HIV Cure - Basic Science Overview

2025 Women's Research Initiative on HIV/AIDS (WRI)

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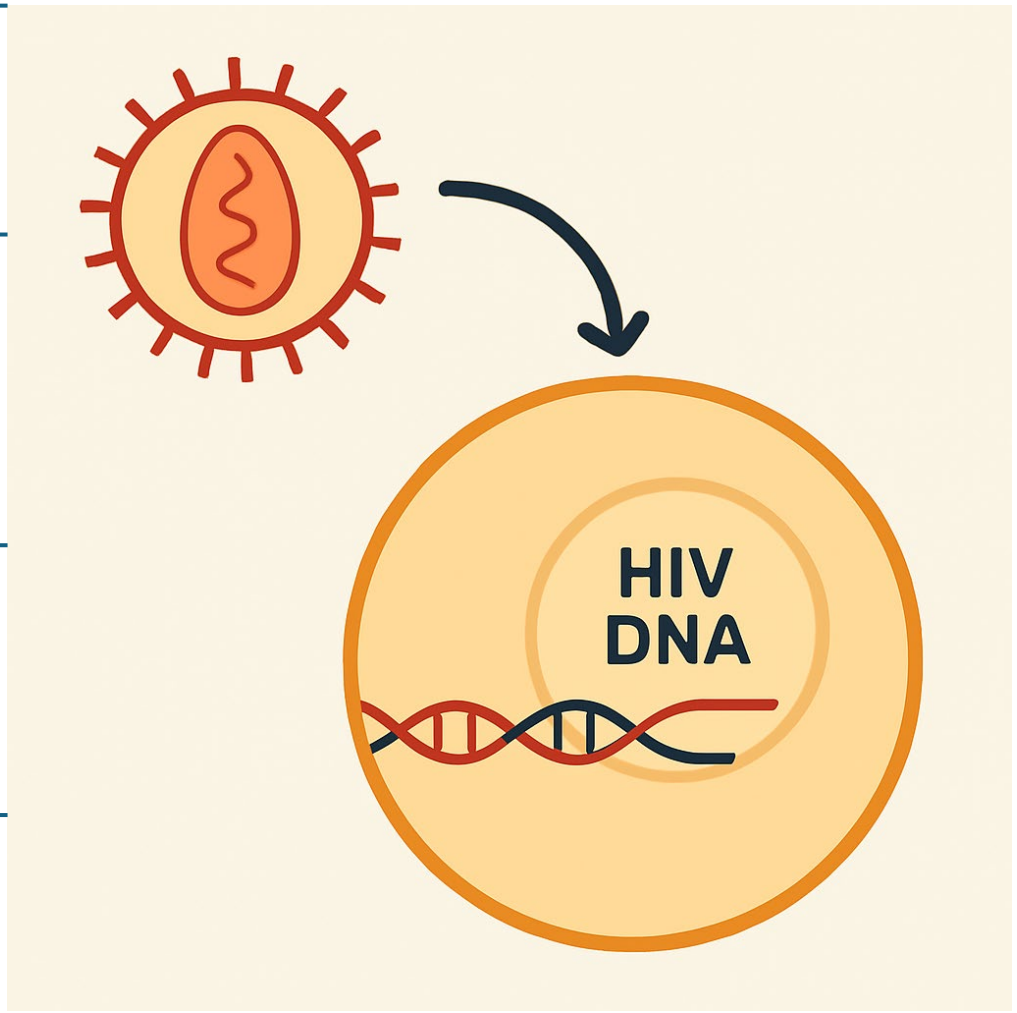
What is the HIV Reservoir?

HIV Reservoir: Places in the body where HIV hides, even when people are on HIV medicines.

Virus Hides in Cells: HIV hides inside our cells by combining with our DNA, which makes it difficult to get rid of completely.

Silenced by Medicine: HIV doesn’t make new copies of itself while on medicine, but it’s still there, quietly hidden.

Comes Back After Stopping Medicine: If someone stops their HIV medicine, the virus will "wake up" and start making new copies.

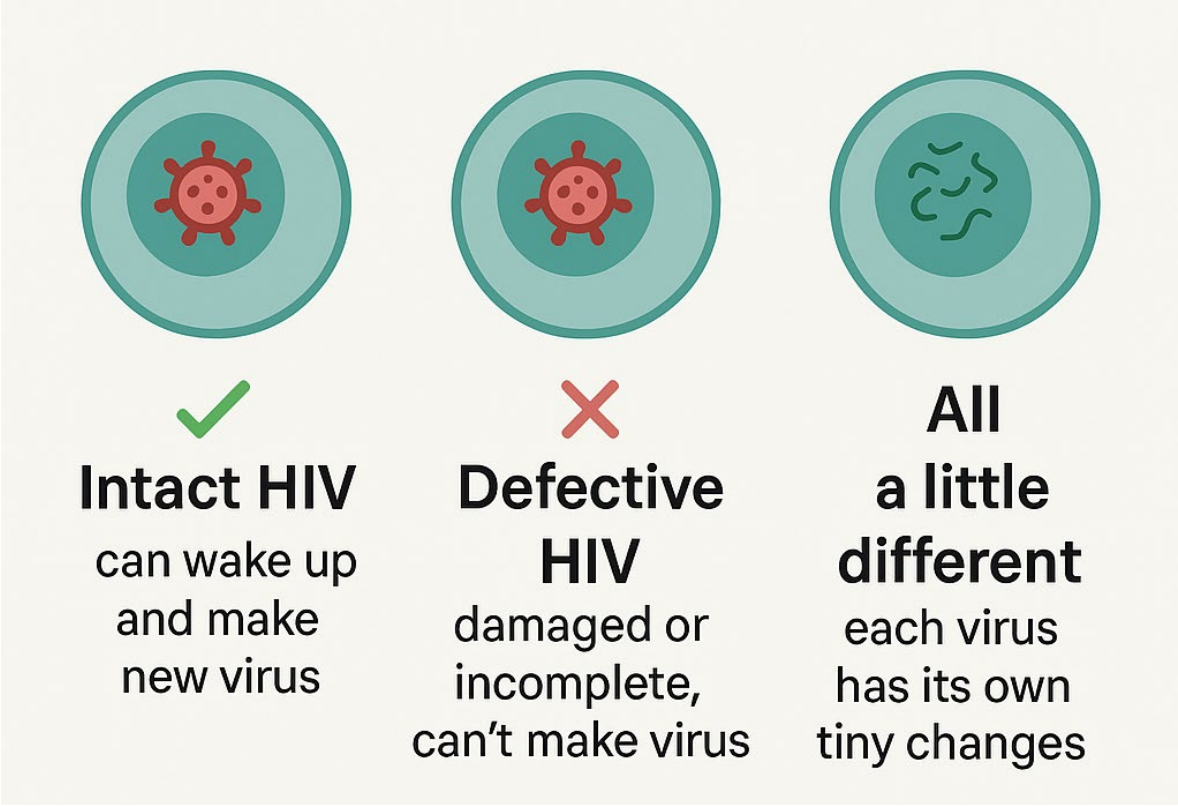


HIV Reservoir Composition

Most of the HIV is defective and can’t make new virus (might still do some proteins)

A small amount is intact and could come back if treatment stops.

Each copy of HIV is a bit different, like tiny fingerprints.



HIV Reservoir Persists during ART

Cell Proliferation: Infected cells divide and pass HIV DNA to daughter cells, allowing the virus to persist without needing new copies. This is the main way the reservoir survives during ART.

Ongoing Replication: HIV can still make new virus particles, but ART typically blocks this. In most patients on ART, ongoing replication is rare or absent.

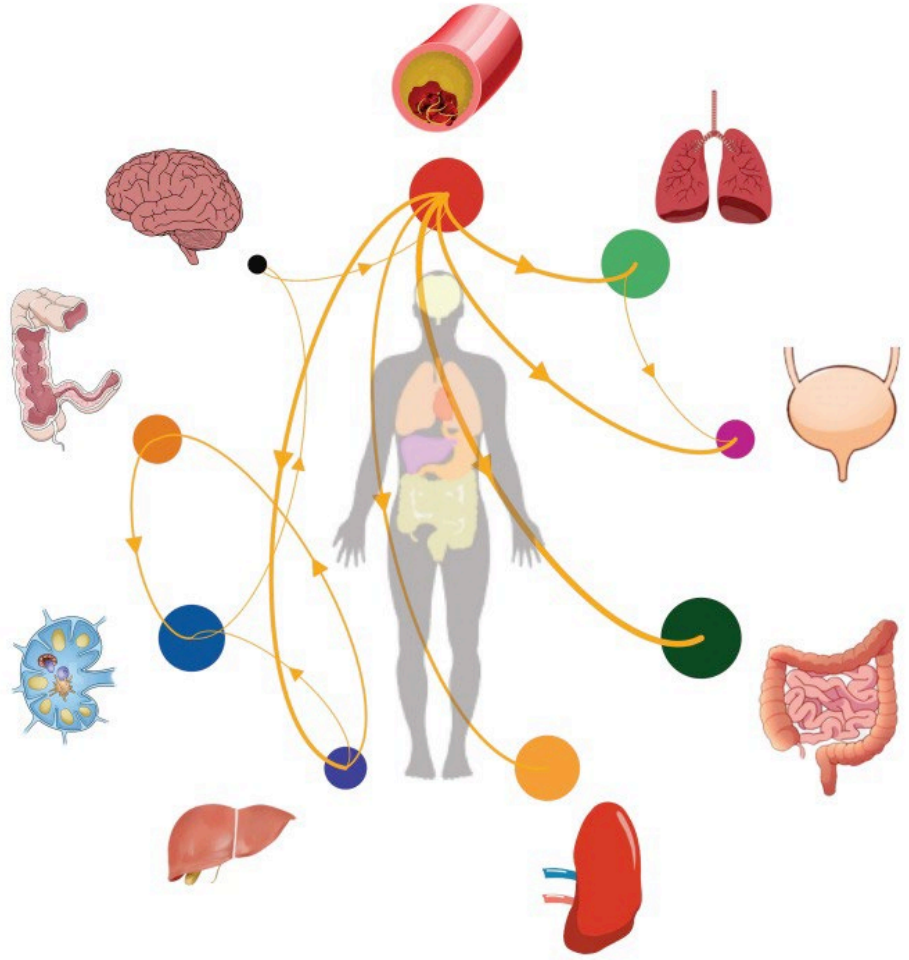
Where does the HIV Reservoir persist?

HIV Integration in Immune Cells

- HIV integrates its DNA into the genetic material of immune cells, particularly $CD4^+$ T cells.
- These immune cells are essential for the body's defense, but HIV uses them to hide and persist.

