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Research Enterprise to Advance a Cure for HIV

HIV Cure and the Environment

How location informs cure research

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02/08/2024
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Poll

Have you attended the previous cure webinars?

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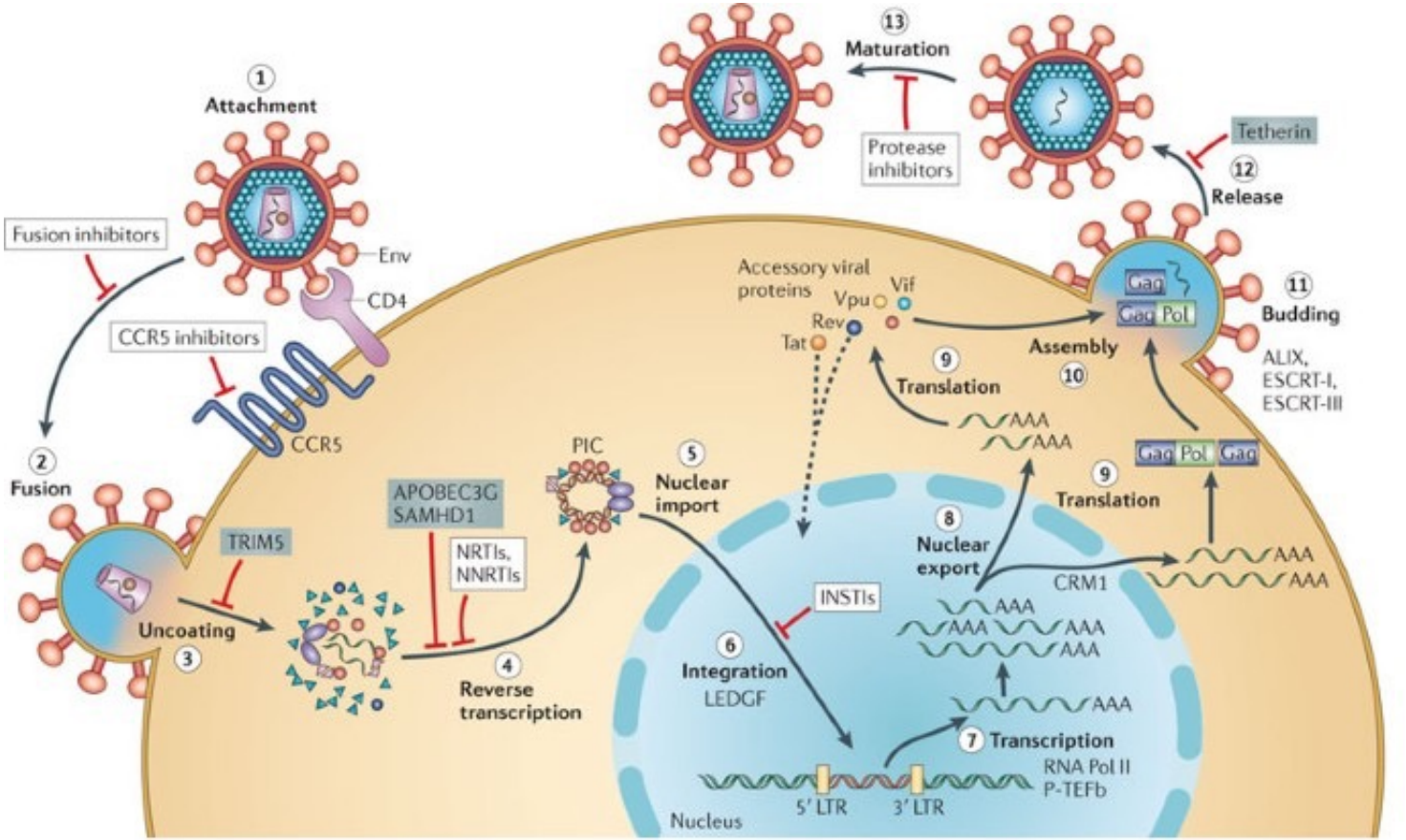
HIV Cure 101 Review

