FDA Meeting:
Drug Interactions with Hormonal Contraceptives; Public Health and Drug Development Implications; Public Meeting

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DHHS/NIH Required Disclaimer

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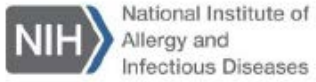

DHHS → NIH → NIAID → **DAIDS** → **PSP** → **PMPRB**

—Create a sustainable pipeline of prevention products and strategies

Single and combination Microbicides, Topical and Systemic PrEP and Multipurpose Prevention Technologies (MPTs)

— Support innovative, proof-of-concept research to enable and facilitate current and future prevention product development:

- ***Windows of Protection:***

  Develop non-coital (1 dose provides 7 days of protection) and sustained delivery (> 30 day window of protection for either continuous delivery or single dose).

- ***PK/PD:***

  Relationship of target tissue and secretion drug concentration to efficacy.

- ***Acceptability and Adherence:***

  Quantitative biomedical methods to measure adherence to prevention placebos and products.

- **HIV Susceptibility/Ecological Prevention**

  Understand in the context of HIV prevention the factors and biological processes which determine HIV susceptibility, using this knowledge to creating safer and more efficient prevention strategies.

— Facilitate the advancement of “best” products and drug delivery systems to first in human testing.

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Who we coordinate with:

NIAID:
Division of AIDS
Division of Microbiology and Infectious Disease -STI Branch

NIH Institutes and Offices:
- National Institute of Mental Health (NIMH)
- National Institute of Child and Human Development (NICHD)
- Office of AIDS Research (OAR)
- Office of Research on Women's Health (ORWH)

Other U.S. Gov't Agencies:
- USAID
- CDC
- FDA

Other Funders:
- Bill and Melinda Gates Foundation (BMGF)

Who we support:

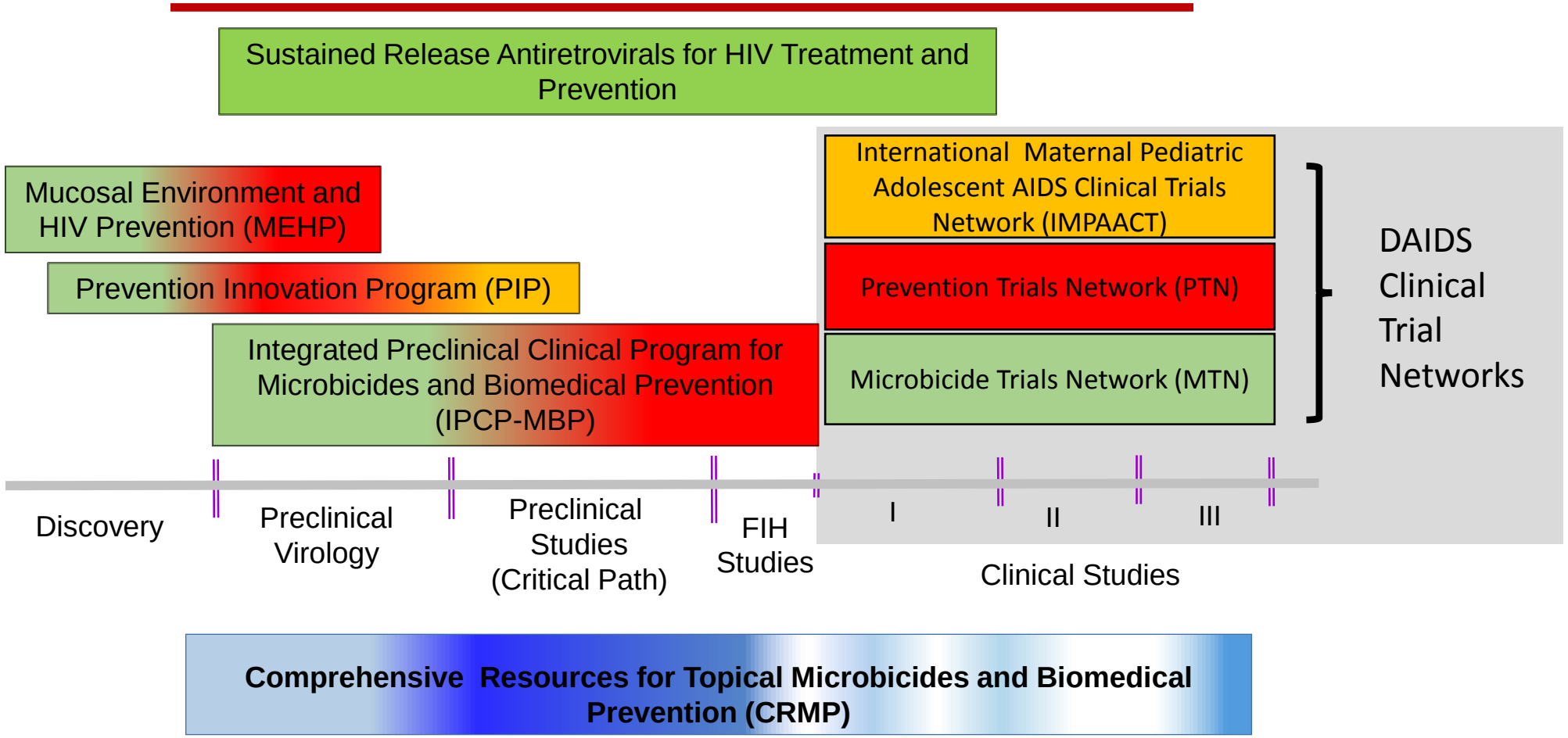
Academic and Small Business Investigators/Researchers
- Unsolicited grants (R01, R21, SBIRs)
- Grants to address specific research gaps (RFAs)

