MACS/WIHS Combined Cohort Study

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ACKNOWLEDGMENTS

• Catalina Ramirez
• MACS/WIHS CCS Investigators
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  Steven Wolinsky
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  Roger Detels
  Seble Kassaye and Daniel Merenstein
  Maria Alcaide, Margaret Fischl and Deborah Jones
  Jeremy Martinson and Charles Rinaldo
  Mirjam-Colette Kempf and Deborah Konkle-Parker

MACS AND WIHS PARTICIPANTS!
Webinar Overview

- Brief history of the MACS and WIHS cohorts
- Types of data collected
- Characteristics of active participants
- Selected recent scientific contributions of the cohort
- Resources for collaboration
Brief History of the MACS and WIHS Cohorts
A.I.D.S.: WE NEED RESEARCH, NOT HYSTERIA!
1984: The Multicenter Aids Cohort Study (MACS): investigate impact and progression of HIV among men
When I was told I had HIV, there was no counseling, testing, or referral. I was told straight out I had 5–6 months to live. MACS was a way to put a face to HIV—a way to build community.

CARLTON
1993: Women’s Interagency HIV Study (WIHS): funded by NIAID to investigate progression of HIV among women
MACS and WIHS are the largest, and longest running cohorts of men and women with – and at risk for – HIV


Plasma Viral Load and CD4 Count Are the Best Predictors of Developing AIDS

Mellors JW, …Rinaldo CR. Ann Int Med 1997
Association of Race and Gender with HIV-1 RNA

Relative Difference of HIV-1 RNA in WIHS Women relative to MACS Men

CD4 < 200 200 ≤ CD4 < 350 350 ≤ CD4 < 500 500 ≤ CD4
13% -32% a 350 -50% b 500 -46% b

Relative Difference of HIV-1 RNA in Whites relative to Non-whites

41% b

a P < 0.05  b P < 0.005

Short Term Bone Loss in HIV+ Premenopausal Women

Yin MT, ...Anastos K, J Acquir Immune Defic Syndr 2010; 53:202-208
Racial Disparities in Mortality Rates – Despite HAART

Murphy K, ...Anastos K, AIDS 2013;27(15):2413-2423
Incidence of Cervical Precancers among HIV-seropositive Women

MWCCS Research Sites

Emory University
• Igho Ofotokun, Anandi Sheth, and Gina Wingood

Johns Hopkins
• Todd Brown and Joseph Margolick

Data Coordinating Center (JHU)
• Amber D’Souza, Stephen Gange and Elizabeth Golub

Albert Einstein/Montefiore
• Kathryn Anastos and Anjali Sharma

SUNY Downstate
• Deb Gustafson and Tracey Wilson

Chicago-Cook County
• Mardge Cohen and Audrey French

Northwestern
• Steven Wolinsky

UCSF
• Bradley Aouizerat and Phyllis Tien

UCLA
• Roger Detels

Georgetown
• Seble Kassaye and Daniel Merenstein

University of Miami
• Maria Alcaide, Margaret Fischl and Deborah Jones

University of Pittsburgh
• Jeremy Martinson and Charles Rinaldo

University of Alabama- Birmingham
• Mirjam-Colette Kempf and Deborah Konkle-Parker

University of North Carolina- Chapel Hill
• Adaora Adimora
MWCCS Research Sites

- 4 MACS sites
- 9 WIHS sites
- 1 Data Center (JHU)

80-Member Executive Committee
>30 Scientific & Operational Working Groups
WIHS Eligibility Criteria (2013, most recent enrollment)

Enrollment only at NEW Southern Sites
3:1 ratio of HIV+: HIV- (same as prior waves)

**WWH**
- Ages 35-60
- Started ART after 2006 (i.e., HAART) and not exposed to monotherapy except for PEP or pregnancy

**Seronegative:**
- 30-55
- Confirmed seronegative within 2 weeks of baseline
- Reported at least one high-risk exposure in the preceding 5 years [e.g. STI diagnosis; sex without a condom with 3+ men; sex with a condom with 6+ men; trading sex; sex with an HIV+ man; IDU or use of crack cocaine, cocaine, heroin or meth; or any partner who had any of the previously mentioned risk characteristics].

