HIV & AGING: FROM MITOCHONDRIA TO THE METROPOLIS
Keratinocyte Carcinoma Treatments Among Veterans Living with HIV: Comparison with Current National Guidelines
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Disclosures

No relevant financial conflicts of interest

Honorarium:
Syneos (InVentiv) Health

Supported in part by the Dermatology Foundation and NIH NCATS under UL1TR002378 and KL2TR002381 awards.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.
Keratinocyte Carcinomas
(Non-melanoma Skin Cancers)

BASAL CELL CARCINOMA
SQUAMOUS CELL CARCINOMA
MELANOMA

Photo Credits: Skin Cancer Foundation
Background

Keratinocyte carcinomas (KC) include basal cell carcinomas (BCC) and cutaneous squamous cell carcinomas (cSCC)
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Background

Keratinocyte carcinomas (KC) include basal cell carcinomas (BCC) and cutaneous squamous cell carcinomas (cSCC)

Extrinsic
- Blistering sunburns

Intrinsic
- PTCH1 mutations
- Basal cell nevus syndrome
- Telomere function gene variants

Extrinsic
- Chronic UV exposure
- Ionizing radiation
- Tanning bed use

Intrinsic
- Fair skin
- Blue/green eyes
- Blond/red hair
- Age > 70 y
- Male sex
- Pigment gene variants
- Immunosuppression
- Chronic inflammation
- Inflammatory bowel disease

Extrinsic
- HPV infection
- Drugs:
  - Immunosuppressives
  - Voriconazole
  - Arsenic

Intrinsic
- Lymphomas
- Oculocutaneous albinism
- Recessive dystrophic epidermolysis bullosa
- Xeroderma pigmentosum
Background

Persons living with HIV are aging
Persons aging with HIV face higher burden of non-AIDS defining malignancies, as compared with HIV-negative persons.

Table 1. Standard Incidence Ratios of Selected Non–AIDS-Defining Cancers [2, 5–8]

<table>
<thead>
<tr>
<th>Non–AIDS-Defining Cancer</th>
<th>Cancer Risk (Standardized Incidence Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal</td>
<td>33.4–42.9</td>
</tr>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>14.7–31.7</td>
</tr>
<tr>
<td>Liver</td>
<td>7.0–7.7</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma/Basal cell</td>
<td>3.2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.1–2.6</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>1.0–4.1</td>
</tr>
<tr>
<td>Lung</td>
<td>2.2–6.6</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2.2–2.5</td>
</tr>
<tr>
<td>Renal</td>
<td>1.8–2.2</td>
</tr>
</tbody>
</table>

Background

KC are the most common non-AIDS defining malignancies in persons living with HIV

<table>
<thead>
<tr>
<th>Primary type of malignancy</th>
<th>No. of malignancies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell skin carcinoma</td>
<td>43 (32.3)</td>
</tr>
<tr>
<td>Squamous cell skin carcinoma</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>15 (9.8)</td>
</tr>
<tr>
<td>Anal carcinoma</td>
<td>10 (7.5)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>9 (6.8)</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>6 (4.5)</td>
</tr>
<tr>
<td>Renal carcinoma</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Salivary gland carcinoma</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Brain carcinoma</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Bone carcinoma</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Male genitalia carcinoma</td>
<td>2 (1.5)</td>
</tr>
</tbody>
</table>

4,144 HIV+ persons in the U.S. military followed for a mean of 6.5 years
Background

KC are common, burdensome, and costly

- KC are the most common cancers worldwide and in the U.S.\(^1\)
  - Annual incidence exceed 3x of all other cancers combined\(^1\)

- >5.4 million new KCs diagnosed in 3.3 million U.S. adults in 2012\(^2\)
  - 35% increase from 2006 to 2012\(^2\)
  - 6.9% of U.S. adults age 65+ are treated for KC\(^1\)
  - Cost of KC treatments are estimated at $4.8 billion\(^1\)

- Veterans Health Administration cared for 89,465 veterans with KC and 197,041 with actinic keratoses (KC precursors) in FY2012\(^3\)
  - $356 million ~2% of all VHA outpatient cost

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\(^1\) US Dept of Health and Human Services. The Surgeon General's Call to Action to Prevent Skin Cancer, 2013
Discussion

National Guidelines:

All KC in persons living with HIV are considered high risk warranting more aggressive treatment

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Basal Cell Skin Cancer

Version 1.2019 — August 31, 2018

Squamous Cell Skin Cancer

Version 2.2019 — October 23, 2018

1 NCCN. 2018; 2 NCCN. 2018
Discussion

National Guidelines:

All KC in persons living with HIV are considered high risk warranting more aggressive treatment

Guidelines of care for the management of basal cell carcinoma

Work Group: Christopher Bichakjian, MD, (Co-Chair);4 April Armstrong, MD, MPH;3 Christi Baum, MD,4
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Invited Reviewers: John Y. S. Kim, MD,1 Jeffrey H. Knofl, MD, MS, Bharat Mittal, MD,8
Jeffrey Moyer, MD,9 Thomas Olencki, DO,9,10 and Phillip Rodgers, MD10

Ann Arbor, Michigan; Denver, Colorado; Rochester, Minnesota; Cleveland, Rootstown, Burton, and Columbus, Ohio; Rochester and New York; New York; Sacramento, San Francisco, Yorba Linda, and Stanford, California; Chicago and Schaumburg, Illinois; Kissimmee and Tampa, Florida; Philadelphia, Pennsylvania; Towson and Danville, Maryland; Phoenix, Arizona; and Birmingham, Alabama

Basal cell carcinoma (BCC) is the most common form of human cancer, with a continually increasing annual incidence in the United States. When diagnosed early, the majority of BCCs are readily treated with office-based therapy, which is highly curative. In these evidence-based guidelines of care, we provide recommendations for the management of patients with BCC, as well as an in-depth review of the best available evidence in support of these recommendations. We discuss biopsy techniques for a clinically suspicious lesion and offer recommendations for the histopathologic interpretation of BCC. In the absence of a formal staging system, the best available stratification based on risk for recurrence is reviewed. With regard to treatment, we provide recommendations on treatment modalities along a broad therapeutic spectrum, ranging from topical agents and superficially destructive modalities to surgical techniques and systemic therapy. Finally, we review the available literature and provide recommendations on prevention and the most appropriate follow-up for patients in whom BCC has been diagnosed. (J Am Acad Dermatol 2018;78:540-59.)

Key words: basal cell carcinoma; biopsy; cutaneous; metastasis; phototherapy; radiotherapy; staging; surgery; surveillance; topical therapy

Guidelines of care for the management of cutaneous squamous cell carcinoma

Work Group: Murali Alam, MD, (Co-Chair);4 April Armstrong, MD, MPH,3 Christian Baum, MD,4
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Cutaneous squamous cell carcinoma (cSCC) is the second most common form of human cancer and has an increasing annual incidence. Although most cSCC is cured with office-based therapy, advanced cSCC poses a significant risk for morbidity, impact on quality of life, and death. This document provides evidence-based recommendations for the management of patients with cSCC. Topics addressed include biopsy techniques and histopathologic assessment, tumor staging, surgical and nonsurgical management, follow-up and prevention of recurrence, and management of advanced disease. The primary focus of these recommendations is on evaluation and management of primary cSCC and localized disease, but where relevant, applicability to recurrent cSCC is noted, as is general information on the management of patients with metastatic disease. (J Am Acad Dermatol 2018;78:560-78.)

Key words: biopsy; cutaneous; metastasis; phototherapy; radiotherapy; squamous cell carcinoma; staging; surgery; surveillance; topical therapy

Discussion

National Guidelines: All KC in persons living with HIV are considered high risk warranting more aggressive treatment

- All KC in persons living with HIV are categorized as “high-risk” based on current American Academy of Dermatology and National Cancer Comprehensive Network guidelines

  - Regardless of immunologic parameters or KC histologic subtypes

- Standard surgical excision and Mohs micrographic surgery recommended
  - Electrodessication and curettage not recommended

<p>| Table IX. Level of evidence and strength of recommendations for the surgical treatment of cSCC |</p>
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Level of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment plan</td>
<td>A</td>
<td>II</td>
<td>53</td>
</tr>
<tr>
<td>Standard excision with 4- to 6-mm margins for low-risk primary SCC</td>
<td>B</td>
<td>II</td>
<td>54</td>
</tr>
<tr>
<td>Standard excision for high-risk SCC</td>
<td>B</td>
<td>II</td>
<td>54</td>
</tr>
<tr>
<td>C&amp;E for low-risk primary SCC*</td>
<td>B</td>
<td>II, III</td>
<td>54</td>
</tr>
<tr>
<td>MMS for high-risk SCC*</td>
<td>B</td>
<td>II, III</td>
<td>41,54,57,58</td>
</tr>
</tbody>
</table>

<p>| Table VIII. Level of evidence and strength of recommendations for the surgical treatment of BCC |</p>
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Level of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment plan</td>
<td>A</td>
<td>II</td>
<td>31,41</td>
</tr>
<tr>
<td>Standard excision with 4-mm margins</td>
<td>A</td>
<td>I</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Low-risk BCC</td>
<td>C</td>
<td>III</td>
<td>17,32,33,42,43,49,50</td>
</tr>
<tr>
<td>High-risk BCC</td>
<td>A</td>
<td>I, II</td>
<td></td>
</tr>
<tr>
<td>MMS for high-risk BCC</td>
<td>A</td>
<td>I, II</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

National Guideline & Major Review:

Cancer in PLWH & LGBTQ+ Persons...

Cancer in People Living with HIV

Version 1.2019 — October 19, 2018

Cancer and Lesbian, Gay, Bisexual, Transgender/Transsexual, and Queer/Questioning (LGBTQ) Populations

Gwendolyn P. Quinn, PhD; Julian A. Sanchez, MD; Steven K. Sutton, PhD; Susan T. Vadaparampil, PhD, MPH; Giang T. Nguyen, MD, MPH; B. Lee Green, PhD; Peter A. Kanetsky, PhD, MPH; Matthew B. Schabath, PhD

1 NCCN. 2018; 2 Quinn et al. CA Cancer J Clin 2015
Prostate Cancer

Descriptive epidemiology

Other than skin cancer, prostate cancer is the most frequently diagnosed cancer in men ...

Breast Cancer

Descriptive epidemiology

Excluding cancers of the skin, breast cancer is the most frequently diagnosed cancer in women.\textsuperscript{18} ...

No discussion on skin cancers ????
Keratinocyte carcinomas (KC) are common in persons aging with HIV and impose high and rising treatment burden.

KC epidemiologic studies are limited by the lack of cancer registry data.

Current guidelines categorize all KC in people living with HIV as high-risk and recommend aggressive surgical treatments, regardless of the patient’s age, comorbidity, frailty, immune status, or the KC’s histologic pattern.
Keratinocyte carcinomas (KC) are common in persons aging with HIV and impose high and rising treatment burden.

KC epidemiologic studies are limited by the lack of cancer registry data.