HIV Life Cycle



Source: Engelman et al. 2012

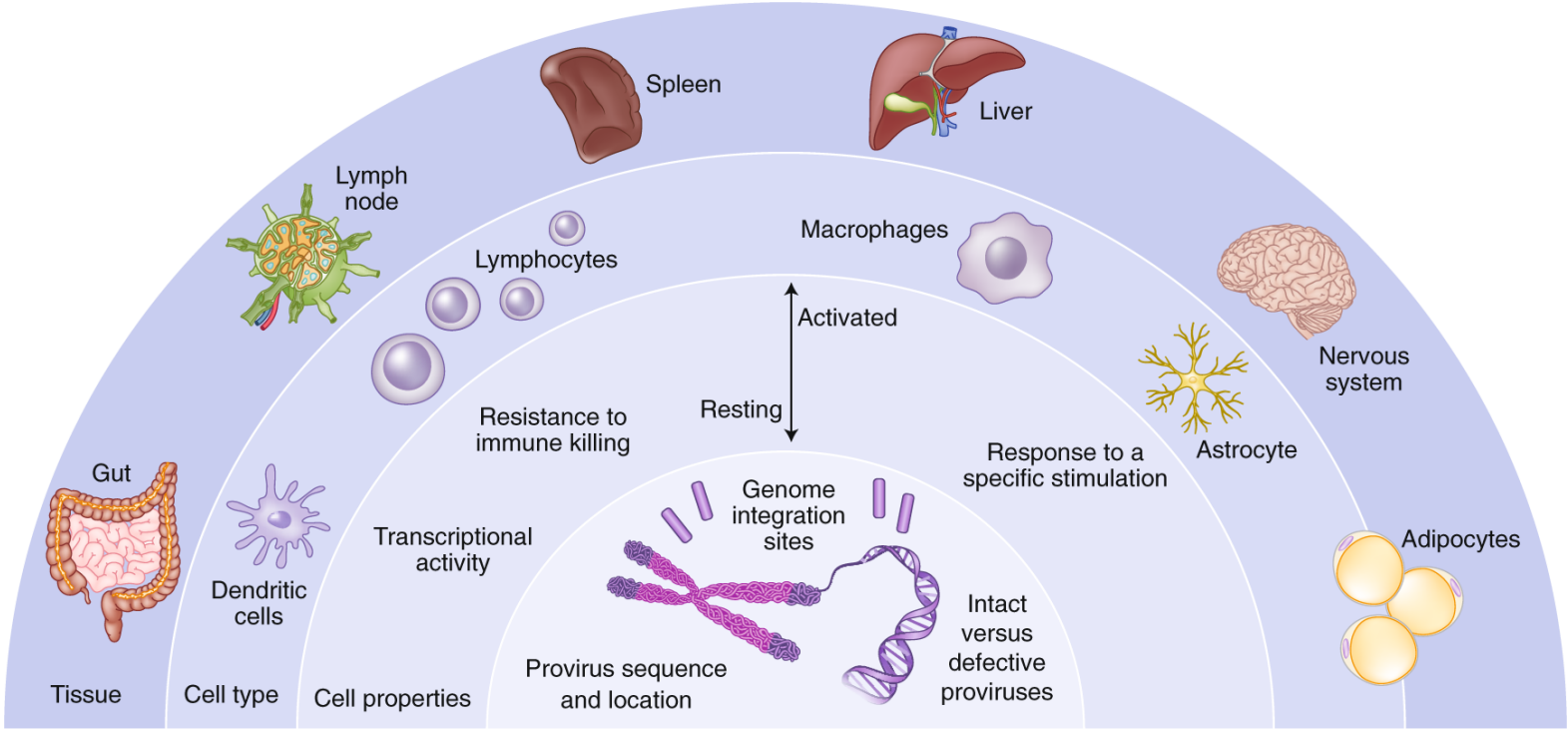
Nature Reviews | Microbiology

The HIV Reservoir

What is the '**HIV reservoir**'?

- Narrow definition: All infected cells in the body with genetically intact provirus capable of causing rebound viremia if ART is interrupted
  - 'Latently' infected cells – no HIV RNA produced from integrated provirus
  - Emerging evidence suggests latency is a continuum ranging from little or no viral transcription, to transcription, translation, and active virion production (Pace et al., Virology, 2011; Yukl et al., Sci Transl Med, 2018; Astorga-Gamaza et al., Curr Opin HIV AIDS, 2021)
  - Defective proviruses are capable of producing HIV transcripts and proteins, and may be clinically relevant (Imamichi et al., PNAS, 2016; Imamichi et al., PNAS, 2020) – *more research needed*
- Broader definition: all infected cells regardless of genomic intactness and transcriptional activity
- $CD4^+$ T-cells are the primary target of infection and are the primary reservoir-harboring cells
  - Other cell types in the body may also be reservoir-harboring (microglia, macrophages, astrocytes)

The HIV Reservoir

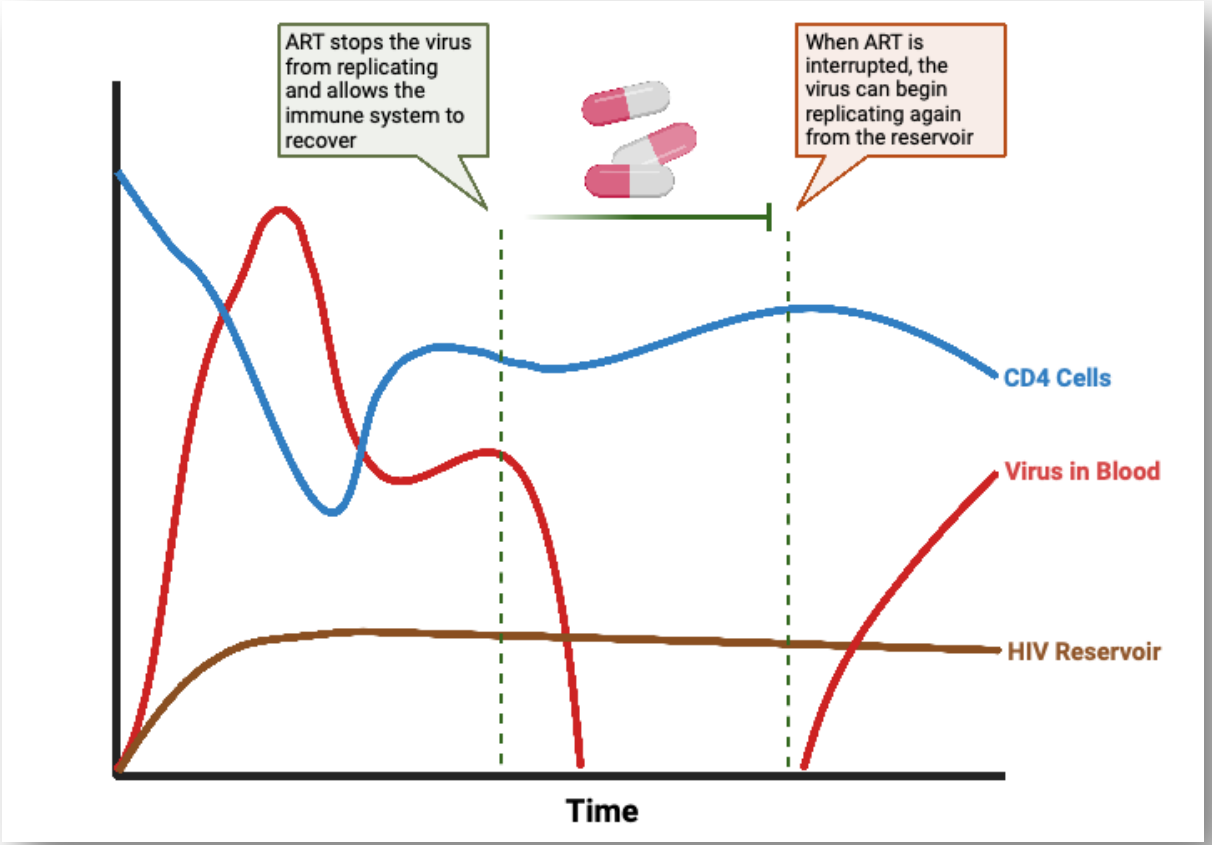


Landscape of the HIV reservoir

Source:

Research Priorities for an HIV Cure: International AIDS Society Global Scientific Strategy 2021

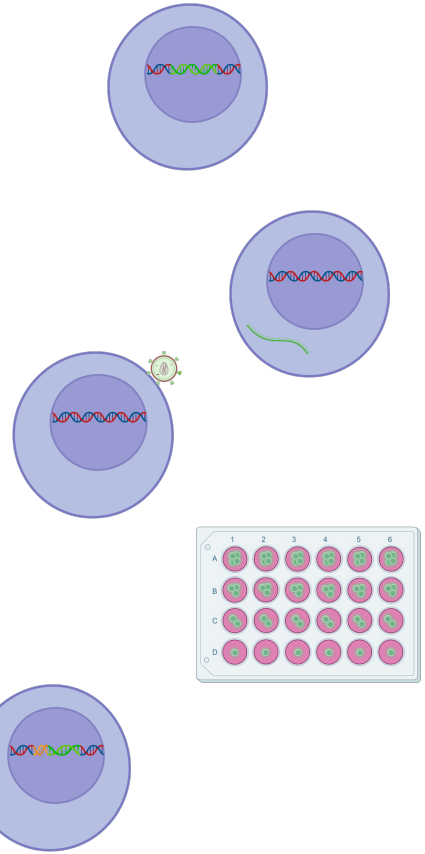
The HIV Reservoir



Measuring the HIV Reservoir

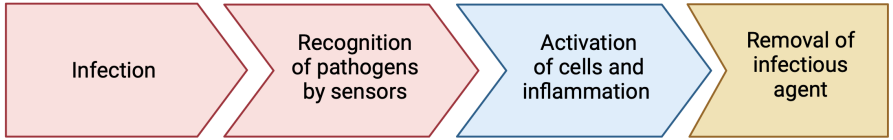
Multiple measures to quantify different aspects of HIV persistence and the reservoir:

- **Cell-associated HIV DNA (CA-DNA)** – measures total HIV DNA levels, including all intact and defective proviruses together (i.e. all HIV genetic material)
- **Cell-associated HIV RNA (CA-RNA)** – measures levels of various HIV RNA forms (i.e. HIV transcription)
- **Plasma HIV RNA** – amount of cell-free virus in blood (i.e. HIV virus production)
- **Quantitative viral outgrowth assay (QVOA)** – measures inducible, replication-competent virus levels after stimulating cells *ex vivo*
- **Intact proviral DNA assay (IPDA)** – separately quantifies genetically intact and defective HIV DNA levels

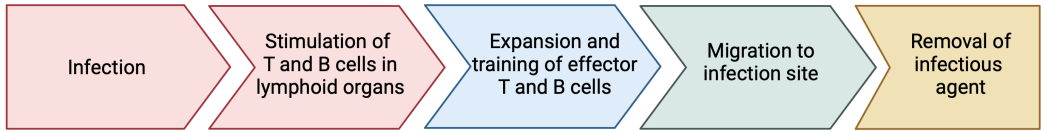


Immune Responses to HIV

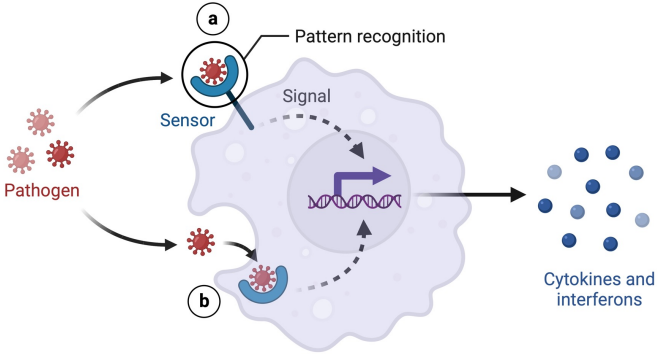
Innate immunity (quick, non-specific)



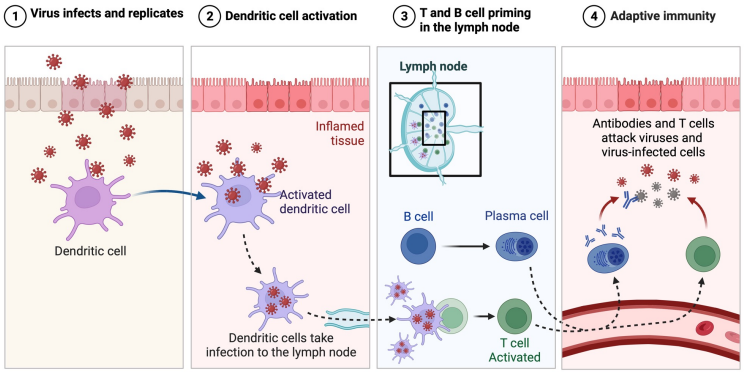
Adaptive immunity (long-term, specific)



Innate Immunity



Adaptive Immunity



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Language for HIV Cure

Defining HIV Cure

Classic cure

DEFINITION:

Removal of all replication-competent virus

This term is used to describe:

1. An individual who has received a stem cell transplant with a donor who has a natural immunity to HIV
2. An individual who has cleared the virus through immune mechanisms in the absence of antiretroviral therapy

Remission is an acceptable term to use when it is uncertain if a classic cure has been achieved. If virus is detectable, the community preferred terminology is "viral control".

PREFERRED ALTERNATIVE PHRASES

"classic cure", "cure", "eradication", "spontaneous cure", "traditional cure"

PHRASES TO AVOID

"Sterilizing cure", "Natural cure"

Viral Control

DEFINITION:

Immunologic suppression of the virus to undetectable levels off therapy

This term is used to describe:

1. A person with HIV-specific immune markers and a detectable inducible reservoir using non-commercial assays

PREFERRED ALTERNATIVE PHRASES

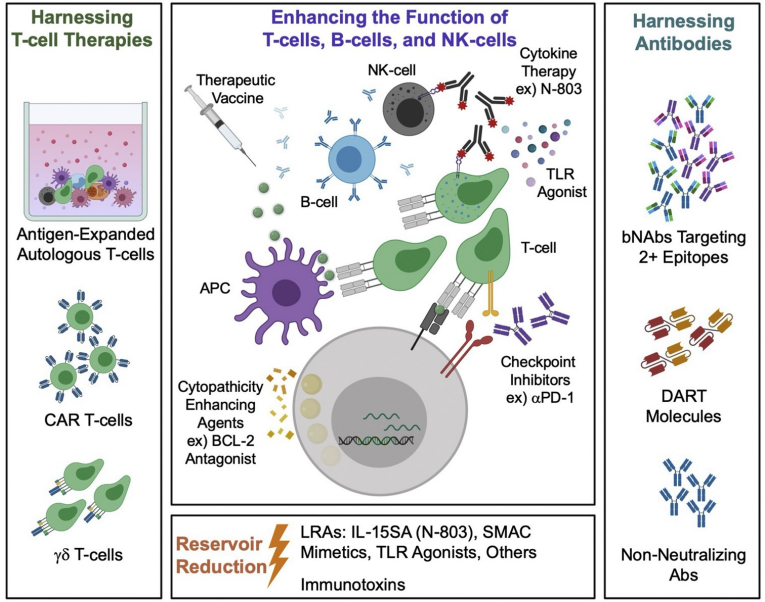
"Durable control", "Viral control off therapy", "immune-based control", "ART free virologic control"

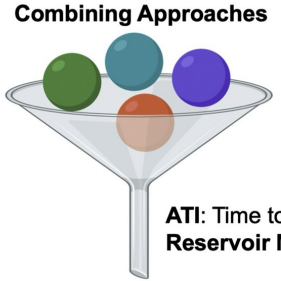
PHRASES TO AVOID

"Functional cure", "Remission"