Seronegatives matched for age, race, and comorbidities (HTN, diabetes, HBV, HCV) and risk behavior (IDU) to WWH
MACS Eligibility Criteria (2010, recent enrollment)

2:1 ratio of HIV+: HIV-

MWH:  
• 18+ years  
• MSM or MSMW  
• ART Naïve; or HAART recipient with documentation of HAART initiation  
• No AIDS diagnosis prior to HAART initiation  
• No IDU in past 12 mos or perinatally acquired HIV infection

Seronegative:  
• 18+ years  
• Confirmed seronegative within 2 weeks of baseline  
• MSM or MSMW race and age matched to HIV+ counterparts
Multicenter AIDS Cohort Study (MACS, 1983-2020)
Women's Interagency HIV Study (WIHS, 1993-2020)
MACS/WIHS Combined Cohort Study (MWCCS)

- **January 1, 2019**: the MACS and WIHS cohorts combined to form the MACS/WIHS Combined Cohort Study (MWCCS)
  - Shift in focus to study co-morbidities
  - Administered by NHLBI and co-funded by 13 institutes (NIAID, NICHD, NHGRI, NIA, NIDCR, NINDS, NIMH, NIDA, NINR, NCI, NIAAA, NIDCD and NIDDK)

- MWCCS cohort will include *all active MACS and WIHS participants* and *new recruits from underrepresented groups*
  - Special focus on African American and Hispanic populations and residents of southern states

- Recruitment slated to start May 2020 -> now Oct 2020 due to SARS-Cov-2
## Current Cohort Status

<table>
<thead>
<tr>
<th>Status</th>
<th>WIHS</th>
<th>MACS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-</td>
<td>HIV+</td>
<td>HIV-</td>
<td>HIV+</td>
</tr>
<tr>
<td>Status</td>
<td>N=1,305</td>
<td>N=3,677</td>
<td>N=4,211</td>
<td>N=3,147</td>
</tr>
<tr>
<td>Active</td>
<td>659 (50)</td>
<td>1,495 (41)</td>
<td>1,257 (29)</td>
<td>826 (26)</td>
</tr>
<tr>
<td>Deceased</td>
<td>145 (11)</td>
<td>1,228 (33)</td>
<td>586 (14)</td>
<td>1,789 (57)</td>
</tr>
<tr>
<td>Administrative disenrollment*</td>
<td>269 (21)</td>
<td>537 (15)</td>
<td>1,689 (40)</td>
<td>-</td>
</tr>
<tr>
<td>Withdrew from the study or lost to follow-up</td>
<td>232 (17)</td>
<td>417 (11)</td>
<td>679 (16)</td>
<td>532 (17)</td>
</tr>
</tbody>
</table>

* 1995: ~1700 HIV-negative men were administratively censored from further follow-up, per an NIH decision; 2012: LA WIHS site was closed and 100 participants from Brooklyn site were disenrolled.

4,106 active participants (contributed data during previous year)

30% of active participants were enrolled in first enrollment waves (25+ years of follow-up)
MWCCS Data Collection
## Types of Data Collection

<table>
<thead>
<tr>
<th>Routine Collection</th>
<th>Intermittent Assessments</th>
<th>Ancillary Grants (&gt; 70 linked NIH awards)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACS/WIHS: every 6 mos; MWCCS: annual</td>
<td></td>
<td></td>
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<tr>
<td>• Interviewer administered questionnaires</td>
<td></td>
<td></td>
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<tr>
<td>• Physical exam and clinical assessments</td>
<td></td>
<td></td>
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<tr>
<td>• Specimen collection (laboratory testing and repository)</td>
<td></td>
<td></td>
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<tr>
<td>• Registry matching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Geocoding</td>
<td>e.g.,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2016-2018: EKGs, echocardiogram and pulmonary function testing on all active participants</td>
<td></td>
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<tr>
<td></td>
<td>• 2016-2018: Polysomnography and actigraphy on all MACS men</td>
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<tr>
<td></td>
<td>• 2010-current: neurocognitive battery every 2 years</td>
<td>e.g.,</td>
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<tr>
<td></td>
<td>• Leukapheresis and tissue collection for HIV viral reservoir studies</td>
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<tr>
<td></td>
<td>• Carotid artery intima media thickness (cIMT) measures</td>
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<tr>
<td></td>
<td>• DXA scans and CTs to assess musculoskeletal changes</td>
<td></td>
</tr>
</tbody>
</table>
Interviewer Administered Questionnaires

Annual Administration

- Demographic info
- Medical conditions and medication use
  - Ascertainment and adjudication of key outcomes, including: hospitalizations, new dx of AIDS, cancer, CVD-related dxs
- HIV medication and adherence
- Healthcare utilization
- Psychosocial domains, including: quality of life, depression, perceived stress, loneliness, stigma
- Behaviors (substance use and sexual behavior)
Physical Exam and Clinical Assessments

