Understanding the Unique Challenges of Cisgender Women Living with HIV

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International Maternal Pediatric Adolescent AIDS Clinical Trials Network

ANNUAL MEETING

2024

Disclosures

- Investigator-sponsored research awards from Gilead Sciences and ViiV Healthcare. Research awards are managed by MedStar Health Research Institute or the IMPAACT Network

Terminology

- Focus on cisgender women and individuals assigned female at birth, subsequently referred to as “women” (unless otherwise specified in the publication being discussed)

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Key Messages

- Inclusion of women with HIV in clinical trials, especially during pregnancy, is critical to equitable and optimal medical care
- Exclusion of women with HIV from research, including during pregnancy, does not *protect* women (and their fetuses)– but rather *neglects* them
- Despite significant improvements in inclusion of women over last 30 years, we still know far less about how medications and diseases affect women due to historical underrepresentation
- There is still an urgent need for continued advocacy for timely and equitable enrollment in clinical trials, especially during pregnancy

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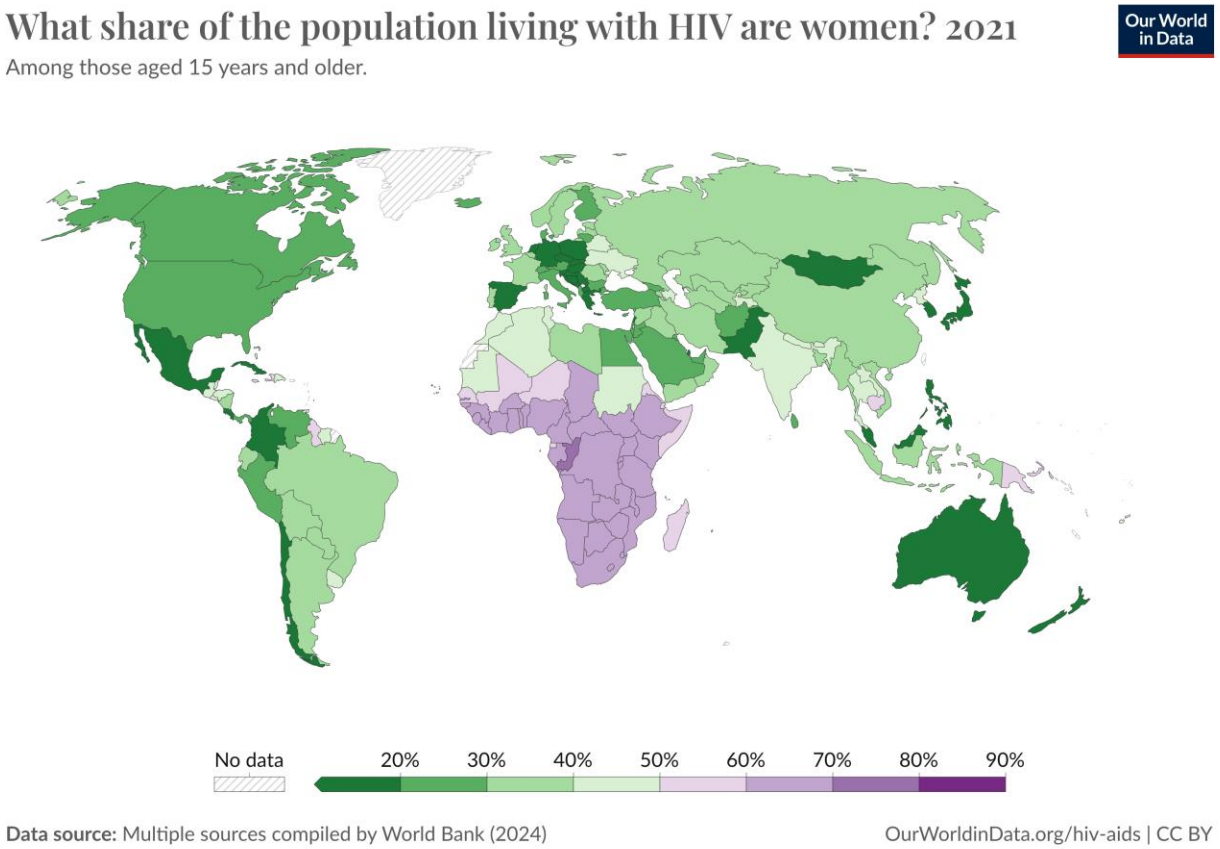
Global perspective

- 39.9 million people living with HIV worldwide
  - 53% women and girls
- Since 2009, HIV/AIDS has been the **leading cause of death** among women of reproductive age
- Historical under representation of women in HIV prevention and treatment research



- https://www.unaids.org/en/resources/fact-sheet
- https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics

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Underrepresentation of Women in Clinical Trials

