Accelerated ageing in young adults infected with HIV since childhood?

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Aging and HIV

- Prolonged survival in HIV infection is accompanied by an increased frequency of non-HIV-related comorbidities which occur earlier in HIV-infected patients than in individuals without HIV infection.

- This "accelerated aging" appears to be largely related to chronic inflammation, chronic immune activation, and immunosenescence in HIV infection.

- HIV infection - increased incidence of:
  - neurocognitive decline
  - CVD
  - malignancy
  - infection and chronic viral reactivation
  - osteoporosis
  - frailty

(Desquilbet L. et al, 2009)
Pathogenesis of HIVE in children


- Although HAART has profoundly impacted the incidence of severe neurocognitive impairments, **HIV-infected children on suppressive regimens still experience neurocognitive deficits** (Parameswaran et al. 2010)
  - irreversible neuronal injury prior to initiation of ARV medications
  - neuronal injury from exposure to inflammatory responses
  - neurotoxic effects of the treatment itself
  - poor CNS penetration of ARV - ongoing CNS viral replication and/or inflammation not reflected systemically (Heaton et al., 2011)

- **CNS penetration effectiveness (CPE)** of a particular regimen (Cysique LA et al. 2011, Eisfeld et al. 2013)
- “**viral escape**” within the autonomous CNS compartment (Tamula et al. 2003)
In children, CSF HIV replication is associated with neurocognitive impairment and HIVE severity - importance of early control of CSF virus (Pratt et al, 1996, Sei et al, 1996)

Children require lifelong treatment → neurologic/ neurocognitive effects of HAART

Risk factors associated with HIV-associated neurocognitive disorders in adults - vascular disease, premature neurodegeneration, or comorbidities such as hepatitis C (Letendre et al, 2010, Wright et al, 2010) - not known to be significant contributors to neurocognitive deficits in children and adolescents

HIV-infected children now survive to adulthood → influence on existing neurocognitive deficits

Pathogenesis of HIVE in children
Pathogenesis of HIVE in children - HIV neuroinvasion

- Spread of HIV into the CNS is thought to occur within weeks after infection (An et al, 1999, Davis et al, 1992)

- Structural changes are detectable by MRI within the first year (Ragin et al, 2012)

- Neuronal damage caused by HIV in the CNS is largely attributed to inflammatory responses (Kaul et al, 2001, Gonzalez-Scarano et al, 2005)

- Autopsy evidence suggests that neuroinflammation persists despite effective ART (Anthony et al, 2005, Garvey et al, 2014)

- 1) "Trojan Horse hypothesis" - via migration of infected monocytes which differentiate into perivascular macrophage

- 2) The passage of infected CD4+ T cells into the brain

- 3) The direct entrance of the virus via tight junctions across the membrane

- 4) Entrance of HIV-1 by transcytosis phenomenon
The normal range of white blood cell counts in the newborn CSF is higher than in adults - leukocytes translocate more easily this barrier in newborns (Greenlee JE, Carroll KC, 2004).

HIV infection in neural progenitor cells (Schwartz L, Civitello L, Dunn-Pirio A, et al., 2007, Krathwohl MD, Kaiser JL, 2004) and developing neurons (Canto-Nogues et al, 2005) in brain tissue from HIV-infected children has been described.

Neurotoxic effects of chemokines and HIV proteins may be of greater importance in the developing brain.