HIV Cure Strategies Under Development

- **Immune-based strategies**
  - Shock-and-Kill (or Kick-and-Kill)
    - Related concept: Reduce-and-Control
  - Broadly neutralizing antibodies (bNAbs)
  - CAR and other engineered T cells
  - Therapeutic vaccination
  - Immunomodulatory drugs (IL-15, immune checkpoint inhibitors, etc.)
- **Gene editing strategies**
  - Block-and-lock
  - Viral excision/silencing by CRISPR
  - CCR5-Δ32 mutation
- **Combination approaches**
  - *Likely needed to achieve cure*

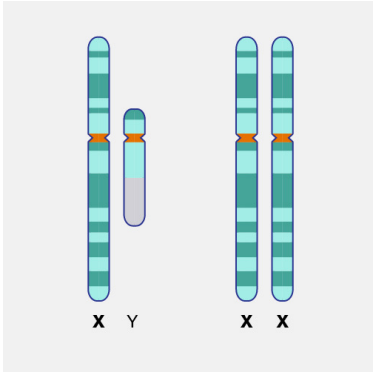


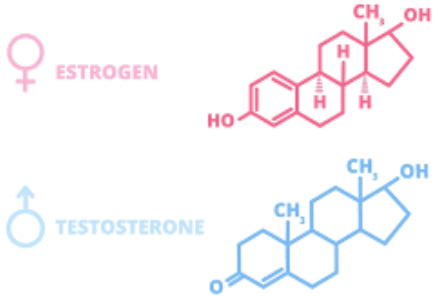


ATI: Time to Viral Rebound
Reservoir Measurements: QVOA, IPDA

Sex and HIV Cure

- **Biological sex can influence:**
  - HIV pathogenesis
  - Immune responses to HIV
  - Response to antiviral therapy
  - Reservoirs
    - May be less transcriptionally active in women
    - May be less inducible in women
  - Differences driven by multiple factors:
    - Influence of sex hormones
    - Sex-specific epigenetic profiles
    - Genetic differences derived from chromosomes
    - Behavioral and socioeconomic dynamics





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Additional Concepts in HIV Cure

Additional Concepts in HIV Cure


Multi-stakeholder consensus on a target product profile for an HIV cure

Sharon R Lewin*, Timothy Attoye, Cathy Bansbach, Brian Doehle, Karine Dubé, Mark Dybul, Devi SenGupta, Adam Jiang, Rowena Johnston, Rosanne Lamplough, Joseph M McCune, Gary J Nabel, Thumbi Ndung'u, John Pottage, David Ripin, James F Rooney, Izukanji Sikazwe, Moses Nsubuga, Mitchell Warren, Steven G Deeks*, on behalf of the Sunnylands 2019 Working Group

- **Safety**
  - Intervention is safe with few or no serious adverse events in most people
- **Efficacy**
  - Intervention: i) maintains viral load below transmission level (conservatively set at <200 cps/mL) or at some low level, and ii) promotes the health of PLWH off ART – in a proportion of PLWH (minimal 20%, optimal >90%)
- **Durability**
  - Intervention induces long-term control without the need for frequent or any subsequent interventions (minimal once/year, optimal never)
- **Scalability**
  - Intervention is cost-effective and can be scaled to the entire population of PLWH

Additional Concepts in HIV Cure

- **39 million people globally were living with HIV in 2022**
  - 29.8 million people (76%) were accessing antiretroviral therapy
    - 9.2 million people did not have access to ART
    - Only 57% of children aged 0-14 years were estimated to have access to ART
  - Sub-Saharan Africa accounted for 15% of the global population, but 68% of PLWH and 57% new infections

- **An HIV cure could:**
  - Help PLWH who cannot access or adhere to ART
  - Improve the individual's quality of life by reducing comorbidities, treatment burden, stigma, and socioeconomic burdens
  - Be a financially sustainable solution to ending the epidemic

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Q&A Break

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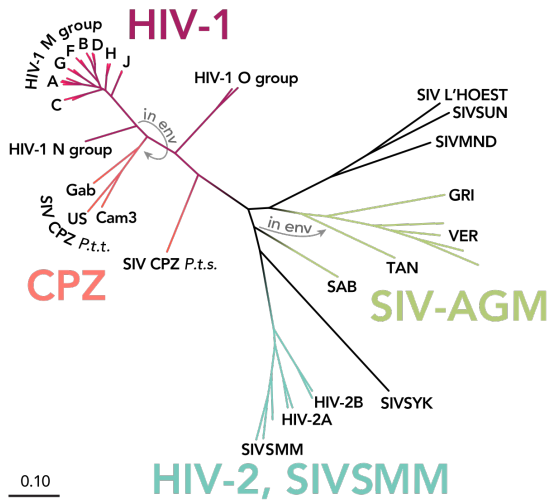
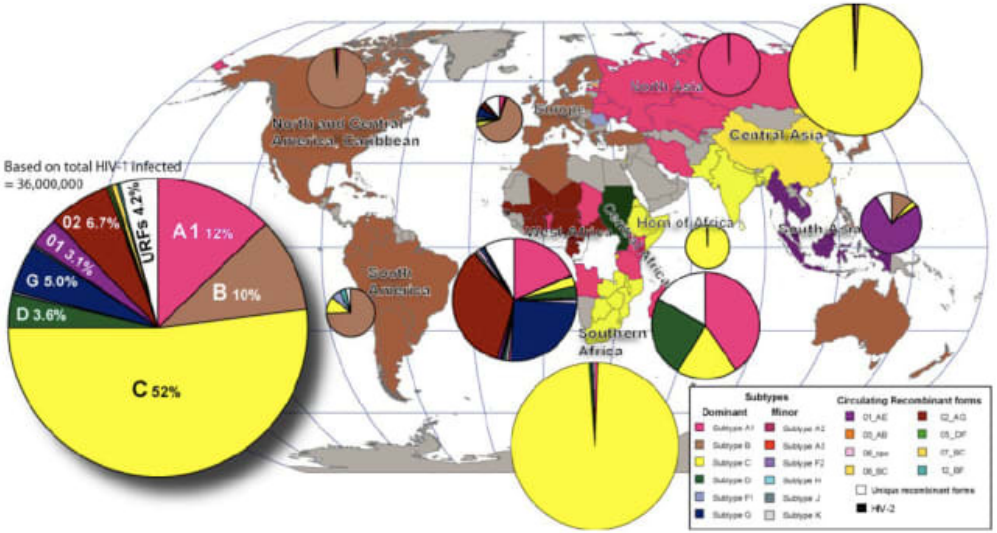
“Environment” – Location, Clade, Co-infections and Comorbidities, and ART Access