- 41% of participants in clinical trials globally
  - 41% in cardiovascular trials (vs. 49% of cardiovascular disease)
  - 41% in cancer trials (vs. 51% of cancer burden)
  - 42% in mental health trials (vs. 60% of individuals with psychiatric disorders)
  - **11-23% in HIV trials (vs. 53% of individuals living with HIV)**
- Excluded due to hormone fluctuations and potential for pregnancy complications

Image: https://helloclue.com/articles/culture/why-are-women-and-people-with-cycles-underrepresented-in-health-research

- Johnston CD, et al. Inclusion of women in HIV research and clinical trials. AIDS. 2023 May 1;37(6):995-7
- Sosinsky AZ, et al. Enrollment of female participants in United States drug and device phase 1–3 clinical trials between 2016 and 2019. Contemporary Clinical Trials. 2022 Apr 1;115:106718.

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Historical Context for the Exclusion of Women

- Minimal regulation of drug research and licensing in the early 20th century
  - Tragic examples of Thalidomide and Diethylstilbestrol (DES)
- 1977 US Food and Drug Administration (FDA) ban on inclusion of women of child bearing potential in early-phase drug trials
- De facto exclusion of women from most drug trials
- NIH Revitalization Act of 1993: mandated inclusion of women and minorities
- FDA Safety and Innovation Act of 2012: sex-specific analysis of clinical trial data and better reporting of outcomes by gender

Image: via Luciana Christiante / Flickr (CC BY-NC-ND)

- Mastroianni AC, et al. NIH revitalization act of 1993 public law 103-43. Institute of Medicine, Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. 1994.
- https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/food-and-drug-administration-safety-and-innovation-act-fdasia

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The Impact of Underrepresentation of Women

- Majority of drugs for both treatment and prevention primarily researched in men
- Fewer and less effective treatments for women
- Dosing guidelines are based upon data in men with a **higher risk of adverse drug reactions**

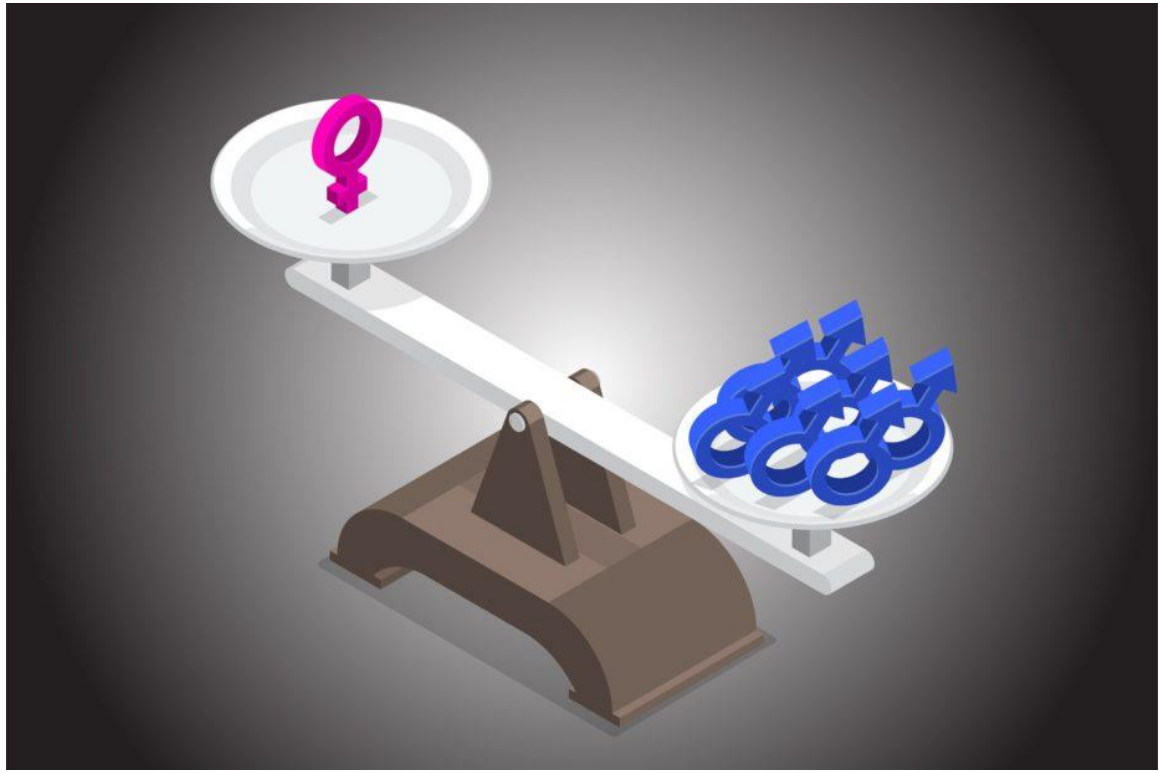

Image: MCLEAN/SHUTTERSTOCK.COM

- Zucker I, et al. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biology of sex differences. 2020 Dec;11:1-4..
- https://www.fda.gov/consumers/diverse-women-clinical-trials/women-clinical-trials-research-and-policy

