Disclosures

• I have no Relevant Financial Relationships with Commercial Interests, but I will offer two irrelevant disclosures to make up for my lack of relevant ones.
  – 1. I am starting to have a few doubts about this managed care thing
  – 2. I think George Harrison was the best Beatle
Objectives

• Describe the aging nature of the patients with HIV and AIDS
• Discuss depression in patients with HIV
• Describe the cognitive impairment associate with aging and HIV
Two ways to think about depression

Categorical
- Demoralization (Sadness/Grief)
- Major Depression

Dimensional
- Demoralization (Sadness/Grief)
- Severity
- Major Depression
Demoralization

- Distractible from loss (Maintains rewards from activity)
- Initial insomnia
- No family history
- Unique episode
- Stable life course
- Responsive to positive events

Major Depression

- Anhedonia (Pervasive loss of rewards from activity)
- AM insomnia
- Family history
- Similar episodes
- Disrupted life course
- Unresponsive to positive events
Decreased neurogenesis in stressed rats that act depressed

Mean Standardized Improvement as a Function of Initial Severity, Treatment Group

Patients With ≥50% Improvement on SSRI, TCA, or Placebo

## Prevalence of Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Depression Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiologic Catchment Area Study</td>
<td>4-6</td>
</tr>
<tr>
<td>National Comorbidity Survey</td>
<td>16</td>
</tr>
</tbody>
</table>
Reward sensitivity
Cytokines
Stress transmitters
Immune system
(Poor adherence and treatment failure)

Depression

HIV

Reward sensitivity
Cytokines
Stress transmitters
Immune system
(Poor adherence and treatment failure)
More Rapid Discontinuation of ART in Depressed Persons

Bangsberg DR et al. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; December 16-21, 2001; Chicago, Ill. Abstract 1721.

BDI ≥ 15
BDI ≥ 15-censored
BDI < 15
BDI < 15-censored

Cumulative survival

$P = 0.0001$

Months on highly active ART

Bangsberg DR et al. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; December 16-21, 2001; Chicago, Ill. Abstract 1721.
Depression Decreases AIDS-Free Survival in Patients on ART

- HERS cohort: 765 participants
- Longitudinal depression (CES-D): none, intermittent, chronic
- Mortality predictors: depression, CD4 cell count, ART duration, age

HIV

Neuroinflammation
Accelerated Aging
Co-morbidities

HIV promotes neuroinflammation and co-morbidities which can result in accelerated cognitive aging.

HAART

If HAART can cross the blood brain barrier, it can reduce the negative effects of HIV in the brain.

Treatment of Co-morbidities

Treating co-morbidities can reduce their negative impact on brain health.

Treatment of Mood

Depression and anxiety negatively impact brain health; thus, treating such mood problems can improve brain health.

Psychostimulants

Several medications have been shown to be effective in promoting better cognitive functioning in adults with HIV.

Cognitive Remediation Therapy

Cognitive remediation therapies have been used in many clinical populations; a recent study shows it may be helpful in adults with HIV as well.

Lifestyle Factors

Generally, that which is good for the body is good for the brain; therefore, lifestyle factors that promote general health will improve cognitive health.
Increasing medical co-morbidity in aging HIV patients

Increasing medical co-morbidity in aging HIV patients

Immune dysfunction as a primary cause of accelerated aging in HIV?

- HIV production and replication
- ART toxicity, lipodystrophy, and traditional risk factors
- Cytomegalovirus and other copathogens
- Loss of regulatory cells
- Inflammation
  - ↑ Monocyte activation
  - ↑ T-cell activation
  - ↑ Endothelium adhesion
  - Dyslipidaemia
  - Hypercoagulation
- Comorbidities
  - Cardiovascular disease
  - Cancer
  - Kidney disease
  - Liver disease
  - Osteopenia/osteoporosis
  - Neurocognitive disease

Steven G Deeks, Sharon R Lewin, Diane V Havlir The end of AIDS: HIV infection as a chronic disease The Lancet Volume 382, Issue 9903 2013 1525 - 1533
## Illicit drug effects on neuro-inflammation

<table>
<thead>
<tr>
<th></th>
<th>Cocaine</th>
<th>Meth</th>
<th>Opioids</th>
<th>Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known increase cog impairment in HIV+ pts</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>ND</td>
</tr>
<tr>
<td>HIV replication in human macrophages</td>
<td>↑?</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Monocyte/macrophage CCR5 expression</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>ND</td>
</tr>
<tr>
<td>Monocyte/macrophages CXCR4 expression</td>
<td>↑</td>
<td>↑</td>
<td>↑?</td>
<td>ND</td>
</tr>
<tr>
<td>HIV replication in human T-lymphocytes</td>
<td>↑↑</td>
<td>↑?</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>CSF/brain SIV viral load in macaque model</td>
<td>↓?</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Proinflammatory cytokine release</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑ ↓</td>
</tr>
<tr>
<td>Anti-inflammatory cytokine release</td>
<td>↑?</td>
<td>ND</td>
<td>↓?</td>
<td>↓</td>
</tr>
<tr>
<td>Blood brain Barrier breakdown in rodents</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>ND</td>
</tr>
</tbody>
</table>

Interactions of Age and Psychiatric Conditions

Depression
Substance use
Cognitive impairment
Disenfranchisement

Adherence
Viral load and T-cells
CNS inflammation
CNS infection

Adherence
Health care access
Subtypes of HIV impairment
The Triad Associated with Subcortical Dementia