HIV Clades and Diversity

Two major types of HIV: HIV-1 and HIV-2

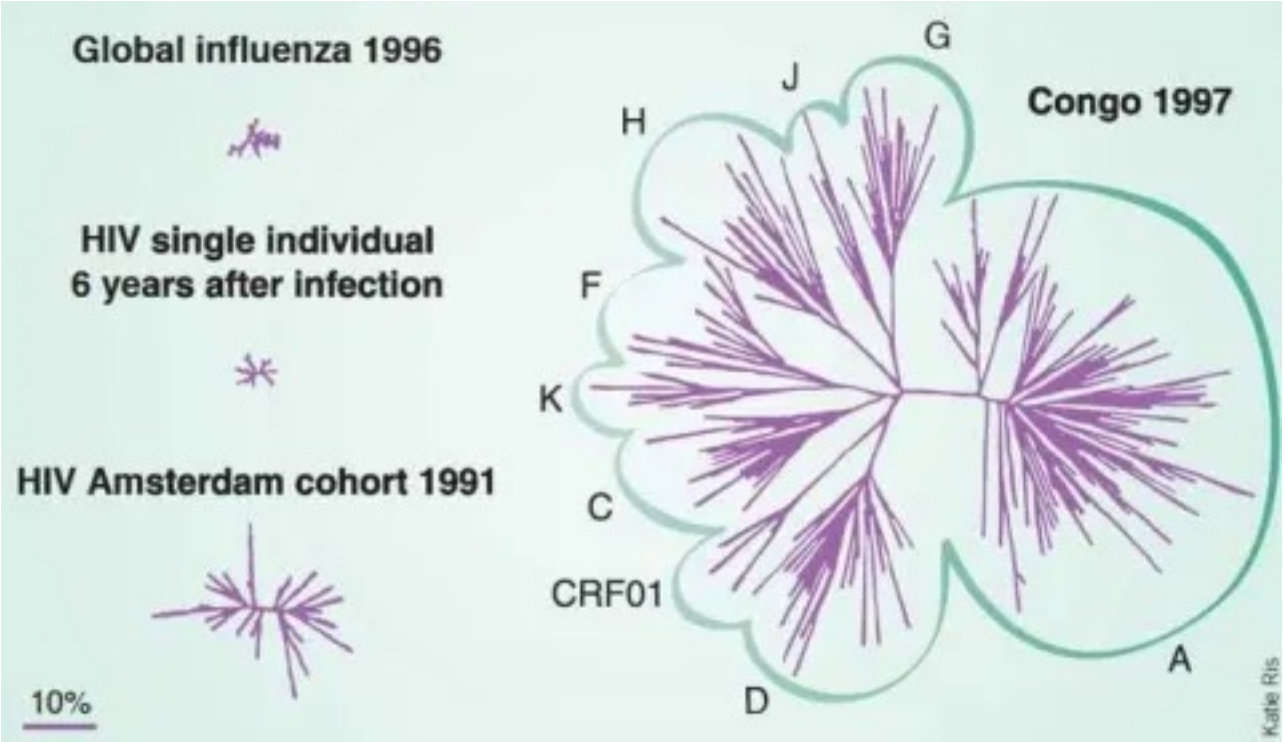
- HIV-1 responsible for >95% of all infections globally
    - HIV-1 divided into four groups: M, N, O, and P
        - Group M is the most widespread worldwide
        - Group M HIV-1 divided into nine distinct subtypes
            - **Subtype C dominates the global epidemic**
- Two or more subtypes can combine to form a hybrid known as a ‘circulating recombinant form’





Source: Hemelaar et al., Lancet Infect Dis 2018

HIV Clades and Diversity



Source: Hemelaar et al., Lancet Infect Dis 2018

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Challenge:

Most persistence and cure studies to-date conducted on populations living with subtype B HIV

- Few comparative studies on subtype B vs. non-B
- Need to adapt some reservoir assays to non-B HIV
- Need to build capacity for basic research and clinical trials in high-burden, resource-limited settings (primarily non-B)
- Role of viral subtype (and geography, ethnicity) on effectiveness of cure interventions?

HIV Clades & Diversity in Cure Research

- Few comparative studies between B vs. non-B
  - One study compared IUPM by QVOA in a cohort of PLWH in Rakai, Uganda (subtype A/D) vs. a cohort from Baltimore, USA (subtype B)
    - Ugandan participants had a 3-fold lower IUPM vs. Baltimorean participants
    - Difference in IUPM persisted despite controlling for differences in multiple relevant clinical factors – biological mechanism unknown

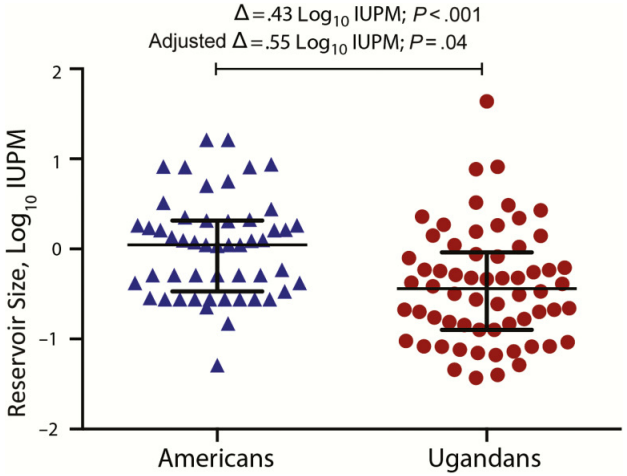
JOURNAL ARTICLE

Reduced Frequency of Cells Latently Infected With Replication-Competent Human Immunodeficiency Virus-1 in Virally Suppressed Individuals Living in Rakai, Uganda

Jessica L Prodger, Jun Lai, Steven J Reynolds, Jeanne C Keruly, Richard D Moore, Jingo Kasule, Taddeo Kityamuweesi, Paul Buule, David Serwadda, Martha Nason ... Show more

Clinical Infectious Diseases, Volume 65, Issue 8, 15 October 2017, Pages 1308–1315, https://doi.org/10.1093/cid/cix478

Published: 23 May 2017 **Article history**



HIV Clades & Diversity in Cure Research

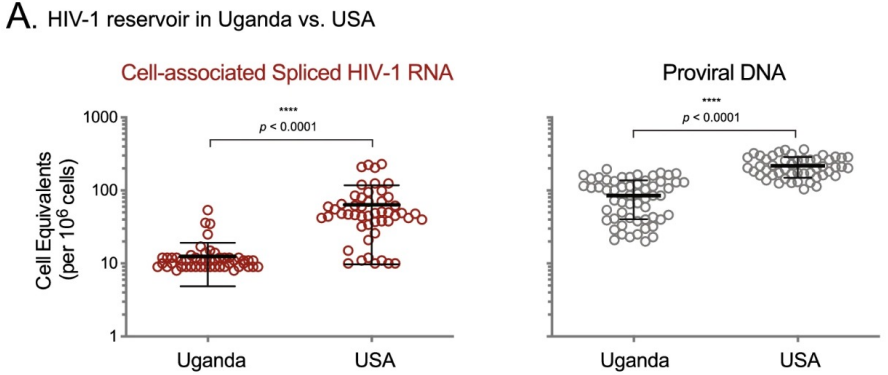
- Few comparative studies between B vs. non-B
  - Another study compared inducible reservoir size by EDITS assay and total HIV DNA in a cohort of PLWH from Kampala, Uganda (subtype A/D/C) vs. a cohort from Cleveland, USA (subtype B)
    - Ugandan participants had a lower: inducible reservoir (11 vs. 48 cell equivalents/M cells) and total HIV DNA level (88 vs. 206 cell equivalents/M cells)
    - Ugandan participants had greater reservoir genetic diversity, however