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Sex-differences between Women and Men

- Physiologic differences:
  - Increased fat mass
  - Decreased lean mass
  - Decreased total body water
  - Higher resting heartrate and variation
  - Slower digestion in the stomach (and less acidity) and in the intestines
  - Differences in liver enzymes which breakdown drugs
  - Slower kidney function which excretes drugs
- Differences in pharmacokinetics (PK): *what the body does to the drug*
- Differences in pharmacodynamics (PD): *what the drug does to the body*

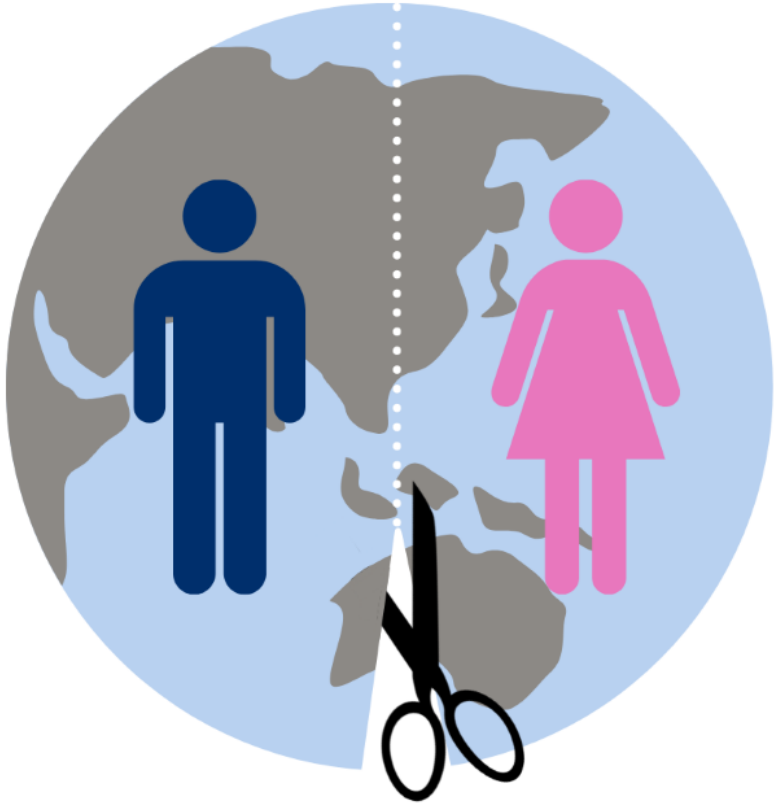

Image: https://www.mtapsprogram.org/news-blog/we-can-only-fix-what-we-know-about-why-sex-disaggregated-data-in-pharmaceutical-systems-is-crucial/

- Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clinical pharmacokinetics. 2009 Mar;48(3):143-57.
- Gandhi M, et al Sex differences in pharmacokinetics and pharmacodynamics. Annu. Rev. Pharmacol. Toxicol.. 2004 Feb 10;44(1):499-523.

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Sex differences in Drug Processing

- Absorption
  - Women may experience higher absorption rates for certain medications due to factors like slower gastric emptying or differences in gastrointestinal pH
  - Other drugs have lower absorption rates, influenced by hormonal cycles or variations in body composition
- Distribution
  - For fat-soluble drugs, women may experience higher distribution volumes due to greater % body fat, which can lead to prolonged drug effects
  - For water-soluble drugs, distribution volume may be lower in women due to lower total body water, resulting in higher concentrations of the drug
- Metabolism/Elimination
  - Women may metabolize certain drugs more quickly due to higher activity of specific liver enzymes, particularly when influenced by hormonal levels
  - For other drugs, women may experience slower metabolism, often due to lower activity of liver enzymes or the effects of hormonal fluctuations
- Example of nevirapine-induced increased liver toxicity in women

Image: PeopleImages/iStock via Getty Images Plus

- Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clinical pharmacokinetics. 2009 Mar;48(3):143-57.
- Gandhi M, et al Sex differences in pharmacokinetics and pharmacodynamics. Annu. Rev. Pharmacol. Toxicol.. 2004 Feb 10;44(1):499-523.