Current guidelines categorize all KC in people living with HIV as high-risk and recommend aggressive surgical treatments, regardless of the patient’s age, comorbidity, frailty, immune status, or the KC’s histologic pattern.
Specific Aim

To understand real-world treatment patterns of keratinocyte carcinomas among veterans living with HIV
Cohort Profile

Cohort Profile: The HIV Atlanta Veterans Affairs Cohort Study (HAVACS)

Jodie L. Guest,1,2,3,* Abeer Moanna,1,3 Susan Schlueter Wirtz,1,3 Edwin C. Caruth,1 Christopher Rentsch,4,5 Vince D. Marconi1,2,3 and David Rimland1,3

1Atlanta VA Medical Center, Decatur, GA, USA, 2Rollins School of Public Health at Emory University, Atlanta, GA, USA, 3Emory School of Medicine, Atlanta, GA, USA, 4VA Connecticut Healthcare System, West Haven, CT, USA and Yale School of Medicine, New Haven, CT, USA
Methods

HIV Atlanta Veterans Affairs Cohort Study (HAVACS)

- 4,664 HIV+ veterans who have sought care at the Atlanta VA Medical Center from 1982 to 2017
- >60% of active HAVACS participants are >50 of age by 2017
- Demographic and clinical factors were prospectively collected during visits in the HAVACS database
- Diagnostic and procedures codes relevant to skin cancers collected via the VA HIV Clinical Case Registry

1 Guest et al. Int J Epidemiol. 2017
• Biopsy-confirmed KC based on manual chart review of patients with ≥1 compatible code in the VA HIV Clinical Case Registry in Jan 2002-Aug 2017
  • CPRS implemented in Atlanta VA Dermatology clinic in 2001-2002
  • ICD-9 173.x & ICD-10 C44.x
    • “Other and unspecified malignant neoplasm of skin”
  • Chart review performed by trained data analyst (C.H.A.) and board-certified dermatologist (H.Y.). Discrepancies were discussed with second board-certified dermatologist (S.C.C.) to reach consensus
  • Restricted biopsy-confirmed cutaneous SCC and BCC
    • Excluded mucosal and anogenital sites
• Documented definitive treatment was described and compared by histologic subtype, age at biopsy, and CD4 count at biopsy using Fisher’s exact tests.
  • $P < 0.05$ considered significant in 2-sided tests
Results

Figure 1. Participants Flow Diagram

HIV Atlanta VA Cohort Study as of 8/15/2017 (N = 4,664)

Analytic sample (N = 3,353)

Skin cancer ICD-9/-10 & CPT codes (N = 84; 280 distinct codes)

Validated biopsy-confirmed KC (N = 45; 159 distinct KC’s)

Missing date for first ID clinic visit (N = 1,187)

No follow up visit (N = 92)

Error in visit dates (N = 32)
### Results

#### Table 1. Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>≥1 KC diagnosed in 2002-2017</th>
<th>No KC diagnosed in 2002-2017</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sample size (N)</td>
<td>45</td>
<td>3,308</td>
<td></td>
</tr>
<tr>
<td>Age at Enrollment, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-44</td>
<td>19 (42.2%)</td>
<td>1,860 (56.2%)</td>
<td>0.03</td>
</tr>
<tr>
<td>45-54</td>
<td>13 (28.9%)</td>
<td>917 (27.7%)</td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>8 (17.8%)</td>
<td>422 (12.8%)</td>
<td></td>
</tr>
<tr>
<td>65+</td>
<td>5 (11.1%)</td>
<td>109 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (100%)</td>
<td>3,198 (96.7%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>110 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Race / Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Caucasian/White</td>
<td>44 (97.8%)</td>
<td>643 (19.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Hispanic African American/Black</td>
<td>1 (2.2%)</td>
<td>2,583 (78.1%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>43 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Other or unknown</td>
<td>0</td>
<td>39 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>Follow Up Time, years</td>
<td>15.9</td>
<td>8.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Table 2. KC Treatment Patterns

<table>
<thead>
<tr>
<th></th>
<th>N = 159 KC lesions in 45 patients</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative treatments:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrodessication &amp; Curettage</td>
<td>40 (25.2%)</td>
<td></td>
</tr>
<tr>
<td>Topical therapy (e.g., 5-fluorouracil, imiquimod)</td>
<td>14 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>2 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Active monitoring</td>
<td>2 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Declined active treatment</td>
<td>1 (0.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical treatments:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard excision</td>
<td>47 (29.6%)</td>
<td></td>
</tr>
<tr>
<td>Mohs micrographic surgery</td>
<td>47 (29.6%)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy / Radiation therapy</td>
<td>2 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4 (3.1%)</td>
<td></td>
</tr>
</tbody>
</table>
## Results

### Table 3.
Factors Associated with Treatment Selection

<table>
<thead>
<tr>
<th></th>
<th>Conservative Treatment</th>
<th>Standard Excision</th>
<th>Mohs Micrographic Surgery</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histologic subtypes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>5 (71.4%)</td>
<td>1 (14.3%)</td>
<td>1 (14.3%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Medium risk</td>
<td>49 (40.8%)</td>
<td>39 (32.5%)</td>
<td>32 (26.7%)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>7 (28.0%)</td>
<td>6 (24.0%)</td>
<td>12 (48.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at the time of skin biopsy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years old</td>
<td>9 (56.3%)</td>
<td>3 (18.8%)</td>
<td>4 (25.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50-65 years old</td>
<td>42 (48.8%)</td>
<td>29 (33.7%)</td>
<td>15 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>&gt;65 years old</td>
<td>10 (23.8%)</td>
<td>9 (21.4%)</td>
<td>23 (54.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 count at the time of skin biopsy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200 cells/mm(^3)</td>
<td>8 (53.3%)</td>
<td>4 (26.7%)</td>
<td>3 (20.0%)</td>
<td>0.57</td>
</tr>
<tr>
<td>200-500 cells/mm(^3)</td>
<td>31 (46.2%)</td>
<td>19 (28.4%)</td>
<td>17 (25.4%)</td>
<td></td>
</tr>
<tr>
<td>&gt;500 cells/mm(^3)</td>
<td>22 (36.1%)</td>
<td>17 (27.9%)</td>
<td>22 (36.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Histologic subtypes are categorized based on NCCN guidelines into low risk (superficial BCC and SCC in situ or Bowenoid SCC), medium risk (nodular or superficial and nodular BCC and invasive SCC or SCC NOS), or high risk (morpheaform, ulcerated, basosquamous, or micronodular BCC and acantholytic or poorly differentiated SCC).
Contrary to national guidelines, more than 1 of 3 keratinocyte carcinomas diagnosed in veterans living with HIV were treated conservatively using electrodessication and curettage, topical therapies, or cryotherapy. More aggressive treatment was associated with older age at the time of diagnosis, but not with aggressive histologic subtype or CD4 count.

To provide clinically meaningful risk stratification and to guide KC treatment selection in persons aging with HIV, further understanding of how tumor- and host-level risk factors influence KC outcomes will be required.

The morbidity, recurrence, quality of life impact, and cost from KC and various KC treatments in aging persons living with HIV should be further elucidated.
Acknowledgements & Funding

Mentors
• Suephy C. Chen, MD MS
• Amita Manatunga, PhD
• Aaron W. Trammell, MD MSc
• Jodie L. Guest, PhD MPH
• Vincent C. Marconi, MD
• Robert A. Swerlick, MD
• Ragini R. Kudchadkar, MD
• Patrick S. Sullivan, PhD DVM

Research Team
• Colin H. Adler, MPH
• Mona Rai, MPH
• Rincy Varughese, MS MPH
• Chao Zhang, PhD
• Bridget Bradley, RN

NIH NCATS UL1TR002378 & KL2TR002381
Dermatologist Investigator Research Fellowship

American Skin Association
Research Grant for Quality of Life/Health Services/Outcome Studies

Pilot Award on Understanding, Preventing and Managing Immunotherapy-Related Adverse Events Associated with Checkpoint Inhibition for Melanoma and Other Cancers

NIH NIAID P30AI050409
Association Between HIV Serostatus, Metabolic Syndrome, and Neurobehavioral Disturbances Among Aging Adults

Caitlin Pope, PhD
Association between HIV serostatus, metabolic syndrome, and neurobehavioral disturbances among aging adults

Caitlin N. Pope, PhD

Postdoctoral Research Scientist
Center for Injury Research and Policy
The Research Institute at Nationwide Children’s Hospital

HIV and Aging: From Mitochondria to the Metropolis - Special Populations | April 12th, 2019
An Aging HIV Population

Increased life expectancy
cART

Most common comorbidities:
(Gallant et al., 2017)
Hypertension
Hyperlipidemia
Endocrine disease

Metabolic Syndrome (MetS)

Metabolic Risk Factors (at least 3 out of 5)

- **Abdominal obesity**
  - ≥ 35 inches women
  - ≥ 40 inches for men

- **High Triglycerides**
  - ≥ 150 mg/dL

- **Low HDL Cholesterol**
  - ≤ 50 mg/dL women
  - ≤ 40 mg/dL men

- **High Blood Pressure**
  - ≥ 130/85 mmHg

- **High Fasting Blood Sugar**
  - ≥ 100 mg/dL
MetS

MetS and HIV
Prevalence ranges 11.2% - 45.4% (Paula et al., 2013)

Increased risk for MetS

Interactions with cART (Calza et al., 2017)

MetS and brain health
General population – Volume reduction in the hippocampus and frontal lobes, white matter alterations (Yates et al., 2012)

MetS significantly associated with global neurocognitive deficits in PLWH, but not in HIV-controls (Yu et al., 2019)
Neurobehavioral Disturbances

Along with disease-related neurocognitive impairment, we also know that brain injury can be accompanied with behavioral changes.

Behaviors linked to dysregulation in the frontal-subcortical circuits (Cummings, 1993; Grace et al., 1999)

Increased neurobehavioral disturbances in PLWH (Kamat et al., 2016)

- Apathy
  - Diminished initiation, loss of interest, blunted affect

- Disinhibition
  - Impulsivity and issues with self-regulation

- Executive Dysfunction
  - Difficulties with goal-driven behavior
To investigate the effects of HIV serostatus and MetS on neurobehavioral disturbances (apathy, disinhibition, and executive dysfunction).

H1: After controlling for necessary covariates, having HIV and MetS would be independently associated with increased neurobehavioral disturbances.

H2: The association between MetS and neurobehavioral disturbances would be greater for PLWH compared to those without HIV.
Multi-Dimensional Successful Aging Among HIV-Infected Adults Study

Inclusion criteria: between age 35-65, English-speaking, capable of providing informed consent

Exclusion criteria: Hx of non-HIV neurological disorder, current psychotic disorder, Hx of learning disability, acute or early HIV-infection*

215 participants from the San Diego area (117 PLWH, 98 HIV-)
Methods: Materials

Metabolic Syndrome (MetS)
Presence of 3 or more of the metabolic risk factors determined by laboratory assessment (phlebotomy and anthropometric measurement) and current medication use

Frontal Systems Behavior Scale (FrSBe) – Self rating form
46-item, 3 subscales: apathy, disinhibition, executive dysfunction

5-point scale: 1 (almost never), 2 (seldom), 3 (sometimes), 4 (frequently), 5 (almost always)

T-score (M = 50, SD = 10) adjusted for age, gender, and education

2 time points: before illness or injury, at the present time
<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>PLWH (n = 117)</th>
<th>HIV- (n = 98)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M (SD)</td>
<td>51.1 (8.4)</td>
<td>51.1 (7.6)</td>
<td>0.90</td>
</tr>
<tr>
<td>Education, M (SD)</td>
<td>14.1 (2.5)</td>
<td>15.0 (2.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>83.8%</td>
<td>68.4%</td>
<td>0.01</td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>56.4%</td>
<td>68.4%</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>19.7%</td>
<td>13.3%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>17.1%</td>
<td>17.4%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6.8%</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>LT Psychiatric Characteristics (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
<td>55.9%</td>
<td>19.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Substance Use</td>
<td>70.3%</td>
<td>37.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol Use Disorder</td>
<td>54.1%</td>
<td>29.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cannabis Use Disorder</td>
<td>27.0%</td>
<td>17.3%</td>
<td>0.092</td>
</tr>
<tr>
<td>Methamphetamine Use Disorder</td>
<td>34.2%</td>
<td>0.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Other Drug Use Disorder</td>
<td>49.5%</td>
<td>18.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note. PLWH = people living with HIV, HIV- = HIV-negative, LT = lifetime.
### HIV Disease Characteristics

**PLWH**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of infection (years), Median (IQR)</td>
<td>18.8 (10.7, 25.4)</td>
</tr>
<tr>
<td>Current CD4, Median (IQR)</td>
<td>638 (432, 853)</td>
</tr>
<tr>
<td>Nadir CD4, Median (IQR)</td>
<td>180 (45, 322)</td>
</tr>
<tr>
<td>AIDS (%)</td>
<td>61.5%</td>
</tr>
<tr>
<td>On antiretroviral therapy (%)</td>
<td>95.7%</td>
</tr>
<tr>
<td>Detectable plasma RNA (%)</td>
<td>8.7%</td>
</tr>
<tr>
<td>Metabolic risk factors</td>
<td>PLWH</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>MetS (%)</td>
<td>37.6%</td>
</tr>
<tr>
<td>Elevated waist circumference (%)</td>
<td>41.2%</td>
</tr>
<tr>
<td>Elevated triglycerides (%)</td>
<td>39.3%</td>
</tr>
<tr>
<td>Reduced HDL-C (%)</td>
<td>51.8%</td>
</tr>
<tr>
<td>Elevated blood pressure (%)</td>
<td>50.4%</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>26.5%</td>
</tr>
<tr>
<td>BMI M (SD)</td>
<td>27.6 (5.3)</td>
</tr>
</tbody>
</table>

Note. BMI = body mass index.
Apathy

Disinhibition

Executive Dysfunction

PLWH

HIV-

MetS (Yes)
The table shows the results of multivariable linear regressions with main effects of HIV serostatus and MetS while controlling for sociodemographic covariates. The regressions were conducted using a stepwise backwards selection method based on Akaike information criterion (AIC).

