Disclosures

Research funds were paid to UC San Diego on behalf of Dr. Letendre:
- National Institutes of Health
- Gilead Sciences

Dr. Letendre was paid for an advisory board:
- ViiV Healthcare

Dr. Letendre was paid for a lecture:
- None
HIV+ Adults Are Ageing but Survival Has Not Yet Normalized

Graphs Courtesy Sara Gianella & Peter Hunt

Smit, Lancet Inf Dis 2015, 15(7):810-8

Legarth et al, JAIDS 2016, 71(2):213-8

~9 years shorter life expectancy even among those with no comorbidity
Evidence of Premature Ageing Has Been Found in Nearly Every Organ System

- **Nervous System**
  - Cognitive Disorders
  - Depression
  - Neuropathy
  - Sleep Disorders
- **Vascular System**
  - Cardiovascular
  - Cerebrovascular
- **Endocrine/Metabolic**
  - Diabetes
  - Hypogonadism
- **Liver**
  - ↓ Drug Metabolism
  - ↓ Synthetic Function
- **Kidney**
  - ↓ Drug Elimination
- **Musculoskeletal**
  - Osteoporosis
  - Frailty
- **Pulmonary**
- **Hematopoietic**
- (Cancer)

*Brooks et al, American Journal of Public Health 2012, 102(8): 1516-26*  
HIV+ Adults are at Greater Risk for Multiple Ageing-Related Diseases than the General Population

Schouten, IAC 2012, Abstract THAB0205

Schouten et al, Clin Infect Dis 2014; 59(12):1787–97

Adapted from Todd Brown, Johns Hopkins
Frailty Phenotype Integrates Multiple Elements of Ageing

Increasing Polypharmacy in Ageing HIV+ Adults

Smit, Lancet Inf Dis 2015, 15(7):810-8
Unifying Model of Premature Ageing During HIV Disease

Deeks, Tracy, & Douek, Immunity 2013, 39: 633-45
Gianella & Letendre, J Inf Dis 2016
HIV and Methamphetamine May Shorten Telomeres

Mehta et al, CROI 2018, Abstract 1062
HIV Accelerates Ageing of Blood Cells by DNA Methylation

Horvath & Levine, J Infect Dis 2015, 212:1563–73
p16^{INK4a} is a Marker of Cellular Senescence and Does Not Normalize in CD8+ T-Cells with Suppressive ART

HC = HIV Negative Control
HS = HIV Suppressed on ART
C = HIV Controller off ART
NC = HIV Non-Controller off ART
IP = Immunologic Progressor off ART

# Definitions of Metabolic Syndrome

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Any 3</strong></td>
<td><strong>IR + ≥ 2 Others</strong></td>
<td><strong>↑Ins + ≥ 2 Others</strong></td>
<td><strong>Obesity + ≥ 2 Others</strong></td>
</tr>
<tr>
<td>🌊: WC &gt; 35 in</td>
<td>🌊: WHR &gt; 0.85</td>
<td>🌊: WC &gt; 80 cm</td>
<td>🌊: WC &gt; 80 cm</td>
</tr>
<tr>
<td>🌊: WC &gt; 40 in</td>
<td>🌊: WC &gt; 0.90 or BMI &gt; 30</td>
<td>🌊: WC &gt; 94 cm</td>
<td>🌊: WC &gt; 94 cm</td>
</tr>
</tbody>
</table>

- **Fasting ≥ 100 or Rx**
- **TG ≥ 150 or Rx**
- **♀: HDL < 50 or Rx**
- **♂: WC < 40 or Rx**
- **> 130 SBP > 85 DBP or Rx**
- **Insulin Resistance (required)**
- **TG ≥ 150**
- **♀: HDL < 39 or Rx**
- **♂: WC < 30 or Rx**
- **≥ 140/90 or Rx**
- **≥ 140/90 or Rx**
- **HDL < 39**
- **♀: HDL < 39 or Rx**
- **♂: WC < 30 or Rx**
- **≥ 140/90 or Rx**