Microbicide Developers:
- International Partnership for Microbicides (IPM)
- CONRAD

Large Pharma:
- Merck/GSK/Shinogi
- Gilead
- Viiv Health Care

Small Pharma:
- Particle Sciences
- Imquest Biosciences
- Mapp Biopharmaceutical
- Intrucep

Selected Non-vaccine Biomedical Prevention Development Programs*



*Showing only those Programs housed in PMPRB

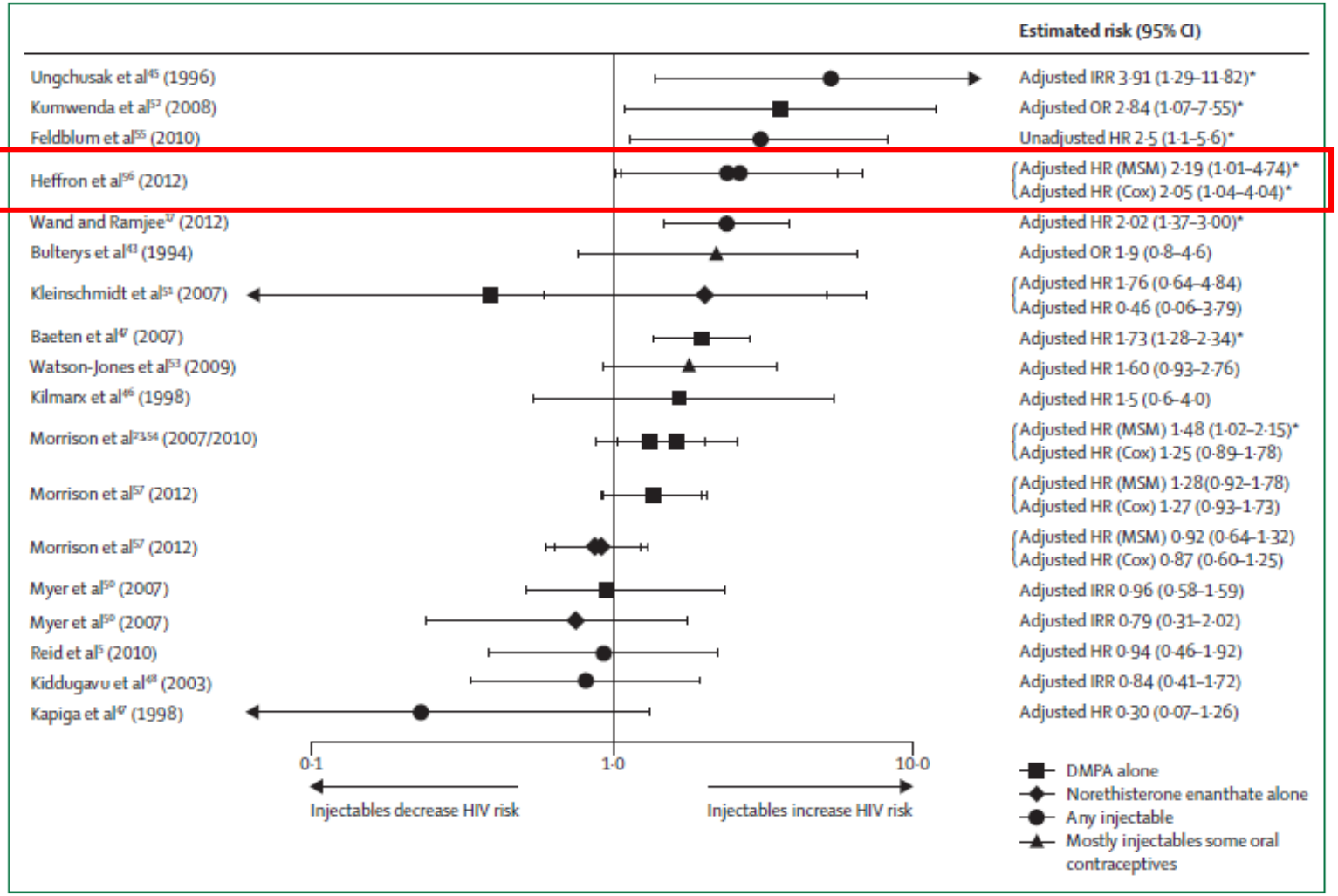
Background

Why are we interested in endogenous and exogenous hormones and their effect on the female genital tract?