Routinely collected

• Height/Weight/Vital Signs
• Body circumference
• Gynecologic exam for women (with colposcopy as indicated)
• Liver Cirrhosis/Fibrosis via Fibroscan™ (every 3 years, annually on those with kPA>9.5 or undergoing Hep C Rx)
• Frailty assessments (grip strength, standing balance, time walk)

+Planned for MWCCS

• Body composition via InBody™

Previously collected in WIHS

• Bioelectric Impedance Analysis (2013-2019, every two years)
• Arterial Brachial Index Measurement (2013-2019 every two years on women >40)
Specimen Collection

**Laboratory Assessments**
- HIV Ab (for HIV-)
- Renal Chemistries
- CBC
- T-Cell (CD4, CD8, CD4/CD8)
- HIV Viral Load
- Lipid Panel
- HgbA1C
- Insulin
- ThinPrep per clinical indication

**Covid-19 Response**
- IgG/IgM (Oct 2020)
- Biomarkers (pre and post)

**+Baseline**
- Hep C (Ab, sAg, RNA→ Genotype)
- Hep B (Core and Surface Ab, sAg, DNA)
- STIs (GC/CT, RPR)

**Repository**
- Serum, EDTA Plasma, PBMCs (viable and cell pellets)
- Urine
- Saliva
- Hair
- Genital tract samples (swabs and CVL)
## Specimens in Central Repository

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>MACS Men</th>
<th>WIHS Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma (CPT, 1.0mL, 1.8mL)</td>
<td>NA</td>
<td>829,523</td>
</tr>
<tr>
<td>Plasma (Heparin, 1.0mL, 1.8mL)</td>
<td>719,074</td>
<td>NA</td>
</tr>
<tr>
<td>Plasma (EDTA, 1.0mL)</td>
<td>198,945**</td>
<td>12,453**</td>
</tr>
<tr>
<td>Serum (1.0mL, 1.8mL)</td>
<td>953,522</td>
<td>562,441</td>
</tr>
<tr>
<td>Cells (1x10E7 cells/ml)</td>
<td>345,823</td>
<td>365,955</td>
</tr>
<tr>
<td>Cell Pellets (5x10E5 cells/ml)</td>
<td>50,580</td>
<td>478,472</td>
</tr>
<tr>
<td>Urine, clean void (1.5mL)</td>
<td>89,876</td>
<td>96,903</td>
</tr>
<tr>
<td>Urine, supernatant (1.0mL, 1.5mL)</td>
<td>NA</td>
<td>95,833</td>
</tr>
<tr>
<td>Cervical Vaginal Lavage (CVL, 1.5mL)</td>
<td>NA</td>
<td>559,792</td>
</tr>
<tr>
<td>Stimulated Saliva</td>
<td>NA</td>
<td>5,372</td>
</tr>
<tr>
<td>Semen</td>
<td>58,782</td>
<td>NA</td>
</tr>
</tbody>
</table>
Other Data Collection/Resources

Registry matching:
- National Death Index
- Cancer Registry
- Renal Disease Registry

Ascertainment and Adjudication of Events
- Cancer
- Hospitalizations
- CVD Events
- Pulmonary diagnoses (COPD, asthma, sleep apnea)
- Cause of Death

Genomic Data
- Includes GWAS
- Datasets prepared by MWCCS Genomic Repository (Dr. Brad Aouizerat, NYU)
Other Data: Contextual datasets

All sites geocode addresses and provide matching block group to MWCCS Geocoding Data Center (UNC). UNC provided limited datasets to investigators which include the study ID number and the characteristics that describe where the participant resides.

For example:

- **Decennial Census & American Communities Survey (annual)**
  - % of people below federal poverty line in a participant’s census tract
  - % of people with health insurance coverage in a participant’s census tract

- BRFSS, NHANES, NSFG
  - % of individuals with STI in a participant’s county

- Air quality index in a participant’s tract or county
Previously Collected

- PFTs on ~60% men (n=1,178) and ~70% of women (n=1,536)
- Echocardiograms on ~60% men (n=1,195) and ~80% of women (n=1,476)
- Ziopatch on 60% of men (n=1,281)
- EKGs on all ~80% men (n=1,633) and ~90% women (n=2,011)

Planned for MWCCS

- PFTs (2x over 7 years)
- Echocardiogram (1x on new recruits and repeat on existing recruits >40)

- Brain MRIs on a subset of cognitively impaired participants (and demographically matched controls)
- Cardiac MRIs on symptomatic Covid+ participants+ matched controls
- Polysomnography and actigraphy on 200 women
Covid-19 Protocol