<table>
<thead>
<tr>
<th></th>
<th>Apathy</th>
<th>Executive Dysfunction</th>
<th>Disinhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (SE)</td>
<td>p</td>
<td>β (SE)</td>
</tr>
<tr>
<td>HIV serostatus</td>
<td>6.70</td>
<td>0.012</td>
<td>4.98</td>
</tr>
<tr>
<td></td>
<td>(2.634)</td>
<td></td>
<td>(2.162)</td>
</tr>
<tr>
<td>MetS</td>
<td>5.30</td>
<td>0.047</td>
<td>4.57</td>
</tr>
<tr>
<td></td>
<td>(2.656)</td>
<td></td>
<td>(2.141)</td>
</tr>
</tbody>
</table>

Notes. MetS = metabolic syndrome.
Multivariable linear regressions with main effects of HIV serostatus and MetS while controlling for sociodemographic covariates were conducted using stepwise backwards selection method based on Akaike information criterion (AIC).
The apathy model controlled for lifetime major depressive disorder.
The executive dysfunction model controlled for lifetime major depressive disorder and lifetime alcohol use disorder.
The disinhibition model controlled for lifetime major depressive disorder, lifetime cannabis use disorder, and ethnicity (White vs. Hispanic, White vs. Black).
HIV serostatus and MetS was statistically associated with more apathy and executive dysfunction, but only HIV serostatus was significantly associated with more disinhibition.

May suggest frontal-subcortical circuits and brain regions are not uniformly impacted by the two diseases (Cummings, 1993).

Supports previous findings documenting associations between HIV and neurobehavioral disturbances and extends the research on MetS and brain health in those with HIV (Kamat et al., 2016; Yu et al., 2019).

Longitudinal data and functional imaging is needed to determine temporality and localization of disease-related brain injury.
Clinical Implications

PLWH and MetS may require more attention from healthcare teams

Diagnostic screening should include both performance-based cognitive tasks as well as behavioral screeners

Enhanced health-related education and alternative disease management strategies to minimize risk behaviors and improve quality of life
Acknowledgments

Sustained Training on Aging and HIV Research (STAHR) Program 5R25MH108389-02 (PIs: Jeste, Dilip V.; Letendre, Scott L.)

UC San Diego Stein Institute for Research on Aging

UC San Diego Department of Psychiatry

HIV Neurobehavioral Research Program (HNRP)

The Research Institute at Nationwide Children’s Hospital / The Ohio State University

University at Albany State University of New York

Comprehensive Cancer Center, University of Puerto Rico

David Yassai- Gonzalez, B.S.

Jessica Montoya, PhD

Elizabeth Vasquez, DrPH, MPH

Josué Pérez-Santiago, PhD

Ronald Ellis, MD, PhD

Dilip V. Jeste, MD

David Moore, PhD

María J. Marquine, PhD
Appendix
Effect size of differences (Cohen’s D)

![Bar chart showing effect size differences (Cohen’s D) for HIV serostatus across Apathy, Disinhibition, and Executive functions.](chart.png)
Model Covariates

Apathy
- Lifetime Major Depressive Disorder
- Lifetime Alcohol Use Disorder
- Lifetime Methamphetamine Use Disorder

Disinhibition
- Ethnicity
- Lifetime Major Depressive Disorder
- Lifetime Alcohol Use Disorder
- Lifetime Cannabis Use Disorder
- Lifetime Methamphetamine Use Disorder

Executive Dysfunction
- Lifetime Major Depressive Disorder
- Lifetime Alcohol Use Disorder
- Lifetime Methamphetamine Use Disorder
- Lifetime Other Substance Use Disorder
<table>
<thead>
<tr>
<th></th>
<th>Apathy β (SE)</th>
<th>p</th>
<th>Disinhibition β (SE)</th>
<th>p</th>
<th>Executive Dysfunction β (SE)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV serostatus</td>
<td>6.70 (2.634)</td>
<td>0.012</td>
<td>5.25 (2.485)</td>
<td>0.036</td>
<td>4.98 (2.162)</td>
<td>0.022</td>
</tr>
<tr>
<td>MetS</td>
<td>5.30 (2.656)</td>
<td>0.047</td>
<td>--</td>
<td>--</td>
<td>4.57 (2.141)</td>
<td>0.034</td>
</tr>
<tr>
<td>LT Major Depression</td>
<td>5.58 (2.671)</td>
<td>0.038</td>
<td>6.60 (2.556)</td>
<td>0.011</td>
<td>5.21 (2.160)</td>
<td>0.017</td>
</tr>
<tr>
<td>LT Alcohol Use Disorder</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>2.95 (2.041)</td>
<td>0.150</td>
</tr>
<tr>
<td>LT Cannabis Use Disorder</td>
<td>---</td>
<td>---</td>
<td>6.22 (2.782)</td>
<td>0.027</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Ethnicity (White vs. Hispanic)</td>
<td>---</td>
<td>---</td>
<td>8.23 (3.100)</td>
<td>0.009</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Ethnicity (White vs. Black)</td>
<td>---</td>
<td>---</td>
<td>-5.70 (3.110)</td>
<td>0.069</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Notes. MetS = metabolic syndrome, LT = lifetime.
Multivariable linear regressions with main effects of HIV serostatus and MetS while controlling for sociodemographic covariates were conducting using stepwise backwards selection method based on Akaike information criterion (AIC).
The apathy model controlled for lifetime major depressive disorder.
The disinhibition model controlled for lifetime major depressive disorder, lifetime cannabis use disorder, and ethnicity (white vs. Hispanic, White vs. Black).
The executive dysfunction model controlled for lifetime major depressive disorder and lifetime alcohol use disorder.
Senescent Phenotype Induced by p9ORSK-NRF2 Signaling Sensitizes Monocytes and Macrophages to Oxidative Stress in HIV+ Individuals: Implications for Atherogenesis

Meera Singh, PhD
Senescent phenotype induced by p90RSK-NRF2 signaling sensitizes monocytes and macrophages to oxidative stress in HIV+ individuals: implications for atherogenesis

Meera Singh
Research Assistant Professor
Microbiology and Immunology
University of Rochester, Rochester NY
meera_singh@urmc.rochester.edu
The major cellular events in the progression of atherosclerosis

1. Endothelial permeability
2. Monocyte adhesion and transmigration
3. Macrophage transformation into foam cells
4. SMC migration

[Diagram showing cellular events in atherosclerosis]
p90RSK-ERK5 signaling in endothelial cells

- Oxidative stress
- p90RSK phosphorylation
- ERK5: phosphorylation of S496 residue
- ERK5 transcriptional activity
- EC inflammation, apoptosis
- Plaque formation

Sun Heo et al, 2016, Abe et al 2017
Primary human Monocytes

- Increased Oxidative stress
- p90RSK phosphorylation
- ERK5: phosphorylation of S496 residue
- ERK5 transcriptional activity
- Phagocytosis by Monocyte/Macrophages
- Plaque formation

Courtesy: Dr. Jun-Ichi Abe’s group, MD Anderson, TX
Study Design

**URMC, Rochester, NY**

**Study participants:** HIV infected, cART treated (n=94) and HIV uninfected (n=86)

- Carotid Intima Media Thickness (CIMT) and Carotid Artery Stenosis (CAS-plaque formation)
- Reynold’s Risk Score
- Measurement of intracellular phospho-p90RSK in monocytes by Flow Cytometry

**In vitro experiments:** primary human monocytes, bone marrow derived mouse macrophages

Singh at el, 2019 Circulation

**MD Anderson, Texas**

**Mouse Models:**
- Low density lipoprotein receptor knock out mice (Ldlr−/−)- treated with cART
- Dominant Negative p90RSK knock out mice (DN-p90rsk-MTg)
- p90RSK overexpression mice (WT-p90rsk-MTg/ldlr−/−)
Monocytes-p90RSK of HIV+ individuals is more sensitive to oxidative damage

HIV infected, cART treated (n=94) and HIV uninfected (n=86)

cART treatment and increased ph-p90RSK levels were significant determinants of plaque formation by Multivariate logistic regression.
Ldlr-/- mice: Low Density Lipoprotein receptor knock out mice

High Fat diet for 2 weeks → Partial Carotid Ligation

IHC analysis for Plaque formation → Two weeks post treatment → cART treatment

Vehicle Treatment → One week after PCL

cART regimen used: ATV/RTV/TDF/FTC

* ECA: External Carotid artery, ICA: Internal carotid artery, OA: Occipital artery, STA: Superior thoracic artery
cART treated *Ldlr*⁻/⁻ mice show increased plaque formation.
cART treated $Ldlr^{-/-}$ mice show increased plaque formation
Mice which overexpress p90RSK also show increased plaque formation

ORO: Oil red O
Conclusions and Clinical Implications

- cART initiates a cycle of p90RSK activation/sensitization via increasing the production of mitochondrial reactive oxygen species (ROS) in monocytes/macrophages.

- p90RSK activation inhibits nuclear factor erythroid 2-related factor 2 (NRF2)-antioxidant response element (ARE) transcriptional activity, which is known to accelerate the vascular aging process.

- Novel therapeutic approaches aimed at reducing p90RSK activity should be investigated for preventing future CVD events.