Why the Concern about Contraceptive Hormones and HIV?

Heffron et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study, Lancet Infect. Dis. 2012 12:19-26

"Women should be counselled about potentially increased risk of HIV-1 acquisition and transmission with hormonal contraception, especially injectable methods."



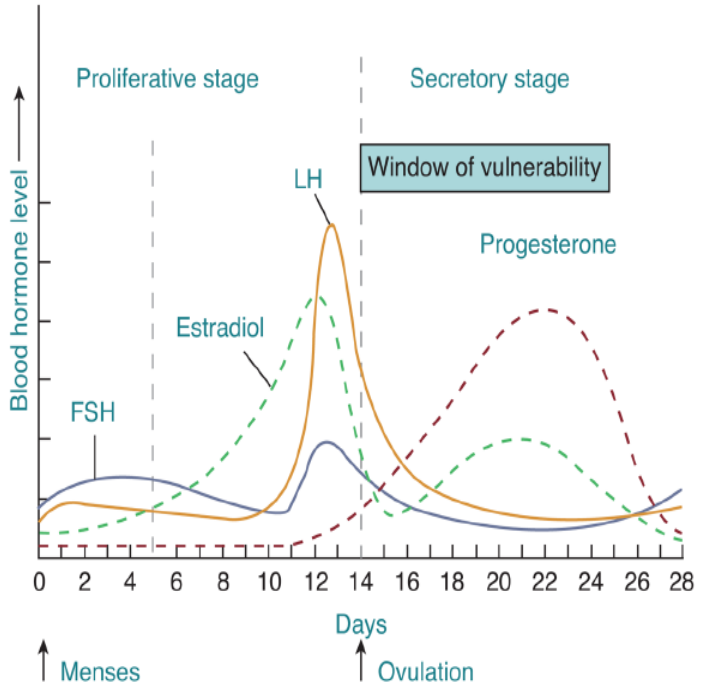
Polis and Curtis Lancet 2013 13:797

Number of recent prevention studies have done prospective cohort analysis for HIV/DMPA risk