## Definitions of Metabolic Syndrome

<table>
<thead>
<tr>
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<td><strong>Obesity + ≥ 2 Others</strong></td>
</tr>
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<td>♂: WC &gt; 35 in</td>
<td>♂: WHR &gt; 0.85</td>
<td>♂: WC &gt; 80 cm</td>
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<td>♀: WC &gt; 0.90 or BMI &gt; 30</td>
<td>♀: WC &gt; 94 cm</td>
<td>♀: WC &gt; 94 cm</td>
</tr>
<tr>
<td>Fasting ≥ 100 or Rx</td>
<td>Insulin Resistance (required)</td>
<td>Plasma Insulin &gt; 75th Percentile</td>
<td>Fasting ≥ 100 or Rx</td>
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<tr>
<td>TG ≥ 150 or Rx</td>
<td>TG ≥ 150</td>
<td>TG ≥ 177</td>
<td>TG ≥ 150 or Rx</td>
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<tr>
<td>♂: HDL &lt; 50 ♀: HDL &lt; 39</td>
<td>HDL &lt; 39</td>
<td>♂: WC &lt; 40 or Rx</td>
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<tr>
<td>♀: WC &lt; 40 or Rx</td>
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<tr>
<td>&gt; 130 SBP &gt; 85 DBP</td>
<td>≥ 140/90 or Rx</td>
<td>&gt; 130 SBP &gt; 85 DBP or Rx</td>
<td></td>
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</tbody>
</table>

Meta-Analysis of Prevalence of Metabolic Syndrome in HIV

Overall prevalence varied by definition: 16.7% - 31.3%

11.8% (9.3, 14.7) Off ART
18.4% (15.9, 21.1) On ART

Nguyen et al, PLOS ONE 2016, 11(3):e0150970
ART and Components of Metabolic Syndrome

3.85-Increased Odds of Diabetes with ART

<table>
<thead>
<tr>
<th>ID</th>
<th>Odds Ratio (95% CI)</th>
<th>Scenario</th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
<th>IR</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Untreated HIV infection</td>
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<td>Treated HIV infection</td>
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<td>NRTI ( stavudine, didanosine, zidovudine)</td>
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<td>Lamivudine/entricitabine</td>
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<td>Tenofovir disoproxi fumarate</td>
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<td>Tenofovir alafenamide fumarate</td>
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<td>Abacavir</td>
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<td>NRTI</td>
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<td>Protease inhibitor</td>
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<td></td>
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<td>Lopinavir</td>
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<td>Fosamprenavir</td>
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<td>Atazanavir</td>
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<td>Darunavir</td>
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<td>NNRTI</td>
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<td>Nevirapine</td>
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<td>Etavirenz</td>
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<td>Rilpivirine</td>
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<td>Integrase inhibitor</td>
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<td>Raltegravir</td>
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<td>Elvitegravir</td>
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<td>Dolitegravir</td>
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<td></td>
<td>Lifestyle effects (eg, metabolic syndrome, et al)</td>
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</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

TC = Total cholesterol, LDL = Low density lipoprotein, HDL = High density lipoprotein, TG = Triglycerides, IR = Insulin resistance

Nduka et al, Diabetes Metab Res Rev. 2017;33:e2902

Non et al, Translational Research 2017;183:41–56
Protease Inhibitors are Associated with Vascular Disease

- Carotid artery wall thickness measured by 3.0 Tesla MRI
- Longer duration of protease inhibitor therapy associated with thicker carotid wall
- Carotid intima media thickness measured by ultrasound
- DRV/r was associated with faster progression than ATV/r

LaBounty et al, HIV Medicine (2015)

Stein et al, AIDS 2015, 29:1775–1783
Acute Myocardial Infarctions Are More Common in HIV+ Adults

- 871 acute MIs in ~80,000 veterans over ~6 years
- Across 3 decades of age, mean acute MIs per 1000 person-years was consistently higher for HIV+ than HIV- adults
- Hazard ratio for acute MI: 1.5 after adjusting for Framingham risk factors, comorbidities, and substance use

Higher Ischemic Stroke Risk in HIV-Infected Women

Model A: Unadjusted
Model B: Demographics
Model C: +Traditional Risk Factors
Model D: +Sex-specific Risk Factors

1,212 HIV+, 12,040 HIV- women

<table>
<thead>
<tr>
<th>All</th>
<th>HIV-infected</th>
<th>HIV-uninfected</th>
<th>Incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.09</td>
<td>4.36</td>
<td>1.86</td>
<td>2.34 (1.60-3.35)</td>
</tr>
</tbody>
</table>

Chow et al, CROI 2016, Abstract 638
Metabolic and Vascular Disease Increase Risk for Neurocognitive Impairment

**CHARTER**

<table>
<thead>
<tr>
<th>Risk</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Yes</td>
<td>49.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>17.6</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>Larger</td>
<td>1.3</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Lower</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI</td>
<td>Smaller</td>
<td>0.69</td>
</tr>
</tbody>
</table>

McCutchan et al. Neurology 2012. 78: 485

**START**

![Graph showing estimated difference in QNPZ-8 and p-values](image)

**SMART**

<table>
<thead>
<tr>
<th>Risk</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior CVD</td>
<td>Yes</td>
<td>6.2</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Higher</td>
<td>1.1</td>
</tr>
<tr>
<td>AIDS</td>
<td>No</td>
<td>0.41</td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Wright et al, HIV Medicine 2015, 16 (S1), 97–108