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Hormonal changes: lifetime and monthly

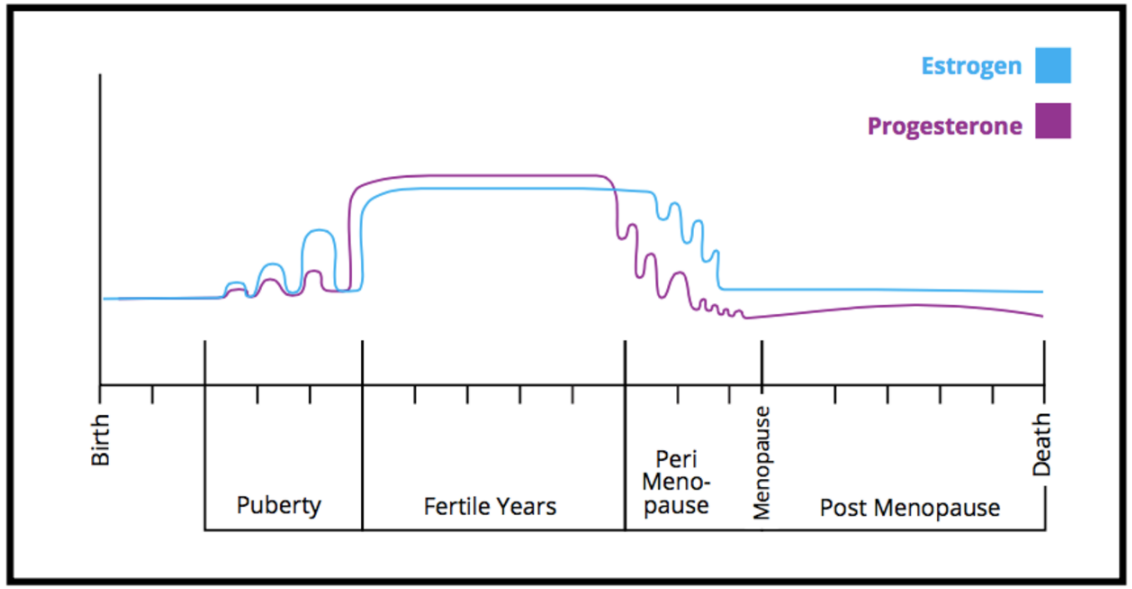

Image: https://www.menopausenaturalsolutions.com/blog/female-hormone-lifecycle

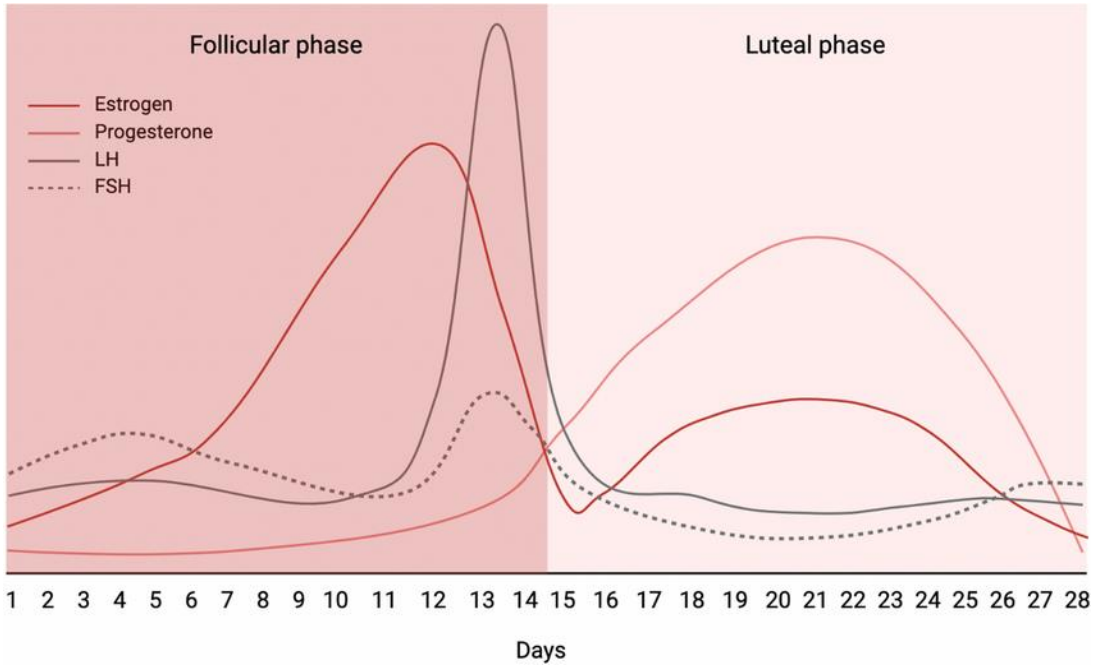

Image: Kissow J, et al. Effects of follicular and luteal phase-based menstrual cycle resistance training on muscle strength and mass. Sports Medicine. 2022 Dec;52(12):2813-9.

