Endocrinopathy and Leukocyte Telomere Length in HIV+ Individuals in the CARMA Cohort

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Oak Tree Clinic

**Children’s & Women’s Health Centre of BC**
- Provincial multidisciplinary clinic
- Vancouver
- Referral centre for HIV+ women and children
- Adults: 75% women

**CARMA:**
- Children & Women Antiretrovirals & Mechanism of Aging
- 2008-present
Background

**pre-HAART:**
-HIV a significant cause of **MORTALITY** and **MORBIDITY**

**post-HAART:**
-decline in mortality, **MORBIDITY** associated with HIV infection
- HIV+ patients develop age associated co-morbid conditions 5-10 years earlier than HIV- patients

Co-morbidities associated with HIV treatment and aging:
- cardio/cerebrovascular disease
- renal & liver disease
- bone metabolism disorders/osteoporosis
- endocrine and metabolic disorders "endocrinopathies"
Figure 1. Increased Prevalence of Endocrinopathies in HIV+ Patients
Endocrinopathies were prevalent in the pre-HAART era too!
Despite sustained HIV suppression by HAART

- Residual HIV replication
- Residual viral co-replication (hepatitis C, CMV)
- Residual bacterial translocation

Persistent immune activation and CHRONIC INFLAMMATION

- “INFLAMMAGING”
  - Accelerated cellular aging
  - Organ Dysfunction
    - CVD & CNS disease
    - Kidney & Liver disease
    - Cancers & Bone disease

Drug toxicity (PIs, TA-NRTI)

Immune senescence

Adapted from Reiss, P. Clin. Infect. Dis. 2009
Deeks, Annu. Rev. Med. 2011
TELOMERS:
- DNA sequences located at the ends of chromosomes
- Prevents loss of genomic information during cell division

Shorter telomere length = Cellular aging (senescence)

- Measured as leukocyte telomere length (LTL)
- Shorter LTL independently associated with¹:
  - Cardiovascular disease
  - Type 2 diabetes mellitus (men)
  - Ovarian aging
  - Kidney disease

¹References at end
Objectives

1. To assess the prevalence of endocrinopathies in the HIV+ adult men and **women**
   - thyroid dysfunction (hypo/hyper)
   - adrenal insufficiency
   - glucose intolerance and diabetes
   - hyperlipidemia
   - hypogonadism (hypotestosteronism, premature ovarian failure, polycystic ovarian syndrome, premature menopause)

2. To correlate endocrine dysfunction with various factors

3. To determine whether is an association between shorter LTL and endocrinopathies
Methods

192 HIV+ women, 45 HIV+ men from CARMA cohort

Annual CARMA-2 visits (Jan. 2008-July 2012)

Any time (Jan. 2008-July 2012)

Self-report data
- Demographic info
- Reported health history (diagnosis of endocrinopathy)
- Substance use
- Prescription medication
- Menstrual cycle

Blood work
- LTL
- HIV status, CD4 nadir
- Hepatitis B/C status

Chart review
- Blood work reviewed for prevalence of endocrinopathy
- Physician diagnosis
- Antiretroviral exposure
**Methods**

**Presence of an endocrinopathy**
- Self reported, physician diagnosis, patient took medication consistent with diagnosis, conclusive blood work:

**Laboratory inclusion criteria to determine the presence of an endocrinopathy**

<table>
<thead>
<tr>
<th>Endocrinopathy</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>TSH &gt;10 mIU/L</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>TSH &lt;0.3 mIU/L</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>2 times: FBG: 5.7-7; or HbA1C: 6.5-6.9%</td>
</tr>
<tr>
<td>Diabetes mellitus T2</td>
<td>FBG &gt;7.0 or HbA1C &gt;7%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1 of: Total Chol &gt;5.6mmol/L, LDL &gt;3.5mmol/L, HDL &lt;1mmol/L, TGs &gt;1.7mmol/L</td>
</tr>
<tr>
<td>Hypotestosteronism</td>
<td>Testosterone &lt;9.7 nmol/L</td>
</tr>
<tr>
<td>Pre-mature menopause or Pre-mature Ovarian Failure</td>
<td>FSH &gt;22.5IU/L &amp; age 40-45 yrs, FSH &gt;22.5IU/L &amp; age &lt;40 yrs</td>
</tr>
<tr>
<td>Low cortisol</td>
<td>A.M. cortisol &lt;240 nmol/L</td>
</tr>
</tbody>
</table>
Results, n=237

Variables Analyzed:
- Gender, ethnicity
- Age, BMI
- Viral load, CD4+ nadir
- ART duration & class
- Active hepatitis C (PCR+)
- Smoking
- Stimulants
- Opiates
- Leukocyte telomere length

Age:
- Female mean: 42.9
- Male mean: 49.5
- Mean: 44.1

Ethnicity
- 43% Caucasian
- 28% Aboriginal
- 16% African Canadian

HIV infection
- 62% undetectable viral load (<50 copies/mL)
- 88% CD4+ >200 cells/mm³

Hepatitis C
- 23% HCV PCR +
Figure 2. Comparing the prevalence of endocrinopathies in the CARMA cohort, to other studies in HIV+ and HIV- individuals
Table 1. Prevalence of endocrinopathies in HIV+ women and men in the CARMA-2 cohort

