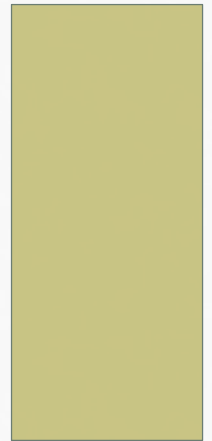


EXPLORING THE IMPACT OF SEX DISCREPANCIES IN HIV TREATMENT AND CURE

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OUTLINE

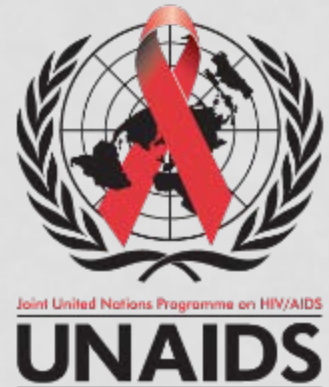
- Describe discrepancy between HIV burden and clinical study inclusion in women
- Review knowledge of known sex differences in HIV infection and relevance to cure agenda
- Give overview of ongoing research projects investigating sex discrepancies in HIV
 - Women's HIV Interagency Study (WIHS)
 - Dolutegravir in Reservoirs



WORLDWIDE BURDEN OF HIV DISEASE IN WOMEN IS HIGH

2014 UNAIDS

- **>50% of 36.9 million** people worldwide living with HIV/AIDS
- Women are particularly vulnerable to HIV infection
 - lack of financial independence
 - Inability to negotiate safer sex (condom use)
 - Intimate partner violence
 - Cultural factors
 - Lack of education



UNAIDS. Global AIDS Response Progress Reporting. 2015;
http://www.unaids.org/en/resources/documents/2015/GARPR_2015_guidelines.

WOMEN ARE UNDER-REPRESENTED IN TRIALS OF HIV CURE

Systematic review looked at participation of women in clinical studies of HIV curative interventions

- 159 studies published between 1995-2013
- Clinical studies looked at early treatment, immune modification, treatment intensification, reactivation, treatment interruption, and vaccines
 - **58% included ≥ 1 woman**
 - **20% had 0 women**
 - **21% had insufficient data on women**
- Of the 79% of studies that reported data on sex, **only 18%** of participants were women

SEX DIFFERENCES RELATED TO HIV CURE HAVE BEEN IDENTIFIED

Female sex is associated with:

- Lower HIV viral load (JAIDS 2002; 31: 11-19)
- Higher CD4+ count (AIDS 1997; 11: 1071-3)
- More pronounced immune and vaccine responses (JAIDS 2011; 57: 9-15)
- Higher levels of immune activation (JID 2013; 208: 830-8)
- More frequent antiretroviral therapy (ART) side effects and discontinuation (J Antimicrob Chemother 2007; 60: 724-32)



SEX DIFFERENCES IN ART PHARMACOLOGY

Sex differences in pharmacology of antiretroviral medications can have clinical significance.

- Females have increased maximal concentrations (C_{max}) of nevirapine compared to males
 - May explain higher propensity for females to develop cutaneous hypersensitivity reactions (AIDS 2003; 17: 2399-400)
- Females showed higher intracellular concentrations of phosphorylated nucleoside reverse transcriptase inhibitors (NRTIs)
 - Associated with more rapid HIV VL decay and shorter time to virologic suppression (AIDS 2003; 17: 2159-68; AIDS 2002; 16: 1196-97)

