NATIONAL INSTITUTE ON AGING
UPDATE ON HIV/AIDS ACTIVITIES

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HIV: AN AGING EPIDEMIC: CONVERGENCE OF AGE- AND HIV-RELATED CO-MORBIDITY

Credit: thegrayingofaids.org
Support and conduct genetic, biological, clinical, behavioral, social, and economic research on aging.

Foster the development of research and clinician scientists in aging.

Provide research resources.

Disseminate information about aging and advances in research to the public, health care professionals, and the scientific community, among a variety of audiences.
PREVALENCE OF HIV IN THE US

CDC. HIV Surveillance Reports, 2005 - 2014
In 2012, people aged 55 or older accounted for 24% of the estimated 1.2 million people living with HIV in the US (CDC, October 2015)

- In 2013, people aged 50 and over were
  - 21% of HIV-1 diagnoses
  - 27% of AIDS diagnoses and 37% of deaths related to AIDS

Immune changes that occur during normal aging may occur earlier in chronically HIV-infected individuals

Potential for ‘synergistic’ effects of aging and HIV-infection driving further immune decline

Long-term ART-treated HIV-infected subjects have excess risk of a number of ‘HIV-associated non-AIDS’ (HANA) conditions including cardiovascular disease, osteoporosis, cognitive impairment – conditions that typically associate with advancing age.
ALTHOUGH ART PREVENTS AIDS AND IMPROVES HEALTH, THE RISK FOR DEVELOPING MANY MORBIDITIES REMAINS HIGHER THAN EXPECTED (~1.5 TO 2.0 FOLD)

- Cardiovascular disease [1-3]
- Cancer (non-AIDS) [4]
- Bone fractures / osteoporosis [5,6]
- COPD [12]
- Liver disease [7]
- Kidney disease [8]
- Cognitive decline [9]
- Non-AIDS infections [10]
- Frailty [11]

National Institute on Aging (NIA) is interested in understanding how biological, clinical, and socio-behavioral processes affect older individuals with HIV and their caregivers, and the social, economic, and health consequences of HIV.

- Interactions among aging-related genetic, molecular, and cellular changes with HIV risk, infection, and pathogenesis (DAB);

- Interactions among HIV infection, treatment, and development or progression of cognitive decline, dementia, and other disabilities in older adults (DN);

- Interactions of HIV infection and treatment with other aging-related diseases, conditions, and syndromes and “geriatric” approaches to assessment and management of older adults with HIV (GCG);

- Interactions among HIV/AIDS, other diseases, social structural variables, and population aging (including in low-income areas such as sub-Saharan Africa) to understand how individual, intergenerational, and structural levels of factors contribute to biological, behavioral and social consequences in older adults.
MANY HIV-ASSOCIATED FACTORS COULD CONCEIVABLY PREVENT HEALTHY AGING

**INITIATORS OF INFLAMMATION**
- HIV replication/production
- Co-pathogen excess (CMV, HCV)
- Microbial translocation
- Loss of regulatory responses
- Obesity
- Lipodystrophy
- Metabolic syndrome
- Substance abuse

**OTHER RISK FACTORS**
- Antiretroviral/HIV toxicity
  - Mitochondrial toxicity
  - Telomerase/telomere dysfunction
  - Metabolic abnormalities
  - Kidney dysfunction
  - Neuropathy
  - Sarcopenia
  - Osteopenia
  - Immunosenescence
- Substance abuse
- Social isolation
- Polypharmacy

**MICROBIAL TRANSLOCATION**
- Loss of CD4+ T cells
- Loss of epithelial cells
- Altered bowel flora
- Loss of Th17 cells
- Local inflammation (IFN-α, IDO)

**INNATE IMMUNITY**
- Activated monocytes and macrophages

**LIVER FIBROSIS OR DYSFUNCTION**
- Microbial translocation
- HIV infection of liver cells
- Inflammation
- ARV toxicity
- HCV
- HBV
- Alcohol

**CARIOVASCULAR DISEASE**
- Atherosclerosis
- Plaque Rupture
- Vascular dysfunction

**HYPERCOAGULATION**
- Microclotting
- VTE, MI, CVA

**Tissue factor expression**

**ALTERED COAGULOME**

**AGE ASSOCIATED DISEASES**

Deeks, Tracy, Douek. Immunity 2013
ARE THERE COMMON MECHANISMS DRIVING INFLAMMATION IN HIV INFECTION AND AGING?
HIV INFECTION AND AGING SHARE FEATURES OF CHRONIC INFLAMMATION AND IMMUNE ACTIVATION

- Increased pro-inflammatory cytokines and acute phase reactants (IL-6, TNF-a, CRP) termed “inflammaging” (Franschechi et al, 2000)
- Elevated levels of pro-coagulant factors
- Increase in cellular and soluble markers of monocyte activation (CD16+ monocytes, sCD14, sCD163)
- Increased markers of T cell activation and immune senescence
- Shared clinical outcomes include: dementia, CVD, strokes, metabolic alterations, frailty and sarcopenia, impaired immune responses and immune surveillance, cancers

Reviewed in Aberg, Top Antivir Med 2012
EPIGENETICS

Changes to DNA, such as methylation at CpG sites, that alter gene expression without changing the inherited genetic code.