Interviewer Administered Phone Interviews

- Monthly questionnaires including:
  - Covid-19 symptoms, testing, treatment and hospitalizations
  - Resource changes (i.e., insurance, housing, employment)
  - Psychosocial impact (depression symptoms, loneliness, perceived stress and resiliency)

+ Planned at first in-person visit
- Antibody testing (IgG and IgM)
- PFTs
- Immunologic and pathogenesis studies proposed

All Covid-19 instruments (English and Spanish) and protocols are available on the MWCCS public website (https://mwccs.org/covid-forms/)
Resources for additional information about WIHS and MACS data collection

Cohort Profile: The Women’s Interagency HIV Study (WIHS)
Adaora A Adimora, Catalina Ramirez, Lorie Benning, Ruth M Greenblatt, Mirjam-Colette Kempf, Phyllis C Tien, Seble G Kassaye, Kathryn Anastos, Mardge Cohen, Howard Minkoff... Show more

International Journal of Epidemiology, Volume 47, Issue 2, April 2018, Pages 393–394i,

The Multicenter AIDS Cohort Study: Rationale, Organization, and Selected Characteristics of the Participants
Richard A Kaslow, David G. Ostrow, Roger Detels, John P. Phair, B Frank Polk, Charles R. Rinaldo, Jr., for the Multicenter AIDS Cohort Study

American Journal of Epidemiology, Volume 126, Issue 2, August 1987, Pages 310–318,
Characteristics of Active Participants (N=4,106)
Age Distribution of Active Participants

<table>
<thead>
<tr>
<th>Age Range</th>
<th>WIHS HIV-</th>
<th>WIHS PLWH</th>
<th>MACS HIV-</th>
<th>MACS PLWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
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<tr>
<td>30-34</td>
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<tr>
<td>35-39</td>
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<tr>
<td>40-44</td>
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<tr>
<td>45-49</td>
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<tr>
<td>50-54</td>
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<tr>
<td>55-59</td>
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<tr>
<td>60-64</td>
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<tr>
<td>65+</td>
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</table>

Median Age (IQR):
- WIHS HIV-: 50 (43, 57)
- WIHS PLWH: 52 (46, 58)
- MACS HIV-: 63 (57, 70)
- MACS PLWH: 58 (50, 64)

Age ≥ 60%
- WIHS HIV-: 18%
- WIHS PLWH: 20%
- MACS HIV-: 64%
- MACS PLWH: 42%
## Demographic Characteristics of Active Participants

<table>
<thead>
<tr>
<th></th>
<th>MACS Men</th>
<th>WIHS Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLWH N=1,024 HIV- N=915</td>
<td>PLWH N=1,516 HIV- N=651</td>
</tr>
<tr>
<td><strong>Median Age (IQR)</strong></td>
<td>58 (50, 64)</td>
<td>63 (57, 70)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>27%</td>
<td>17%</td>
</tr>
<tr>
<td>Hispanic/Latino, any race</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>White</td>
<td>53%</td>
<td>73%</td>
</tr>
<tr>
<td>Multiple Races/Other</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Annual Income &lt; $19,000</strong></td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>&lt;High School Education</strong></td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Currently Insured (Any)</strong></td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Median (mean) Follow-up Time, yrs</strong></td>
<td>16.7 (21.5)</td>
<td>34.0 (27.9)</td>
</tr>
</tbody>
</table>
## Chronic Disease Indicators

<table>
<thead>
<tr>
<th></th>
<th>MACS Men</th>
<th>WIHS Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLWH N=1,024</td>
<td>HIV- N=915</td>
</tr>
<tr>
<td>Current Smoker % (Former Smoker %)</td>
<td>22% (47%)</td>
<td>14% (53%)</td>
</tr>
<tr>
<td>BMI Median, IQR (% BMI &gt;30 [&gt;40])</td>
<td>26 (24, 30)</td>
<td>27 (24, 30)</td>
</tr>
<tr>
<td></td>
<td>23% [2%]</td>
<td>26% [3%]</td>
</tr>
<tr>
<td>HTN (SBP≥140, DBP≥90, meds)</td>
<td>50%</td>
<td>55%</td>
</tr>
<tr>
<td>Diabetes (A1C≥6.5%, FG≥126, meds)</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Dyslipidemia (LDL≥130, HDL&lt;40)</td>
<td>34%</td>
<td>28%</td>
</tr>
<tr>
<td>CKD (eGFR &lt;60 [&lt;30])</td>
<td>14% [1%]</td>
<td>8% [0.1%]</td>
</tr>
<tr>
<td>% w/Confirmed Cancers</td>
<td>11%</td>
<td>8%</td>
</tr>
</tbody>
</table>
## Antiretroviral Medication Exposure*

