ CBZ (3A4)	PIs may ↓ lamotrigine (gluc)
Other		CBZ ↓ maraviroc	



### 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 higherrisk 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