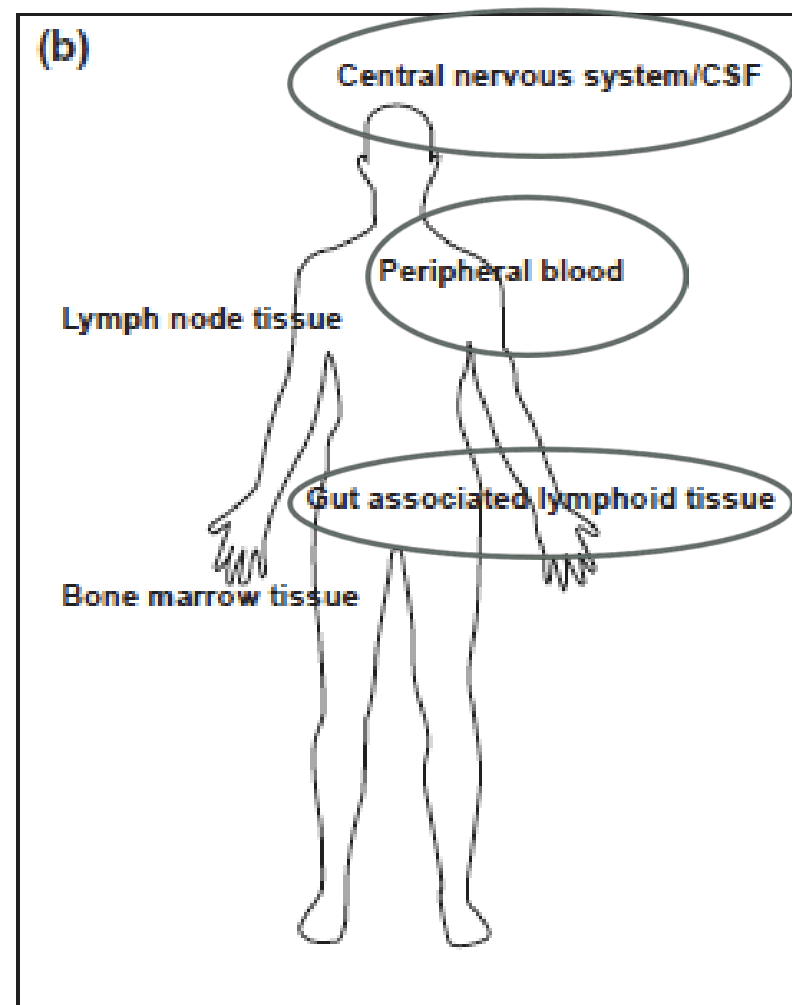
These studies are all limited by examination of sex differences only in secondary analyses

PHARMACOLOGICAL BARRIERS TO HIV ERADICATION

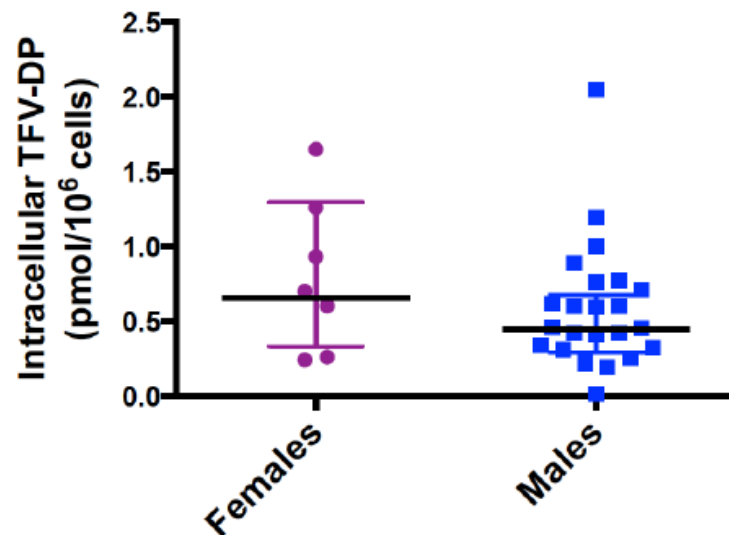
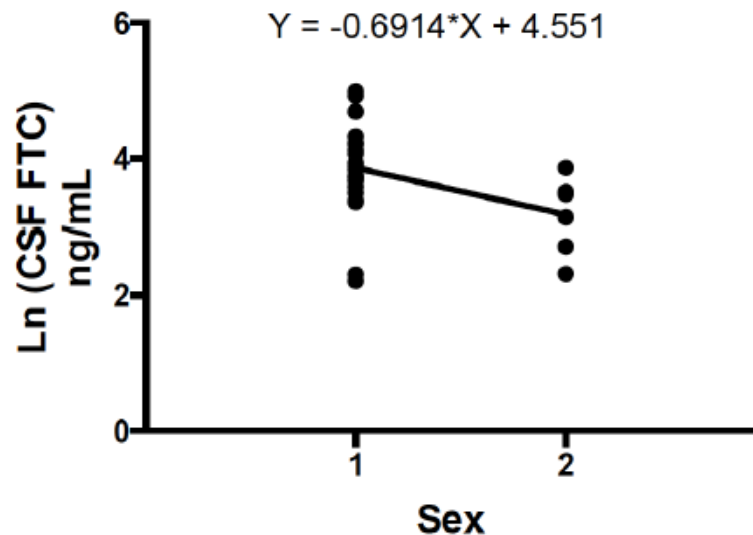
How has HIV-1 eluded eradication?