HIV Can Persist in Any Tissue

- HIV reservoirs can hide in all tissues, including lymph nodes, gut, brain (and many more).
- This ability to persist in multiple tissues makes it difficult to fully eliminate the virus.



Is a HIV Cure Possible?

As of now, **10 people** (2 woman) have been considered "cured" of HIV after receiving a **stem cell transplant** mostly with cells from a donor who is resistant to HIV **(primarily to treat malignancies)**.

The first public case was **Timothy Ray Brown** (the Berlin patient), followed by:

- **Adam Castillejo** (the London patient)
- **Mark Franke** (the Düsseldorf patient)
- **Paul Edmunds** (City of Hope patient)

Why This Approach Isn't for Everyone

- Stem cell transplants are **complex** and involve significant **risks**, making it an impractical option for most people with HIV.
- The procedure requires finding a **compatible donor** and is a **high-risk** process that is difficult to apply to the general population.

Exceptional Cases: Possible Natural HIV Cures

Esperanza Patient (Argentina)
Diagnosed in 2013; took ART only briefly during two pregnancies
No intact or replication-competent HIV detected despite extensive testing
Loreen Willenberg (San Francisco Patient)
Diagnosed in 1992; never needed ART
In 2020, researchers found no intact HIV in over 1 billion cells
→ Suggests their immune system may have eliminated the virus

Timothy Ray Brown

Adam Castillejo

Paul Edmunds

Mark Franke

#HIVHEROES EDITION

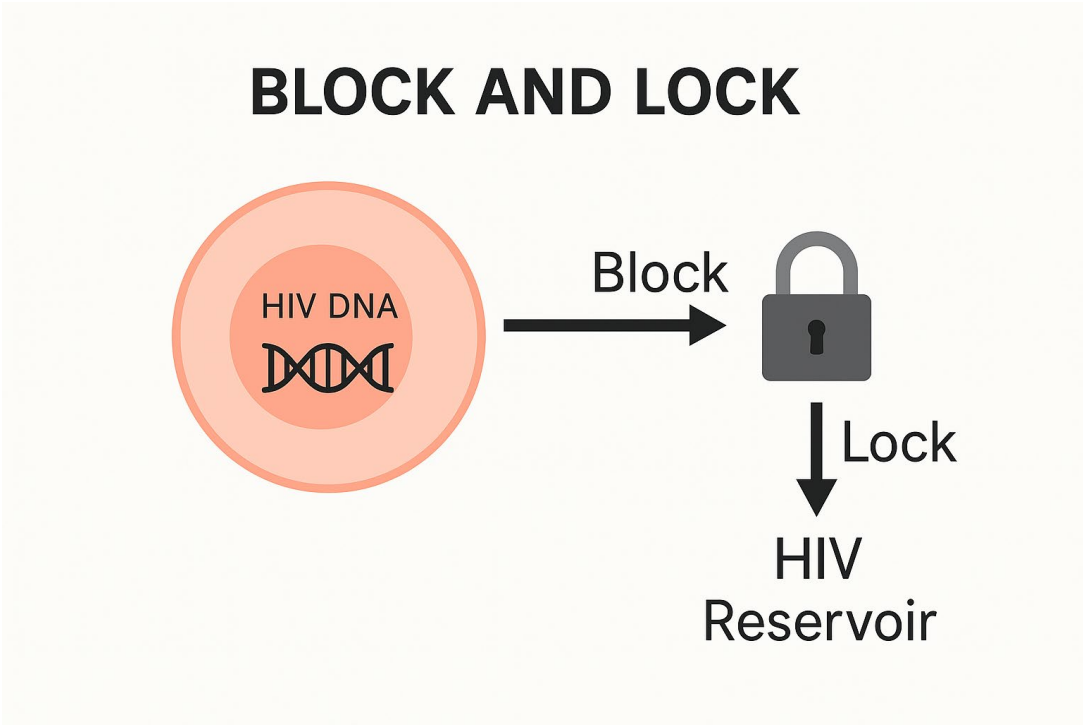
Loreen Willenberg

Block and Lock

Silence HIV in reservoirs and **lock** it in a dormant state, preventing the virus from reactivating without completely eradicating it.

The goal is to maintain long-term remission without the need for ongoing ART.

For example, Tat inhibitors

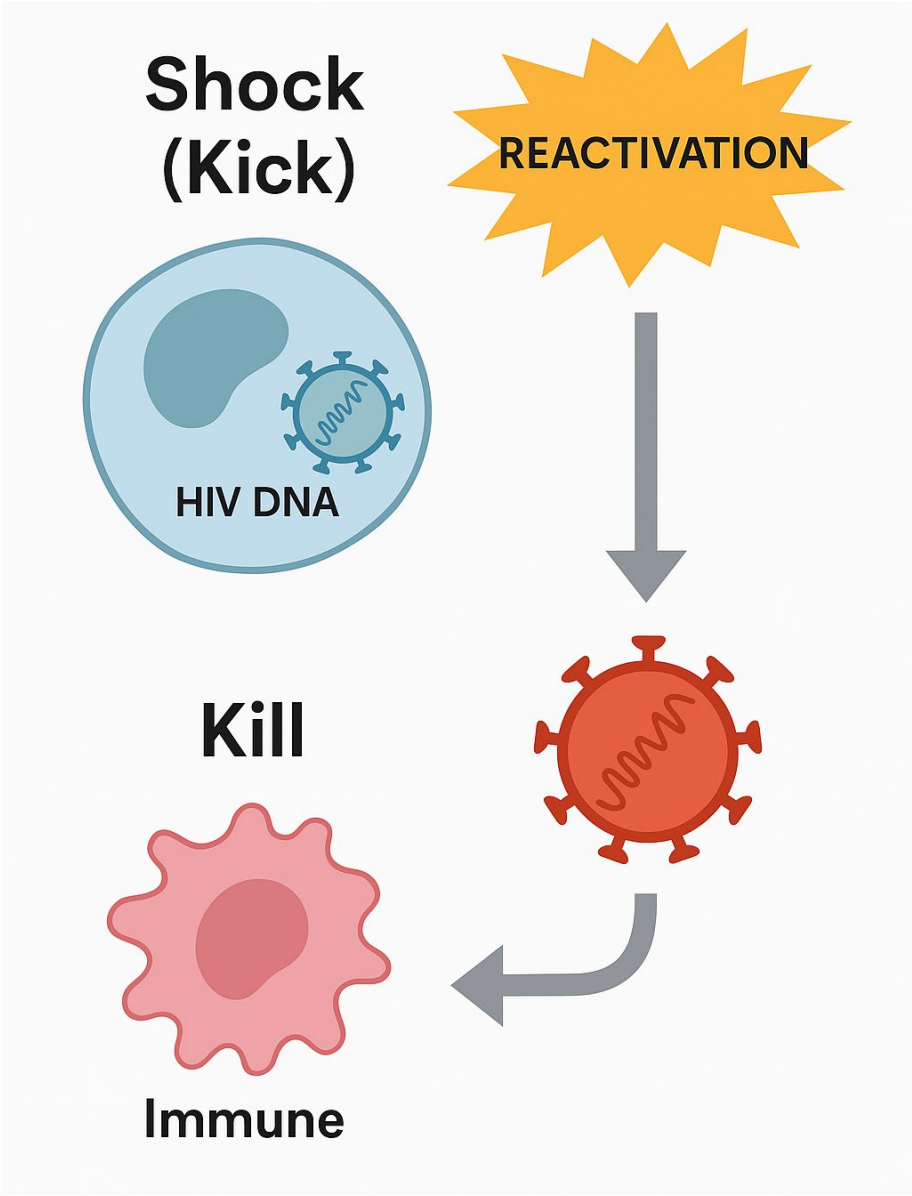


Shock (or Kick) and Kill

Reactivating dormant HIV, using Latency Reversing Agents to "kick" the virus out of hiding.

Once the virus is awakened, it can be targeted and eliminated by the immune system (“kill”).

For example, HDAC inhibitors, protein kinase C agonists, and Toll-like receptor agonists.



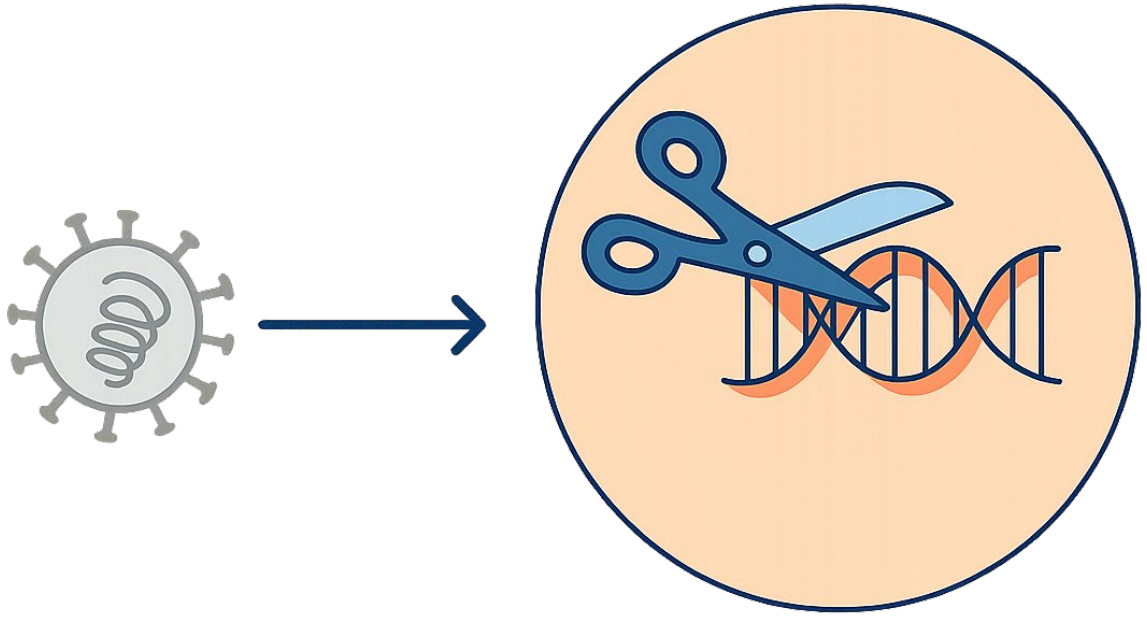
Gene Editing

CRISPR/Cas9 and other gene-editing technologies can be used to **cut** HIV DNA directly from the host cell's genome.

The virus is **disrupted or removed**, preventing it from replicating.

Gene Editing targets the HIV genome, potentially **curing** infected cells.

This strategy is still in the **experimental stage**, but it holds great promise for eradicating HIV from the body.