- H$_2$O$_2$-induced p90RSK activation in CD14$^+$ monocytes obtained from patients may serve as a viable biomarker to predict future CVD events in HIV$^+$ patients.
Acknowledgements

Maggirwar lab

Sanjay Maggirwar, MBA, PhD
Vir Singh, PhD
Sumanun Suwunnakorn, PhD
Emily Weber
Sydney Simpson
Edward Sambrano
Dorota Piekna

Dr. Jun-ichi Abe
Dr. Giovanni Schifitto
Abe Lab Members
Ultrasound Team
Biostatistics Team
Clinical Research Center Team

Funding: NIH RO1s HL123346, HL128155, NS054578, NS066801, AG054328

University of Rochester –Center For AIDS Research NIH P30 AI078498

Rochester Victory Alliance and Infectious Disease Unit

Department of Microbiology and Immunology
HIV & AGING:
FROM MITOCHONDRIA TO THE METROPOLIS
Kevin P. High
MD, MS

High has been a faculty member at Wake Forest since 1993 and is currently President, Health System for Wake Forest Baptist Health. Previous positions include: Tinsley R. Harrison Professor and Chair of the Department of Internal Medicine, Associate Dean for Clinical and Community Research, and Chief, Section on Infectious Diseases. He is a member of the National Advisory Council for the National Institute on Aging (NIA), served as a member of the Board of Directors of the American Board of Internal Medicine (ABIM) from 2006-2010 and as Chair of the Education Committee of the Infectious Diseases Society of America from 2008-2010. He is also a Past President of the Association of Specialty Professors.
Aging with HIV:
life-long lessons

Kevin P. High, MD, MS
Professor of Medicine and Translational Science
Wake Forest School of Medicine
President, Health System
Wake Forest Baptist Health
Disclosures/Acknowledgements

• Research Funding
  – NIA
  – John A. Hartford Foundation

• Royalties
  – Associate Editor, Hazzard’s *Geriatric Medicine and Gerontology, 6th and 7th editions*

• Consultant
  – ViiV Healthcare
JK

- 1996 – 49 yo man initial Dx of HIV; severe weight loss, but no OI or other serious illness
  - Started on clinical trial of stavudine/lamivudine/indinavir
  - Gained 40 lbs. in 6 months
- 1997-99 – one episode of bacterial pneumonia; some depression, occasional herpes keratitis
- 2003 – diabetes mellitus w/ hyperlipidemia
- 2004 – LE pain c/w neuropathy
- 2005 – BPH severe enough to require TURP
JK

- 2006 – severe LLE pain → popliteal aneurysm requiring surgical repair
- 2007 – constipation and rectal discharge → sigmoidoscopy → rectal carcinoma → surgery/XRT
- 2009 – disabling sweats/hot flushes → venlafaxine, testosterone
- 2012 – lost his balance and fell; unrelenting back pain → thoracic vertebral compression fracture
- 2016 – acute myocardial infarction
- 2018 – CKD (Creat 1.9)
• Treated with multiple ART’s over the years
  – zidovudine, didanosine, stavudine, abacavir, lamivudine, tenofovir, nevirapine, indinavir, nelfinavir, ritonavir, fosamprenavir – VL nearly always undetectable

• At least 9 morbidities developed from ages 52-68
  – Diabetes, HTN, Hyperlipidemia, BPH, peripheral vascular disease, rectal carcinoma, fragility fracture, coronary artery disease, renal disease
  – Became very depressed, lost his job, social isolation – complained of severe fatigue from day 1 that never resolved
• As humans have increasingly controlled their environment, their life expectancy has ↑ dramatically ("Rectangularization" of the survival curve)
Life Expectancy with/without ART

http://www.vox.com/2015/12/1/9814026/world-aids-day-2015-hiv-awareness
ART “rectangularized” the survival curve for HIV by “controlling the environment”
Trends in the Percentage Distribution of Deaths due to HIV Infection by Age Group, United States, 1987–2015

Note. For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
So . . . . what does it mean to age with HIV infection?

Are there life-long lessons for HIV from aging research?
"You’re looking old Indy . . ."
Marian

"It’s not the years, Honey, it’s the mileage . . . ." Indiana Jones
Aging mechanisms link to the development of chronic disease

Slide courtesy Felipe Sierra, PhD
Aging and incidence of CV disease, Dementia, Cancer in the general population

A. England cardiovascular disease rates

B. Europe dementia rates

C. UK cancer rates

Current Biology 22, R741–R752, September 11, 2012
<table>
<thead>
<tr>
<th>Disease</th>
<th>HIV</th>
<th>Risk Factors Among HIV+</th>
<th>ART Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Direct injury, HBV and HCV progress rapidly</td>
<td>Alcohol, IDU, steatosis from obesity and diabetes</td>
<td>DDI, nevaripine, AZT, D4T</td>
</tr>
<tr>
<td>Heart</td>
<td>Direct injury (MI and CHD), also increases inflammation</td>
<td>Smoking, alcohol, hypertension, obesity, cocaine use</td>
<td>Hyperlipidemia (PIs), EFV, thymidine analogues, ABC</td>
</tr>
<tr>
<td>Kidney</td>
<td>Direct injury, progress rapidly</td>
<td>Smoking, hypertension, diabetes, HCV, Black race</td>
<td>Tenofovir, and some other ARVs</td>
</tr>
<tr>
<td>Lung</td>
<td>Pneumonia, pulmonary HTN</td>
<td></td>
<td>Smoking, other inhalants</td>
</tr>
<tr>
<td>Anemia</td>
<td>Direct injury, inflammation</td>
<td></td>
<td>Smoking, other inhalants</td>
</tr>
<tr>
<td>Brain</td>
<td>Wet and dry stroke</td>
<td></td>
<td>Smoking, hypertension, brain lesions</td>
</tr>
<tr>
<td>Cancer</td>
<td>Direct injury, chronic inflammation</td>
<td></td>
<td>Smoking, alcohol, infections (HPV, CMV, HCV, HBV, etc.)</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteopenia and falls</td>
<td>Smoking, wasting, inactivity</td>
<td>??</td>
</tr>
</tbody>
</table>

Age is a major risk factor for ALL of these co-morbidities
The risk for developing many morbidities remains higher than expected (~1.5 to 2.0 fold) even in those with “well-controlled” HIV

- Cardiovascular disease [1-3]
- Cancer (non-AIDS) [4]
- Bone fractures / osteoporosis [5,6]
- Liver disease [7]
- Kidney disease [8]
- Cognitive decline [9]

83 years old; HTN, Hyperlipidemia, prior MI

83 years old; HTN, Hyperlipidemia, prior MI
What do integrative functional assessments add?
Examples of Functional “biomarkers”

- Physical function
  - Gait speed, grip strength, SPPB/other composite functions, 6 min walk distance
- Cognitive function
  - MOCA, many others
- Multi-morbidity/Cumulative deficit scores
  - Rockwood, VACS (for HIV)
- Vulnerability/Resilience
  - Fried Frailty Index, Resilience (Psychosocial)
Death and Disability Rate by Modified Physiologic Index score: The Health ABC Study

Score based on tertiles of:
1. Systolic Blood Pressure
2. Forced Vital Capacity
3. Digit Symbol Substitution Test
4. Cystatin-C
   And *a priori* cut-points of
5. Serum Fasting Glucose
   (<126; 126-142,≥142)

Trajectories of functional decline
Gait Speed & Grip Strength

Grip Strength and Age by HIV-serostatus

Usual Gait Speed and Age by HIV Status


Conceptualization: Mechanism of Aging

Slide courtesy Felipe Sierra, PhD

Sierra & Kohanski
J Gerontol June 2014

López-Otín et al.
Cell 153:1194 (2013)
The Goal of Aging Research: A New Kind of Old Person

Slide courtesy of Richard Miller, U Michigan

Normal person, age 70  Normal person, age 114
A new paradigm – address the most common risk factor for all chronic disease, simultaneously, not one at a time.
Aging mechanisms link to the development of chronic disease.

Slide courtesy Felipe Sierra, PhD
EXAMPLE: Epigenetics

Changes in methylation at CpG sites alter gene expression without changing the inherited genetic code.

Methylation patterns can be used to predict a person’s chronologic age.

(S. Horvath Genome Biol. 2013)

Methylation patterns are also beginning to reveal differences between chronologic and biologic age.

DNA Methylation – may be the single best marker of “passing time,” i.e. Chronologic Age
DNA Methylation and Age Verified in nearly all tissues (prostate, head & neck, cartilage?)
Epigenetic “clock” shows age acceleration in those with HIV in both blood and brain

- Examined both brain and blood; age acceleration on average:
  - Brain 7.4 years
  - Blood 5.2 years
- Not controlled for cell type
VACS Cohort – similar exposures other than HIV Infection

 Avg. 9 years between visits (HIV+)
And one more . . . . COBRA

Fig. 1. (a) Age advancement (biological minus chronological age) in HIV-positive and HIV-negative COBRA participants and blood donors (Ps from linear regression); (b) Correlation between age advancement and chronological age in HIV-positive and HIV-negative COBRA participants and blood donors (no interaction between chronological age and HIV-status/group, \( P = 0.66 \)). BD, blood donors; COBRA, Co-morBidity in Relation to AIDS.

AIDS 2019, 33:259–268
Summary of Increased DNA Methylation in blood cells of PAWH

Figure 1. Treated HIV-Infected Individuals' Display Accelerated Aging as Assessed by 5mC Patterns
May also be true in kids/adolescents . . . .

Some studies say yes . . . . But effect is greatly attenuated (eliminated?) by ART.
EXAMPLE: ACCUMULATION OF SENESCENT CELLS

Peripheral T-cell pool
3x10^{11} cells

- Influx of newly generated T cells
- Thymus
- Bone marrow
- Input of precursors

- Autoproliferation
- Cell loss

Daily replacement
1% of the pool

Daily need
3x10^9 T cells

Slide courtesy Jorg Goronzy, MD
Aging and T cell Regeneration

Peripheral T-cell pool
3x10^{11} cells

- Influx of newly generated T cells
- Thymus
- Input of precursors
- Bone marrow
- Autoproliferation

- Cell loss

Daily replacement
1% of the pool

Daily need
3 x 10^9 T cells

Slide courtesy Jorg Goronzy, MD
Increased “senescent” T cells, particularly CD8; indicated by lack of CD28 expression

Aging and T cell Regeneration in the presence of HIV/CMV/Other chronic viruses
Cellular Senescence 1.0 – A Primer

- First described by Hayflick (1965)
- “Irreversible growth and proliferation arrest induced by stress”

SASP – strongly pro-inflammatory and has many bystander effects!
Is senescence a final common pathway?

Is anything practical on the horizon for humans?

• “The senolytic cocktail, dasatinib plus quercetin, which causes selective elimination of senescent cells, decreased the number of naturally occurring senescent cells and their secretion of frailty-related proinflammatory cytokines in explants of human adipose tissue. Moreover, intermittent oral administration of senolytics to both senescent cell–transplanted young mice and naturally aged mice alleviated physical dysfunction and increased post-treatment survival by 36% while reducing mortality hazard to 65.”