Lancet HIV. 2015 2:e279
Microbicide Trials Network: VOICE Study
5 arms
Tenofovir and Truvada Gels and Pills 1x day
DMPA [aHR] 1·41
95% CI 1·06-1·89; p=0·02
HSV at enrollment [Ahr] 2.02

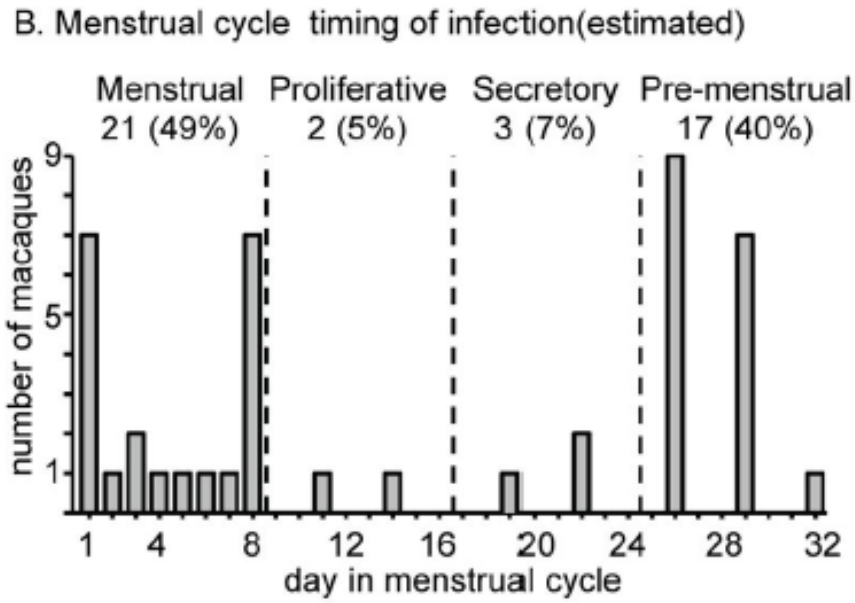
MTN actively working to increase the contraceptive mix at clinical sites

Menstrual Cycle and HIV Susceptibility



Wira and Fahey, AIDS 2008 22:1909

CDC



Kersh et al J. Med. Primatol. 2014 43:310

NOTE: Precise determinations of the *in vivo* timing virus infection are complicated by the lag between infection and the sensitivity of virus detection methods.

Multipurpose Prevention Strategies (MPT)

MPT: Contraceptive strategy either co-formulated or co-administered with another prevention strategy

The Initiative for Multipurpose Prevention Technologies (IMPT) http://www.cami-health.org/mpts/impt

Supports all forms of MPT development

Contraception combined with prevention for:

- HIV (HC/HIV)
- STIs e.g. Papilloma virus, Herpes Virus
- Vaccines
- Enhanced barriers: *Microbicide gel + diaphragm*

Activities

- Development of MPT Targeted Product Profiles (TPP)
- Coordinate funders
- Supports workshops
  - Clinical design
  - Regulatory
  - Implementation issues

Current status of HC/HIV MPTs

- CONRAD: Tenofovir/LNG IVR, Phase 1 nearing completion
- IPM: Dapivirine/LNG IVR, proposed Phase 1
- Population Council: IVR MPT in development

Critical issues in MPT development

- All one drug delivery system-Intravaginal Ring
- All using LNG
- Hormone and antiretroviral interactions
- Regulatory issues

Questions/Gaps from the Prevention Perspective

- What is the role of endogenous and exogenous hormones on:
  - HIV susceptibility,
  - PK and PD of prevention drug products.