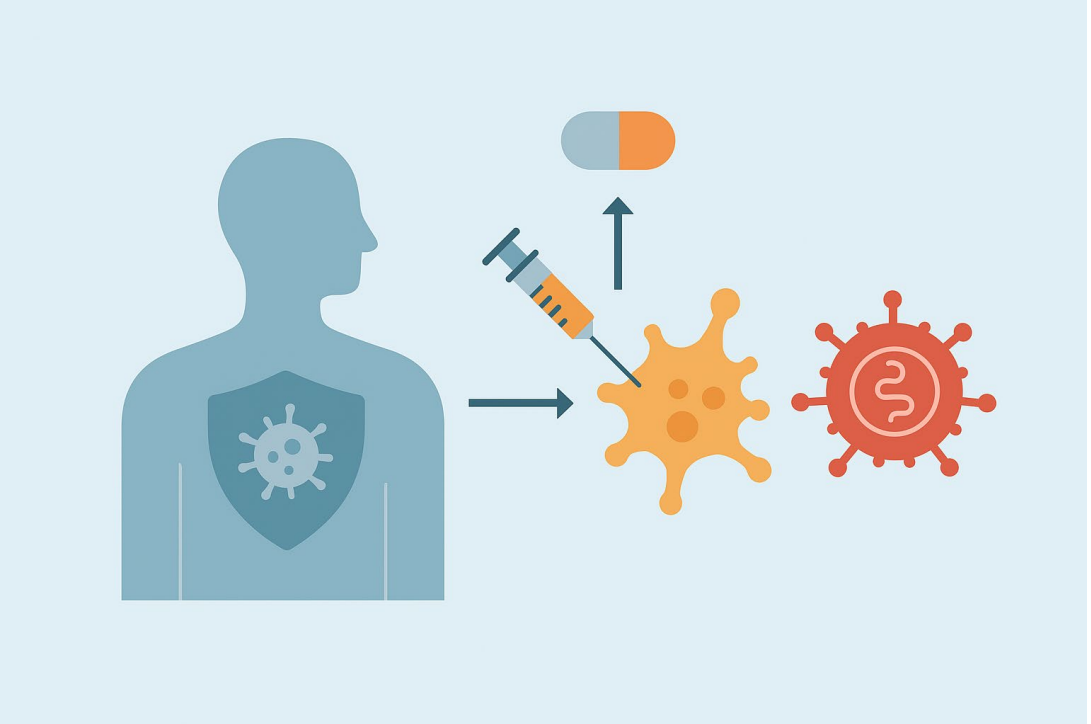
Boosting the Immune Response

Strengthening the body's natural defenses to better recognize and eliminate HIV-infected cells.

Therapeutic vaccines can train the immune system to target HIV more effectively.

Immune checkpoint inhibitors are used to remove blocks that prevent the immune system from attacking HIV.

The goal is to help the immune system control or clear HIV without the need for ongoing ART.



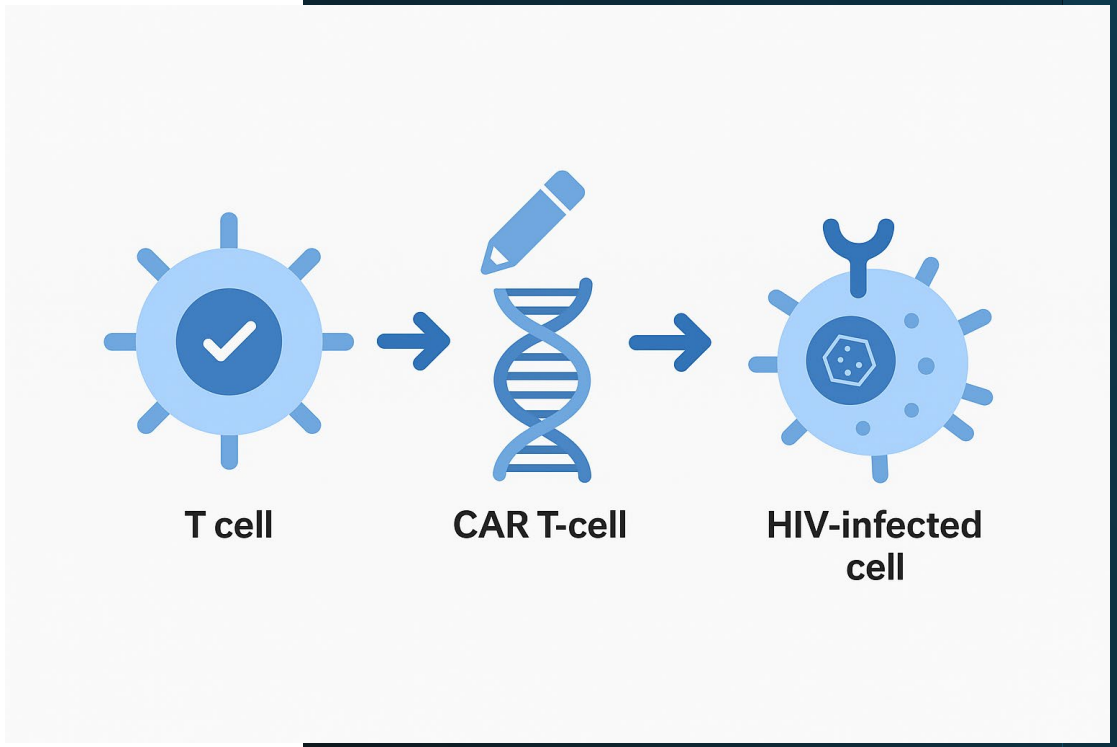
Immune Cell Modification

This strategy involves **modifying immune cells** to enhance their ability to fight HIV.

CAR T-cell therapy: T cells are genetically engineered to better **recognize and target HIV-infected cells**.

Gene modification may also be used to make immune cells resistant to HIV or better equipped to attack infected cells.

The goal is to create a **stronger immune response** that can clear HIV from the body.



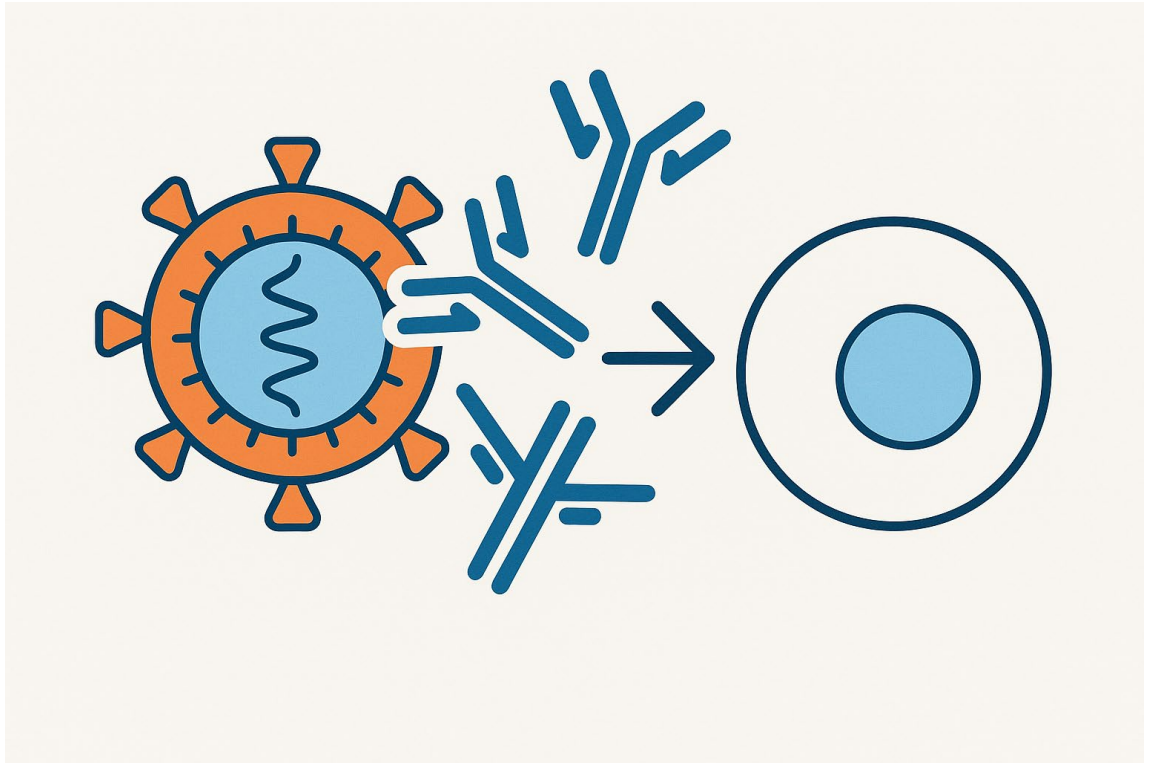
Antibody-based Therapies

This strategy uses **broadly neutralizing antibodies** (bNAbs) to block HIV from infecting cells.

bNAbs target parts of the virus that are critical for entry into the host cell, preventing the virus from spreading.

These therapies can **boost the immune system's ability** to fight HIV by recognizing and neutralizing the virus.

Monoclonal antibodies may also be used to target and eliminate HIV-infected cells.



Why is HIV so hard to eliminate?

HIV Hides in Tissues and Compartments

- HIV integrates into immune cells and hides in various tissues, making it difficult for treatments to reach and eliminate the virus.

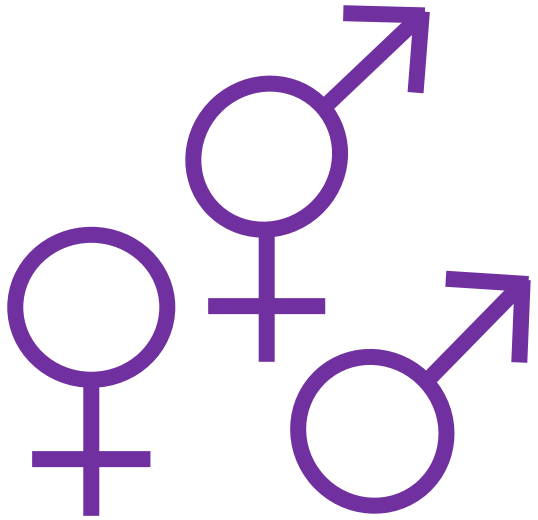
Resistance Development

- HIV can mutate rapidly, leading to drug resistance. This makes it harder for single treatments to remain effective over time.
- Combination therapy (using multiple drugs) is necessary to target different stages of the virus and reduce the chance of resistance.

Need for Safe and Effective Treatments

- Any cure or therapy must be safe, with minimal side effects, to avoid damaging the body or triggering harmful responses.
- Long-term safety is crucial, as patients would need to take these therapies for extended periods or even lifelong.
- One cure might not fit all (need to account for race, sex, gender, clade and much more).