Research | Open access | Published: 15 January 2022

Reduced and highly diverse peripheral HIV-1 reservoir in virally suppressed patients infected with non-B HIV-1 strains in Uganda

Samira Joussef-Piña, Immaculate Nankya, Sophie Nalukwago, Joy Baseke, Sandra Rwambuya, Dane Winner, Fred Kyeyune, Keith Chervenak, Bonnie Thiel, Robert Asaad, Curtis Dobrowolski, Benjamin Luttge, Blair Lawley, Cissy M. Kityo, W. Henry Boom, Jonathan Karn & Miguel E. Quiñones-Mateu

Retrovirology **19**, Article number: 1 (2022) | Cite this article



HIV Clades & Diversity in Cure Research

- Need to adapt some reservoir assays to non-B HIV

STAR Protocols

CellPress

Volume 3, Issue 4, 16 December 2022, 101681

Protocol

Protocol for high-throughput reservoir quantification across global HIV subtypes using a cross-subtype intact proviral DNA assay

Carolyn S. Fish [1 7], Noah A.J. Cassidy [1 7], Claire N. Levy [2], Sean M. Hughes [2], Keith R. Jerome [3 4], Julie Overbaugh [1], Florian Hladik [2 3 5], Dara A. Lehman [1 6 8 9]

Methodology | Open access | Published: 31 January 2024

Development of a highly sensitive and specific intact proviral DNA assay for HIV-1 subtype B and C

N. V. E. J. Buchholtz, M. M. Nühn, T. C. M. de Jong, T. A. T. Stienstra, K. Reddy, T. Ndung'u, Z. M. Ndhlovu, K. Fisher, S. Palmer, A. M. J. Wensing, J. Symons & M. Nijhuis

Virology Journal **21**, Article number: 36 (2024) | Cite this article

Cohort-specific adaptation of the Intact Proviral DNA Assay (IPDA) to HIV-1 subtypes A1, D, and recombinants

Sarah N. Gowanlock
Ph.D Student, Western University

Dennis C. Copertino
Research Specialist, Weill Cornell Medicine

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HIV Persistence During Therapy, 2022

HIV Clades & Diversity in Cure Research

- Need to build capacity for basic research and clinical trials in high-burden, resource-limited settings (primarily non-B)

The case for an HIV cure and how to get there

Mark Dybul, Timothy Attoye, Solange Baptiste, Peter Cherutich, François Dabis, Steven G Deeks, Carl Dieffenbach, Brian Doehle, Maureen M Goodenow, Adam Jiang, Dominic Kemps, Sharon R Lewin, Murray M Lumpkin, Lauren Mathae, Joseph M McCune, Thumbi Ndung'u, Moses Nsubuga, Holly L Peay, John Pottage, Mitchell Warren, Izukanji Sikazwe, on behalf of the Sunnylands 2019 Working Group*

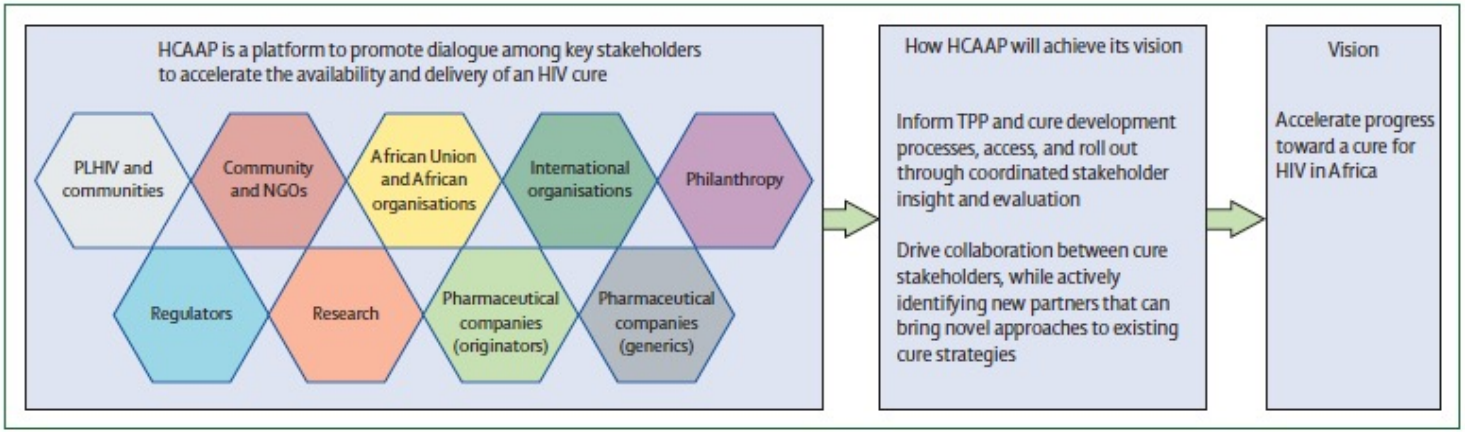


Figure 3: **The HCAAP model**
HCAAP=HIV Cure Africa Acceleration Partnership. NGOs=non-governmental organisations. TPP=target product profile. PLHIV=people living with HIV.

HIV Clades & Diversity in Cure Research

Notice of Special Interest (NOSI): HIV Cure-Related Research in Diverse Populations

Notice Number:

NOT-AI-23-046

Key Dates

Release Date: June 23, 2023

Purpose

This Notice of Special Interest (NOSI) is to highlight NIAID's interest in HIV cure-related research in diverse cohorts of people living with HIV to determine similarities and differences in the establishment and dynamics of persistent non-subtype B HIV reservoirs, as well as in post-treatment control of viremia.

Research Objectives

National Institute of Allergy and Infectious Diseases (NIAID) encourages applications in basic, preclinical, or clinical research studies using existing human samples to analyze and compare HIV human reservoir establishment, dynamics, persistence, and post-treatment control in diverse cohorts of people living with HIV. The proposed studies should include particular emphasis on the impact of viral subtype, sex, age, coinfections and comorbidities, and geography. Studies including samples from people living with HIV in low- and middle-income countries (LMICs) are encouraged.