Pathogenesis of HIVE
- differences in children vs adults
Pathogenesis of HIVE
- neurologic/neurocognitive effects of HAART

- An early AIDS-defining illness increased the risk of chronic static encephalopathy during the preschool and early school age years (Smith et al, 2006)

- Treated HIV-infected children with no prior class C event - similar cognitive performance as their HIV-exposed uninfected peers (Smith R et al, 2012)

- Youth with HIV infection but no history of severe HIV disease exhibit low average to average cognitive performance similar to their HIV-exposed but uninfected peers (Smith R et al, 2012)

- Early treated infants have significantly better neurodevelopmental scores, compared with HIV-infected infants for whom treatment was deferred until clinical or immunological progression (Laughton et al, 2012)

CNS penetration effectiveness (CPE)
Mechanisms of ART-associated neurotoxicity:

- metabolic derangements associated with a variety of ARV medications (Jayadev S, et al, 2009)
- proteasomal dysfunction associated with protease inhibitors (Piccinini et al, 2005)
- and exacerbation of CNS vascular disease (Mothobi et al, 2012)

- Certain ARV drugs produce well-described neurologic side effects
Compartmentalization of HIV infection in the CSF - “viral escape”

- Neurocognitive deficits can emerge among HIV infected adults on ART with undetectable plasma viral loads

- Virus recovered from the CSF and plasma of individual patients is often genetically diverse (Antinori et al, 2005, Liu et al, 2013, Canestri et al, 2010)

- Adult patients on suppressive ART regimens with new or worsening neurologic symptoms not infrequently have detectable CSF viral load (Canestri et al, 2010, Peluso et al, 2012)
CSF and plasma levels in patients with HIVE from Romania

- 16 of 32 pts diagnosed with HIV encephalopathy had higher CSF levels
- 3 of 11 patients with HIVE had altered BBB

Duiculescu D et al IAS 2011 MOPE259
Brain CT – 8 y.o. child with cortical and subcortical atrophy and calcifications
Demyelinating aspect and cortical atrophy in a 18 y.o with HIVE, cognitive deficit and paraparesis
Why is neurocognitive impairment important in children and adolescents?

- Neurocognitive impairment impacts
  - quality of life
  - school performance
  - risk behaviors
  - productivity in adulthood

- Neurocognitive impairment has practical implications
  - diminished ability to comprehend
Challenges to describe neurocognitive impairment in adults infected with HIV since childhood

- Aim - to identify patients with more subtle deficits

- Detection of mild deficits needs more difficult tests that often take longer than the simple timed motor tests of the pre-ART era

- Global cognitive scores may overlook subtle deficits in one or more areas specific to PHIV children and may affect their performance on a different level (Laughton B et al. 2013)

- Additional reliable biomarkers with more pathophysiological validity are needed to transform this area of research
Adolescents with chronic HIV- infection

- Vertically infected
  - treated with cART
  - long-term non-progressors
- Horizontally infected - roughly comparable developmentally to their peers until late in their course *(Mitchell, W. (2001))*
  - Blood transfusion
  - Unsterilized needles
- Romanian pediatric cohort
  - Unique, homogenous
  - F-clade infection in the same period (1987-1990)
  - Similar genetic background
  - Similar length of exposure to ART (~15 years)
- Current age - 20-29 ans
- Sex ratio male/female=54/46
- HBV co-infection
- TB co-infection
General characteristics of the participants tested between 2012 and 2015

<table>
<thead>
<tr>
<th></th>
<th>HIV+ group n=222</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of infection years, date of infection based</td>
<td>23.6 (22.8-24.6)</td>
</tr>
<tr>
<td>Duration of infection years, diagnosis based</td>
<td>15.8 (10.2-18.3)</td>
</tr>
<tr>
<td>Plasma ND (&lt;34 c/ml) (%)</td>
<td>59.5%</td>
</tr>
<tr>
<td>CSF ND (&lt;34 c/ml) (%)</td>
<td>86.6%</td>
</tr>
<tr>
<td>Current CD4 cell/ml, median (IQR)</td>
<td>479 (259-709)</td>
</tr>
<tr>
<td>Nadir CD4, median (IQR)</td>
<td>87.5 (22-190)</td>
</tr>
<tr>
<td>GDS imp (%)</td>
<td>35.05%</td>
</tr>
</tbody>
</table>