Sex



Male, Female
Intersex
Penis, Vagina
Estrogen, Testosterone
Ovaries, Testis

Gender

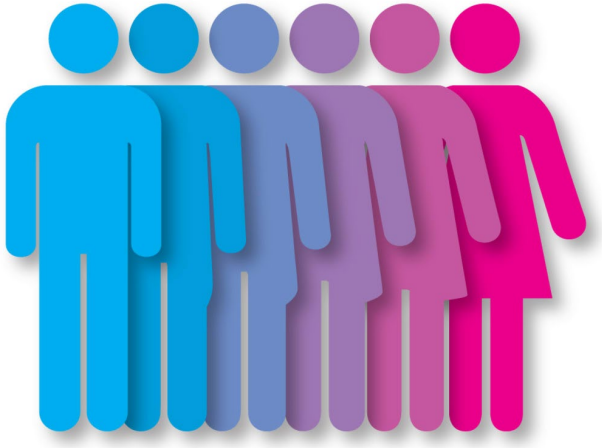


Image credit: Radio New Zealand

Man, Women
Non-binary, Gender fluid
He/She/They
Gender expression:
Pants, dress, pink, blue

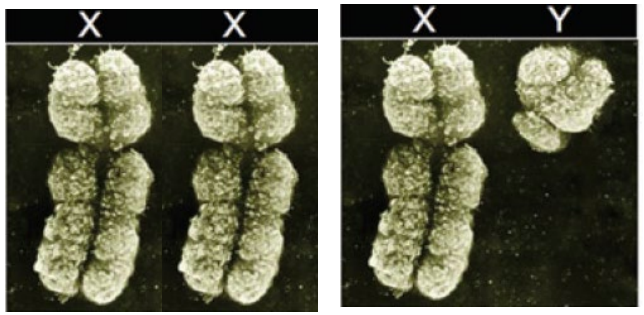
Sexuality

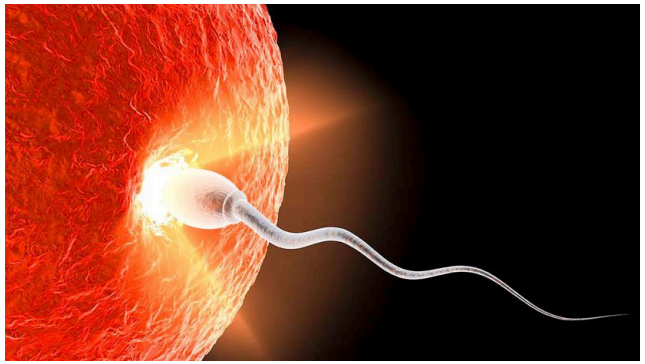
Image credit: Radio New Zealand

Heterosexual
Gay, Lesbian
Bi-sexual, Asexual
Love, Intimacy,
Attraction, Partner

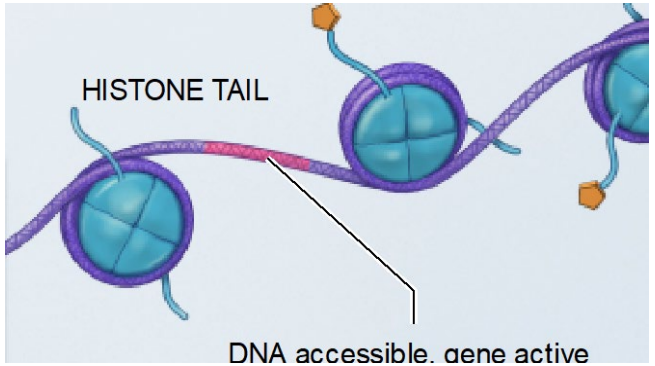
What determines “sex” (the boring kind)

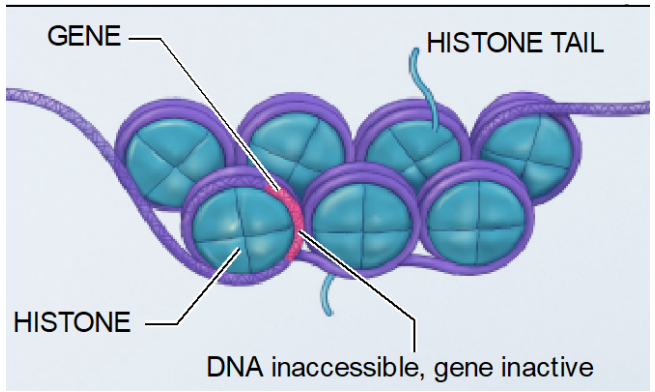
1. X & Y Chromosomes



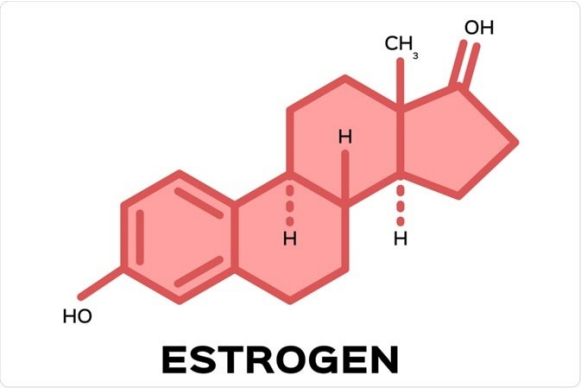


2. Epigenetic modification

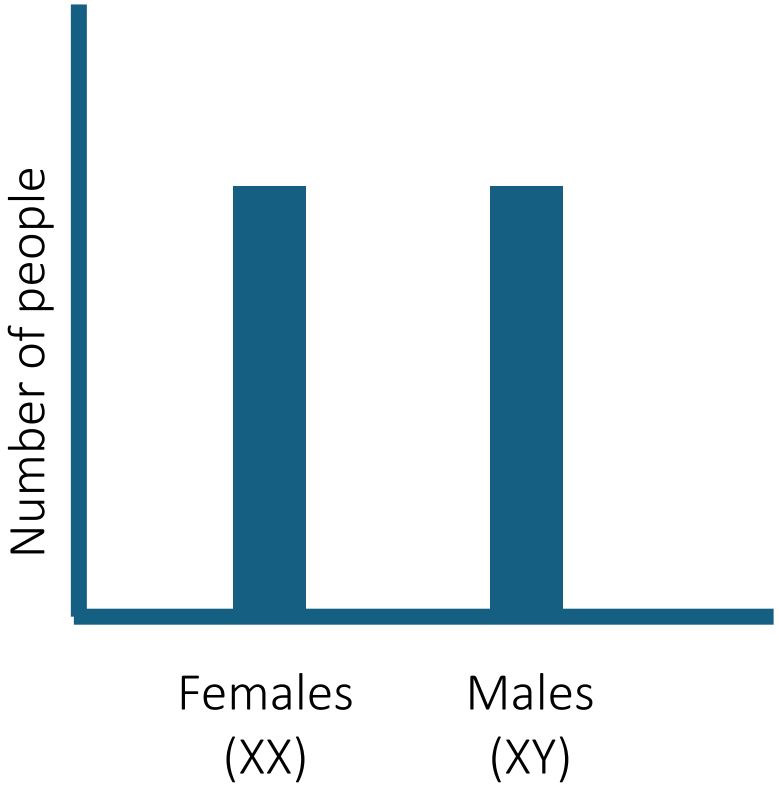


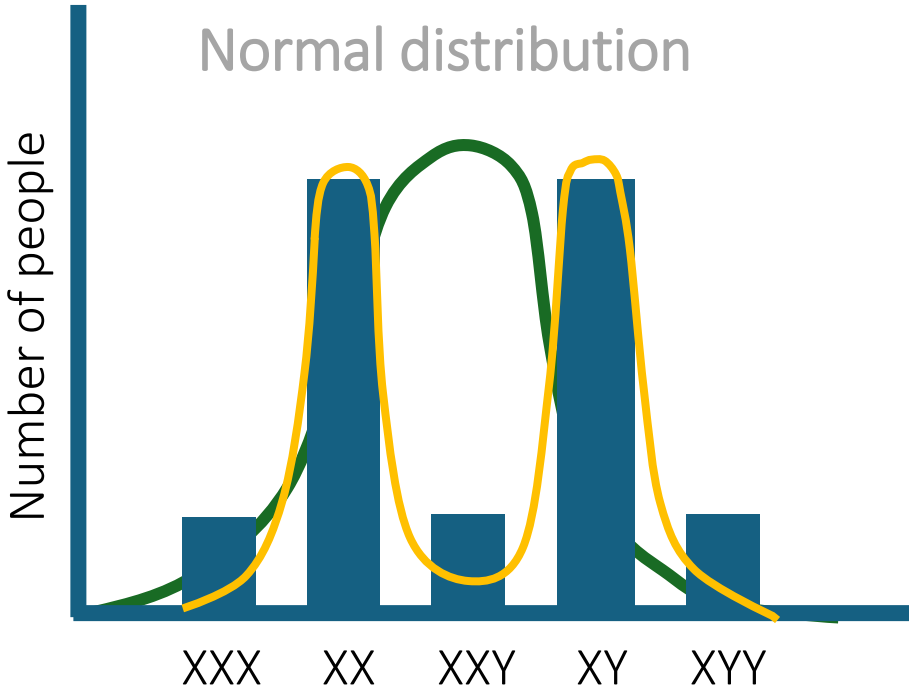


3. Sex Hormones



Nothing is binary - including karyotype!