• Nature Medicine | VOL 24 1246 | AUGUST 2018 | 1246–1256 | www.nature.com/naturemedicine
Senolytics and/or anti-SASP compounds

Ageing Research Reviews 46 (2018) 14–31

**Natural:**
- Tocotrienols
- Quercetin
- Piperlongumine

**Synthetic:**
- Dasatinib
- Navitoclax and other Bcl family inhibitors
- Panobinostat
- HSP90 inhibitors
- FOXO4-p53 targeting peptide
- 2-Deoxy-D-glucose

**Senolytic**

**Apoptosis resistance**

**Senescence-associated secretory phenotype**

**Natural:**
- Naringenin
- Apigenin
- Epigallocatechin gallate

**Synthetic:**
- Metformin
- Rapamycin
- JAK inhibitors
- Aspirin

**Natural:**
- Curcumin
- Quercetin
- Naringenin
- Apigenin
- Kaempferol
- Epigallocatechin gallate
- Catechin
- Genistein
- Resveratrol
- Pterostilbene
- Phloroglucinol
- Ginsenosides
- Oleuropein and oleacein
- Spermidine
- Urolithins
- NAD+
Transplanted Senescent Cells accelerate disability and reduce median survival
Senolytics reduce disability and increase median survival (both healthspan and lifespan improved!) at 20 months, but not as effective at 24 months.
Yeah, but that’s mice; what about humans?
No change in pulmonary Fxn, but Physical Fxn improved in a number of ways

<table>
<thead>
<tr>
<th>Functional measure</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Difference</th>
<th>Within-subjects</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Δ ± SD</td>
<td>p-Value</td>
<td>r</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (L/s)</td>
<td>2.1 ± 0.9</td>
<td>2.2 ± 0.7</td>
<td>+0.1 ± 0.3</td>
<td>0.38</td>
<td>0.95*</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>72.3 ± 26.3</td>
<td>73.4 ± 20.1</td>
<td>+1.14 ± 11</td>
<td>0.71</td>
<td>0.92*</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.7 ± 1.0</td>
<td>2.6 ± 1.0</td>
<td>−0.2 ± 0.9</td>
<td>0.53</td>
<td>0.74*</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>67.3 ± 23.5</td>
<td>67 ± 17.9</td>
<td>−0.29 ± 9.1</td>
<td>0.91</td>
<td>0.94*</td>
</tr>
<tr>
<td>FEV1: FVC (%)</td>
<td>92.4 ± 8.3</td>
<td>91.6 ± 4.1</td>
<td>−0.7 ± 10</td>
<td>0.78</td>
<td>−0.27</td>
</tr>
<tr>
<td>Physical function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-min walk distance (m)</td>
<td>447 ± 83</td>
<td>468 ± 81</td>
<td>+21.5 ± 28</td>
<td>0.012*</td>
<td>0.94*</td>
</tr>
<tr>
<td>4-m gait speed (m/s)</td>
<td>1.1 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>+0.12 ± 0.2</td>
<td>0.024*</td>
<td>0.54*</td>
</tr>
<tr>
<td>Timed chair-stands (s)</td>
<td>14.8 ± 3</td>
<td>12.6 ± 2</td>
<td>−2.2 ± 3</td>
<td>0.013*</td>
<td>0.51*</td>
</tr>
<tr>
<td>SPPB score</td>
<td>10 ± 1</td>
<td>11 ± 0.9</td>
<td>+0.9 ± 1</td>
<td>0.003*</td>
<td>0.38</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>12.7 ± 5</td>
<td>12.1 ± 4</td>
<td>−0.6 ± 2</td>
<td>0.314</td>
<td>0.94*</td>
</tr>
</tbody>
</table>
Effect of 3-week senolytic therapy in IPF patients – Physical Function

Chart Title

- 6 min walk (x0.01)
- 4m gait spd
- timed chair stands
- SPPB score

Pre: 0 2 4 6 8 10 12 14 16
Post: 0 2 4 6 8 10 12 14 16

p=0.012
p=0.024
p=0.01
p=0.003
SPRINT Research Question

Randomized controlled clinical trial to examine effect of more intensive high blood pressure treatment strategy than is currently recommended (standard treatment)

Target Systolic BP

Intensive Treatment
Goal SBP < 120 mm Hg

Standard Treatment
Goal SBP < 140 mm Hg

SPRINT design details available at:
- ClinicalTrials.gov (NCT01206062)
Systolic Blood Pressure in the Two Treatment Groups during the treatment phased of the Trial

<table>
<thead>
<tr>
<th>Years</th>
<th>Standard treatment</th>
<th>Intensive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>1</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>2</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>4</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

No. with Data
- Standard treatment: 4683 4345 4222 4092 3997 3904 3115 1974 1000 274
- Intensive treatment: 4678 4375 4231 4091 4029 3920 3204 2035 1048 286

Mean No. of Medications
- Standard treatment: 1.9 1.8 1.8 1.8 1.8 1.8 1.8 1.8 1.8 1.9
- Intensive treatment: 2.3 2.7 2.8 2.8 2.8 2.8 2.8 2.8 3.0

Incidence of the Primary Cardiovascular Outcome and Death from Any Cause in SPRINT

Primary composite outcome includes myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death.

Effects of Blood Pressure Lowering on the Incidence of Dementia in Placebo-Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>ΔSBP</th>
<th>FU</th>
<th>Control</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP</td>
<td>12.0</td>
<td>4.9</td>
<td>44 / 2371</td>
<td>37 / 2365</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>10.1</td>
<td>2.0</td>
<td>21 / 1180</td>
<td>11 / 1238</td>
</tr>
<tr>
<td>PROGRESS/Com</td>
<td>12.8</td>
<td>3.9</td>
<td>136 / 1774</td>
<td>106 / 1770</td>
</tr>
<tr>
<td>HYVET-COG</td>
<td>15.0</td>
<td>2.2</td>
<td>137 / 1649</td>
<td>126 / 1687</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5.6</td>
<td>4.3</td>
<td>37 / 5571</td>
<td>39 / 5569</td>
</tr>
<tr>
<td>All DIUs/CCBs</td>
<td>9.9</td>
<td>3.5</td>
<td>375 / 12545</td>
<td>319 / 12269</td>
</tr>
</tbody>
</table>

Heterogeneity: Q=3.49, p=0.32

<table>
<thead>
<tr>
<th>Study</th>
<th>ΔSBP</th>
<th>FU</th>
<th>Control</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESS/Per</td>
<td>4.9</td>
<td>3.9</td>
<td>81 / 1280</td>
<td>87 / 1281</td>
</tr>
<tr>
<td>SCOPE</td>
<td>3.2</td>
<td>3.9</td>
<td>57 / 2460</td>
<td>62 / 2477</td>
</tr>
<tr>
<td>PROfESS</td>
<td>3.8</td>
<td>2.5</td>
<td>409 / 8646</td>
<td>408 / 8624</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>4.0</td>
<td>4.7</td>
<td>245 / 2699</td>
<td>239 / 2694</td>
</tr>
<tr>
<td>All ACEs/ARBs</td>
<td>4.1</td>
<td>3.8</td>
<td>792 / 15075</td>
<td>796 / 15076</td>
</tr>
</tbody>
</table>

Heterogeneity: Q=0.49, p=0.92

<table>
<thead>
<tr>
<th>All trials</th>
<th>ΔSBP</th>
<th>FU</th>
<th>Control</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.6</td>
<td>3.6</td>
<td>1167 / 27620</td>
<td>1115 / 27705</td>
</tr>
</tbody>
</table>

Heterogeneity: Q=7.95, p=0.44

Jan A. Staessen et al. Hypertension. 2011;57:e6-e7

Copyright © American Heart Association, Inc. All rights reserved.
Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Treatment Group</th>
<th></th>
<th></th>
<th></th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. With</td>
<td>No. With</td>
<td>Cases per 1000</td>
<td>Cases per 1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outcome/Person-Years</td>
<td>Outcome/Person-Years</td>
<td>Person-Years</td>
<td>Person-Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable dementia</td>
<td>149/20 569</td>
<td>176/20 378</td>
<td>7.2</td>
<td>8.6</td>
<td>0.83 (0.67-1.04)</td>
<td>.10</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>287/19 690</td>
<td>353/19 281</td>
<td>14.6</td>
<td>18.3</td>
<td>0.81 (0.69-0.95)</td>
<td>.007</td>
</tr>
<tr>
<td>Composite of mild cognitive impairment or probable dementia</td>
<td>402/19 873</td>
<td>469/19 488</td>
<td>20.2</td>
<td>24.1</td>
<td>0.85 (0.74-0.97)</td>
<td>.01</td>
</tr>
</tbody>
</table>

A Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

B Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.
Conclusions: Lessons learned from aging research for HIV

• Outward signs of aging (multi-morbidity, frailty, other geriatric syndromes) are prevalent in those with HIV – occur 5-15 years earlier than in well-matched HIV-uninfected cohorts

• Retarding aging is more likely to extend health span than curing any single disease

• There is no single biomarker of aging; functional assessments of integrated physiology perform best, but focusing on hallmarks/pathways of aging show promise (e.g., “DNA methylome”)


Conclusions: Lessons learned from aging research for HIV

• Addressing mechanisms of aging is THE key to reducing multimorbidity efficiently

• Potential mechanisms such as senolytics hold promise, but a long way to go

• In the interim, the major issues for changing current HIV care is to focus on prevention of co-morbidities common with aging:
  – Treat hypertension!! (goal < 120 systolic?)
  – Stop smoking, Cancer screening, CVD mitigation, frailty screening and interventions (see Appendix slides)
### Summary of screening and monitoring for common comorbid conditions and complications in the older PLWH

<table>
<thead>
<tr>
<th>Condition or complication</th>
<th>Summary of recommendations</th>
</tr>
</thead>
</table>
| **CVD**                   | • Check fasting lipid profile prior to starting ART.  
                            • Check fasting lipid profile 3 to 6 months after initiating or switching ART, then every 12 months thereafter.  
                            • Check BP, weight, and BMI at least annually. |
| **Diabetes**              | • Check FBG or A1C prior to starting ART.  
                            • Repeat FBG or A1C 3 to 6 months after ART initiation or after modifying ART.  
                            • If FBG or A1C is abnormal, continue to monitor every 3 to 6 months.  
                            • If FBG or A1C is normal, may repeat annually. |
| **Kidney disease**        | • Assess kidney function with eGFR and urinalysis prior to initiating ART.  
                            • Check kidney function 2 to 8 weeks after initiating or modifying ART.  
                            • If kidney function is normal, monitor every 3 to 6 months. |
| **Osteopenia/osteoporosis**| • Assess for fragility fracture with the FRAX for all PLWH 40 to 49 years of age.  
                            • DXA:  
                              ◦ in men over 50  
                              ◦ postmenopausal women  
                              ◦ patients with a history of fragility fracture  
                              ◦ patients receiving chronic glucocorticoid treatment  
                              ◦ patients at high risk for falls. |

<table>
<thead>
<tr>
<th>HAND</th>
<th>No single definitive screening tool exists. Some experts recommend use of the MoCA. This test may miss more milder forms of cognitive impairment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>Screen at least annually. Inquire if patient has experienced: Two or more falls in prior 12 months Difficulty with walking or balance.</td>
</tr>
<tr>
<td>Depression</td>
<td>Screen all patients. Several tools available including: GDS Patient Health Questionnaire (PHQ) (PHQ2 or PHQ9). Recommendations on frequency vary based on guidelines, some recommend screening at every visit.</td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>Screen all patients at least annually. Several standard tools available including: Alcohol Use Disorders Identification Test (AUDIT), Michigan Alcoholism Screening Test – Geriatric Version (MAST-G).</td>
</tr>
</tbody>
</table>
Clinical Care Appendix


<table>
<thead>
<tr>
<th>Cancer screening recommendations in older PLWH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervical</strong></td>
<td></td>
</tr>
<tr>
<td>• Screen with cytology (Pap) or cytology plus HPV cotesting.</td>
<td></td>
</tr>
<tr>
<td>• If using cytology screening alone, screen annually. May extend to every 3 years after 3 consecutive negative tests.</td>
<td></td>
</tr>
<tr>
<td>• If using cytology screening plus HPV cotesting, screening interval is every 3 years.</td>
<td></td>
</tr>
<tr>
<td>• Screening should continue after age 65, taking into account life expectancy and risk of developing cancer.</td>
<td></td>
</tr>
<tr>
<td><strong>Anal</strong></td>
<td></td>
</tr>
<tr>
<td>• Annual digital exam may be useful in detecting masses.</td>
<td></td>
</tr>
<tr>
<td>• Use of cytology testing of anal canal is recommended by some experts.</td>
<td></td>
</tr>
<tr>
<td>• Abnormal anal cytology results need to be followed up by high-resolution anoscopy (HRA), which is similar to cervical colposcopy.</td>
<td></td>
</tr>
<tr>
<td>• It is recommended to defer anal cytology if HRA is not available.</td>
<td></td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td></td>
</tr>
<tr>
<td>• The American Cancer Society (ACS) recommends low-dose computed tomography (CT) scan for current or former smokers ages 55-74 in good health with at least 30-pack-year of smoking or who have quit within the past 15 years and have at least a 30-pack-year smoking history.</td>
<td></td>
</tr>
<tr>
<td>• Individuals should also receive evidence-based smoking cessation counseling, if they are current smokers.</td>
<td></td>
</tr>
</tbody>
</table>
| • Candidates should also have undergone a process of informed/shared decision-making that includes the benefits, limitations, harms of screening with low-dose CT and have access to a high-volume, high-quality lung cancer screening and treatment center.
Clinical Care Appendix


**Colorectal**

Several guidelines exist regarding age at which to begin screening. All guidelines agree that screening should begin no later than age 50, and the ACS recommends screening beginning at age 45 through age 75 for average-risk asymptomatic adults. Several screening options are available including colonoscopy, fecal immunochemical test, CT colonography, and sigmoidoscopy. Refer to the guidelines below for additional information:

- **American College of Gastroenterology**

- **US Preventive Services Task Force (USPSTF) guidelines**

- **American Cancer Society**

**Prostate**

Several guidelines exist regarding utility and age parameters for routine screening. Consult the following sources for additional information.