(Katerina Karavodin)
HIV-INFECTION ACCELERATES EPIGENETIC AGING

- Weighted gene co-expression network analysis (WGCNA) was applied to the data.

- Using a multivariate model that includes methylation patterns, age, and HIV status, we published that HIV-1-infection accelerates aging by 13.7 to 14.7 years.

ART ONLY PARTIALLY RESTORES AGE-APPROPRIATE METHYLATION PATTERNS

- Longitudinal samples
- 3 time-points, spanning ART initiation
- 15 HIV+ MACS participants
- 15 SN age-matched MACS controls
- 39 to 50 years of age

DNA Methylation age – chronological age

Pre-ART (p = 0.00062) 2 Years Post-ART (p = 0.017)
Intramural Research Program

Division of Extramural Activities

- Division of Aging Biology
- Division of Neuroscience
- Division of Geriatrics and Clinical Gerontology
- Division of Behavioral and Social Research
Heterogeneity of neuro-HIV clinical presentations in older adults.

Mechanisms and pathways modulating patterns of HIV-induced CNS symptoms in older adults e.g., the role of microvascular disease in HIV neurodegeneration, or the degree of neuronal and/or epithelial dysfunction in neuro-HIV.

Risks, phenotypes and likely progression of age-associated neurodegenerative disorders in HIV; AD and ADRD, in particular.

Causes and consequences of metabolic syndrome on neuro-HIV and mitigation methods.

Multimodal imaging of and novel MRI sequences in neuro-HIV.
ALZHEIMER’S DISEASE AND NEURO-HIV: 
CONTROVERSY EXISTS AS TO WHAT FEATURES OF AD ARE PRESENT IN NEURO-HIV

- Disagreement exists as to whether brain deposition of Aβ42 and/or Tau is a common pathologic feature in HIV positive patients.

- There are discrepancies regarding the level of Aβ42 in the CSF of HIV positive individuals.

- Results of β-Amyloid imaging in patients with HIV remain controversial.

- There is a divergence in opinion whether the antiretroviral therapies contribute to the etiology of Alzheimer’s disease.
Goals of this FOA are to encourage basic and clinical research on delineating Alzheimer’s disease etiology in neuro-HIV in the setting of chronic viral suppression and antiretroviral therapies.

The request is highly focused with specialized review, it will promote collaborative and integrative efforts between investigators with different perspectives and backgrounds.

Combines NIA and OAR resources.

POTENTIAL AREAS OF INTEREST

- Reevaluate the AD and ADRD neuropathological indices in HIV patients on ART.
- Study neuronal dysfunction focusing on and synapto-dendritic damage in models with concurrent AD- and HIV-related neurodegenerative processes.
- Evaluate whether deficits in molecular and cellular mechanisms observed in AD, such as deficits in autophagy, are compromised in HIV.
- Assess AD biomarkers in neurological disorders associated with HIV infection.
- Evaluate whether neuronal circuits that are specifically compromised in HIV-induced CNS dysfunction involve mechanisms that play a role in AD; develop and adapt in-vitro/in-vivo AD models to investigate the abnormalities in both functional and structural neuronal connectivity caused by HIV.
- Develop novel models for investigating concurrent neurodegenerative processes in AD and HIV. A key need is the development of models that consider the effect of chronicity of viral infection and persistence in the CNS in the context of AD.
Aim 1: Harmonize processes for data collection of function/disability measures across the OAICs and CFARs, and provide a coordinated platform for gathering such data in supported pilot studies.

Aim 2: Validate key instruments/measures of functional outcomes and geriatric phenotypes derived in senior populations (age > 65 years) for use in HIV-infected subjects age > 50 years.

Aim 3: Support pilot projects at the interface of HIV and aging in high-priority areas of focus:

- Mechanisms and risk factors for accelerated organ system aging and functional decline
- Biomarkers and clinical indices as predictors and surrogate outcome markers
- Multi-morbidity and clinical interventions to preserve or recover function
- Societal infrastructure/support and caregiver issues

Aim 4: Identify and mentor junior faculty with a research focus in HIV and aging

Aim 5: Disseminate information regarding network research and data sharing opportunities to the larger scientific community in the fields of HIV, geriatrics, and gerontology.
A key geriatric functional performance measure (Short Physical Performance Battery) deployed in several cohort studies (MACS, WIHS, ALRT) and clinical sites (University of Alabama Birmingham, University of Washington, Wake Forest).

- Approximately 250 subjects have undergone testing in all locations to date. Analyses are underway.

- Pilot project funding (n=16): Early Stage Investigators (NIH definition) submit approximately half of all pilot concept proposals.

- R24 leadership contributed to organization of an R13 conference in October 2014: “HIV and Aging: from the Mitochondria to the Metropolis” (PI’s Marcia Holstad, Molly Perkins).