- How do hormones (endogenous and exogenous) impact the male and female genital and GI tracts:
  - HIV target cells—activation state, migration and infection,
  - Adaptive and innate immunity to HIV,
  - Microbiome,
  - Wound repair and resolution?

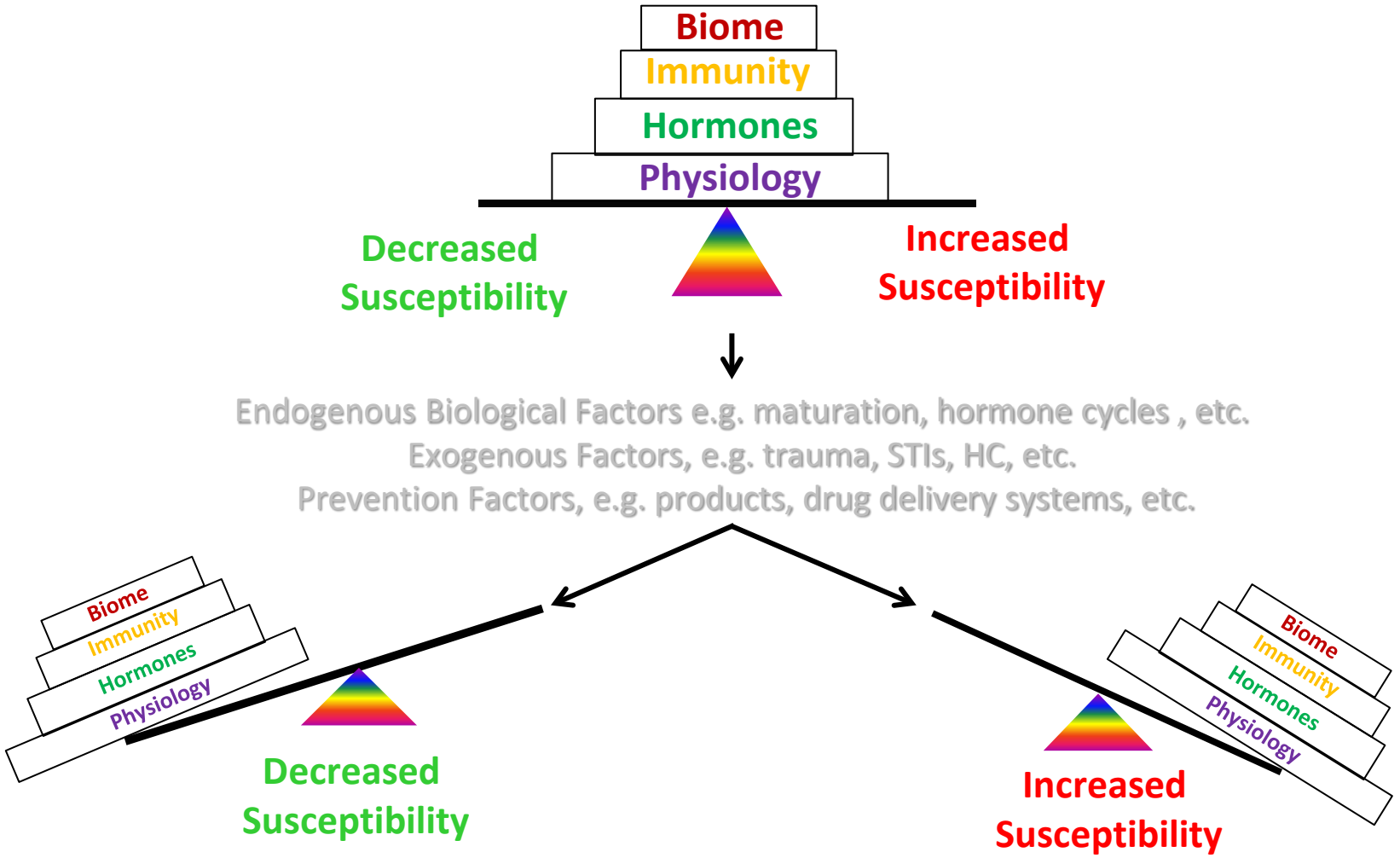
- How to best create a safe and effective HC/HIV MPT?