- **American Urologic Association (AUA)**

- **US Preventive Services Task Force (USPSTF) guidelines**

**Breast**

Screening recommendations differ on the age and frequency of screening. Consult current guidelines for additional information.

- **US Preventive Services Task Force (USPSTF) guidelines**
  www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/breast-cancer-screening1

- **American Cancer Society**
## Recommended vaccines for older PLWH

### Influenza
Administer inactivated, adjuvant inactivated, or high-dose inactivated influenza annually. Live attenuated influenza is not recommended.

### Tdap/Td
One dose of Tdap if not previously vaccinated, then Td booster every 10 years.

### Hepatitis A
- Hepatitis A vaccine: initial dose, then the second dose at 6 to 12 months.
- (Hepatitis A vaccine, inactivated): initial dose, then the second dose at 6 to 18 months.
- Hepatitis A-hepatitis B: initial dose, then the second dose in 1 month, and third dose in 6 months.

### Hepatitis B
Single-antigen hepatitis B vaccine: two or three doses depending on the vaccine or administer the combined hepatitis A and hepatitis B vaccine: initial dose, then the second dose 1 month later, and third dose 6 months later.

### Meningitis
- Two doses of serogroup A, C, W, and Y meningococcal vaccine (MenACWY) 2 months apart; revaccinate every 5 years through age 55.
- Serogroup B meningococcal vaccine (MenB) is not recommended.
<table>
<thead>
<tr>
<th>Measles, mumps, rubella</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Two doses if born after 1957 and/or CD4+ count ≥200 cells/mcL (if not previously vaccinated).</td>
</tr>
<tr>
<td>• Do not administer if CD4+ count &lt;200 cells/mcL.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Varicella</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Two doses if CD4+ count is ≥200 cells/mcL.</td>
</tr>
<tr>
<td>• Do not administer if CD4+ count is &lt;200 cells/mcL.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Herpes zoster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not administer the zoster vaccine live if CD4+ counts &lt;200 cell/mcL. Consider the zoster vaccine recombinant for PLWH age 60 or older with CD4+ counts ≥200 cells/mcL.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pneumococcal disease</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Under age 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pneumococcal 13-valent conjugate vaccine (PCV13) x one dose followed by pneumococcal 23-valent polysaccharide vaccine (PPSV23) at least 8 weeks after.</td>
</tr>
<tr>
<td>• Revaccinate with PPSV23 after 5 years (max two doses of PPSV23 under age 65).</td>
</tr>
<tr>
<td>• Administer final dose after age 65. Final dose should be at least 5 years after second dose.</td>
</tr>
<tr>
<td>• Total of three lifetime doses of PPSV23.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 65 or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>If not previously vaccinated:</td>
</tr>
<tr>
<td>• give one dose PCV13 followed by PPSV23 at least 8 weeks after.</td>
</tr>
<tr>
<td>• If PPSV23 is administered first, wait at least 1 year before administering PCV13.</td>
</tr>
</tbody>
</table>
Questions?
HIV & AGING: FROM MITOCHONDRIA TO THE METROPOLIS
Damani Piggott, MD, PhD is Assistant Professor of Medicine and Epidemiology, Associate Faculty in the Center on Aging and Health, Affiliate Faculty in the Cellular and Molecular Medicine Program, and Assistant Dean for Graduate Biomedical Education at Johns Hopkins University. Dr. Piggott received his MD and PhD in Immunology from Yale University. He is board certified in Internal Medicine, Pediatrics and Infectious Diseases, having completed residency at Yale and fellowship in Infectious Diseases and Epidemiology at Johns Hopkins.
Frailty: Targeting Vulnerability and Disparity among Persons Aging with HIV and Injection Drug Use

Damani A. Piggott, MD, PhD
Division of Infectious Diseases, Johns Hopkins University School of Medicine
Department of Epidemiology, Johns Hopkins University School of Public Health
Associate Faculty, Johns Hopkins Center on Aging and Health
Financial Disclosures

• None
Objectives

• To describe the epidemiology of frailty in HIV and persons with injection drug use (PWID)

• To describe putative biological pathways to frailty in HIV and PWID

• To define the role of frailty as a target to reduce disparity and vulnerability to adverse clinical outcomes in HIV and PWID
Global Burden of the HIV Epidemic & PWID

- 35 million have died of HIV
- 37 million living with HIV worldwide (~0.005% global population)
- ~1.3 to 3 million HIV+ PWID worldwide (~12-18% total PWID population)

Aceijas C et al. AIDS 2004
Mathers BM et al. Lancet 2008
UNAIDS 2019
Increasing Number of Older HIV+ Adults with ↑ ART

HIV-infected persons 50+ : 4 million now ➔ 12 million in 2040
Increasing Number of Older HIV-infected Adults in the U.S.

- 45% of U.S. Persons Living with HIV ≥ 50 years of age
Persistent Gaps in Survival for HIV+ vs. HIV- Adults

Decreasing mortality rates and increasing life expectancy for HIV+, while stable for HIV-

Marcus JL et al. JAIDS 2016
Kaiser Permanente California cohort
Survival Gaps Most Severe for HIV+ Racial/Ethnic Minorities and Persons with Injection Drug Use

Life Expectancy from Age 20 for HIV-infected Participants in NA-Accord

By Race

<table>
<thead>
<tr>
<th>Year</th>
<th>WHITE</th>
<th>NON-WHITE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>52.7</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>53.6</td>
<td>46.4</td>
</tr>
<tr>
<td>2003</td>
<td>56.9</td>
<td>46.4</td>
</tr>
<tr>
<td>2005</td>
<td>52.4</td>
<td></td>
</tr>
</tbody>
</table>

By Transmission Group

<table>
<thead>
<tr>
<th>Year</th>
<th>MSM</th>
<th>IDU</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>53.3</td>
<td></td>
<td>69.3</td>
</tr>
<tr>
<td>2002</td>
<td>57.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>52.4</td>
<td></td>
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</tr>
<tr>
<td>2007</td>
<td>56.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Samji H et al. PLoS One 2013
North American Accord: Collaboration of HIV Cohorts in the U.S. and Canada
Survival Gaps Most Severe for HIV+ Persons with Injection Drug Use

Probability of Death for HIV-infected Participants by Risk Group
Swiss HIV Cohort Study

Weber R et al. HIV Med 2014
Why do Disparities in Survival Still Exist for HIV+ vs. HIV- Adults?

- Gaps in antiretroviral therapy coverage to achieve and maintain virologic suppression
  - HIV cascade of care

Burden of aging-related disease and aging-related syndromes

FRAILTY
Frailty: Target to Reduce Disparities among Persons Aging with HIV

- Frailty is a critical syndrome of vulnerability to adverse health outcomes
  - Mortality
  - New or worsening chronic disease → hospitalization
  - Disability

- First characterized among HIV-uninfected adults 65 years and older

- Decreased resilience to internal and external stressors

- Physiologic dysregulation/cumulative decline in physiologic reserve

- Frailty: aging-related ≠ chronologic age
Early Conceptual Model of Frailty

- Lipsitz LA, Goldberger AL. Loss of ‘complexity’ and aging: Potential applications of fractals and chaos theory to senescence. JAMA 1992


Buchner DM & Wagner EH. Clinics in Geriatric Medicine 1992
Physical Frailty Phenotype


- Weight loss/ Shrinking
- Weakness (↓ grip strength)
- Exhaustion/ Poor endurance
- Slow gait speed
- Low physical activity

Frail if ≥3 of 5 present (critical mass)
Prefrail if 1-2 present
Robust 0 present
Frailty and HIV share Geographic, Racial/Ethnic and Socioeconomic Disparities

Frailty Burden among U.S. Adults 65 Years and Older

White
Lowest Income Quartile

29.6%

White
Highest Income Quartile

5.6%

Black
Lowest Income Quartile

39.1%

Black
Highest Income Quartile

8.3%

Overall Burden 15%

National Health & Aging Trends Study
Disproportionate HIV Burden Persists among Racial/Ethnic Minorities, Low SES and PWID

- **U.S. blacks***
  - 13% of U.S. Population
  - 43% of new HIV infections
  - 42% of persons living with HIV

- **↑ HIV prevalence with ↓ SES***
  - Income, education, employment

- **U.S. PWID***
  - ~17% persons living with HIV

*Centers for Disease Control and Prevention

**UNAIDS 2019**
Frailty: Target to Reduce Vulnerability and Disparity in HIV & PWID

AIDS Linked to the IntraVenous Experience (ALIVE) Cohort

- Baltimore community based, prospective observational cohort
- Enrollment: 1988 - present
- HIV+ and HIV- Adults with prior or current injection drug use
- 90% African American with high socioeconomic disadvantage
  - 60% <high school education; 60% annual income<$2500
- Frailty assessments incorporated in 2005
  - Median age 48 years
Frailty, HIV Infection, and Mortality in an Aging Cohort of Injection Drug Users

Damani A. Piggott¹,²*, Abimereki D. Muzaale¹,², Shruti H. Mehta², Todd T. Brown¹,², Kushang V. Patel³, Sean X. Leng¹, Gregory D. Kirk¹,²

¹ Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, ² Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, ³ University of Washington School of Medicine, Seattle, Washington, United States of America

PLoS One 2013; 8: e54910

HIV+
66% More Likely to Be Frail
Frailty Predicts Increased Hospitalization Risk in HIV & PWID Independent of HIV Disease Stage & Comorbidity

Hospitalization Risk by Frailty Status in ALIVE

Adj Hazard ratio  95% CI

Frailty Predicts Increased Risk of Death in HIV & PWID
Independent of HIV Disease Stage & Comorbidity


7 Fold More Likely to Die If you have HIV and are FRAIL
Frailty Outcomes in HIV Cohorts

- Mortality
- Hospitalization
- Falls
- Fractures
- Incident comorbid chronic disease
- IADL disability
- ↓ Quality of life
Reducing Disparities in HIV Outcomes: Understanding Pathways to Frailty in HIV & PWID

HIV → Frailty → \(\uparrow\) Hospitalization, \(\uparrow\) Mortality
Understanding Pathways to Frailty: Frailty is a Dynamic State

Nonfrail ⇄ Frail

Understanding Pathways to Frailty in HIV: Frailty Transitions in ALIVE

- Markov transition models
- 1353 ALIVE participants
- 9559 frailty transitions
- 2005 to 2013

Frail if $\geq 3$ of 5 present
Nonfrail if 0-2 present

\[ \text{Nonfrail} \quad 699 (8\%) \quad \text{Frail} \quad 660 (68\%) \]
## Individual Socioeconomic Disadvantage & ↓ Comorbidity is Associated with ↓ Frailty Progression & ↑ Frailty Recovery