**WIHS**

![Graph showing adjusted T-score and Stroop 1&2](image)

Wright et al. Neurology 2010; 75: 864

HIV May Accelerate White Matter Injury in the Brain

**Unpublished CHARTER Data**

**HIV x Age Interaction p = 0.003**

Metabolic Syndrome Components Influence BBB Permeability

- LDL Cholesterol, Serum (mg/dL) with CSF-Serum Albumin Ratio ($\log_{10}$)
- HDL Cholesterol, Serum ($\log_{10}$ mg/dL) with CSF-Serum Albumin Ratio ($\log_{10}$)
- Glucose, Serum ($\log_{10}$ mg/dL) with CSF-Serum Albumin Ratio ($\log_{10}$)
- Diastolic Blood Pressure (mmHg) with CSF-Serum Albumin Ratio ($\log_{10}$)

- Multivariate Regression Predicted Value with CSF-Serum Albumin Ratio ($\log_{10}$)
- CSF-Serum Albumin Ratio ($\log_{10}$) with CSF-Serum Albumin Ratio ($\log_{10}$) of Lopinavir
- CSF-Serum Albumin Ratio ($\log_{10}$) with CSF-Serum Albumin Ratio ($\log_{10}$) of Efavirenz

Correlation coefficients and p-values:
- LDL Cholesterol: $r = 0.21, p = 0.01$
- HDL Cholesterol: $r = -0.23, p = 0.0032$
- Glucose: $r = 0.22, p = 0.0042$
- Diastolic Blood Pressure: $r = 0.20, p = 0.0092$
- Multivariate Regression: $r = 0.40, p < 0.0001$
- CSF-Serum Albumin Ratio with Lopinavir: $r = 0.57, p < 0.0001$
- CSF-Serum Albumin Ratio with Efavirenz: $r = 0.33, p = 0.02$
Age and NRTI Metabolite/Endogenous Nucleotide Ratios

- Cellular senescence may alter intracellular metabolism of NRTIs
- The ratio of NRTI metabolites to their endogenous nucleotides may be a marker of toxicity
- **Hypothesis:** Older age will be associated with higher TFVdp:dATP and FTCtp:dCTP ratios

*Gumond et al, CROI 2018, Abstract 464*
Mechanisms of Premature Ageing May Differ Between Women and Men

• Estrogen has neuroprotective effects so its loss may increase neuronal vulnerability

• Lower antioxidants in women

• Insulin resistance more common in women and linked to cognitive impairment

• Women more likely to have altered iron metabolism, which can affect the CNS
Possible Interventions

- “Lifestyle” modification
  - Exercise, Weight loss
  - Smoking Cessation
  - Moderate Alcohol Use
  - Alter Microbiome
- Modify Existing Medications
- Target components of the metabolic syndrome
  - Pitavastatin (REPRIEVE)
  - Metformin
- Treat coinfections
  - HCV
- Adjunctive therapy
  - Tesamorelin
  - Intranasal insulin
  - Intranasal IGF-1

Graphic courtesy of Peter Hunt, UCSF (and ulead.org)
Stopping Smoking Reduces Risk for Cardiovascular Events

- More than 27,000 HIV+ patients had a total of 3,680 CVEs or mortality
- Adjusted incidence rate ratio in patients who stopped smoking decreased from 2.3 within the first year to 1.5 after > 3 years compared with those who never smoked

Benefits of Exercise, Diabetes Management, & Probiotics

Dufour et al, J Neurovirol 2013, 19(5):410-7


OR 0.38 for Global NCI

DSST = Digit Symbol Substitution Test
TBV = Total Brain Volume

Weitzman et al, Circulation. 2005;112:862-869

d’Ettorre et al, PLoS ONE 2015, 10(9): e0137200

Vrieze et al, Gastroenterology 2012;143:913–916
Conclusions

• Evidence of premature aging exists in persons living with HIV but are not entirely consistent
  – Clinical data
  – Biological data
  – Pharmacological data

• Roles of disease severity and ART should become more clear with time

• Distinguishing the effects of HIV from syndemic conditions is essential
  – Definitional issues
  – Careful assessment of and control for syndemic factors
Acknowledgements

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• Sheela Godbole
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• Ramesh Paranjape

• Ajay Bharti
• Ronald Ellis
• Igor Grant
• Allen McCutchan
• Robert Heaton
• Tom Marcotte

• …Mental Health
• …Drug Abuse
• …Allergy and Infectious Disease

\[\text{NIH}\]
National Institutes of Health
Turning Discovery Into Health

\[\text{CHARTER}\]
CMRP Antiretroviral Therapy Effects Research