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Shifts in pregnancy

ABSORPTION

- Nausea = difficulty with adherence
- Vomiting = reduction in drug intake
- ↓ gastric emptying = ↓ maximal drug concentration
- ↑gastric pH = ↓absorption of weak acid and base molecules

DISTRIBUTION

- ↑ total body water and expanded plasma volume = ↑volume of distribution of hydrophilic drugs
- ↑ body fat = ↑volume of distribution of lipophilic drugs
- ↓maternal albumin and albumin occupied by steroids/hormones = ↑ free drug fraction

METABOLISM

- Enzyme induction/inhibition by progesterone/oestrogen = ↑↓ metabolism depending on drug
- Inhibited enzymes = CYP1A2, CYP2C19
- Induced enzymes = CYP2B6, CYP2C8, CYP2C9,CYP2D6, CYP2E1, CYP3A4, UGT

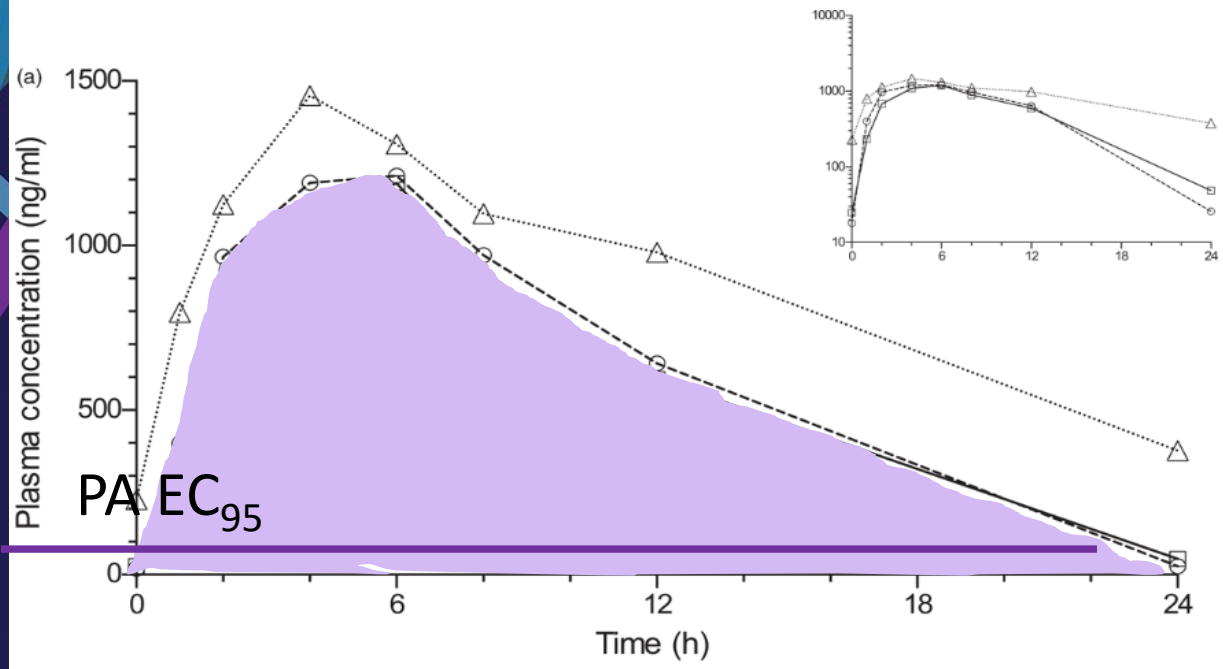
ELIMINATION

- ↑ renal blood flow and ↑ glomerular filtration rate = ↑ elimination of renally eliminated drugs
- ↑hepatic blood flow = ↑ elimination of high hepatic extraction drugs