<table>
<thead>
<tr>
<th></th>
<th>FRAILTY PROGRESSION</th>
<th>FRAILTY RECOVERY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonfrail -&gt; Frail</td>
<td>Frail -&gt; Nonfrail</td>
</tr>
<tr>
<td>Adj OR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 5yr ↓)</td>
<td>0.93 (0.88, 0.98)</td>
<td>1.08 (1.02, 1.13)</td>
</tr>
<tr>
<td>High school education or greater</td>
<td>0.87 (0.75, 1.00)</td>
<td>1.15 (1.00, 1.33)</td>
</tr>
<tr>
<td>Employed</td>
<td>0.56 (0.45, 0.69)</td>
<td>1.78 (1.44, 2.22)</td>
</tr>
<tr>
<td>Absence of depressive symptoms</td>
<td>0.61 (0.51, 0.73)</td>
<td>1.64 (1.37, 1.96)</td>
</tr>
<tr>
<td># Comorbid conditions*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>Ref</td>
<td>1.59 (1.29, 1.95)</td>
</tr>
<tr>
<td>2</td>
<td>0.63 (0.51, 0.78)</td>
<td>1.80 (1.48, 2.20)</td>
</tr>
<tr>
<td>1</td>
<td>0.55 (0.46, 0.68)</td>
<td>2.44 (1.97, 3.03)</td>
</tr>
<tr>
<td>0</td>
<td>0.41 (0.33, 0.51)</td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>1.23 (1.06, 1.43)</td>
<td>0.81 (0.70, 0.94)</td>
</tr>
</tbody>
</table>

*Diabetes, Hypertension, Stroke, Heart Disease, Chronic Kidney Disease, Obesity, Liver disease, COPD, Cancer
# Virologic Suppression & Early HIV Control Reduces Frailty Progression & Promotes Frailty Recovery

<table>
<thead>
<tr>
<th></th>
<th>Frailty Progression</th>
<th>Frailty Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonfrail -&gt; Frail</td>
<td>Frail -&gt; Nonfrail</td>
</tr>
<tr>
<td></td>
<td>Adj OR (95% CI)</td>
<td>Adj OR (95% CI)</td>
</tr>
<tr>
<td><strong>MODEL A:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV+, viremic</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>HIV+, suppressed (VL&lt;50)</td>
<td>0.74 (0.58, 0.95)</td>
<td>1.34 (1.05, 1.72)</td>
</tr>
<tr>
<td>HIV negative</td>
<td>0.71 (0.59, 0.85)</td>
<td>1.42 (1.18, 1.72)</td>
</tr>
<tr>
<td><strong>MODEL B:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV+, prior AIDS</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>HIV+, no AIDS</td>
<td>0.67 (0.51, 0.88)</td>
<td>1.53 (1.16, 2.02)</td>
</tr>
<tr>
<td>HIV negative</td>
<td>0.60 (0.46, 0.77)</td>
<td>1.72 (1.33, 2.23)</td>
</tr>
</tbody>
</table>
Frailty Associations in HIV Cohorts

- Increased age
- Non-white
- Socioeconomic challenge
  - Low educational attainment
  - Low income
  - Unemployment
- Depressive symptoms
- Increased comorbid chronic disease
- Poorly controlled HIV infection/AIDS
Biological Pathways to Frailty in HIV & PWID
Inflammation is Central to HIV Pathophysiology

Untreated HIV Infection
- Immune Activation
- Loss of immunoregulatory cells
- Immunosenescence
- Loss of gut mucosal integrity and microbial translocation

Antiretroviral Therapy
- Decreased but Persistent Defects
- Chronic Inflammation
- Clinical Disease

Adapted from Deeks SG et al. Annu Rev Med 2011
Inflammatory Index

Simple Biologically Informed Inflammatory Index of Two Serum Cytokines Predicts 10 Year All-Cause Mortality in Older Adults

Ravi Varadhan,1 Wenliang Yao,1 Amy Matteini,1 Brock A. Beamer,2 Qian-li Xue,1 Huanle Yang,1 Bhavish Manwani,1 Alexander Reiner,3 Nancy Jenny,4 Neel Parekh,1 M. Daniele Fallin,5 Anne Newman,6 Karen Bandeen-Roche,7 Russell Tracy,4 Luigi Ferrucci,8 and Jeremy Walston1


- Biologically informed aggregate marker derived from NFkB related cytokines
- Validated to best capture inflammation effect on mortality (InCHIANTI/CHS: adults 65+)

**Inflammatory Index Score = (ln IL-6 + 2*ln sTNFR1)/3**
Decreased Survival with Increased Inflammatory Index Score in HIV & PWID

\[
\text{Inflammatory Index Score} = \frac{\ln \text{IL-6} + 2 \ln \text{sTNFR1}}{3}
\]

Heightened Inflammation is Associated with Frailty Independent of HIV Disease Stage & Comorbidity

Research Article

Frailty, Inflammation, and Mortality Among Persons Aging With HIV Infection and Injection Drug Use

Damani A. Piggott,¹,² Ravi Varadhan,³ Shruti H. Mehta,² Todd T. Brown,¹,² Huifen Li,¹ Jeremy D. Walston,¹ Sean X. Leng,¹ and Gregory D. Kirk¹,²,³

Increased Inflammation is Associated with Frailty in HIV
Reduced Inflammation Decreases Frailty Progression & Promotes Frailty Recovery

<table>
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<tr>
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<th>FRAILTY PROGRESSION</th>
<th>FRAILTY RECOVERY</th>
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<tbody>
<tr>
<td></td>
<td>Nonfrail -&gt; Frail</td>
<td>Frail -&gt; Nonfrail</td>
</tr>
<tr>
<td></td>
<td>Adj OR (95% CI)</td>
<td>Adj OR (95% CI)</td>
</tr>
<tr>
<td>Inflammatory index score (per standard deviation ↓)*</td>
<td>0.78 (0.65, 0.92)</td>
<td>1.29 (1.08, 1.53)</td>
</tr>
</tbody>
</table>

*Adjusting for age, sociodemographics, depressive symptoms, # chronic comorbid diseases, HIV status

800 Participants
2400 Person visits

\[ \text{Inflammatory Index Score} = \frac{(\ln IL-6 + 2\ln sTNFRI)}{3} \]
Biological Correlates of Frailty in HIV Cohorts

• Inflammation
  – IL-6, sTNFR1, CRP

• Immune activation
  – HLA-DR+/CD38+/CD8+

• Δ Hormone levels
  – DHEA-S, free testosterone

• Bone metabolism
  – Fibroblast growth factor (FGF-23)

• DNA methylation
Frailty and Neurocognitive Impairment in HIV & PWID
Potential Shared Pathophysiology between Neurocognitive Impairment and Frailty

Robertson DA et al. Ageing Research Reviews 2013
Frailty and Neurocognitive Impairment

- Bidirectional associations proposed between physical frailty & cognitive impairment in older HIV-uninfected populations
- Same or related domains
### Neurocognitive Assessments in ALIVE

<table>
<thead>
<tr>
<th>Category</th>
<th>Test Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premorbid IQ</td>
<td>New adult reading test</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Trail making test part b</td>
</tr>
<tr>
<td></td>
<td>Digit span backward</td>
</tr>
<tr>
<td>Speed of Information Processing</td>
<td>Trail making test part a</td>
</tr>
<tr>
<td></td>
<td>Symbol digit</td>
</tr>
<tr>
<td>Attention/Working Memory</td>
<td>Digit span forward</td>
</tr>
<tr>
<td></td>
<td>Hopkins verbal learning test trial 1</td>
</tr>
<tr>
<td>Learning/Memory</td>
<td>Hopkins verbal learning test trials 1-3 (immediate recall)</td>
</tr>
<tr>
<td></td>
<td>Hopkins verbal learning test trial 4 (delayed recall)</td>
</tr>
<tr>
<td></td>
<td>Symbol digit paired recall</td>
</tr>
<tr>
<td>Motor Processing</td>
<td>Grooved pegboard dominant hand</td>
</tr>
<tr>
<td></td>
<td>Grooved pegboard nondominant hand</td>
</tr>
</tbody>
</table>
Intersection of Frailty & Neurocognitive Impairment in HIV & PWID

- Neurocognitive Impairment
  - 83.6%
  - 25.6%

- Frailty
  - 16.4%
  - 75.4%
Frailty and Neurocognitive Impairment Independently Predict ↑ Risk of Death in HIV & PWID

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognitive impairment</td>
<td>1.93 (1.19, 3.14)</td>
</tr>
<tr>
<td>Frail</td>
<td>2.32 (1.03, 5.20)</td>
</tr>
</tbody>
</table>

‡ Adjusted for age, gender, race, premorbid IQ, HIV status/disease stage and comorbid conditions
Summary

• Frailty burden is heightened in HIV among PWID

• In HIV & PWID, frailty is associated with
  – ↑ hospitalization risk
  – ↑ death
  (independent of comorbidity and HIV disease stage)

• Physical frailty and neurocognitive impairment are independent predictors of mortality in HIV & PWID
Summary: Reducing Disparity and Vulnerability through Frailty in HIV & PWID

• Prevent or reduce chronic comorbid disease
• Modulate socioeconomic factors
  – Education
  – Employment
• Attain virologic suppression
  – Improve HIV cascade of care
• Pursue early and consistent antiretroviral therapy
  – Prevent ↓CD4 nadir/progression to AIDS
• Reduce chronic inflammation
Framework for Frailty in HIV

Underlying factors

Cell/Molecular
- Shortened telomeres
- Immune dysfunction
- Mitochondrial dysfunction
- DNA methylation
- Gut dysbiosis
- Genotype

Comorbidities
- Co-infections
- HAND and/or MCI
- Fat/Metabolic disorders
- Pro-inflammatory conditions
- Polypharmacy

Psychosocial/environmental
- Mental health disorders
- Nutrition & physical activity
- Socioeconomic stressors
- Psychological resilience
- Substance abuse

Pathways

- Altered energy metabolism
- Inflammation
- Immune activation
- Neuroendocrine dysfunction
- Renin/Angiotensin system alteration

Pathophysiology

- Insulin resistance
- Lipodystrophy/obesity
- Anorexia
- Sarcopenia/dynapenia
- Osteoporosis
- Cognitive impairment
- Anemia
- Hypercoagulable

Clinical Findings

- Slow gait
- Muscle weakness
- Weight loss
- Low activity
- Fatigue

Outcomes

- Mobility limitations
- Disability
- Falls/fractures
- Social isolation
- Hospitalizations
- Mortality

Acknowledgments

• ALIVE study participants & providers
• ALIVE investigators & staff

• Hopkins Center on Aging and Health
• Hopkins Older Americans Independence Center
• Hopkins Center for AIDS Research
• Hopkins Frailty Working Group

• Robert Wood Johnson Foundation Harold Amos Award

• National Institute of Allergy and Infectious Diseases
  – K23-AI-108357
  – RC1-AI-086053

• National Institute on Drug Abuse
  – ROI-DA-04334
  – ROI-DA-12568

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Jacquie Astemborski
Karen Bandeen-Roche
Todd Brown
Jason Creighton
Sean Leng
Huifen Li
Abimereki Muzaale
Kushang Patel
Vincent Rogalski
David Roth
Ned Sacktor
Ola Selnes
Ravi Varadhan
Jeremy Walston
Ryan Westergaard
Shruti Mehta
Greg Kirk
Russell Van Dyke is Professor of Pediatrics and Section Head, Pediatric Infectious Diseases at the Tulane University School of Medicine. His research interests include the epidemiology and management of HIV-infected and HIV-exposed pregnant women, children, and youth, mother-to-child transmission of HIV, and antiviral chemotherapy. He directs the Tulane Pediatric AIDS Clinical Trials Unit, which was funded as an NIH International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) clinical site from 1990-2015. He is Principal Investigator (PI) of the Coordinating Center of the NIH-funded Pediatrics HIV/AIDS Cohort Study (PHACS), a multicentered longitudinal cohort study of HIV-infected and HIV-exposed infants and children. He is also the site PI for the PHACS SMARTT study of the long-term safety of in utero exposure to antiretroviral agents.
Growing Up With Perinatal HIV