<table>
<thead>
<tr>
<th></th>
<th>MACS Men</th>
<th>WIHS Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLWH N=1024</td>
<td>PLWH N=1,516</td>
</tr>
<tr>
<td>% currently on any Therapy</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>% with previous exposure to d4T, ddI, ddC</td>
<td>48%</td>
<td>29%</td>
</tr>
<tr>
<td>% with previous exposure to Monotherapy</td>
<td>29%</td>
<td>21%</td>
</tr>
<tr>
<td>% Ever with Low CD4:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500 cells/mm³</td>
<td>88%</td>
<td>90%</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>32%</td>
<td>44%</td>
</tr>
</tbody>
</table>

* At most recent visit
Antiretroviral Therapy Use Among MACS and WIHS PLWH (active participants only)

- **Mono/Dual Therapy**
- **NNRTI-based/3+ NRTI Regimens**
- **PI-based Regimens**
- **Integrase Inhibitor-based Regimens**

Calendar Time

Jan 95 Jan 97 Jan 99 Jan 01 Jan 03 Jan 05 Jan 07 Jan 09 Jan 11 Jan 13 Jan 15 Jan 17 Jan 19

% Receiving Therapy

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Viral Load Among PLWH (active participants only)

Year

- **VL > 10,000**
- **VL ≤ 10,000**
- **VL ≤ 1,000**
- **VL ≤ 80**
- **VL ≤ 20**

* *TaqMan v2.0 HIV-1, sensitive to 20 copies HIV RNA/mL, implemented in 2009*
CD4 Cell Counts Among PLWH
(active participants only)

- CD4 ≥ 500
- CD4 < 500
- CD4 < 350
- CD4 < 200

Year: Jan 95, Jan 97, Jan 99, Jan 01, Jan 03, Jan 05, Jan 07, Jan 09, Jan 11, Jan 13, Jan 15, Jan 17, Jan 19

Percentage: 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%
<table>
<thead>
<tr>
<th></th>
<th>MACS Men</th>
<th>WIHS Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLWH</td>
<td>HIV-</td>
</tr>
<tr>
<td><strong>Baseline:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV+</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>HCV RNA+</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>HBsAg+</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Last Test Result</strong></td>
<td>N=3,873</td>
<td>N=3,485</td>
</tr>
<tr>
<td>Anti-HCV+</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>HCV RNA+</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>HBsAg+</td>
<td>7%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Recent Scientific Contributions of the Cohorts
Background: Cost of DAAs for HCV led many payers to restrict treatment to patients who met non–evidence-based criteria (e.g., fibrosis and cirrhosis). These restrictions have implications for survival of people with HCV, especially for people with HIV/HCV coinfection, who are at high risk for liver disease progression.

Purpose: Estimate effects of DAA access policies on 10-yr all-cause mortality among people with HIV.

Methods: Among WIHS and MACS participants with HIV, investigators used the parametric g-formula to estimate 10-year all-cause mortality under DAA access policies that included treating

(i) all people with HCV;
(ii) only people with suppressed HIV;
(iii) only people with severe fibrosis; and
(iv) only people with HIV suppression and severe fibrosis.
Results: The 10-year risk difference of treating

- all coinfected persons with DAAs compared with no treatment was -3.7% (95% CI: -9.1% - 0.6%)  **NNT= 27**, (27 PWH treated to prevent 1 death over 10 years)

- treating only those with suppressed HIV and severe fibrosis yielded a risk difference of -1.1% (95% CI: -2.8% -0.6%), with 51% (95% CI, 38%-59%) of coinfected persons receiving DAAs. **NNT=94**

- treating a **random selection** of 51% of coinfected persons at baseline decreased the risk by -1.9% (95% CI, –4.7% - 0.3%) **NNT=53**
Conclusion

• Restrictive DAA access policies may decrease survival compared to treating similar proportions of people with HIV/HCV coinfection with DAAs at random – suggesting that thoughtfully revising access policies could save lives.
Background: The HIV care continuum can estimate effectiveness of HIV services. Universal and early treatment have been adopted in the US, but many PWH do not maintain viral suppression.