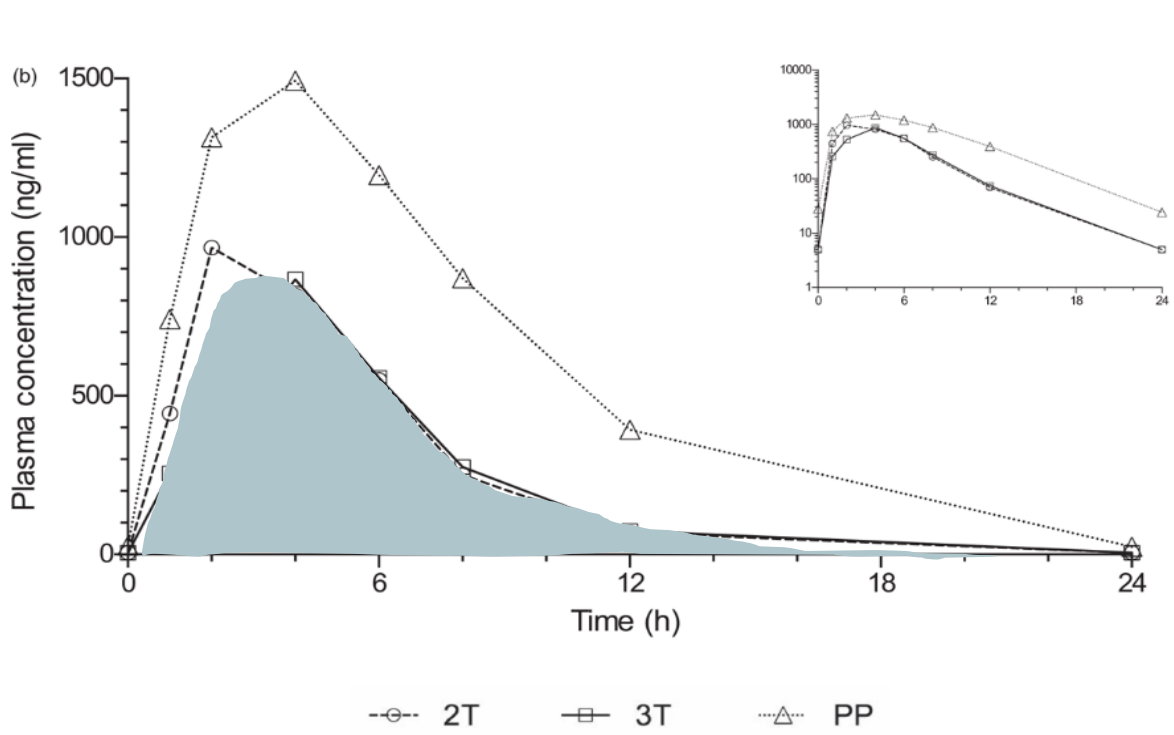
From Hazenberg et al 2021 Clinical Pharmacology and Therapeutics; Slide courtesy of Catriona Waitt

Momper 2018, AIDS ; 32(17):2507-2516
Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV

Elvitegravir



Cobicistat



C_{24} 81% lower (T2) and 89% lower (T3) compared with paired postpartum

C_{24} 60% lower (T2) and 76% lower (T3) compared with paired postpartum

Slide adapted from Catriona Waitt

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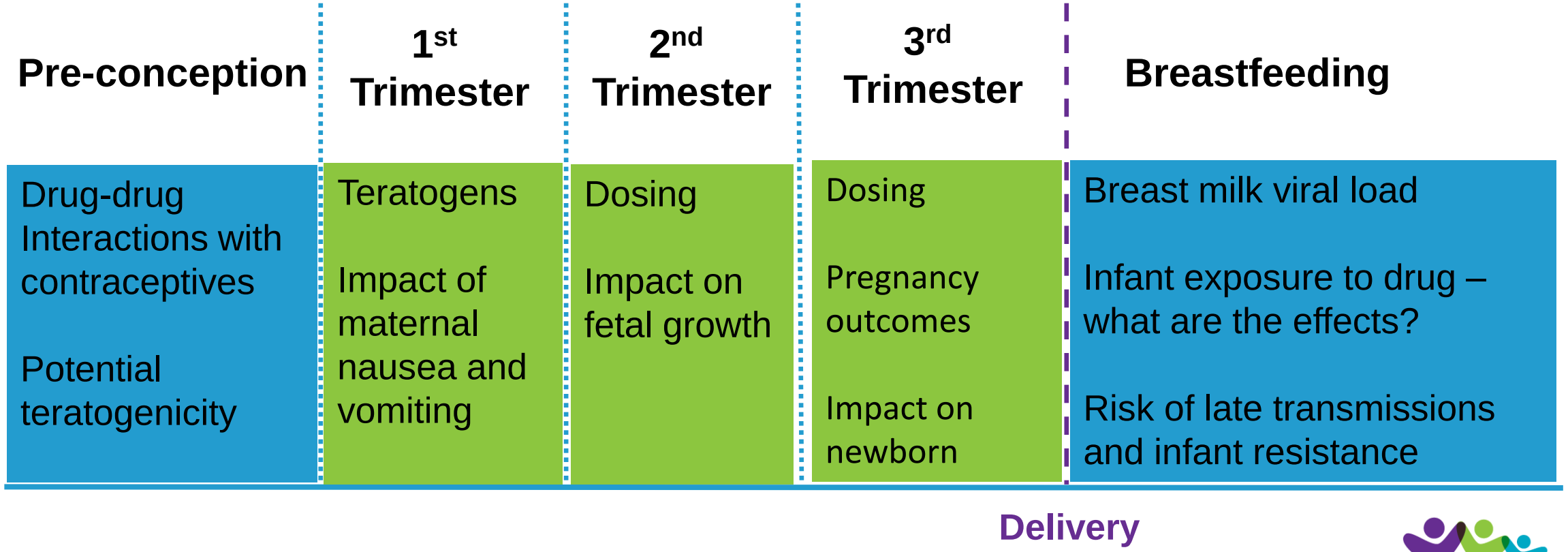
Risk-benefit Considerations with Maternal Drug Exposure before/during/after Pregnancy