  - Conference focused on science at the intersection of HIV/AIDS and aging across basic, clinical, and socio-behavioral levels.

  - R24 leadership invited to serve on Executive Board of R13 renewal; most recent conference October 16-17, 2017.
Increased inflammation is believed to be a fundamental aging process.

Losartan, an angiotensin II receptor blocker, is best known for its use as an antihypertensive, but it also has immunomodulatory and anti-fibrotic properties.

This phase II randomized placebo-controlled trial is testing the effects of losartan (100 mg/d) over 12 months in subjects aged ≥ 50y with ART-treated HIV and CD4 counts less than 600 cells/mm3.

Primary and secondary outcomes are 12-month average IL-6 and change in CD4 count.

Study completion expected December 2018.

R01AG045032, PI: Jason Baker, Minneapolis Medical Research Foundation
NIA

Office of the Director/Deputy Director
- Office of Special Populations
- Office of Legislation/Policy/International Activities
- Office of Communications and Public Liaison
- Office of Planning, Analysis, and Evaluation

Intramural Research Program

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BSR-SUPPORTED HIV/AIDS PROJECTS: STUDY LOCATION

- U.S.: 60%
- International: 40%
BSR PROJECT HIGHLIGHT: HAALSI

- Determine HIV prevalence & incidence and identify HIV risk factors
- Identify extent + predictors of HIV treatment access & ART success
- Establish direct & indirect effects of HIV epidemic on health, social, behavioral, and economic outcomes, and determine how ART modifies these effects.

Baseline data collection in 2015 (Agincourt, S. Africa)

- HIV ELISA test results available for 4,560 participants, aged 40+
- Prevalence=23%♂♀; 38% HIV+ 40-49yrs; 2.8% HIV+ 80yrs+
- Among those HIV+, 76% reported knowing HIV status; only 51% reported being HIV+; 46% of HIV+ people were on treatment and virally suppressed
- Follow-up data collection at 3-year intervals.
BSR PROJECT HIGHLIGHT:
SAGE – WELL-BEING OF OLDER PEOPLE STUDY HIV

- Measure health status, chronic conditions, subjective wellbeing, and frailty
- Assess immune function, cellular senescence and inflammation in HIV-infected and HIV-uninfected older adults
- Assess effect of caregiving on older women impacted by HIV.

WOPS data (epidemiological and biological)
- Wave 1 completed in 2010/11; Wave 2 completed in 2013; Wave 3 completed in 2016, Wave 4 in 2018; data collected in rural and urban South Africa and Uganda community settings
- N = 1,100, aged 50+ (550 HIV seropositive and 550 seronegative)

PIs: Boerma Ties & Somnath Chatterji
**BSR CENTERS: HIV/AIDS-RELATED PILOTS**

- **NBER Roybal Center for Behavior Change in Health and Savings (Roybal, PI: David Laibson)**

- **The Center for Health Improvement of Minority Elderly (RCMAR, PI: Carol Mangione)**
  - Differences in age and ethnicity in HIV testing and perceptions of HIV risk in the Coachella Valley (2016)
  - Accelerated Cognitive Aging as a Function of HIV and Lifetime Stress/Adversity (2017)

- **The Center for the Global Demography of Aging (PI: David Bloom)**
  - Assessment of Neurocognitive Function in Africa's HIV-Infected Oldest Old (2014)
  - HIV Infection, Geriatric Health, and Quality of Life in Rural Uganda (2016)
Data from 2012 Gallup World Poll show a negative relationship between perceived improvements in health care and HIV prevalence where prevalence is low, and a positive relationship in regions with high HIV prevalence in sub-Saharan Africa (Deaton & Tortora 2015, *Health Affairs*).

Overall, the number of persons living with HIV/AIDS steadily increased, while HIV/AIDS mortality decreased in 195 countries between 1980-2015 (GBD 2015 HIV Collaborators 2016, *Lancet HIV*).

Opt-out HIV testing increased patient acceptance of tests compared to opt-in and active choice testing in the emergency department of an urban hospital (Montoy et al. 2016, *BMJ*).

Adult life expectancy increased after the rollout of a public ART program in KwaZulu-Natal, South Africa (Reniers et al. 2017, *Lancet HIV*).

Time since HIV diagnosis, social support, and community engagement were positively associated with resilience and mastery, which were in turn positively associated with psychological well-being in people living with HIV and depression (Endler et al. 2017, *Cerebroahuieria*).
GRANTS FOR EARLY MEDICAL/SURGICAL SPECIALISTS’ TRANSITION TO AGING RESEARCH (GEMSSTAR)

- An NIA “pre-K” award program for junior faculty physicians or dentists interested in a research career bridging their specialty and aging
- R03 mechanism ($75k/year for 2 years) plus an independently-supported Professional Development Plan
- Biennial GEMSSTAR scholar conferences
- Yearly competition

To date, 8 HIV-related GEMSSTAR applications have been received and 3 have been funded.