Purpose: Characterize longitudinal HIV viral load outcomes among women with HIV in the WIHS

Methods: All WIHS women with at least 2.5 years of data between 1994-2017 were included. Categorized women into groups based on their probability of achieving viral load suppression, using logistic trajectory modeling. Multinomial regression analysis was used to identify factors associated with placement in the group with the highest probability of viremia.
Group-based trajectory analysis identified 3 distinct viral trajectories among participants using a cutoff of >200 copies/mL.
The mean (SD) cumulative years of viral suppression were 18.7 (4.0), 12.2 (3.1), and 5.8 (2.9) years in the respective groups.
• Proportion of women who were suppressed improved over time (83.4% suppressed in 2017).
  • Between 2015 to 2017; 89.6% had consistent suppression in the low-viremia group, 83.4% in the intermediate-viremia group, but just 35.2% in the high-viremia group.
• The overall median HIV viral load for individuals who were not always virally suppressed from 2015 to 2017 was: 7,286 copies/mL in the low-viremia group, 5,558 copies/mL in the intermediate-viremia group, and 21,817 copies/mL in the high-viremia group.
Results and Conclusions

The probability of viremia decreased substantially over time for most participants, regardless of group.

Factors associated with high probability of viremia included:
  - Younger age OR: 0.99, 95%CI (0.98-0.99) P = 0.03
  - African American race OR: 2.43, 95%CI (1.75-3.37), P < 0.001
  - Hispanic ethnicity (OR, 1.50; 95%CI, 1.03-2.19; P = .04),
  - Increased depressive symptoms OR: 1.17, 95%CI (1.01-1.36); P = 0.03
  - Drug use OR: 1.23, 95%CI (1.01-1.51), P = .04,
  - Lower CD4+ count OR: 0.82, 95%CI (0.80-0.85), P < 0.001
  - Unstable housing OR: 1.25, 95%CI (1.03-1.50), P = 0.02

Continued efforts are needed to address mental health, social, behavioral and structural factors that are associated with high probability of HIV viremia over time.
Background: PWH have greater risk for sudden arrhythmic death than individuals. HIV-associated abnormal cardiac repolarization may contribute to this risk.

**Purpose:** Determine whether HIV infection is associated with ventricular repolarization lability by using the QT variability index, QTVI (log measure of QT-interval variance indexed to heart rate variance).

**Methods:** 1123 MACS participants (589 HIV+ and 534 HIV−) wore a ZioXT ambulatory electrocardiography patch (Ziopatch) for 4 days. Inflammatory markers were collected. Beat-to-beat analysis of up to 4 full days of electrocardiographic data per participant was performed using an automated algorithm (median analyzed duration [quartile 1–quartile 3]: 78.3 [66.3–83.0] hours/person). QTVI was modeled using linear mixed-effects models adjusted for demographics, cardiac risk factors, and HIV-related and inflammatory biomarkers.
Results

- In comparison with HIV− men, HIV+ men had higher QTVI (adjusted difference of +0.077 [95% CI, +0.032 to +0.123]).
  - The magnitude of this association depended on the degree of viremia, such that in HIV+ men with undetectable VL, adjusted QTVI was +0.064 (95% CI, +0.017 to +0.111) higher than in HIV− men, whereas, in HIV+ men with detectable VL, adjusted QTVI was higher by +0.150 (95% CI, 0.072–0.228) than in HIV− referents.

Table 3. Adjusted Associations Between HIV Serostatus and QTVI

<table>
<thead>
<tr>
<th>Associations</th>
<th>QTVI Model A* (n=1123)</th>
<th>QTVI Model B* (n=983)</th>
<th>P Value</th>
<th>QTVI Model C* (n=983)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept with centered covariates†</td>
<td>−1.55 (−1.61 to −1.49)</td>
<td>−1.57 (−1.69 to −1.45)</td>
<td>&lt;0.001</td>
<td>−1.57 (−1.69 to −1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV+ (vs HIV−)</td>
<td>0.079 (0.034 to 0.124)</td>
<td>0.077 (0.032 to 0.123)</td>
<td>&lt;0.001</td>
<td>HIV+/Undetectable‡</td>
<td>0.064 (0.017 to 0.111)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HIV+/Detectable‡</td>
<td>0.150 (0.072 to 0.228)</td>
</tr>
</tbody>
</table>
• Analysis of QTVI subcomponents showed that HIV+ men had: (1) lower heart rate variability irrespective of VL status, and (2) higher QT variability (only if they had detectable VL)
  • Progressively greater QTVI with higher viral loads could be the result of direct viral effects on electrophysiological properties
• Higher levels of CRP, IL-6, ICAM-1, sTNF-R2, and sCD-163 (borderline), were associated with higher QTVI and partially attenuated the association with HIV serostatus

Table 6. QTVI Differences Associated With Inflammatory Marker Concentrations (n=219 HIV−/344 HIV+) and the Residual Association for HIV