Co-infections & Comorbidities in Cure Research

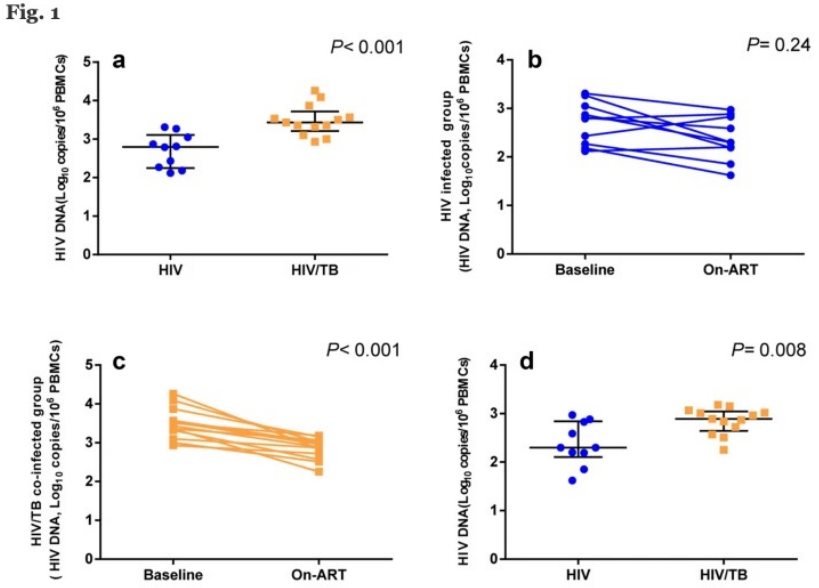
- What is the impact of common co-infections and/or comorbidities on the HIV reservoir and potentially HIV cure?
  - Co-infections: CMV, EBV, HCV, HBV, HSV, TB, others
  - Comorbidities: cardiovascular disease, cancers, diabetes, dyslipidemia, renal disease, others
  - **Very few studies to date**

Research | Open access | Published: 19 October 2020

Mycobacterium tuberculosis co-infection is associated with increased surrogate marker of the HIV reservoir

Jingna Xun, Tangkai Qi, Lei Zou, Qi Tang, Yinzhong Shen, Junyang Yang, Luman Xie, Yongjia Ji, Renfang Zhang, Li Liu, Jiangrong Wang, Corky Steinhart, Zhenyan Wang, Yang Tang, Wei Song, Jianjun Sun, Juan Cheng, Xiaoqin Le, Huanmei Wu, Xiaoqing He, Rong Chen, Jun Chen ✉ & Hongzhou Lu ✉

AIDS Research and Therapy **17**, Article number: 63 (2020) | Cite this article



Co-infections & Comorbidities in Cure Research

- NIDDK concept clearance

Impact of Comorbidities and Co-Infections on HIV Reservoirs

May 2023 Council

Lead Division/Office

DDN, DEM, KUH, OMHRC

Point(s) of Contact

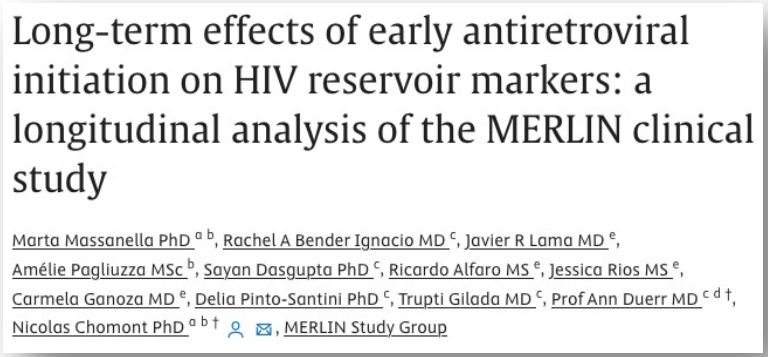
Peter Perrin, Ph.D.; Saul Malozowski, M.D., Ph.D., M.B.A.; Deepak Nihalani, Ph.D.; Khoa Nguyen, PharmD

Executive Summary

Because of advances in HIV science, particularly the development of effective antiretroviral therapy, HIV has evolved into a chronic disease. As people age with HIV they are developing various comorbidities and co-infections that significantly impact their health and quality of life. There is emerging appreciation that these various conditions and co-infections also impact HIV reservoir biology in ways that are likely to interact with potential cure strategies. However, most research on HIV reservoirs does not incorporate the impact of inflammation, metabolic perturbations, or other pathophysiological processes associated with prevalent comorbidities or co-infections. Rigorous research to address this problem will require synergistic, collaborative interactions between experts in HIV science and researchers with primary expertise is the pathobiology of the comorbidities or co-infections being investigated. This initiative will therefore bring together multi-disciplinary teams to address how comorbidities and co-infections that are prevalent in people interact with viral reservoirs in ways that would confound cure strategies at aimed at sustained viral suppression or elimination from the body.

ART Access & Cure Research

- **Early ART initiation:**
  - Limits the size and genetic diversity of the HIV reservoir
  - Limits gut damage and microbial translocation and resulting levels of innate immune activation
  - Limits systemic inflammation
  - Preserves immune function



Long-term effects of early antiretroviral initiation on HIV reservoir markers: a longitudinal analysis of the MERLIN clinical study

Marta Massanella PhD [a b], Rachel A Bender Ignacio MD [c], Javier R Lama MD [e], Amélie Pagliuzza MSc [b], Sayan Dasgupta PhD [c], Ricardo Alfaro MS [e], Jessica Rios MS [e], Carmela Ganoza MD [e], Delia Pinto-Santini PhD [c], Trupti Gilada MD [c], Prof Ann Duerr MD [c d †], Nicolas Chomont PhD [a b †], MERLIN Study Group

Study found:

- Participants who initiated ART within 30 days or less showed steeper and more sustained decay in HIV reservoir measures
- Suggests long-term benefit of acute ART initiation on reservoir clearance

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Challenge:

Current cure-related clinical trials require participants to be on ART and virally suppressed

- If intervention works, will it work in PLWH not virally suppressed?
- Safety of intervention in PLWH off ART?
- Possible advantage: some cure interventions may work better if given at the same time as ART initiation – *need to study*

ART Access & Cure Research

Notice of Special Interest (NOSI): Opportunities for HIV Cure Interventions at the Time of ART Initiation

Notice Number:

NOT-AI-22-072

Purpose

This Notice of Special Interest (NOSI) serves to identify new opportunities for cure strategies during active HIV infection at or near the start of antiretroviral therapy (ART) or as a potential replacement for conventional ART, with the ultimate goal of achieving a sustained ART-free HIV remission.