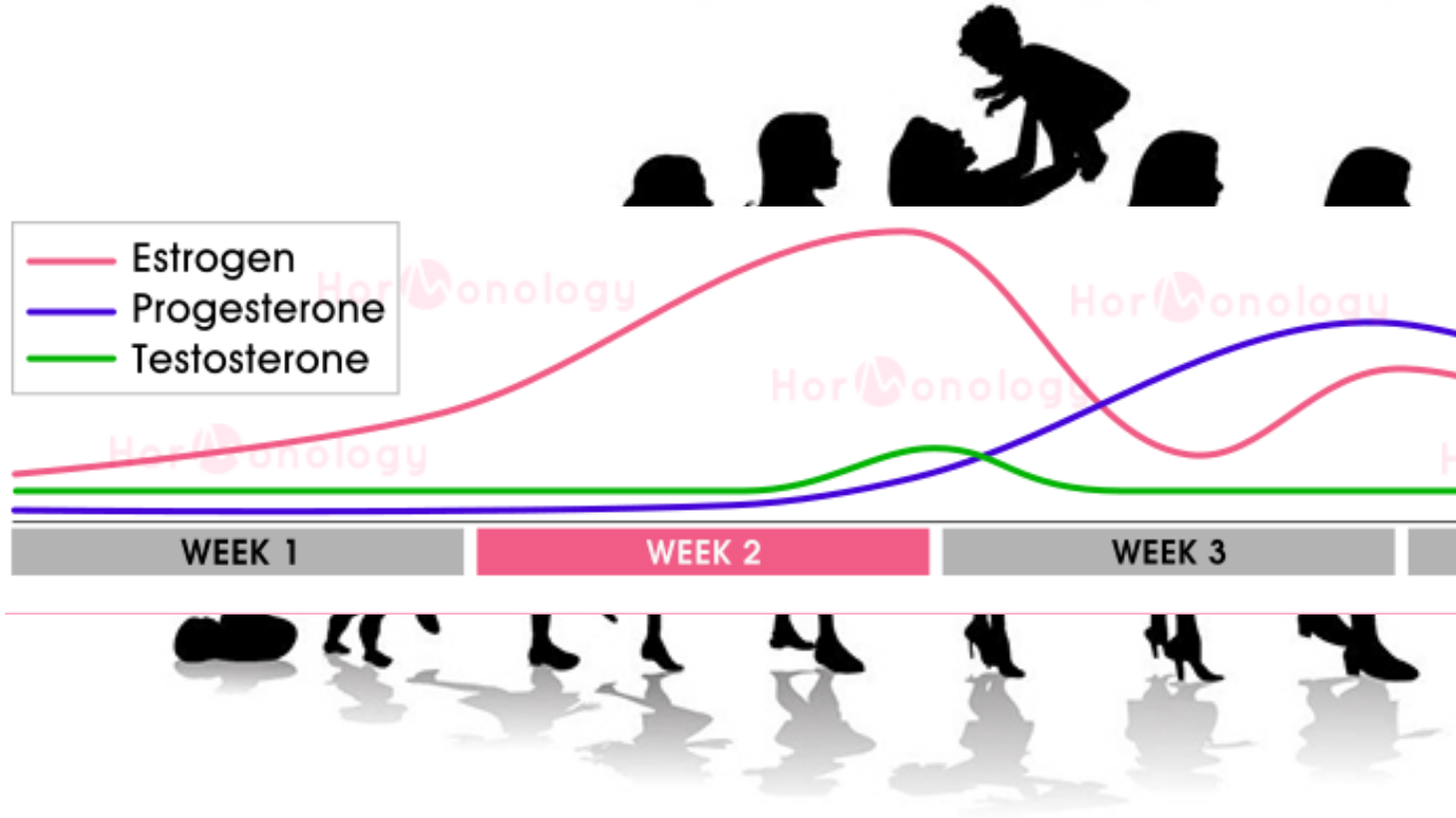


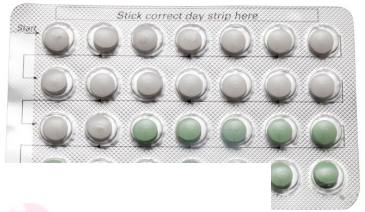


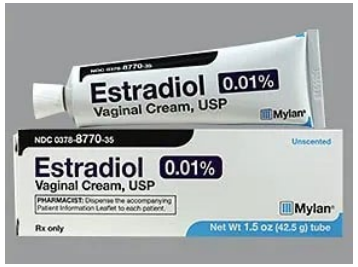
Endogenous Estrogen

Exogenous Estrogen

Birth	Pre-menarche	Menarche	Reproductive Years	Menopause





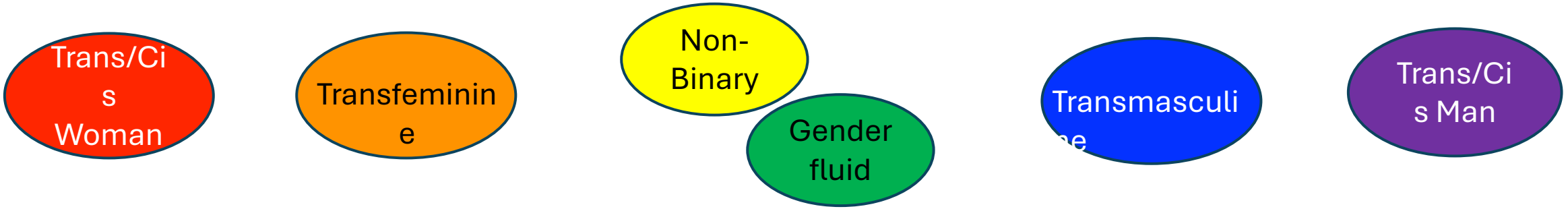


Estrogen

“Not all boys have penises”

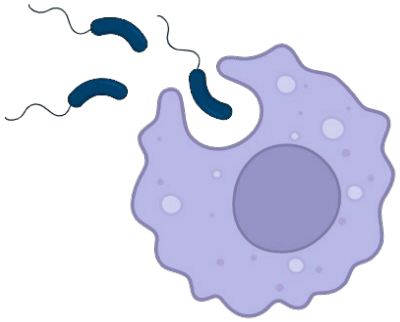
Grant Prodger, 3 yrs

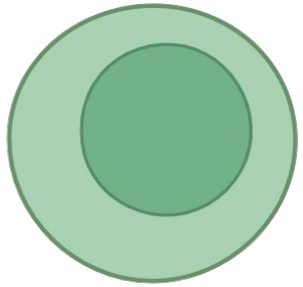
- sex = gender → cisgender (cis woman)
- sex differs from gender → transgender (trans woman)



- Gender affirming medical care: exogenous estrogen, androgen blockers
  - Woman with XY chromosome, low testosterone, and high estrogen.

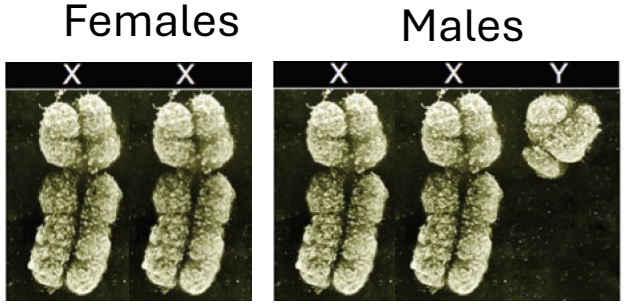
Clues that female sex matters to HIV basic science





More CD4 T cells

Macrophages more phagocytic



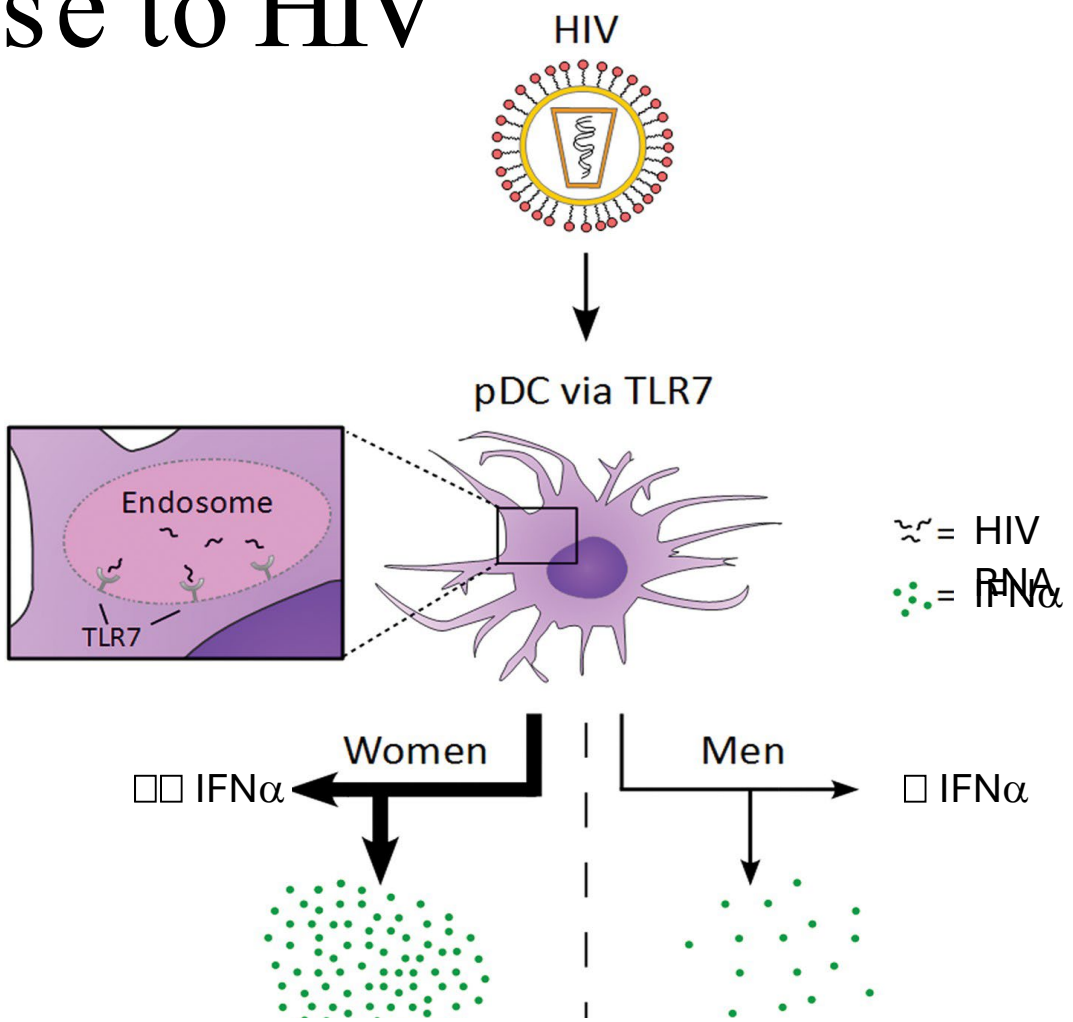
Multiple Sclerosis (MS)

Lupus

Scleroderma

Sex &the immune response to HIV

- X-inactivation as an embryo
  - up to 23% of X-linked <u>not</u> inactivated
  - “Biallelic” expression = more protein
- Immune genes on X chromosome
  - toll-like receptor (TLR) 7
- Female = higher IFNΘto HIV
  - Bi-allelic expression = more TLR7
  - Estrogen enhances response to TLR7



Meier et al Nature 2009; Adapted from Addo et al. JID 2014

Sex &in utero risk

BabyCure Study in South Africa (KZN)

- Of babies born to viremic moms:
- Sex-discordant twins: 5 instances where only one was HIV+
  - all 5 times it was the female twin
- female infants 2.0 – 1.5 times more likely to be HIV+
- Female babies more likely to be infected with IFN-resistant HIV