<table>
<thead>
<tr>
<th>Model B and Adjustments</th>
<th>2nd Tertile (vs 1st)</th>
<th>P Value</th>
<th>3rd Tertile (vs 1st)</th>
<th>P Value</th>
<th>HIV+ (vs HIV−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.089 (0.022 to 0.157)</td>
</tr>
<tr>
<td>Model B + CRP, µg/mL</td>
<td>0.050 (−0.021 to 0.122)</td>
<td>0.17</td>
<td>0.092 (0.016 to 0.168)</td>
<td>0.018</td>
<td>0.081 (0.013 to 0.148)</td>
</tr>
<tr>
<td>Model B + ICAM-1, ng/mL</td>
<td>0.014 (−0.059 to 0.088)</td>
<td>0.70</td>
<td>0.075 (0.001 to 0.149)</td>
<td>0.049</td>
<td>0.079 (0.010 to 0.147)</td>
</tr>
<tr>
<td>Model B + IL-6, pg/mL</td>
<td>0.113 (0.041 to 0.186)</td>
<td>0.002</td>
<td>0.135 (0.059 to 0.211)</td>
<td>&lt;0.001</td>
<td>0.084 (0.016 to 0.151)</td>
</tr>
<tr>
<td>Model B + sCD163, ng/mL</td>
<td>0.029 (−0.045 to 0.103)</td>
<td>0.44</td>
<td>0.074 (−0.006 to 0.154)</td>
<td>0.070</td>
<td>0.081 (0.011 to 0.150)</td>
</tr>
<tr>
<td>Model B + sTNF-R2, ng/mL</td>
<td>0.049 (−0.025 to 0.122)</td>
<td>0.20</td>
<td>0.083 (0.006 to 0.161)</td>
<td>0.035</td>
<td>0.085 (0.017 to 0.153)</td>
</tr>
</tbody>
</table>

Each row corresponds to a separate mixed-effects model of QT variability with adjustments from model B and the tertiles of the inflammatory marker of interest as the independent variable. Fibrinogen, MCP1, sCD14, and sTNF-R1 were also modeled but had P values >0.10 and are not reported. CRP indicates C-reactive protein; HIV, human immunodeficiency virus; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; MCP1, monocyte chemoattractant protein-1; QTVI, QT variability index; sTNF-R1, soluble tumor necrosis factor receptor 1; and sTNF-R2, soluble tumor necrosis factor receptor 2.
Clinical Perspective

What Is New?

• In this largest study of QT variability to date, human immunodeficiency virus (HIV) infection and viral load were progressively associated with a higher QT variability index, a marker of QT interval dynamicity reflecting ventricular repolarization lability and increased arrhythmia risk.
• Elevated levels of inflammatory markers were associated with higher QT variability index and, in part, explained the relationship between HIV and abnormal repolarization.

What Are the Clinical Implications?

• Men living with HIV exhibit lower heart rate variability, regardless of viral load.
• Viremia among men living with HIV is associated with higher QT variability.
• Abnormal heart rate variability reflecting autonomic dysfunction, and abnormal QT variability suggesting ventricular repolarization lability may explain mechanisms for increased sudden cardiac death among people living with HIV.
Background and Methods: Neighborhoods with high poverty have limited resources to support residents' health. Census data from WIHS women was used to describe tract level poverty, interview and laboratory data used to classify all health outcomes (e.g., VL, BP, HgbA1C). The goal of this research was to determine the relationships between tract level variables and clinical outcomes.

Results:

**VL:** Prevalence of unsuppressed VL was higher among HIV+ women living in neighborhoods of extreme poverty in unadjusted analyses (>40-100% vs. ≤20% PR, 1.79; CI,1.30-2.48) and analyses adjusted for individual markers of HIV disease, SES, and demographics (aPR, 1.42; CI,1.04-1.92)

**BP:** No difference in the prevalence of uncontrolled hypertension with increasing neighborhood poverty in either HIV+ or HIV-seronegative women

**Diabetes:** No difference in the prevalence of uncontrolled diabetes in HIV+ women. Among HIV- women with diabetes, neighborhood poverty was associated with uncontrolled diabetes, with a threshold effect in census tracts with >20% poverty (>20-40% vs. ≤20% aPR, 1.75; 95% CI, 1.02-2.98)
Conclusions

We believe these results (lack of observed associations between tract-level poverty and either hypertension or diabetes control among all women) may be due the restricted range of individual income and neighborhood poverty in the sample.

- Study participants generally lived in neighborhoods of concentrated poverty and were themselves overwhelmingly poor, with nearly half of women reporting an annual household income ≤$12,000.

