HIV through the Life Cycle

Dr. Adriana Carvalhal, MD, MSc, PhD
Assistant Professor - Department of Psychiatry
Director Consultation-Liaison Psychiatry - St. Michael's Hospital
Introduction

- Evolution from a fatal disorder to a chronic manageable condition
- Physicians challenges have changed with the advances in the disease
- HIV-positive patients faces:
  - Chronic illness
  - Complex medical demands
  - Extensive social challenges
  - Social stigma and discrimination
Peter – 1992:
36-year-old man

- ICU
- PCP pneumonia
- HIV / AIDS diagnosis
- CD4 count: 30/mm³
- “Get affairs in order”
  - Quits job
  - Sells house
- Imminent death

- Shock to family
- Fear
- Wasted
- Depressed
- Stigma
- Isolated
- Alone
Pater – 2012 (Age 56)

- On HAART since 1996
- Viral load always undetectable
- CD4 count: 450/mm³

- Off work
- On 16 different medications
- Hypertension
- Alcohol daily: 2 drinks
- Depression / “Boredom”
- Crystal meth: 2-3 per month
- Lipodystrophy
- Dyslipidemia
- Osteoporosis – 1 hip replacement
- Anal dysplasia
- Erectile dysfunction
- Coronary artery disease – recent single vessel angioplasty

Is HIV this patient’s #1 medical problem?
The Good News: The impact of HAART

Survival from age 25 years
N = 3,990

- Population controls
- Late HAART (2000–2005)
- Early HAART (1997–1999)

HIV and the ageing population

- By 2015, nearly 50% of persons living with HIV/AIDS will be >50 years\(^1\)
- The number of persons >65 years of age at AIDS diagnosis has grown 10-fold in the last 10 years\(^2\)

---

Causes of death in the D:A:D study

- An international observational study of HIV-infected individuals. This analysis included:
  - 33,347 patients
  - 2,192 deaths over 158,959 person-year
  - 13.8 deaths per 1,000 person-years (95% CI: 13.2–14.4)

- AIDS-related: 32%
- Liver-related: 14%
- CVD-related: 11%
- Non-natural: 9%
- Bacterial infection: 7%
- Lactic Acidosis / Pancreatitis: 1%
- Non-AIDS cancers: 12%
- Renal: 1%
- Other unknown: 13%
- Non-AIDS cancers: 12%

- This study reiterates the importance of addressing traditional, non-HIV specific risk factors in order to further reduce death rates in HIV positive populations.
Peter

• 56 year old man, single, living alone
• Until recently worked as an investor on Bay street (partner in the company)
• Over the last 2-3 years progressively with memory problems
• Coping with several practical strategies and delegating a lot to other ("Not my style!")
• Last year made a huge mistake at work and decided to leave the firm
• “Not sure what to do with my life!”
Peter

- Short-term memory
- Difficulties with concentration
- Difficulties with “multi-task”
- “I’m not so sharp any more!”
- “Everything takes longer!”
- Difficulties to adapt to a different life style
- Feels lonely - crystal meth
- Social withdrawal
- Not enjoying things in the same way – plans for future
Common Mental Health Problems in PHAs

- Depression
- Substance Use Disorder (SUD)
- HIV-Associated Neurocognitive Disorder (HAND)
- Other conditions can affect mental health:
  - Lipodystrophy
  - Social determinants of health
  - Side effects from ARVs
Neurocognitive Changes in HIV

**HIV-related:**
- CNS Lymphoma
- HAND

**Non-HIV related:**
- Aging
- Depression
- Substance Use
- HCV Co-infection
- Dementia:
  - Alzheimer’s
  - Cerebrovascular disease
BACKGROUND

HIV enters CNS shortly after infection

HIV Associated Neurocognitive Disorder (HAND):
- Asymptomatic neurocognitive impairment (ANI)
- HIV-associated mild neurocognitive disorder (MND)
- HIV-associated dementia (HAD)

Introduction of cART, decrease incidence of HAD, increased prevalence of MND and ANI

Detrimental effect of minor neuropsychological deficits in HIV
- Ability to work
- Carry out tasks independently
- Medication adherence
- Mortality rates
HAART Era: Dementia Prevalence Decreased, Milder HAND Persists

ANI: asymptomatic neurocognitive impairment; MND: mild neurocognitive disorder; HAD: HIV-associated dementia
HIV: Potential Mechanisms of Brain Injury

“Trojan Horse”