Limited antiretroviral penetration into reservoir sites



SEX DIFFERENCES IN CSF AND PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCS) PHARMACOLOGY



Lower emtricitabine (FTC) concentrations noted in CSF of females (sex = 2) vs males (sex = 1), $p = 0.03$

Trend toward higher intracellular tenofovir (TFV) concentrations in females vs males.

MECHANISMS OF SEX DIFFERENCES IN ART PHARMACOLOGY?

- **Physiologic?**

- Total body weight
- Fat distribution
- Degree of protein binding
- Influence of sex hormones on drug metabolism
- Gastric emptying time

- **Molecular?**

- cytochrome P450 enzyme activity
- Expression/activity of drug transporter genes



Enrollment of women in studies examining sex differences in ART pharmacology needs to be a PRIORITY.

WOMEN'S INTERAGENCY HIV STUDY (WIHS)

- **Multicenter, prospective, observational study of women who are either HIV infected or at risk for HIV acquisition**
- **Established in 1993 to study the natural and treated history of HIV/AIDS among women in the United States**
- **Originally consisted of 6 sites (East and West Coasts and Midwest)**
- **In 2013, because of the growing impact of the AIDS epidemic in the South, four additional sites were added in the Southeast**



Women's Interagency HIV Study (WIHS) Sites



*WIHS Data Center

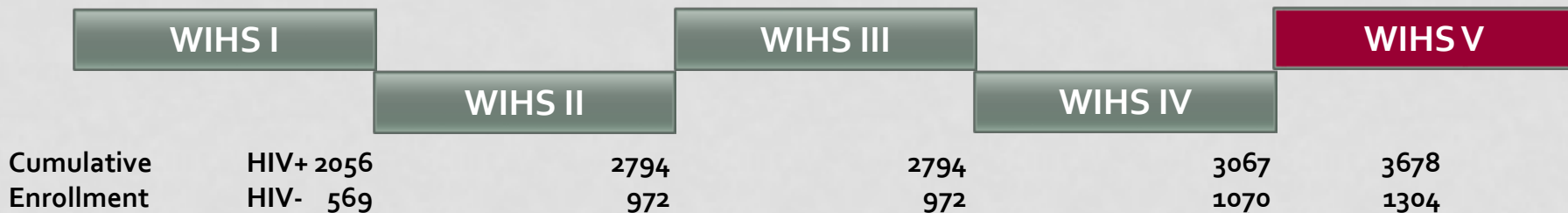


Slide courtesy of Igho Ofotokun.



WIHS Timeline

1993 1996 1999 2002 2005 2008 2011 2014 2017



1st Visit
10/3/94

21.0 years (7,680 days)

43rd Visit
10/13/15

Bronx, NY

Brooklyn, NY

Chicago, IL

Los Angeles, CA

San Francisco, CA

Washington, DC

WDMAC
Baltimore, MD

Atlanta, GA

Birmingham, AL/
Jackson, MS

Chapel Hill, NC

Miami, FL

WIHS



DOLUTEGRAVIR IN RESERVOIRS: A SUBSTUDY OF WIHS



Goals of study? To compare dolutegravir (DTG) pharmacokinetic-pharmacodynamic relationships in 3 anatomical sites, 1) blood plasma, 2) PBMCs, and 3) rectal tissue of males and females