- This is a testimony to the difficult socioeconomic contexts in which women with HIV live and may have limited our ability to observe associations between neighborhood poverty and hypertension and diabetes control.
Background: Dramatic ↑ in STI rates in US in past decade and 7 of 10 states with highest rates are in the South

• Simultaneous ↓ in safety net STI services (budget cuts → clinic closures, ↓ hours, contact tracing, STI screening). Divestment in local STI services → ↓ STI dx and Rx

• ↓ health care access could ↑ risk of women’s exposure to STI

• People with or at ↑ risk for STIs live closer to their partners than people at lower risk
Methods: WIHS data from all Southern recruits, census data used to describe social capitol and voter turnout in 2012 election, Dx/o STIs (CT, GC, trich, or early syphilis) ascertained via labs, relationships between tract level characteristics and STIs evaluated via GEE

Results: County-level voter turnout was associated with not having an STI

- A 4-unit increase in the county-level voter turnout was associated with not having an STI (RR=0.86, 95% CI=0.75-0.99)
- Risk ratios for county-level voter turnout in models controlling for and without county-level poverty were within 1% for all comparisons, suggesting that these relationships were independent of county-level poverty
Background: ART leads to undetectable levels of HIV-1 in the blood and virtually eliminates risk of sexual transmission. Questions persist, however, concerning the amount of virus present in the genital tract of women who receive suppressive ART. There are clinical implications for both sexual transmission and perinatal transmission of HIV-1, particularly in the setting of genital tract infection or inflammation.

Purpose: Determine frequency of genital HIV-1 shedding among WIHS women on long-term suppressive ART and its association with mucosal inflammation.

Methods: HIV-1 was quantified from CVL samples of 332 WIHS participants with and without clinical evidence of genital inflammation at the time of CVL collection; participants had suppressed plasma viral load for a median of 7.1 years (IQR 3.4–9.8, Group 1) or for a median of 1.0 years (IQR = 0.5–1.0, Group 2). Twenty-two biomarkers of inflammation were measured in CVL to compare with clinical markers.
Results:

- HIV-1 detected in 47% of 38 pre-ART CVL samples (median 668 copies/ml); detection in CVL was associated with higher pre-ART PVL.
- HIV-1 detected in only 1 of 38 CVL samples from women on suppressive antiretroviral therapy for 1 year.
- No HIV-1 RNA detected in any of the 294 CVL samples from cross-sectional set of women with suppressed PVL for a median of 7 years.
- Clinical inflammation markers were correlated with inflammatory biomarkers in CVL specimens, although genital inflammation was not associated with measurable genital HIV-1 shedding in these WIHS participants on ART.

Conclusion: **ART that suppresses HIV-1 in plasma of women also prevents genital tract HIV-1 shedding, even in the presence of genital tract inflammation.**
Resources for Collaboration
Investigator How-To’s

1. Submit a Concept Sheet
2. Submit a Revised Concept Sheet
3. Submit a Concept Sheet Addendum
4. Request Data/Specimens
5. Submit a Manuscript or Abstract
6. Submit a Publication

MACS/WIHS CCS WORKING GROUPS

To view upcoming working group calls, click here.

MWCCS Scientific Working Groups

- Aging Working Group—Studies complex characteristics of aging, to include both aging-related diseases and non-organ-specific events that are associated with age, in multiethnic and HIV+ men and women comprising the CCS. Studies the epidemiology of complex aging-related processes including physical/functional status (frailty, walking speed, balance, falls, fractures, endocrine status), mental health (depressive symptoms), the interaction between physical/functional and mental health, and healthy aging and resilience. Studies...
Contact the PI at your Nearest Site

https://airtable.com/shrvTcWBCNozp5t7b/tbIKFk9fzIVc2gXsi?blocks=hide
Type of Collaborations

**Secondary Data Analysis**
- Requires concept sheet and DUA
- Investigator works with MWCCS PI (either at site or assigned liaison) to submit concept sheet
- 2-3 week EC approval
- DACC will provide dataset

**Specimen and Data Request**
- Requires concept sheet, DUA and MTA
- Investigator works with MWCCS PI (either at site or assigned liaison) to submit concept sheet
- 2-3 week EC approval
- DACC will coordinate specimen retrieval and provide dataset

**New Data Collection**
- Requires concept sheet and funding
- Investigator works with MWCCS PI (either at site or assigned liaison) to submit concept sheet
- Approval (for concept and budget) required from all participating sites prior to submission to EC
- Investigator responsible for sIRB
- 2-3 week EC approval
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