BBB

Virus

gp120

Tat

INFLAMMATORY

Nitric oxide

TNF

IL1

IL6

Monocyte

Microglia

RESERVOIR

Astrocytes

Neuron

Inhibition of growth factor production

Glutamate levels

Neuronal Stress

Neuronal Death

Gliosis

Adapt Avison et al, 2002
CNS: distinct virologic compartment for HIV

**Methods**
- Paired CSF and plasma samples collected from HIV-infected patients ARV-naive with middle cognitive impairment
- NPZ-6 (baseline and 6 months): Logical memory, verbal fluency, word span, visual recognition, Stroop test
- Treatment with AZT + 3TC + EFZ

**Results**
- Differences in response in plasma and CSF viral load
- 70% of patients with undetectable viral load in 6 months
- Undetectable CSF viral load was not significantly associated with improvements in cognitive performance

**Conclusion**
- Data support hypothesis: CSF and plasma represent virologically distinct biological compartments
- Limitations: ARV treatment, number of patients, need for longer FU

Carvalhal A et al, 2006 Infection 34(6):357-60
## Definition of HAND

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pre-existing cause</th>
<th>Delirium absent</th>
<th>Acquired impairment in ≥ 2 cognitive abilities</th>
<th>Interferes with daily functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic neurocognitive impairment (ANI)</td>
<td>No</td>
<td>Yes</td>
<td>Mild</td>
<td>No</td>
</tr>
<tr>
<td>Mild neurocognitive disorder (MND)</td>
<td>No</td>
<td>Yes</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>HIV-associated dementia (HAD)</td>
<td>No</td>
<td>Yes</td>
<td>Marked</td>
<td>Marked</td>
</tr>
</tbody>
</table>

# HAND: Prevalence

<table>
<thead>
<tr>
<th></th>
<th>CHARTER 1</th>
<th>ALLRT 2</th>
<th>Neuradapt 3</th>
<th>OCS 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of neurocognitive deficit</td>
<td>51%</td>
<td>39%</td>
<td>23%</td>
<td>59%</td>
</tr>
<tr>
<td>N (% men)</td>
<td>1562 (74%)</td>
<td>1160 (87%)</td>
<td>158 (79%)</td>
<td>834 (73%)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>43</td>
<td>41</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>ARV</td>
<td>83%</td>
<td>100%</td>
<td>86%</td>
<td>100%</td>
</tr>
<tr>
<td>Undetectable VL</td>
<td>40%</td>
<td>70%</td>
<td>54%</td>
<td>92%</td>
</tr>
<tr>
<td>Current CD4/ mm³</td>
<td>461</td>
<td>424</td>
<td>558</td>
<td>530</td>
</tr>
<tr>
<td>Nadir CD4</td>
<td>NA</td>
<td>213</td>
<td>NA</td>
<td>57% &lt;200</td>
</tr>
<tr>
<td>HCV co-infection</td>
<td>26%</td>
<td>NA</td>
<td>22%</td>
<td>11%</td>
</tr>
</tbody>
</table>

4. Carvalhal et *al.* 19th CROI, Seattle 2012, abstract # 484
Pathophysiology and Risk Factors

Pathophysiologic factors

- Inflammation
- Vascular changes
- Direct and/or indirect effects of antiretrovirals
- Accelerated cerebral aging
- HIV replication in CNS

Risk factors

- Co-morbidities (e.g., diabetes, metabolic syndrome)
- Lower nadir CD4
- Family history of dementia
- Age > 50 years

Improvement with ARV

• Greater numbers of CSF-penetrating drugs showed greater reduction in CSF viral load.
• CSF virological suppression demonstrated greater global deficit score (GDS) improvement.
• Including CSF-penetrating drugs in the ART regimen and monitoring CSF viral load may be indicated for individuals with HIV-associated cognitive impairment.

cART that cross the blood brain barrier are both helpful in terms of neurocognitive functioning and toxic at the cerebral metabolism level (Brew, 2010)

Functional MRI shows that brains of patients infected with HIV look 15-20 years older than brains without HIV.
HIV + Aging

- Cause frailty phenotype\(^1\)
  - decreased physical function and ability to maintain homeostasis
  - vulnerability to immunological stressors
  - inflammatory dysregulation
- Age = 50\(^2\)

Dementia - Vascular

- Hypertension 2\textsuperscript{nd} common comorbidity
- HIV+ higher risk for cerebrovascular disease
  - aging
  - direct impact of HIV infection
  - SE from ARVs: mainly dyslipidemic effect of PIs
HAND: Clinical Approach
What happen with Peter?

- Neuropsych testing: MND
- Plasma VL: undetectable
- MRI: middle cortical atrophy
- CSF VL: undetectable
- Rehabilitation: “Brain Fitness Program”
- Support and mindfulness therapy
Thanks!

adriana.carvalhal@utoronto.ca