Approach

Hypothesis:
The potential for HIV infection in the genital and GI tract is controlled by multiple factors which in aggregate determine the overall degree of susceptibility to HIV infection, and understanding these factors will be critical to the development of safe and effective prevention products.

Conceptualizing the Hypothesis

What are the biological and physiological endogenous and exogenous factors that control HIV susceptibility, and if they modulate infection susceptibility do they impact the safety and/or the PK/PD relationship for the prevention product?



Funding Strategy

Year	Research Question	Initiative	Outcome
2012	How do reproductive health factors, especially hormones, impact HIV susceptibility?	NICHD: HIV Transmission/Acquisition through a better understanding of Reproductive Health	• Impact of hormones and contraceptives on: – FRT Immune Function – Drug PK – Timing of the infection event
2014	How do other endogenous and exogenous factors in addition to hormones impact HIV susceptibility and the safety and efficacy of prevention products	NIAID: Mucosal Environment and HIV Prevention (MEHP)	• HIV Susceptibility factors: – Inflammation – Microbiome – Immune system – Other factors • How hormones impact these factors
2016	How does age and anogenital injury impact HIV susceptibility and the safety and efficacy of prevention products?	**UPCOMING** NIAID: Risks of Age and Injury in HIV Susceptibility (RAIS)	• Impact on HIV susceptibility of – Maturation of the genital and GI tracts – Injury/trauma and healing – Role of hormones in these processes

Snap-shots

15 grants in portfolio addressing hormone and HIV interactions

WHAT FOLLOWS ARE:

Brief summaries of selected studies funded by NIAID under the following RFAs:

1. NICHD: HIV Transmission/Acquisition Through a Better Understanding of Reproductive Health,
2. NIAID: Mucosal Environment and HIV Susceptibility (MEHP), and
3. NIAID: Prevention Innovation Program (PIP) RFAs.

All studies are small and designed to provide proof-of-concept insights into hormone interactions with the female reproductive tract.

The highlighted studies are ongoing and in many cases have yet to publish results.

To see more go to NIH RePorter http://report.nih.gov/index.aspx

Chuck Wira: Dartmouth

Basic Research into the interaction of hormones with the Female Reproductive Tract

Estradiol acts directly on CD4+ T-cells and macrophages to reduce *in vitro* HIV-infection, not by reduction in CCR5 expression

Rodriguez-Garcia et al., Estradiol reduces susceptibility of CD4+ T cells and macrophages to HIV-infection. PLoS One. 2013.

Estradiol regulates nucleotidase enzyme expression and activity in epithelial cells and fibroblasts from the upper and lower FRT, but not in endothelial cells or blood CD4+T cells.

Shen Z, et al.,. Estradiol regulation of nucleotidases in female reproductive tract epithelial cells and fibroblasts. PLoS One. 2013

Intracellular Tenofovir diphosphate (TFV-DP) concentrations varies with cell type and location in the FRT.

Estradiol and/or progesterone regulate intracellular concentrations of TFV-DP in FRT epithelial cells and CD4+ T cells

Biswas et al., Effects of tenofovir on cytokines and nucleotidases in HIV-1 target cells and the mucosal tissue environment in the female reproductive tract. Antimicrob Agents Chemother. 2014.

Grant Title: Expression and activity of Tenofovir metabolizing enzymes throughout the female reproductive tract (FRT)

- Impact of MPA, LNG and NET on intracellular tenofovir-diphosphate levels
- Effect on activity/expression of adenylate kinase and phosphatases responsible for degradation

Sharon Achilles: Magee Womens/U. Pitt.