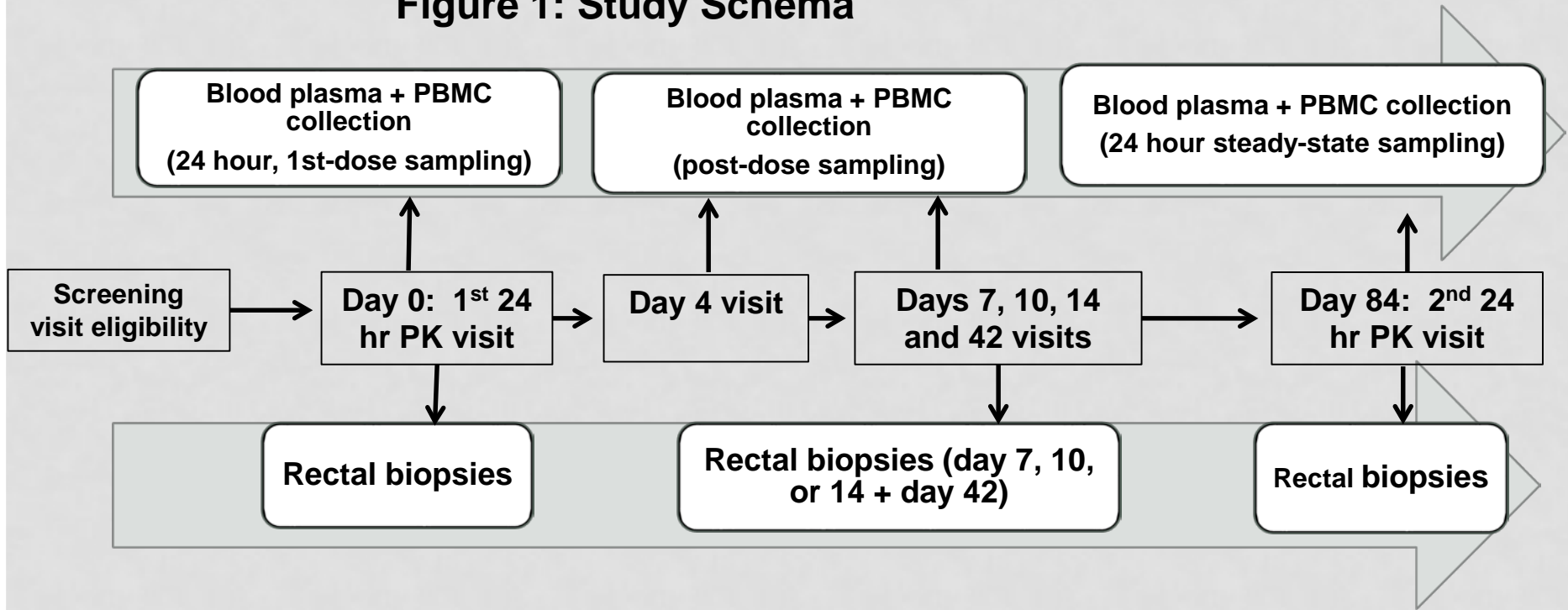
Why? Optimal drug exposure needed for HIV suppression in reservoir sites may differ between males and females, informing cure strategies for both sexes

Who? 40 HIV+ ARV-naïve participants (20 males, 20 females) initiating DTG-based therapy

- Recruitment predominantly from Grady IDP and WIHS

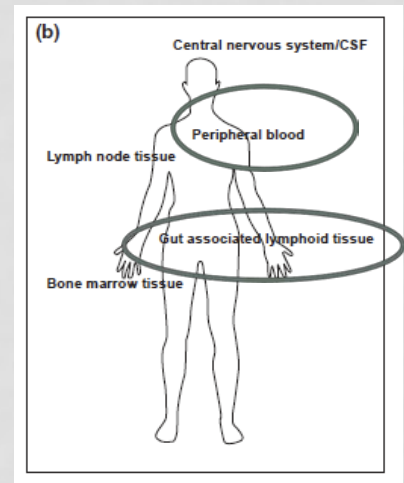
How? 12 week longitudinal cohort study with serial collection of blood, PBMCs, and rectal tissue biopsies

Figure 1: Study Schema



Sex-related covariates:

- Menopausal status
- Menstrual cycle stage
- Exogenous sex hormone use
- Future banking for:
 - Drug transporter gene expression
 - Sex hormone quantification



STUDY PROGRESS

- 8 participants have enrolled and completed all study visits
 - 4 females
 - 4 males
- Preliminary analyses of samples underway
 - Emory CFAR Virology Core Lab (Dr. Colleen Kraft)
 - Biochemical Pharmacology Lab (Dr. Raymond Schinazi)
 - University of Alabama-Birmingham Antiviral Pharmacology Lab (Dr. Edward Acosta)

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