Active viral replication is associated with:
- male sex
- lower CD4 T-cell counts
- longer time on ART
- longer exposure to monotherapy
<table>
<thead>
<tr>
<th>General characteristics participants</th>
<th>2007-2009 (R21)</th>
<th>2012-2014 (R01)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R21 HIV- (n=20)</td>
<td>R21 HIV+ (n=49)</td>
</tr>
<tr>
<td>Age</td>
<td>18.75 (1.02)</td>
<td>18.49 (0.77)</td>
</tr>
<tr>
<td>Education – mean years (SD) *</td>
<td>11.30 (.98)</td>
<td>9.78 (1.75)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>60.00%</td>
<td>46.94%</td>
</tr>
<tr>
<td>Beck Depression Inventory- median (95% CI for median)</td>
<td>4.5* (3-6.8)</td>
<td>8* (6-13)</td>
</tr>
<tr>
<td>Unemployed/not in school°</td>
<td>0.2%</td>
<td>44.9%</td>
</tr>
<tr>
<td>GDS °</td>
<td>9.5%</td>
<td>48.9%</td>
</tr>
</tbody>
</table>

* p<0.05, ° p<0.001
ART experience

<table>
<thead>
<tr>
<th>ARV history % participants treated</th>
<th>Current use</th>
<th>91.2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Past use</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>Never used</td>
<td>2.4</td>
</tr>
<tr>
<td>Cumulative exposure to ARV (months)</td>
<td>129.8 (90.8-165.3)</td>
<td></td>
</tr>
<tr>
<td>Exposure to current regimen (months)</td>
<td>26.2 (10.6-47.5)</td>
<td></td>
</tr>
<tr>
<td>D-drug exposure</td>
<td>Past</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>36.8</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>15.2</td>
</tr>
</tbody>
</table>
No correlates of deficit scores with:

- CD4: nadir, current, increase from nadir
- HIV RNA: zenith, current
- Previous AIDS
- ARV:
  - total exposure time to ARV's
  - exposure to current regimen
  - no of ARV's
- Depression
- Unemployment
Drug Abuse and HAND

- **Substance abuse - co-morbid condition** with HIV - additive or synergistic effects on the persistence and severity of neurocognitive dysfunction in patients with HAND (Martin-Thormeyer EM, et al, 2009)


- Methamphetamine has been linked to **increased neuroinflammation**, which may contribute to its neurotoxic effects (Yamamoto et al. 2010; Clark et al. 2013).

- Participants with histories of substance use (alcohol, cocaine, cannabis, opiates, methamphetamine) **did not have higher rates of neurocognitive impairment** or functional impairment in everyday life (Byrd DA, et al, 2011)

- The relative additive and synergistic effects of drugs of abuse on neuroinflammation in HIV+ individuals is not known
## Drug use

<table>
<thead>
<tr>
<th>Use &gt; 5x (%)</th>
<th>HIV+ (%)</th>
<th>HIV- (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alcohol</td>
<td>81.32</td>
<td>78.05</td>
</tr>
<tr>
<td>tobacco</td>
<td>50.55</td>
<td>51.22</td>
</tr>
<tr>
<td>marijuana</td>
<td>2.75</td>
<td>7.32</td>
</tr>
<tr>
<td>cocaine</td>
<td>1.10</td>
<td>2.44</td>
</tr>
<tr>
<td>methamphetamine</td>
<td>-</td>
<td>2.44</td>
</tr>
<tr>
<td>other stimulants</td>
<td>-</td>
<td>4.88</td>
</tr>
<tr>
<td>heroin</td>
<td>1.10</td>
<td>-</td>
</tr>
<tr>
<td>opioids</td>
<td>-</td>
<td>2.44</td>
</tr>
<tr>
<td>sedatives</td>
<td>0.55</td>
<td>-</td>
</tr>
<tr>
<td>anxiolitics</td>
<td>-</td>
<td>7.32</td>
</tr>
<tr>
<td>hallucinogens</td>
<td>0.55</td>
<td>2.44</td>
</tr>
<tr>
<td>dissociative drugs</td>
<td>-</td>
<td>2.44</td>
</tr>
<tr>
<td>popper</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ecstasy</td>
<td>1.10</td>
<td>-</td>
</tr>
<tr>
<td>legal highs</td>
<td>2.04</td>
<td>5.00</td>
</tr>
</tbody>
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R01
4 controls
8 HIV + with > 1 drugs
### Studies on NCI in children and adolescents with current good CD4 count