Slide adapted from Catriona Waitt

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Global estimate: Half of all women require medication in pregnancy

Women with chronic medical conditions requiring medication will become pregnant and may choose to breastfeed

Women may acquire new acute or chronic medical conditions requiring medication when already pregnant or breastfeeding

Complex and understudied, not ‘special’ or ‘vulnerable’

Slide adapted from Catriona Waitt

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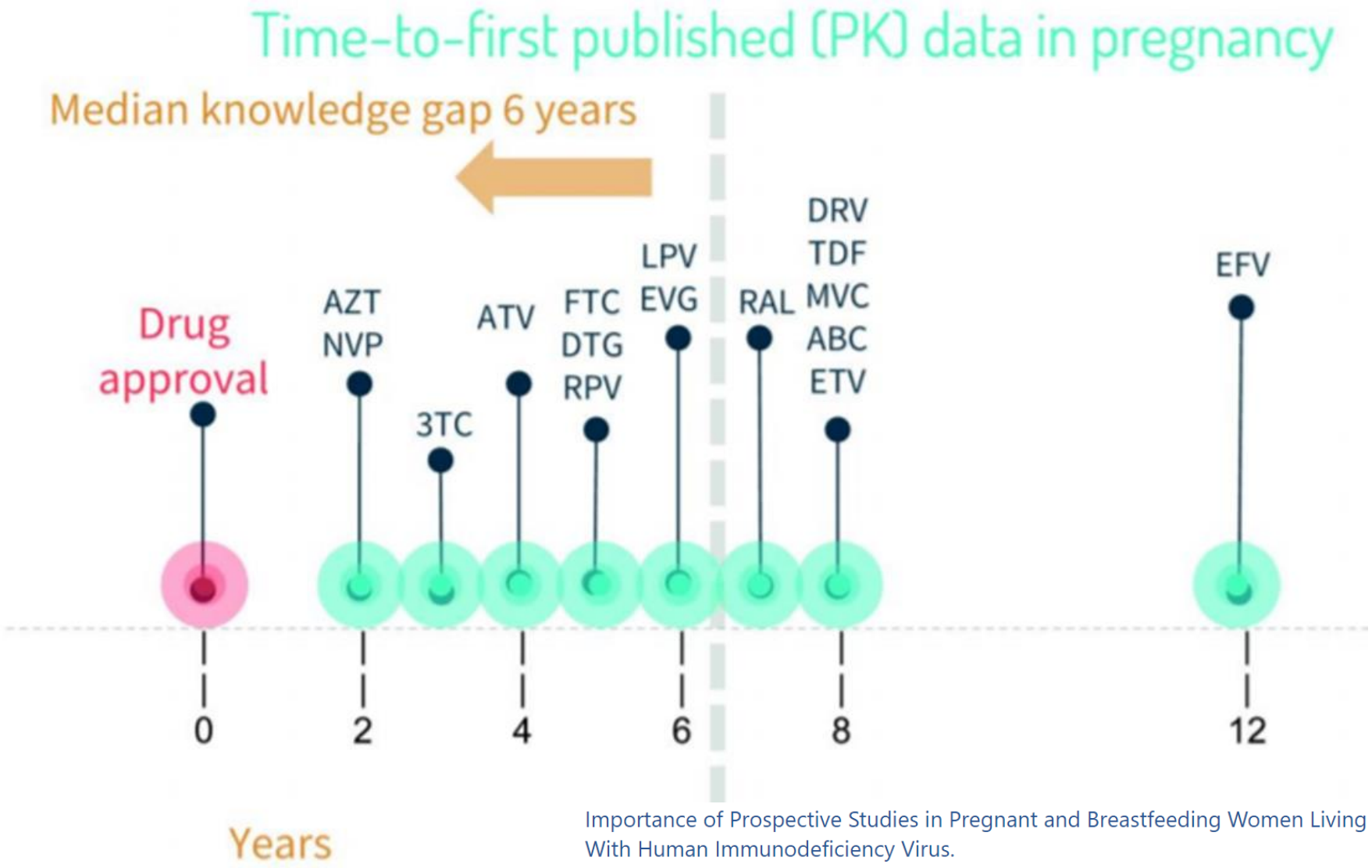
Delay between licensing and pregnancy safety and dosing data



Importance of Prospective Studies in Pregnant and Breastfeeding Women Living With Human Immunodeficiency Virus.