- dyskinesia
- dementia
- depression
Subcortical pattern of dementia

- Memory loss with selective impairment of retrieval
- Impaired manipulation of acquired knowledge
- Personality changes with apathy, inertia, and irritability (personality deterioration or coarsening)
- General slowing of thought processes
A web of co-morbidity

Drug toxicity

Nerve tissue injury

Immune dysregulation

Neuropathy

Disability

Dementia

Social isolation

Depression

Opiate dependence

Disinhibition

Impoverishment

Apathy

Risk Behavior

Poor adherence
Aging, Neurocognition, and Medication Adherence in HIV Infection.
Ettenhofer, Mark; Hinkin, Charles; Castellon, Steven; Durvasula, Ramani; Ullman, Jodi; Lam, Mona; Myers, Hector; Wright, Matthew; Foley, Jessica
DOI: 10.1097/JGP.0b013e31819431bd

FIGURE 1 Latent Model of Cognition and Medication Adherence Among Younger and Older HIV+ Adults Notes: Mem.: memory; Attent.: attention; Exec.: executive; Qual.: qualitative self-report; 30-Day: 30-day self-report; 1-Day: 1-day self-report. Standardized values shown from model C0. Factor loadings of 1-day self-report have been reversed for ease of interpretation.
Depression is increased in patients with HIV

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+¹ (N=2864)</td>
</tr>
<tr>
<td>Major depression</td>
<td>36.0</td>
</tr>
<tr>
<td>Dysthymia (chronic depression)</td>
<td>26.5</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>15.8</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>10.5</td>
</tr>
<tr>
<td>Alcohol and drug use</td>
<td>50.1</td>
</tr>
</tbody>
</table>

¹ Bing p725, Table 2
² Kessler p596, Table 2
Depression in HIV is associated with:

- Decreased survival  Ickovics
- Impaired quality of life  Trepanier
- Decreased HAART adherence  Yun
- Decreased cognition  Ammassari
- Higher treatment costs  Williams
- Unemployment  Rabkin
- Increased risk behaviors  Williams, Bing
- Suicidality  Carrico
- Longer hospital stays  Leserman
- More frequent medical visits (eg, emergency room and/or clinic)  Leserman
DEPRESSION AS AIDS DEVELOPS

MONTHS BEFORE AND AFTER AIDS

TIME OF AIDS

PERCENT DEPRESSED

-48 -36 -24 -12 6 18
HIV

Reward sensitivity
Cytokines
Stress transmitters
Immune system
(Poor adherence and treatment failure)

Depression

Reward sensitivity
Cytokines
Stress transmitters
Immune system
(Poor adherence and treatment failure)
Major depressive disorder

Infection with HIV
Treatment failure

Immune activation from CSF HIV
Inflammation

HI V/ AIDS

Sexual risk behavior
Addiction
Substance use
Non-adherence
Access to care

Hammond E, Treisman G.
Major depressive disorder

Immune activation from CSF HIV
Inflammation

CNS penetration
CNS viral replication
Drug toxicity
Immune reconstitution
Access to care, stigma
Genetics, family history

HI V/ AIDS

Hammond E, Treisman G.
Incidence Rates for Depression by Detectable CSF HIV RNA, N=154

Adjusted HR: 4.76 (95% CI: 1.58—14.3) \( p=0.006 \)

Trajectories of Beck Depression Inventory (BDI) Scores by CSF HIV RNA, N=223

![Graph showing change in depression (BDI) scores by CSF HIV RNA over follow-up months, with significance markers (*P<0.05, **P<0.01).](image_url)

Population Prevalence and Odds Ratios-Depression and CSF Viral Escape, N=803

Adjusted Odds Ratio=2.10
(95% CI: 1.15, 3.84)
\( p=0.016 \)

#Adjusted for CPE2.0: CNS penetration effectiveness score 2.0; adherence by AIDS Clinical Trials Group 4-Day Adherence Questionnaire; cART: combination antiretroviral therapy; lifetime alcohol and substance use disorder based on Diagnostic and Statistical Manual of Mental Disorders, IV using the Composite International Diagnostic Interview (CIDI DSM-IV); cART: combination antiretroviral therapy; SSRI: selective serotonin reuptake inhibitor

Bidirectional Association: MDD \(\leftrightarrow\) HIV

**Immunoactivation?**
- Sexual risk behavior
- Addiction
- Substance use
- Non-adherence
- Access to care

**Major depressive disorder**

**Detectable CNS HIV Inflammation**

**Immune activation from persistent CSF HIV Inflammation**

**HIV/ AIDS**

- CNS penetration
- CNS viral replication
- Drug toxicity
- Immune reconstitution
- Access to care, stigma
- Genetics, family history

Hammond E, Treisman G.
Treatment of depression improves survival
Summary: things we should do

• 1. Diagnose and treat depression
• 2. Screen for HIV cognitive impairment
• 3. Include treatment for addiction
• 4. Include treatment for personality disorder
• 5. Guidelines are aimed at the average trials subject, not at your patient; always individualize treatment
What we need to know and think about

• How important is CNS penetration? (LP?)
• How do we evaluate HAART induced CNS effects (efavirenz)?
• How do we prioritize CNS issues, resilience to resistance, cardiovascular risk, renal risk, hepatic risk and HEP C treatment?
• When do we start treatment with patients with high risk for poor adherence?