The New England Journal of Medicine

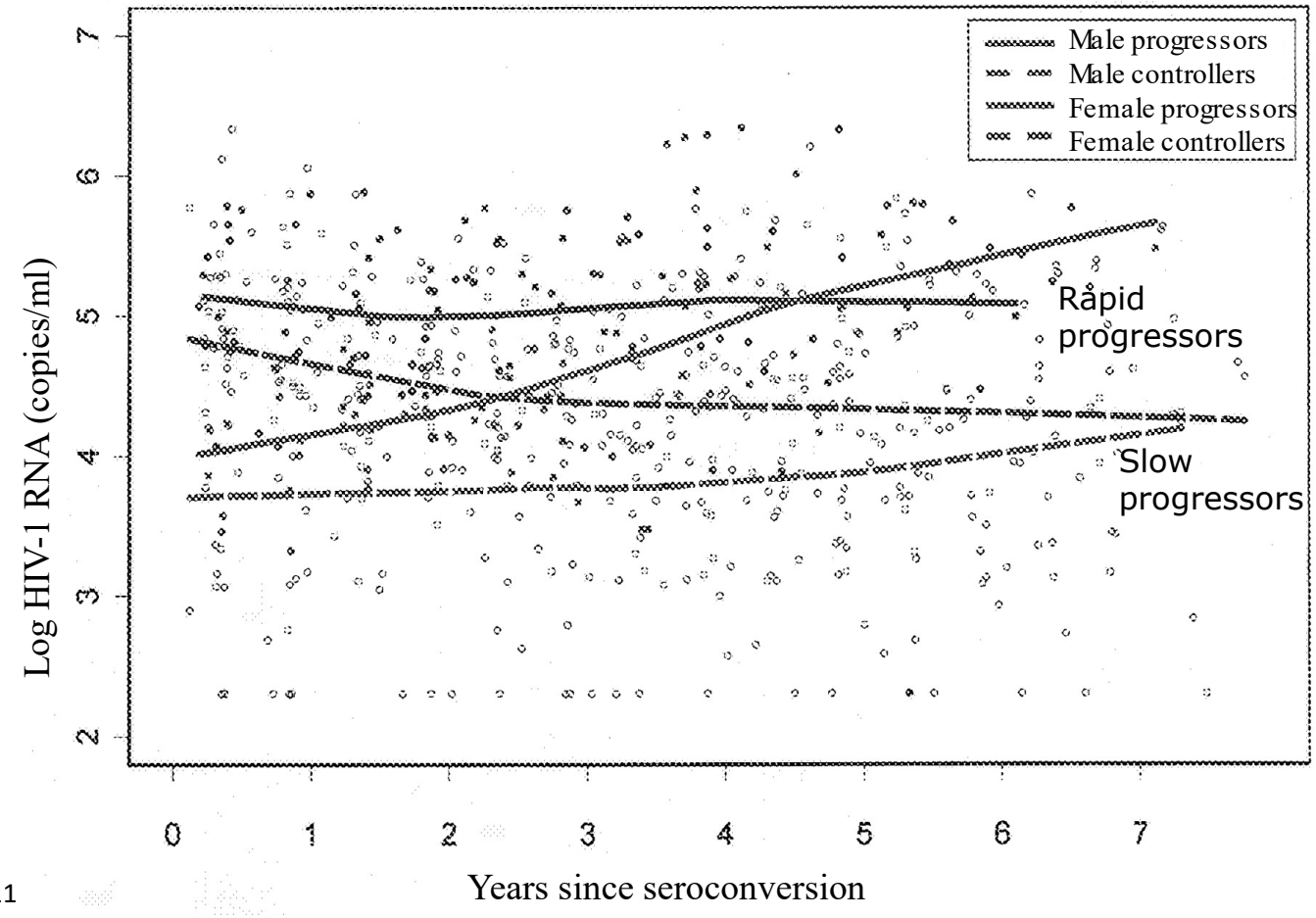
INITIAL PLASMA HIV-1 RNA LEVELS AND PROGRESSION TO AIDS IN WOMEN AND MEN

TIMOTHY R. STERLING, M.D., DAVID VLAHOV, PH.D., JACQUIE ASTEMBORSKI, M.H.S., DONALD R. HOOVER, PH.D., M.P.H., JOSEPH B. MARGOLICK, M.D., PH.D., AND THOMAS C. QUINN, M.D.

TABLE 2. INITIAL PLASMA HIV-1 RNA LEVELS AND CD4+ LYMPHOCYTE COUNTS AFTER SEROCONVERSION.

VARIABLE	MEN	WOMEN	P VALUE*
Median plasma HIV-1 RNA level (copies/ml)	50,766	15,103	<0.001
Median CD4+ lymphocyte count (per mm³)	659	672	0.48

*P values were determined with the Wilcoxon rank-sum test.

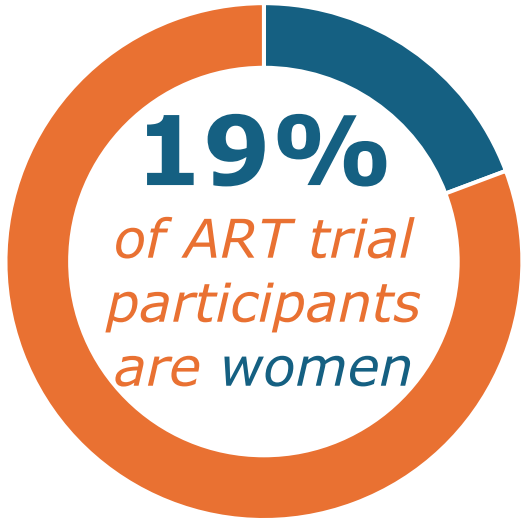


Farzadegan et al. **Lancet** 1998; Sterling et al. **JID** 1999; Prins et al. **AIDS** 1999; Sterling et al. **NEJM** 2001; Toulami et al. **AIDS** 2004; Gandhi et al. **CID** 2002; Meditz et al. **JID** 2011

Sex & Cure Research

- Most ARTs target the virus

- Many curative agents target host factors
  - Boosting the immune system (TLRs, PD-1)
  - Immune cell modification
  - Block and Lock (Epigenetic pathways)
  - Shock and Kill (when reactivation targets host cell)

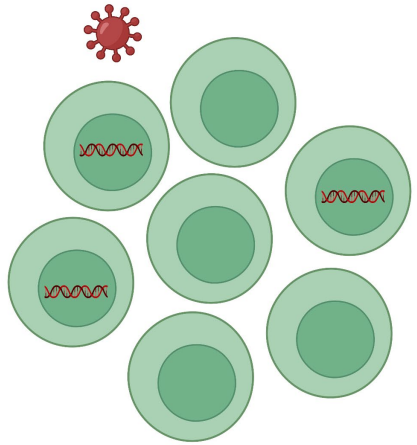


Curno et al JAIDS 2016

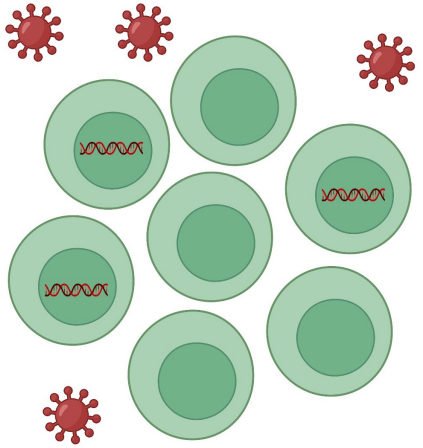
Sex and the HIV reservoir

- Untreated, HIV-1 RNA levels vary with menses
  - lower in follicular when estrogen peaks

- On treatment, females have
  - Same number of cells with any HIV-1 DNA
    - But potentially less cells with intact provirus
  - Less detectable ongoing HIV transcription
    - Less residual viremia (single copy assay) & lower cell-associated HIV RNA
    - Lower levels of inducible RNA & inducible infectious virus



Female



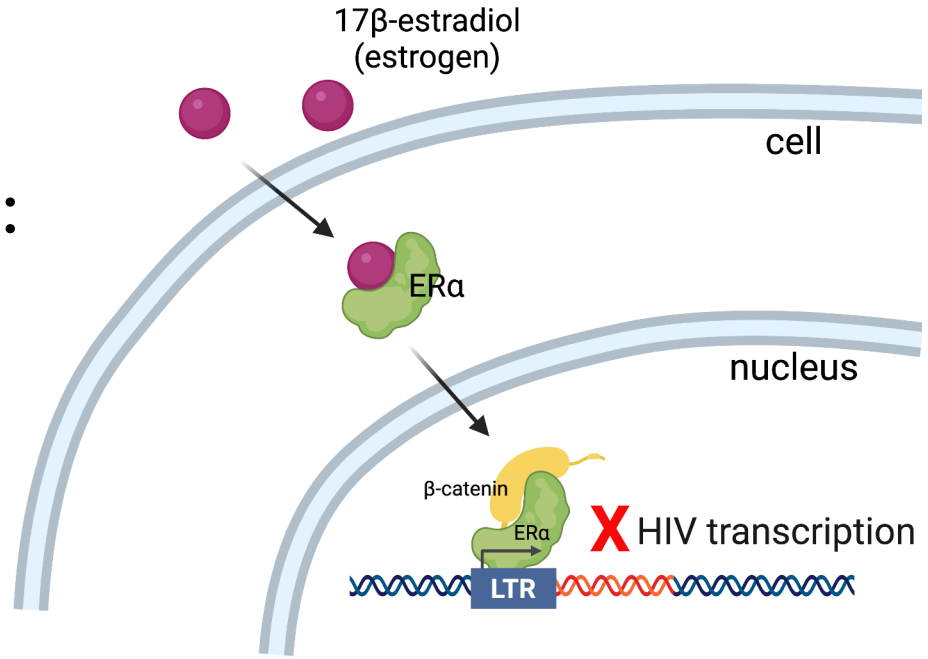
Male

Reichelderfer AIDS 2000; Scully JID 2019; Prodger JCI Insight 2020; Kirk et al. JID 2020; Gandhi et al. JID 2020; Falcinelli et al JID 2020; Gianella et al. OFID 2020; Scully et al. JID 2019

Estrogen receptor maintains latency

- Estrogen signalling inhibits HIV transcription
- Genome-wide screen to identify cellular factors required for latency:

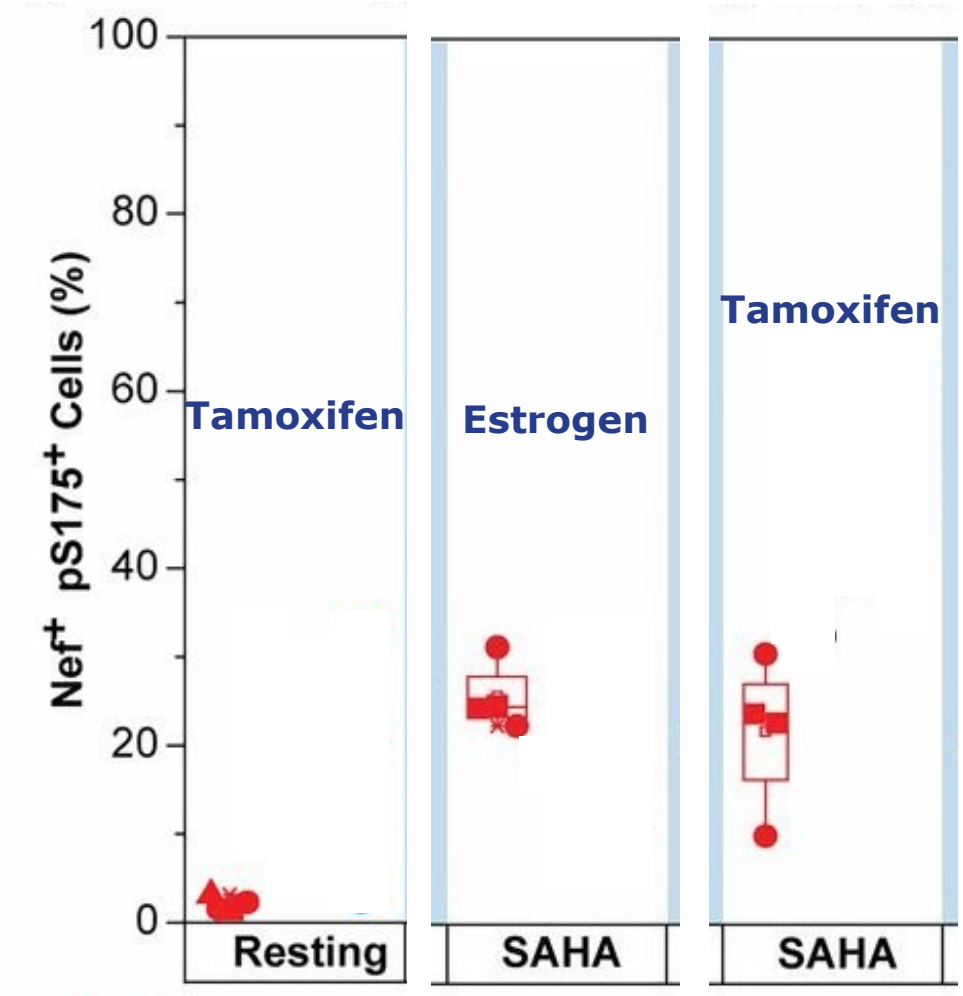
Estrogen receptor is key in regulating latency (!)



Katagiri Int Immunopharmacol 2006; Szotek Virology 2013; Das PNAS 2018; image created in Biorender

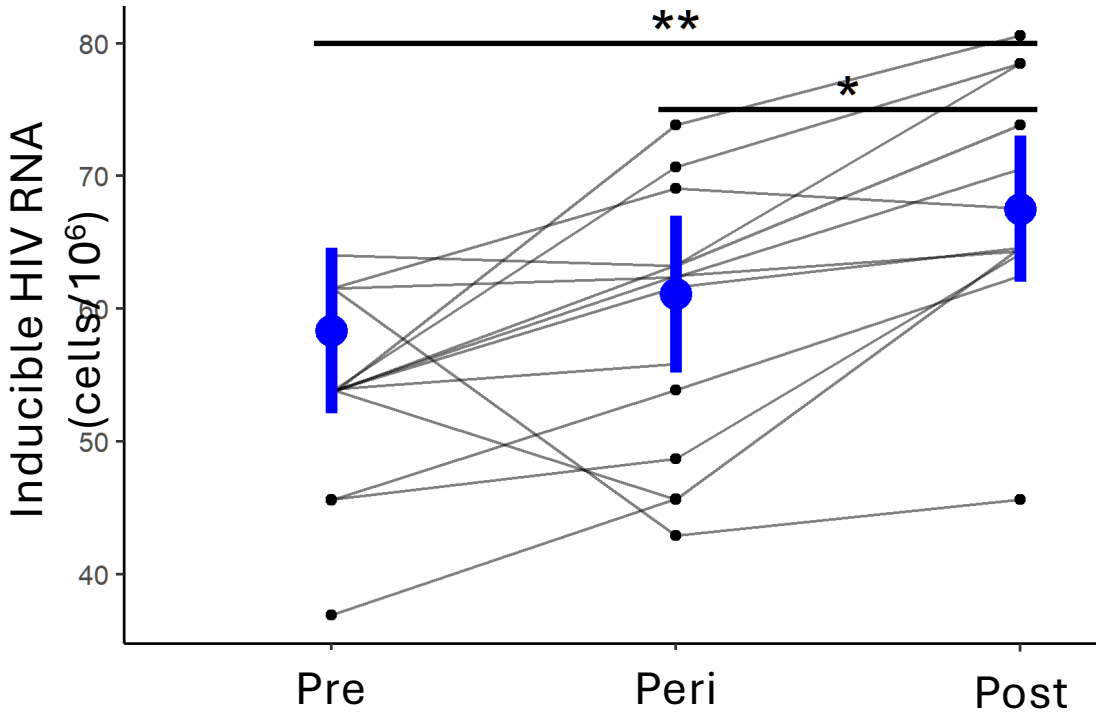
Estrogen & Latency Reversal Agents

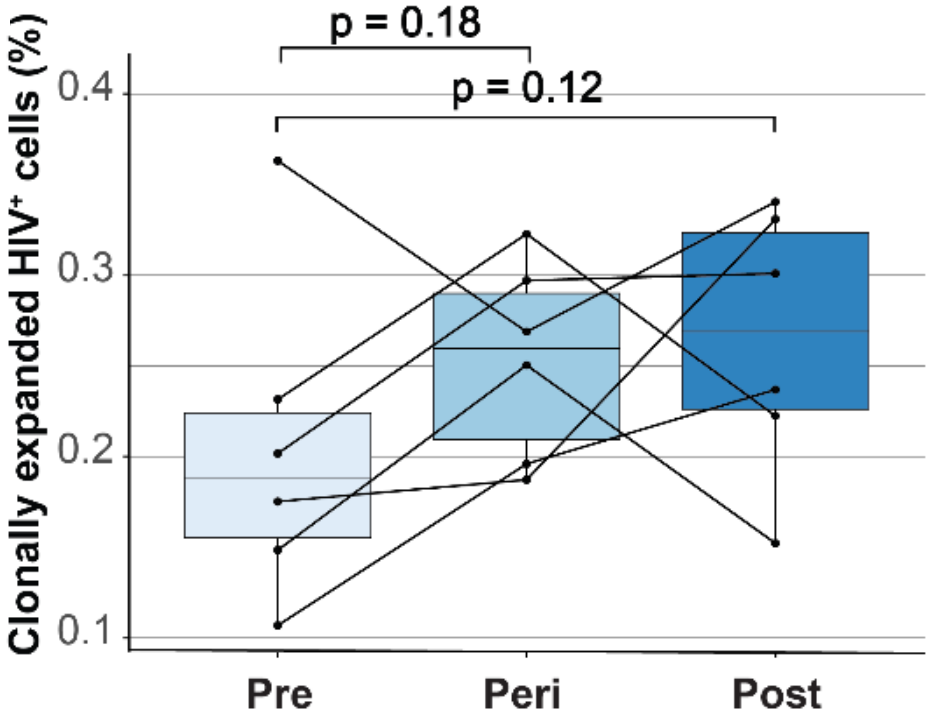
- Vorinostat (SAHA) = HDAC inhibitor
- Tamoxifen = blocks estrogen receptor (ERα)
- Estrogen limits the efficacy of an LRA!
- Most pronounced: reproductive age females
- Modest effects: males and older women



Adapted from Das et al. PNAS 2018

HIV persistence during menopausal stages





Gianella et al, CID, 2022 and unpublished data from Antoine Chaillon

Trans Women in Cure Research?

Transcendendo Study

- trans-specific cohort to longitudinally evaluate the health aspects of trans women aged ≥18 years in Rio de Janeiro, Brazil.
- Nested study: Reservoir and immunology

GET IT RiGHT study (ACTG 5403)

- Impact of ART on gender affirming hormone therapy in transfeminine people.

Ferreira Transgender Health 2019; Razek Transgender Health 2024

Considerations for Cure Research

- Estrogen may limit efficacy of latency reversal agents
  - interfere with reactivation-based quantification assays (QVOA)
- Hormones/chromosomes may impact immunomodulatory cures
  - e.g., TLR7 agonists might be more effective in females
- Need more diversity in cure research
  - Careful design: menses, puberty, pregnancy, menopause, hormonal contraception, transition-related hormone therapy…
  - Community engagement: novel agents with risk

Reduced HIV-1 latent reservoir outgrowth and distinct immune correlates among women in Rakai, Uganda

Jessica L. Prodger,[1,2,3] Adam A. Capoferri,[3] Katherine Yu,[2] Jun Lai,[3] Steven J. Reynolds,[3,4,5] Jingo Kasule,[5] Taddeo Kityamuweesi,[5] Paul Buule,[5] David Serwadda,[5,6] Kyungyoon J. Kwon,[3] Katherine Schlusser,[3] Craig Martens,[7] Eileen Scully,[3] Yun-Hee Choi,[2] Andrew D. Redd,[3,4] and Thomas C. Quinn[3,4]

Effect of pregnancy on the reservoir?

BIOS CLINICAL RESEARCH

Social Determinants of Health

Kimberly Skeete,
Researcher, Lab Tech, CPT 1
Association of Nurses in AIDS Care (ANAC), GPS Chapter President
02 April, 2025

Agenda Overview

01 Social Determinates of Health

02 Collection/ Interpretation of Sex & Gender Data

03 Data on Exogenous hormone use

04 Language - Impacts the quality of data

05 Theoretical Reproductive Toxicity

06 Outreach Strategies - Representation

07 Final Thoughts

What are Social Determinants of Health

Social determinants of health (SDOH) are non-medical factors that influence health outcomes. They encompass the conditions in which people are born, grow, live, work, and age, as well as the broader systems shaping daily life. These include economic policies, social norms, political structures, and environmental factors.

Examples of social determinants include:

- Economic Stability: Access to quality jobs and financial security.
- Education: Availability of educational opportunities and literacy skills.
- Healthcare Access: Accessibility and quality of medical services.
- Neighborhood Environment: Safe housing, transportation, and clean surroundings.
- Social Context: Community support, inclusion, and protection against discrimination.

Collection / Interpretation of Sex and Gender Data

Exogenous Data

- Comprehensive Data Collection: Move beyond surface-level documentation to monitor long-term impacts, medication interactions, and effects across diverse populations.
- Address Research Gaps: Identify representation and methodological gaps in current studies, ensuring better inclusivity.
- Specialized Protocols: Develop study designs to examine how exogenous hormones influence HIV treatment outcomes, considering all physiological variables.
- Contraceptives & Gender-Affirming Treatments: Investigate their impact on treatment efficacy and cure research for personalized approaches.
- Clinical Trials: Incorporate hormone therapy data to ensure diverse representation and tailored strategies in HIV research.