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age</td>
<td>8.7</td>
<td>18.8</td>
<td>18.4</td>
</tr>
<tr>
<td>No of HIV+</td>
<td>93</td>
<td>6</td>
<td>49</td>
</tr>
<tr>
<td>Control group</td>
<td>HIV- age matched</td>
<td>Elderly HIV+ (65 yo)</td>
<td>HIV- age matched</td>
</tr>
<tr>
<td>Nadir CD4</td>
<td>N/A</td>
<td>393</td>
<td>86</td>
</tr>
<tr>
<td>Current CD4</td>
<td>655</td>
<td>619</td>
<td>517</td>
</tr>
<tr>
<td>Current HIV RNA</td>
<td>4.7 (4.2-5.1)</td>
<td>Undetectable in 4 of 6 pts</td>
<td>2.6 (1.6-5.8)</td>
</tr>
<tr>
<td>Subtype</td>
<td>A, D, C</td>
<td>N/A</td>
<td>F</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.7</td>
<td></td>
<td>10.1</td>
</tr>
<tr>
<td>NCI impairment rates</td>
<td>Significant motor and cognitive deficits</td>
<td>67% (Cogstate)</td>
<td>47% (HNRC battery)</td>
</tr>
</tbody>
</table>

NCI: Neurocognitive Impairment

- **Uganda**
  - HIV+ Age: 8.7
  - No of HIV+: 93
  - Control group: HIV- age matched
  - Nadir CD4: N/A
  - Current CD4: 655
  - Current HIV RNA: 4.7 (4.2-5.1)
  - Subtype: A, D, C
  - Years of education: 11.7
  - NCI impairment rates: Significant motor and cognitive deficits

- **UK**
  - HIV+ Age: 18.8
  - No of HIV+: 6
  - Control group: Elderly HIV+ (65 yo)
  - Nadir CD4: 393
  - Current CD4: 619
  - Current HIV RNA: Undetectable in 4 of 6 pts
  - Subtype: N/A
  - Years of education: 11.7

- **Romania**
  - HIV+ Age: 18.4
  - No of HIV+: 49
  - Control group: HIV- age matched
  - Nadir CD4: 86
  - Current CD4: 517
  - Current HIV RNA: 2.6 (1.6-5.8)
  - Subtype: F
  - Years of education: 10.1

NCI impairment rates:
- **Cogstate**: 67%
- **HNRC battery**: 47%
High overall prevalence of NCI in VBH population

VBH cohort
- Normal: 53%  
- ANI: 25%  
- HAD: 2%  
- MNI: 20%

CHARTER cohort
- Normal: 47%  
- Severe impairment: 2%  
- Moderate impairment: 30%  
- Mild impairment: 21%

Duiculescu et al. 16th CROI 2009 # 477
Heaton R et al., 16th CROI 2009
Systemic and plasma markers

- **Low CD4 nadir** → early treatment could substantially prevent the disorder (Heaton et al. 2011, Ellis et al., 2011, Valcour et al., 2006, Lyons et al., 2011, Crum-Cianflone et al., 2013)

- **Plasma-soluble CD14** - impairment in attention and learning (Lyons JL, 2011)


- HIV affects the gut to potentially cause **microbial translocation** driving chronic inflammation, leading to HIV-associated dementia (Ancuta P et al, 2008, Brenchley et al, 2006)