Grant Title: Quantification of Immune Cells in Women Using Contraception

Goal: Understand the Impact of Hormonal Contraceptives on the Female Genital Tract

CHIC II (N=50/group) (NIH)

- Control (condoms)
- COC
- DMPA
- LNG-IUD (Mirena)
- Cu-IUD
- ENG-IUD (Nexplanon, BMGF)

Zim-CHIC (N=50/Group) (BMGF)

- DMPA
- Net-EN
- MPA/E2
- LNG-IUD
- ENG-IUD
- Cu-IUD

Study Visits: Pre-initiation, 3 months, 6 months

Collecting: Fluids (sponge , CVL), cytobrush, cervicovaginal and endometrial biopsy (U.S. only) and plasma

Endpoints:

- Immune cells –presence and activation status by flow cytometry
- Endogenous and exogenous hormone concentrations in blood, fluids and tissues by UPLC/MS/MS and RIA
- Anti-HIV activity in CVL
- Innate immunity factor expression
- Changes in the microbiome

Allison Quayle: Louisiana State Univ. Health Sciences Center

Grant Title: Prevention of HIV transmission/acquisition through informed contraceptive choice

Hypothesis: Progestin glucocorticoid receptor (GR) cross-talk may correlate with immune activation, cervical mucous composition and epithelial/tissue barrier changes which may be associated with changes that increase susceptibility to HIV infection.

N=60
- 20 NuvaRing
- 20 DMPA
- 20 LNG IUD

Samples
- PBMC,
- CVL,
- Explant,
- Plasma.

Endpoints:
- Endocervical concentration of progestins (RIA),
- Numerical, phenotypic and activation state changes in the endocervical leukocyte repertoire,
- Determine the effects of MPA and LNG on:
  - Virus trapping by endocervical mucus,
  - Innate Immunity factor expression,
  - Anti-HIV activity of endocervical secretions,
  - Epithelial cell barrier integrity—impact of cervical secretions on Trans-epithelial resistance (in vitro).

Craig Hendrix: Johns Hopkins University

Grant Title: The effect of Depo-Provera on HIV susceptibility, immune activation, and PrEP PK

Hypothesis:
MPA increases HIV susceptibility by immune activation and HIV co-receptor expression on genital tract target cells.

MPA decreases effective Truvada (TDF/FTC) concentrations through upregulation of hormonally-sensitive drug transporters on CD4+T and kidney cells as well as alteration of drug phosphorylation and activation in CD4+T cells.

N=20
PBMC, CVL, Plasma and Biopsy

Will determine if MPA impacts the blood and cellular concentrations of tenofovir and FTC concentrations by:

1) Increasing glomerular filtration rate,
2) Increasing tubular secretion through upregulation of membrane transporters,
3) Reducing phosphorylation and activation of TFV and/or FTC, and/or
4) Changing intracellular kinase expression.

Karen Smith-McCune: University of CA

Grant Title: Reproductive Tract Effects of the Intrauterine Device: Implications for HIV Risk

Hypothesis: The IUD acting as a foreign body may result in changes in the upper FRT that increase susceptibility to HIV-1 infection.

6 to 18 months after initiation (N=15/group)

- LNG-IUD
- Cu-IUD
- LNG-containing oral contraceptive (OCs);
- Control

Samples

- Cytobrush,
- CVL,
- Endocervical wick,
- Cervical and endometrium biopsy,
- Blood

Endpoints:

- The inflammatory changes attributable to the presence of the IUD.
  - Cytokines/Chemokines /innate factors,
  - Transcription profiling.
- Flow Cytometry –Cell types, numbers and activation,
- Resistance to HIV infection (*in vitro*) of cervical and endocervical mononuclear cells,
- Pyroptosis: Caspase 1 activation and IL-1β and IL-18 secretion in cells and biopsies.

Summary

NIAIDs funded activities are laying the ground work for developing an understanding of the interaction of endogenous and exogenous hormones with the female genital tract in the context of susceptibility to HIV infection.