<table>
<thead>
<tr>
<th>Endocrinopathy</th>
<th>Prevalence (%) (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any disorder</td>
<td>45.6 (39.1-52.1)</td>
</tr>
<tr>
<td>Any thyroid disorder</td>
<td>13.5 (9.5-18.7)</td>
</tr>
<tr>
<td>Any diabetic disorder</td>
<td>10.1 (6.7-14.9)</td>
</tr>
</tbody>
</table>
### Variables significantly associated with the number of endocrinopathies

**Table 2.** Poisson regression results for number of endocrine abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>IRR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.046</td>
<td><strong>1.02 (1.002 – 1.04)</strong></td>
</tr>
<tr>
<td>BMI</td>
<td>0.001</td>
<td><strong>1.04 (1.02 – 1.08)</strong></td>
</tr>
<tr>
<td>log$_2$ (cumulative months of NRTIs)</td>
<td>0.001</td>
<td><strong>1.18 (1.08 – 1.30)</strong></td>
</tr>
</tbody>
</table>
Variables significantly associated with the number of endocrinopathies

Figure 3. The predicted number of endocrinopathies given that the other 2 variables are held at their mean. The grey curves show the 95% CI for the estimates.
Results, n=203

Variables significantly associated with the probability of having any endocrinopathy

Table 3. Logistic regression of the presence of any endocrinopathy

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.01</td>
<td><strong>1.06 (1.01 – 1.12)</strong></td>
</tr>
<tr>
<td>log₂ (cumulative months of PIs)</td>
<td>0.03</td>
<td><strong>1.15 (1.01 – 1.31)</strong></td>
</tr>
<tr>
<td>log₂ (cumulative months of NNRTIs)</td>
<td>0.001</td>
<td><strong>1.20 (1.07 – 1.35)</strong></td>
</tr>
</tbody>
</table>
Variables significantly associated with the probability of having any endocrinopathy.

**Figure 4.** Predicted probability of having any endocrine abnormality for the three significant variables while holding the other two at their mean values. The grey shading indicates the 95% CI for the estimated probabilities.
Variables significantly associated with specific endocrinopathies

1. **Thyroid disorders** (hypo/hyperthyroid) - none

2. **Diabetic disorders** (impaired fasting glucose/T2DM)

**Table 4.** Logistic regression of the presence of any diabetic abnormality

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.01</td>
<td><strong>1.10</strong> (1.02 – 1.19)</td>
</tr>
<tr>
<td>log₂ (cumulative months of PIs) *</td>
<td>0.06</td>
<td><strong>1.25</strong> (0.99 – 1.64)</td>
</tr>
<tr>
<td>Hep C active (PCR+)</td>
<td>0.009</td>
<td><strong>0.13</strong> (0.01 – 0.65)</td>
</tr>
</tbody>
</table>

* not significant
Variables significantly associated with specific endocrinopathies

3. Dyslipidemia

Table 5. Results of the logistic regression on the presence of dyslipidemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>p-value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.04</td>
<td>1.05 (1.00 – 1.11)</td>
</tr>
<tr>
<td>log₂ (cumulative months of NRTIs)</td>
<td>0.0088</td>
<td>1.20 (1.13 – 1.69)</td>
</tr>
</tbody>
</table>
Discussion

Leukocyte telomere length was not associated
- With the **number** of endocrinopathies
- With the probability of having **any** endocrinopathy
- With a **diabetic, thyroid or lipid abnormality**

Lower prevalence of hyperlipidemia
- Rate of active hepatitis C\(^1\)
- Under-represented?
- US higher baseline than Canada (51% vs 14%)\(^2\)

\(^{1}\) Bedimo HIV Medicine 2006
\(^{2}\) Petrella Clin Ther 2008
Toth J Clin Lipidol 2012
Discussion

HAART, age and BMI appear to play role in most endocrinopathies:

- **BMI** and **age** show linear relationship
- **HAART**: greatest effect seen early in treatment and tends to attenuate over time

-> early treatment: inflammatory cytokines elevated  

-> with HAART: HIV infection controlled and inflammation declines  
Keating AIDS 2011
Limitations

- Endocrinopathies were determined retrospectively, rates (esp. of lipid and diabetic abnormalities likely underestimated)

- Single time point assessment
  - Incidence not possible
  - Rate of telomere attrition?

- Presence of endocrinopathy before or after HIV infection?

- Difficult to separate length of HAART and actual length of HIV infection

- Self-report data
**Prospective study**: next 5 years

- Multiple visits, CARMA cohort and new participants

- Questionnaire: personal & family history, drugs/procedures affecting endocrine function

- Additional blood testing at each visit:
  - TSH, AM cortisol, insulin level, apoA and B, HbA1C, anti-Müllerian hormone,
  - FSH, prolactin, estradiol (to diagnose amenorrhea)
  - Fasting glucose, cholesterol
  - LTL and whole blood mitochondrial DNA

- BMI, waist circumference, and blood pressure
  - Framingham risk scores, metabolic syndrome