- **Carotid intima–media thickness and glomerular filtration rate** were associated with performance speed on neuropsychometric tests, and intima–media thickness was also associated with memory impairment (Becker JT et al, 2009)

- Increased presence of **metabolic risk factors** (McCutchan et al, 2012)
CSF markers

- Potentially identify patients at risk of HIV-associated neurocognitive disorder

- **Severity of cortical atrophy reflects the level of viral load in the CSF** (Brouwers P et al, 2000)

- **Virally suppressive ART protects against cortical neurodegeneration** (quantified by measuring microtubule-associated protein (MAP2) and synaptophysin (SYP) density in midfrontal cortex tissue sections) (Bryant AK et al, 2015)

- **Persistent immune activation markers** – IL 6, IL 8, and MCP-1, remain present in successfully treated patients (Kamat et al, 2012)


- **MCP-1 and MMP-9** declined parallel with HIV RNA CSF load in children on ART (McCoig C et al, 2004)
## Biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Plasma (n=144)</th>
<th>CSF (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>IFN-γ</td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>IL-1β</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>IL-8</td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>TNF-α</td>
<td></td>
</tr>
<tr>
<td>Fractalkine</td>
<td>Fractalkine</td>
<td></td>
</tr>
<tr>
<td>IP-10</td>
<td>IP-10</td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td>MCP-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-12 p70</td>
</tr>
</tbody>
</table>
Neurocognitive impaired participants had higher IL1β, IL6 and TNFα levels

- TNF-α, sTNFR-II, and IL-6 have all been previously implicated in HIV disease progression (Nixon and Landay 2010; Crowe et al. 2010, Achim et al. 1993; Mastroianni et al. 1990; Perrella et al. 1992; Vullo et al. 1995)

- Lower sTNFR-II concentrations were associated with neurocognitive worsening and higher IL-6 concentrations were associated with neurocognitive improvement (Marcotte et al, 2013)

- TNF-α may link neurocognitive progression and remission

- SMART - elevated IL-6 at baseline and hs-CRP were significantly associated with mortality

- Greater age and body mass index were associated with higher IL-6  Rodger AJ, 2009

- therapeutic implications?
Correlation between IP 10 and HIV ARN levels

- G-CSF and IP-10 in plasma were significantly higher in HIV-impaired than HIV-normal cognition
- G-CSF, IL-8, IP-10 and MCP-1 in CSF showed significant difference between HIV-impaired and HIV-normal cognition group (Yuan L et al, 2015)
- 2 ACTG - higher IP-10 levels and higher MCP-1 levels correlated with lower cerebral metabolites in the brain regions considered
- higher levels of IP-10 correlated with lower neuronal pattern scores and higher basal ganglia and inflammatory pattern scores, the same pattern which has been associated with (HAND) Letendre et al, 2011
Cardiac disease among HIV-infected children and adolescents

- In HIV-infected pregnant women treated with HAART - no significant changes in fetal cardiac parameters (De la Calle M et al, 2015)

- Significant burden of cardiac disease was seen among children with vertically-acquired HIV infection. Over half of asymptomatic 110 adolescents had significant echocardiographic abnormalities (Miller R et al, 2012)

- HIV-infected adolescents showed higher intima-media thickness (Idris NS et al, 2014, Sainz T et al, 2015)

- Birth defects - 39.34% (Tudor AM, 2014)

- Comparable myocardial function and similar carotid intima-media thickness (Chanthong P et al, 2014)

- No differences regarding cardiac abnormalities - vertically HIV-infected children and adolescents (Sainz T et al, Pediatr Infect Dis J 2015)

- French Perinatal Cohort - specific association between in utero exposure to ZDV and congenital heart disease and a long-lasting postnatal myocardial remodeling in girls (Sibiude J et al, 2015)