Background

The initiation of ART within the first few weeks of HIV infection has been associated with the development of a smaller latent reservoir, reduced viral diversity, preservation of innate as well as T and B cell immune responses, and higher rates of post treatment control. Additional interventions, in combination with the start of ART, may potentially accelerate viral decay, limit reservoir seeding, and induce a vaccinal effect that, in combination, may induce HIV remission. Currently, HIV cure approaches are focused almost exclusively on interventions administered during complete viral suppression on ART. Recent scientific evidence suggests that much of the reservoir is stabilized at the time of ART initiation. It is thought that ART alters the host environment in a way that promotes the formation of most of the long-lived latent HIV reservoir. Therefore, there is an opportunity to explore novel strategies designed to limit the establishment of the HIV reservoir around the time of ART initiation. In more translational studies, some early interventions using broadly neutralizing antibodies in the absence of ART have led to sustained remission in non-human primates (NHP). Therefore, opportunities also exist to intervene before complete ART-mediated viral suppression, when HIV antigen is stimulating the immune response, to improve clinical outcomes toward an HIV cure.

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Challenge:

Treatment interruption

- Need to monitor viral loads carefully following ATI or treatment interruption in eventual cure interventions
- Access to viral load testing?

Additional Diversity Considerations in HIV Cure Research

- Globally, women and girls represent 53% of all PLWH (UNAIDS 2023)
  - Between 1995 and 2020, women represented a median of 11.1% of HIV cure trial participants globally (Barr, Jefferys 2019)
- In the US, Black/African Americans account for over 40% of new HIV diagnoses each year (CDC 2021)
  - A majority of participants in cure-related studies are white
- In the US, an estimated 44% of Black/African American transgender women and 26% of Latinx transgender women live with HIV (CDC 2020)
  - Very few studies report on inclusion of gender minorities (*increasing*)

AIDS RESEARCH AND HUMAN RETROVIRUSES
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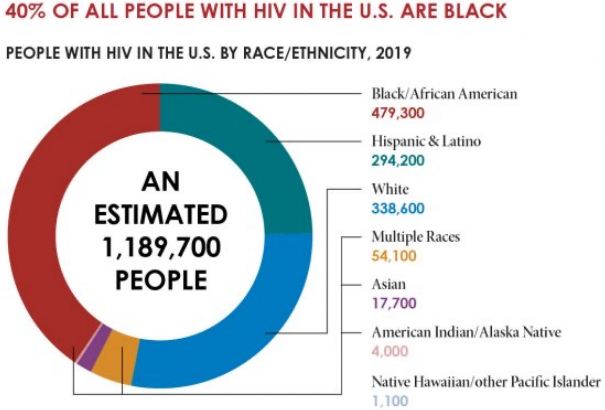
DOI: 10.1089/aid.2021.0023

SOCIO-BEHAVIORAL

Considerations for Increasing Racial, Ethnic, Gender, and Sexual Diversity in HIV Cure-Related Research with Analytical Treatment Interruptions: A Qualitative Inquiry

Karine Dubé,[1,i] John Kanazawa,[1,ii] Chadwick Campbell,[2,3,iii] Cheriko A. Boone,[4] Allysha C. Maragh-Bass,[5] Danielle M. Campbell,[6] Moisés Agosto-Rosario,[7] Jamila K. Stockman,[8] Dázon Dixon Diallo,[9] Tonia Poteat,[10,iv] Mallory Johnson,[2] Parya Saberi,[2] and John A. Sauceda[2]



Additional Diversity Considerations in HIV Cure Research

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 38, Number 1, 2022

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SOCIO-BEHAVIORAL

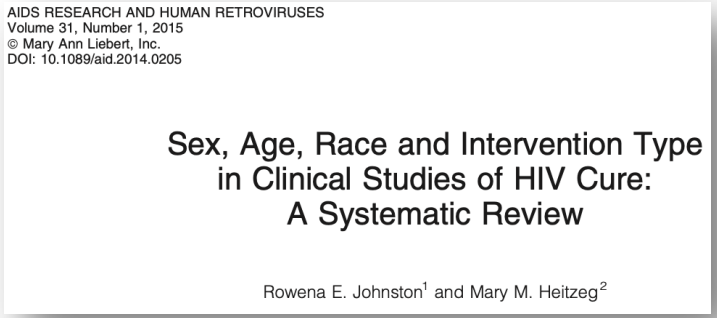
Considerations for Increasing Racial, Ethnic, Gender, and Sexual Diversity in HIV Cure-Related Research with Analytical Treatment Interruptions: A Qualitative Inquiry

Karine Dubé,[1,i] John Kanazawa,[1,ii] Chadwick Campbell,[2,3,iii] Cheriko A. Boone,[4] Allysha C. Maragh-Bass,[5] Danielle M. Campbell,[6] Moisés Agosto-Rosario,[7] Jamila K. Stockman,[8] Dázon Dixon Diallo,[9] Tonia Poteat,[10,iv] Mallory Johnson,[2] Parya Saberi,[2] and John A. Sauceda[2]

"Despite disproportionate incidence and prevalence among transgender individuals, cisgender women, and people from racial and ethnic minorities, all remain underrepresented in HIV clinical research, especially HIV cure research."

Additional Diversity Considerations in HIV Cure Research

- Systematic review undertaken to determine the extent to which adult participants representing sex (female), race (nonwhite), and age (>50 years) categories are included in clinical studies of HIV curative interventions
  - The representation of women, older people, and nonwhites did not reflect national or international burdens of HIV infection

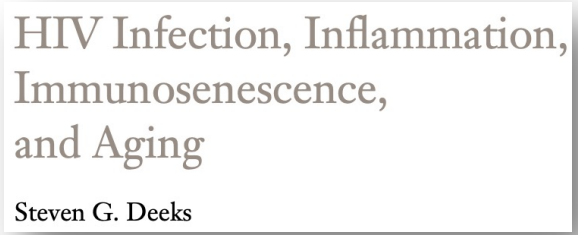

AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 31, Number 1, 2015

DOI: 10.1089/aid.2014.0205

Sex, Age, Race and Intervention Type in Clinical Studies of HIV Cure: A Systematic Review

Rowena E. Johnston[1] and Mary M. Heitzeg[2]

- Impact of age on curative intervention safety and efficacy?
  - Immunosenescence: alteration of immune function due to aging that contributes to the increased susceptibility of the elderly to infection
  - May particularly impact immune-based strategies – *need to conduct trials in PLWH across the age range*


HIV Infection, Inflammation, Immunosenescence, and Aging

Steven G. Deeks

Key Takeaways & Discussion

- **How will these environmental factors impact cure strategies?**
  - Viral clade
  - Co-infections & comorbidities
  - ART access
  - Sex, Race/Ethnicity, age
  - Others: diet, microbiome, HLA type and genetic differences, etc.
- **Much remains unknown**
  - Calls for research in these areas
  - Some recent progress
  - The number of HIV cure-related clinical trials is increasing, diversity considerations

Weill Cornell Medicine

REACH
For the Cure
Research Enterprise to Advance a Cure for HIV

Q&A