Patient First Language

The Power of Inclusive Language in Research

- Impact on Data Quality:
  - Framing questions and communication styles significantly influence the accuracy and inclusivity of collected data.
- Why Inclusive Language Matters:
  - Ensures diverse populations are accurately represented.
  - Enhances the relevance and reliability of research findings.
- Training for Inclusivity:
  - Equip researchers and healthcare providers with skills in inclusive and culturally sensitive communication.
  - Introduce concepts like code-switching to adapt language to different cultural contexts.
- Key Terminology in Study Design:
  - Utilize precise terms, such as “sex assigned at birth” versus “gender identity,” for accurate data representation.
  - Implement people-centered, first-person terminology across protocols, surveys, and study frameworks.
  - This approach directly contributes to improved data quality and better health outcomes.

Reproductive Toxicity

Potential Concerns

- Reproductive toxicity in HIV treatment and prevention drugs is a critical area of concern, especially when considering theoretical risks similar to those posed by cancer drugs.
- Antiretroviral drugs (ART) have been studied for their potential effects on fertility. While many antiretroviral drugs are deemed safe during pregnancy, some may carry risks that require careful evaluation.
- The NIH provides guidelines on the use ART drugs during pregnancy, emphasizing the importance of monitoring for toxicity. These guidelines recommend reporting all cases of prenatal exposure to antiretroviral drugs to the ART Pregnancy Registry.

Navigating Reproductive Toxicity

- Pre-Enrollment Education: Develop orientation sessions for participants to explain the study's reproductive toxicity risks, with tailored information for cisgender women and TGNC individuals.
- Pharmacovigilance Systems: Implement robust systems during trials to monitor and report adverse reproductive outcomes. This real-time data can inform adaptive protocols.
- Collaborative Data Sharing: Partner with institutions researching reproductive health to enhance study designs and share findings, especially on theoretical toxicity.

Advocacy for Policy and Guidelines

- Advancing Policy Discussions: Advocate for stronger FDA guidelines to address reproductive toxicity risks in HIV drugs, ensuring safety across populations.
- Registry Enhancements: Support improvements in registries like the Antiretroviral Pregnancy Registry, making them more inclusive of TGNC and cis women participants.

How Do We Do Better Outreach and Improve Inclusion?

Community Engagement and Feedback Loop

- Community Collaboration: Partner with local organizations, leaders, advocacy groups, and faith-based spaces to align research with community needs using trusted messengers.
- Human-Centered Approaches: Employ strategies proven effective with individuals who have lived experience
- Interactive Education: Host workshops to foster researcher-community dialogue, address questions, and provide ongoing feedback channels.
- Visibility Matters: Attend health fairs and events to raise awareness in accessible, non-clinical settings.
- Inclusive Feedback: Use listening sessions, advisory boards, and anonymous surveys to gather diverse perspectives and improve inclusivity.
- Transparency: Share study outcomes and progress with participants to highlight their contributions' impact.

Address Barriers

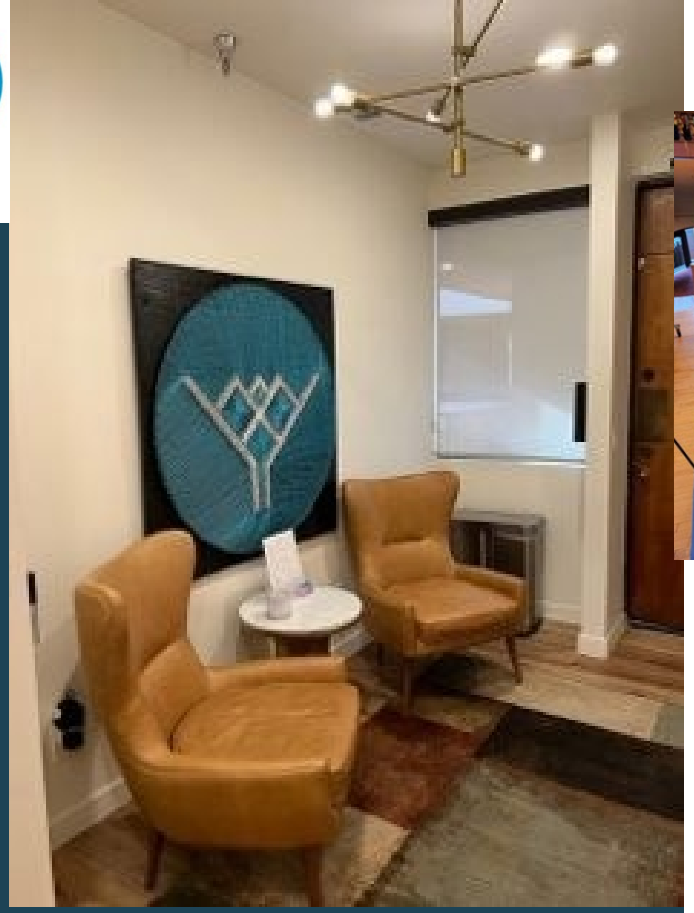
- Identify and mitigate obstacles such as stigma, transportation, childcare, and financial constraints. Providing flexible participation options and support services can make research more accessible.
- Transportation Solutions: Provide stipends for rideshares or arrange shuttles for study visits.
- Childcare Support: Offer on-site childcare or reimburse childcare costs during appointments.
- Flexible Scheduling: Allow evening or weekend study visits to accommodate work schedules.
- Direct Financial Support: Compensate participants fairly, including stipends for their time and effort

Culturally Competent Communication & Structural Interventions

- Inclusive Materials: Design flyers, social media posts, and outreach tools that use gender-inclusive language and represent diverse groups (e.g., cis women, TGNC individuals, BIPOC communities).
- Language Access: Translate materials into languages commonly spoken by your target communities and employ interpreters when needed.
- Access to Services: Partner with clinics to ensure participants can access complementary healthcare, such as PrEP navigation or mental health support
- Reduce Healthcare Disparities: Use your outreach to connect marginalized participants with resources they may lack, such as insurance navigators or housing assistance.

BIOS
CLINICAL RESEARCH

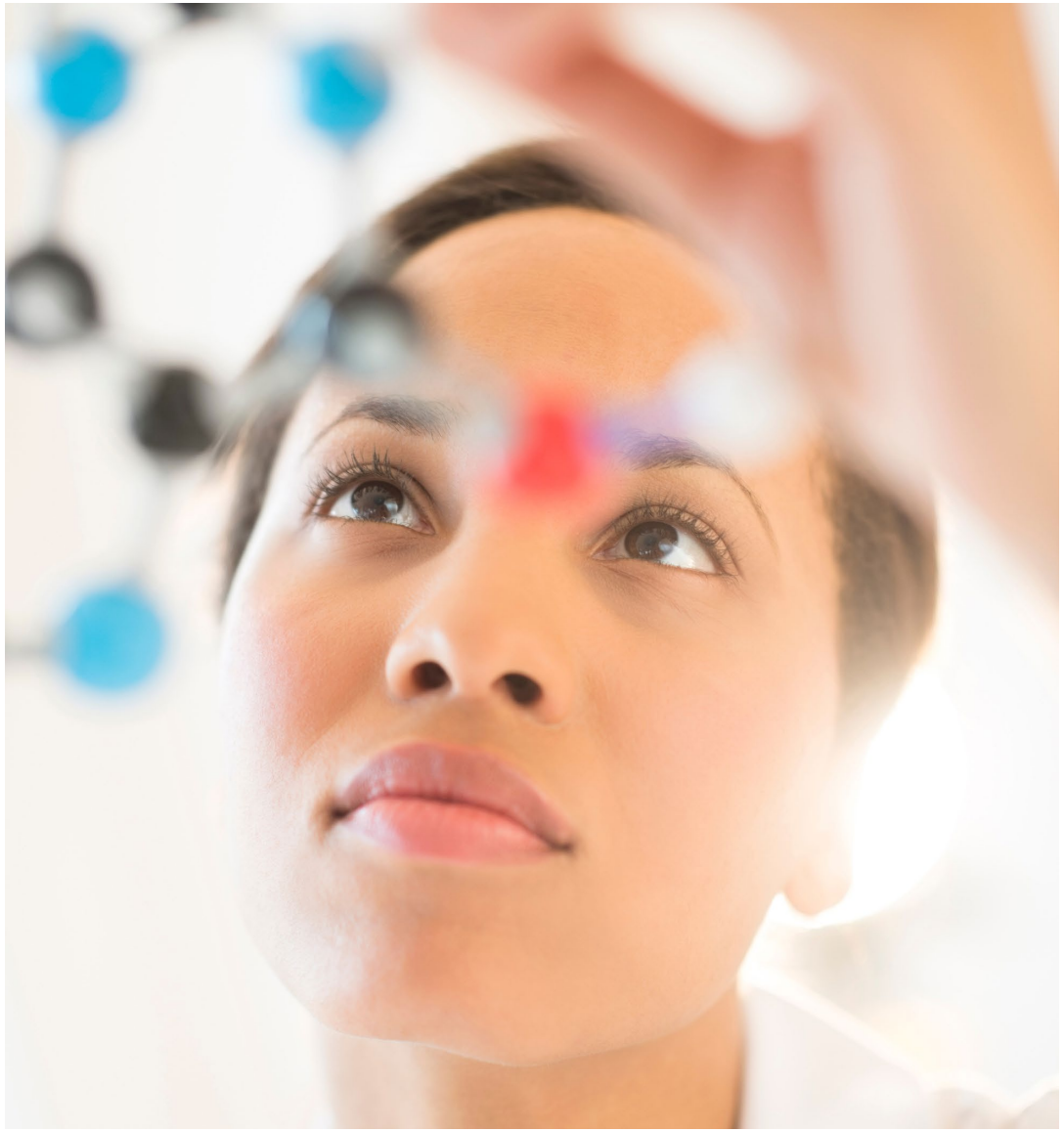
Quick Look



“Nothing about us without us”

Since our start, BIOS has been dedicated to both the highest medical standards and ensuring that all communities in our area, especially historically underserved groups, are represented in our studies. We’re also committed to employing people from all backgrounds and origins, aiming for both studies and staff that are as diverse as our area.

Most importantly, BIOS is a sex-positive, affirming, inclusive, and welcoming space. We welcome people of all genders, identities, and socio-economic statuses.



As we bring today's presentation, The Basic Science of HIV Cure, to a close, I want to express my heartfelt gratitude to Dr. Sara Gianella Weibel from UC San Diego and Dr. Jessica Prodger from Western University for their exceptional contributions to this important discussion.

Thank You

02 April, 2025