- Effects of HIV infection per se and antiretroviral therapy treatment?
HIV-infected children have higher levels of biomarkers of vascular dysfunction (sICAM, sVCAM, MCP-1, IL-6, and fibrinogen levels) than healthy children. Risk factors associated with these biomarkers include higher waist to hip ratios and HIV disease severity. Millet Tr et al, 2010

Vertically HIV-infected subjects on ART with no significant metabolic disturbances displayed increased sCD14 and soluble vascular cell adhesion molecule-1 (sVCAM) but not up-regulation of proinflammatory pathways (C-reactive protein, interleukin-6, myeloperoxidase, monocyte chemoattractant protein-1, P-selectin and tissue plasminogen activator). Sainz et al, 2014

Cardiac disease among HIV-infected children and adolescents
Metabolic risk factors didn’t influence NCI HIV+ group

<table>
<thead>
<tr>
<th>Condition</th>
<th>HIV+ group n=201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl) (N: 11-15) &lt;11</td>
<td>13.8 (8.6-18.3)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl) (N: 50-200) &gt; 200</td>
<td>121 (41-1076)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl) (N: 50-200) &gt;200</td>
<td>173 (89-371)</td>
</tr>
<tr>
<td>Albumin (g/l) (N: 35-50) &lt;35</td>
<td>41 (29-56)</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/l) (N: &lt;100mg/dl) &gt;100</td>
<td>79 (57-144)</td>
</tr>
<tr>
<td>AgHBS pos</td>
<td>29.2% 56%</td>
</tr>
<tr>
<td>VHB DNA pos</td>
<td></td>
</tr>
<tr>
<td>AcVHC pos</td>
<td>2.2%</td>
</tr>
<tr>
<td>BMI &gt; 25</td>
<td>9.45%</td>
</tr>
<tr>
<td>BMI &lt;18.5</td>
<td>24.3%</td>
</tr>
</tbody>
</table>
The Veterans Aging Cohort Study (VACS) index - 7 variables: age, CD4 count, HIV-1 RNA, hemoglobin, FIB-4, eGFR, and hepatitis C status – index for 5-year mortality risk in HIV patients, with a 10-point increase in the VACS score predicting a 10% increase in 5-year mortality (Justice AC et al, 2010, 2013)

Higher VACS Index scores were associated with concurrent risk for global NCI even when adjusting for psychiatric comorbidities for most cognitive domains in adjusted models.

The VACS Index predicted concurrent NCI beyond nadir CD4 and estimated duration of infection

Older age, lower hemoglobin, and lower CD4 counts were the VACS components most strongly linked to NCI (Marquine MJ et al, 2014)

In our cohort, VACS index wasn’t associated with a higher risk for NCI

Hepatitis B?

Median 11.5 (0-54), n=187
Discussion and conclusions

- We found a high prevalence of neurocognitive impairment – neurotropism of clade F?
  - Irreversible brain injury prior to initiating treatment
  - Persistence of low-level HIV replication in the brain
  - Persistence of inflammation and immune activation in the brain
  - Possible neurotoxicity of antiretroviral therapy on a developing brain

- No classical/metabolic risk factors associated with NCI
- Few confounders in terms of drug exposure, HCV coinfection, depression or psychiatric conditions in this group which may interfere with NCI
- NCI didn’t correlate with HIV markers (CD4, HIV RNA)

- Challenges to assess NCI were related to difficulties in assessing functionality, to find an education matched control group

- The rates of NCI seem to decline on longitudinal follow-up
Future directions

- Further analyse longitudinal data (CD4, HIV RNA) and potential correlation with NCI
- New challenges for further studies emerge from this cohort:
  - Cardiac disease evaluation
  - Identify new risk factors
  - What is the clinical significance of the high HBV coinfection for the CNS?
  - Neuroimaging and MRS
  - Follow up
A functional cure for HIV infection will need the virus to be silenced in all body compartments, including the brain. Valcour V, Sithinamsuwan P, Letendre S, Ances B. Curr HIV/AIDS Rep 2011

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