Colbers A, Mirochnick M, Schalkwijk S, Penazzato M, Townsend C, Burger D.

Clin Infect Dis. 2019 Sep 13;69(7):1254-1258. doi: 10.1093/cid/ciz121.

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Why inclusion in clinical trials during pregnancy is critical

- Assessment of drug in among a small number of participants, in a controlled setting, with close follow-up to assess safety and outcomes
  - **Risks of toxicity or ineffectiveness are present but contained**
- In the absence or delay of clinical trial data
  - **Above risks are magnified** as women and their medical providers must make decisions about clinical management without evidence (and without the controlled setting of a clinical trial)
  - **Risk of choosing older, ineffective, or even harmful medications**
  - **Risk of disease harm from under treatment**

Image:https://www.hivaidsexpert.com/pregnancy-with-hiv-infection/

- Weld ED, et al Ethical issues in therapeutic use and research in pregnant and breastfeeding women. British journal of clinical pharmacology. 2022 Jan;88(1):7-21.

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Recent strides and room for growth

- Long acting Cabotegravir (CAB) and Rilpivirine (RPV) for treatment of HIV
- Drug trials: 28% women
- Approved for treatment (CAB + RPV) and prevention (CAB only) in 2021
  - CREATE (IMPAACT 2040) is opening in early 2025
  - Preliminary safety and pharmacokinetic data for CAB in pregnancy from HPTN 084 presented at AIDS 2024
- Lenacapavir
- Drug trials 25-28% women
- Approved for treatment in 2022.
- No clinical trials for treatment in pregnancy
- PURPOSE-1 trial for HIV prevention among cisgender women
  - Allowed continuation during pregnancy
  - Pregnancy data presented concurrent with non-pregnant data (and two months before data in men)

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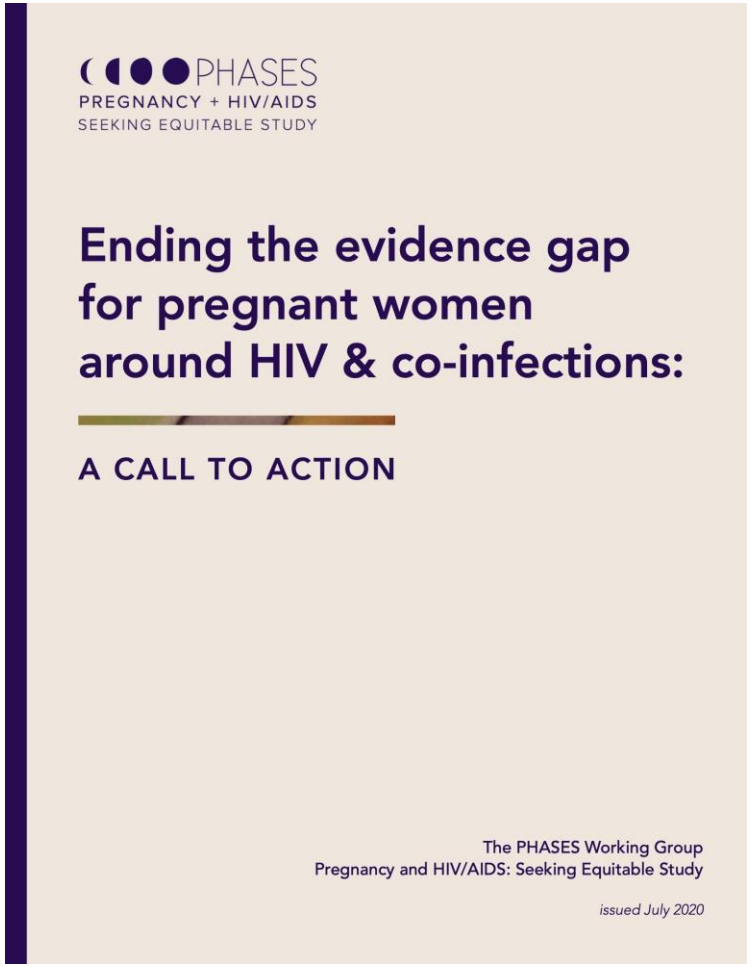
Call for Change in HIV Research

- International task force of community advocates and experts in the field
- Call to “end to the evidence gap for pregnant women around HIV”
- Primary means to achieve equitable protection from drug-related risks and access to first-line medications and equitable respect for pregnant women’s’ own health, not just the health of her fetus



Imagehttp://www.hivpregnancyethics.org/

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THANK YOU!

rachel.k.scott@medstar.net

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Include acknowledgements and thanks!

- Standard IMPAACT acknowledgements can be found here: https://www.impaactnetwork.org/about/funding-acknowledgements

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