Russell Van Dyke, MD
Department of Pediatrics
Tulane University School of Medicine
I have no conflicts
Objectives

• Understand the characteristics of youth with perinatal HIV in the US.
• Understand long-term outcomes of youth with perinatal HIV and nearly lifelong exposure to antiretroviral medications, including immune status, growth and development, end-organ function, and neurocognitive development.
• Appreciate the challenges that these youth face in their transition to adulthood and adult medical care.
Pediatric HIV/AIDS Cohort Study
Estimated Numbers of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2007—United States and Dependent Areas

2013: 69 infants born in US with perinatal HIV

Note: Data have been adjusted for reporting delays and missing risk-factor information.
Hypothetical Current Age Distribution of US Children with Perinatal HIV

[Graph showing the distribution of current ages of children with perinatal HIV, with a peak around age 2 and a decline thereafter.]
Youth with Perinatal HIV in the US

- Approximately 11,000 children currently living with perinatal HIV in the US
- 35% with AIDS diagnosis
- Most 15-32 years of age
- 66% African-American, 20% Hispanic, 12% white
- 53% female
Dramatic Decrease in Opportunistic Infections and Other Complications of HIV
Decline in Incidence of Selected AIDS-Defining Conditions Per 100 HIV-Infected Children at Risk, U.S. Pediatric Spectrum of Disease Project, 1992-2001

Year

1992 Overall 13%
2001 Overall 2%

HAART era
Dramatic Decrease in Mortality With HAART Therapy….

but still >30 fold higher than similarly-aged US children
(0.6 vs. 0.02 deaths/100 children aged 5-14 years)
Yearly Mortality (1994-2006) in HIV-Infected Children Enrolled in PACTG 219 Long-Term Follow-Up Study

Death rate in 1994: 7.2/100 pt-yrs

Death rate in 2006: 0.6/100 pt-yrs

3,553 children Median f/u 5.3 yrs 298 deaths

[Brady, JAIDS 2010; 53: 86]
Survival By Birth Cohort

[Brady, JAIDS 2010; 53: 86]
High Risk of Viral Resistance

• Long-term exposure to antiretroviral therapy
• Initial treatment with suboptimal regimens (prior to cART)
• Challenge of adherence, particularly during adolescence
Prevalence of any viral resistance among those with detectible virus, 2007-2015

<table>
<thead>
<tr>
<th>Category</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>75%</td>
</tr>
<tr>
<td>NRTI</td>
<td>61%</td>
</tr>
<tr>
<td>NNRTI</td>
<td>45%</td>
</tr>
<tr>
<td>PI</td>
<td>34%</td>
</tr>
<tr>
<td>2+ classes</td>
<td>43%</td>
</tr>
<tr>
<td>All 3 classes</td>
<td>18%</td>
</tr>
</tbody>
</table>

2012 overall for testing lab

(Van Dyke, CID 2016)
Ongoing Concerns in the cART Era

• Adherence to lifelong therapy
• Residual impairment of humoral and cellular immunity
• Chronic immune activation, even in those with viral suppression
Measles and Rubella Seroprotection and Mumps Seropositivity Among HEU and PHIV+ Children
Measles and Rubella Seroprotection and Mumps Seropositivity

(Siberry, CID 2015)
Vaccine Dose Response for Doses Received While Receiving cART - PHIV

(Siberry, CID 2015)
Long term Complications Similar to Adults

- Cardiac: increased CV risk, increased intimal media thickness and markers of vascular dysfunction, dyslipidemia.
  - 48% elevated PDAY risk score
  - 15-20% elevated lipids
  - 10% abnormal echocardiograms
- Renal: HIV-associated nephropathy
  - 11% proteinuria
HIV Complications

- Bone: decreased bone mineral density, related to treatment and HIV infection
  - 20% decreased BMD
- Metabolic: insulin resistance, lipodystrophy, dyslipidemia
  - 15% glucose intolerance
- Malignancy: lymphoma
Complications Specific to Children and Youth

- Growth
- Delayed puberty
- Neurodevelopment and encephalopathy
- Mental health and behavioral issues
- Transition to adult care and adult living
Growth

length

weight
Head Circumference
## Growth

<table>
<thead>
<tr>
<th></th>
<th>AMP HEU</th>
<th>AMP HIV+</th>
<th>P2C2 (1990-1997)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>189</td>
<td>325</td>
<td>70</td>
</tr>
<tr>
<td><strong>Age at assessment (yrs)</strong></td>
<td>11.0</td>
<td>13.0</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Mean height z score</strong></td>
<td>0.23</td>
<td>-0.43</td>
<td>-1.49</td>
</tr>
<tr>
<td><strong>Mean weight z score</strong></td>
<td>0.70</td>
<td>0.16</td>
<td>-0.89</td>
</tr>
<tr>
<td><strong>Mean BMI z score</strong></td>
<td>0.70</td>
<td>0.39</td>
<td>-0.31</td>
</tr>
<tr>
<td><strong>HIV viral load &lt; 400 copies/mL</strong></td>
<td>69%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td><strong>Median CD4 count, cells/uL</strong></td>
<td>693</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td><strong>HAART</strong></td>
<td>89%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td><strong>Median duration of HAART, yrs.</strong></td>
<td>9.0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

All p<0.001

(Lipshultz, JAMA Peds 2013)
Delay in Puberty
Mean Age at Sexual Maturity

<table>
<thead>
<tr>
<th>Tanner Stage Measure</th>
<th>PHIV</th>
<th>PHEU</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>F: Breast</td>
<td>15.37</td>
<td>14.79</td>
<td></td>
</tr>
<tr>
<td>F: Pubic Hair</td>
<td>15.41</td>
<td>14.82</td>
<td></td>
</tr>
<tr>
<td>M: Genitalia</td>
<td>15.93</td>
<td>15.02</td>
<td></td>
</tr>
<tr>
<td>M: Pubic Hair</td>
<td>15.79</td>
<td>14.97</td>
<td></td>
</tr>
</tbody>
</table>

(Williams, AIDS 2013)
Mean Age at Sexual Maturity By Age at cART Initiation (PHIV)

<table>
<thead>
<tr>
<th>Tanner Stage Measure</th>
<th>&lt;Age 5yrs</th>
<th>&gt;Age 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>F: Breast</td>
<td>15.12</td>
<td>15.44</td>
</tr>
<tr>
<td>F: Pubic Hair</td>
<td>15.04</td>
<td>15.47</td>
</tr>
<tr>
<td>M: Genitalia</td>
<td>15.57</td>
<td>16.01</td>
</tr>
<tr>
<td>M: Pubic Hair</td>
<td>15.42</td>
<td>15.87</td>
</tr>
</tbody>
</table>

* p=0.1, p=0.0, p=0.02, p=0.01

(Williams, AIDS 2013)
Similar Neurocognitive Impairment in both PHIV and HEU

<table>
<thead>
<tr>
<th></th>
<th>PHIV +</th>
<th>HEU</th>
<th>P =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Comprehension</td>
<td>87</td>
<td>87</td>
<td>NS</td>
</tr>
<tr>
<td>Perceptual Reasoning</td>
<td>90</td>
<td>92</td>
<td>NS</td>
</tr>
<tr>
<td>Working Memory</td>
<td>88</td>
<td>89</td>
<td>NS</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>86</td>
<td>90</td>
<td>0.01</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>85</td>
<td>87</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Wechsler Intelligence Scale for Children (WISC-IV)
- Both HIV+ and HEU have mean scores below average
- Scores are similar in the two groups

(Smith, Ped Inf Dis J 2012)
Proportion Scoring 2 SD Below Mean by HIV Disease Status

(Smith, Ped Inf Dis J 2012)
• Overt HIV encephalopathy is rarely seen with cART

• Both HIV-exposed and HIV-infected subjects are at risk for cognitive, behavioral, and language impairment

• Need to anticipate these difficulties and screen for them.

• Youth with prior encephalopathy and CDC C diagnosis are at increased risk
Behavioral Health Risks for PHIV-Infected Youth

- Maternal HIV infection
- Family disruption
- Poverty
- Mental health problems (28%)
- Non-adherence to therapy (34%)
- Substance use (18%)
- Unprotected sex (65% of sexually active)

[Mellins, AIDS Patient Care STDs 2011]
Mental Health Diagnoses: PHIV and HEU Youth

- Any Disorder
- ADHD
- Mood Disorder
- Anxiety Disorder
- Behavior Disorder
- Trauma Disorder
- ASD
- Other Disorder

Smith, AIDS Patient Care and STDs 2019

PHIV (n=355)
PHEU (n=196)
Prevalence of Mental Health Treatment

Smith, AIDS Patient Care and STDs 2019
Ongoing Concerns

- Long term complications from lifetime exposure to HIV and antiretroviral therapy
- Malignancies
- Reproductive outcomes
- Outcomes of the children of PHIV+ and HEU parents
- Transition to adult care.
Transition to Adult Care – where does it lead?
Mortality in perinatally HIV-infected young people in England following transition to adult care: an HIV Young Persons Network (HYPNet) audit

R Fish,1 A Judd,2 E Jungmann,1 C O’Leary2 and C Foster3 on behalf of the HIV Young Persons Network (HYPNet)

1TEAM Clinic, Mortimer Market Centre, Central Northwest London NHS Foundation Trust, London, UK. 2Medical Research Council Clinical Trials Unit, London, UK and 3The 900 Clinic, Imperial College Healthcare NHS Trust, London, UK

Table 2 Estimated minimum* mortality rates by age and type of HIV care in perinatally HIV-infected young people, 2006–2011

<table>
<thead>
<tr>
<th>Age group and type of care</th>
<th>No. of deaths</th>
<th>Person-years</th>
<th>Rate/100 person-years (95% CI)</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13–15 years, paediatric</td>
<td>3</td>
<td>1689</td>
<td>0.2 (0.1–0.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>16–20 years, paediatric</td>
<td>2</td>
<td>786</td>
<td>0.3 (0.1–1.0)</td>
<td>1.4 (0.2–8.6)</td>
</tr>
<tr>
<td>16–20 years, adult†</td>
<td>4</td>
<td>825</td>
<td>0.5 (0.2–1.3)</td>
<td>2.7 (0.6–12.2)</td>
</tr>
<tr>
<td>≥ 21 years, adult†</td>
<td>4</td>
<td>458</td>
<td>0.9 (0.3–2.3)</td>
<td>4.9 (1.1–22.0)</td>
</tr>
</tbody>
</table>
Summary

• Perinatally HIV-infected youth are living past adolescence but are not reliably tracked
• Even with “elimination” of pediatric HIV, millions will continue to survive into adolescence and young adulthood for many years to come
• Adverse clinical outcomes may only become apparent in adulthood, thus requiring continued surveillance
• We need to consider positive outcomes (resilience) as well negative ones (risk).
Acknowledgements

PHACS is funded by:

Under cooperative agreements HD052104 (PHACS Coordinating Center, Tulane University School of Medicine) and HD052102 (PHACS Data and Operations Center, Harvard School of Public Health).

We thank the study participants, clinical sites, PHACS Community Advisory Board, Frontier Science & Technology Research Foundation, and Westat.

Thanks to Lynne Mofenson, Rohan Hazra, and Paige Williams for sharing slides.
The End     Thanks!
HIV & AGING: FROM MITOCHONDRIA TO THE METROPOLIS