

# The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial: Rationale, Summary of Primary Results & Lessons Learnt

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*on behalf of the ECHO Consortium*

*MTN Regional Meeting, Cape Town, South Africa  
10<sup>th</sup> September 2019*



The ECHO Trial  
is dedicated to the memory of

# Dr. Ward Cates

1942 - 2016

President – Research

FHI 360



Ward would have loved to see the data!

# Outline

## Why we conducted the ECHO trial

- Observational data on hormonal contraceptive and HIV risk
- Biological plausibility

## What we learnt

- HC and HIV risk
- Contraceptive safety and pregnancy outcome
- Clinical data on immune markers and genital microbiome

changes with use of contraceptives in the ECHO trial

## Implications for women globally

# Starting point

Safe and effective  
contraception is essential to  
the health and development  
of women, children and  
communities worldwide



# Context

- Women represent over half of the 37 million persons currently living with HIV; nearly 600,000 new HIV infections occur yearly among adolescent girls and women in Africa.
- Modern contraceptive methods are used by >700 million women worldwide, including >58 million African women.
- Use of these methods substantially improves the health of women and children by averting unintended pregnancy and sequelae and contributes to women's empowerment and to economic and social development.

# 30 years of unresolved questions

## Progesterone implants enhance HIV transmission and early viral load

PRESTON A. MARX<sup>1,2</sup>, ALEXANDER I. SPIRA<sup>1,2</sup>, AGEGNEHU GETTIE<sup>1,2</sup>, RONALD S. VEAZEY<sup>4</sup>, AND LEE E. CLAYTON<sup>1,2</sup> PLOS MEDICINE

RESEARCH ARTICLE  
Hormonal Contraception and HIV Acquisition: A Meta-analysis

Charles S. Morrison<sup>1\*</sup>, Preston A. Marx<sup>1,2</sup>, Angela M. Crook<sup>6</sup>, Lut Van der Pol<sup>3</sup>, Barbara A. Friedland<sup>9</sup>, Richard A. Ismail<sup>10</sup>, Abdool Karim<sup>10</sup>, Stephanie Sheena McCormack<sup>4</sup>, Nuala M. Martin<sup>11</sup>, Straten<sup>15</sup>, Deborah Watson<sup>16</sup>, Nicola Low<sup>18</sup>



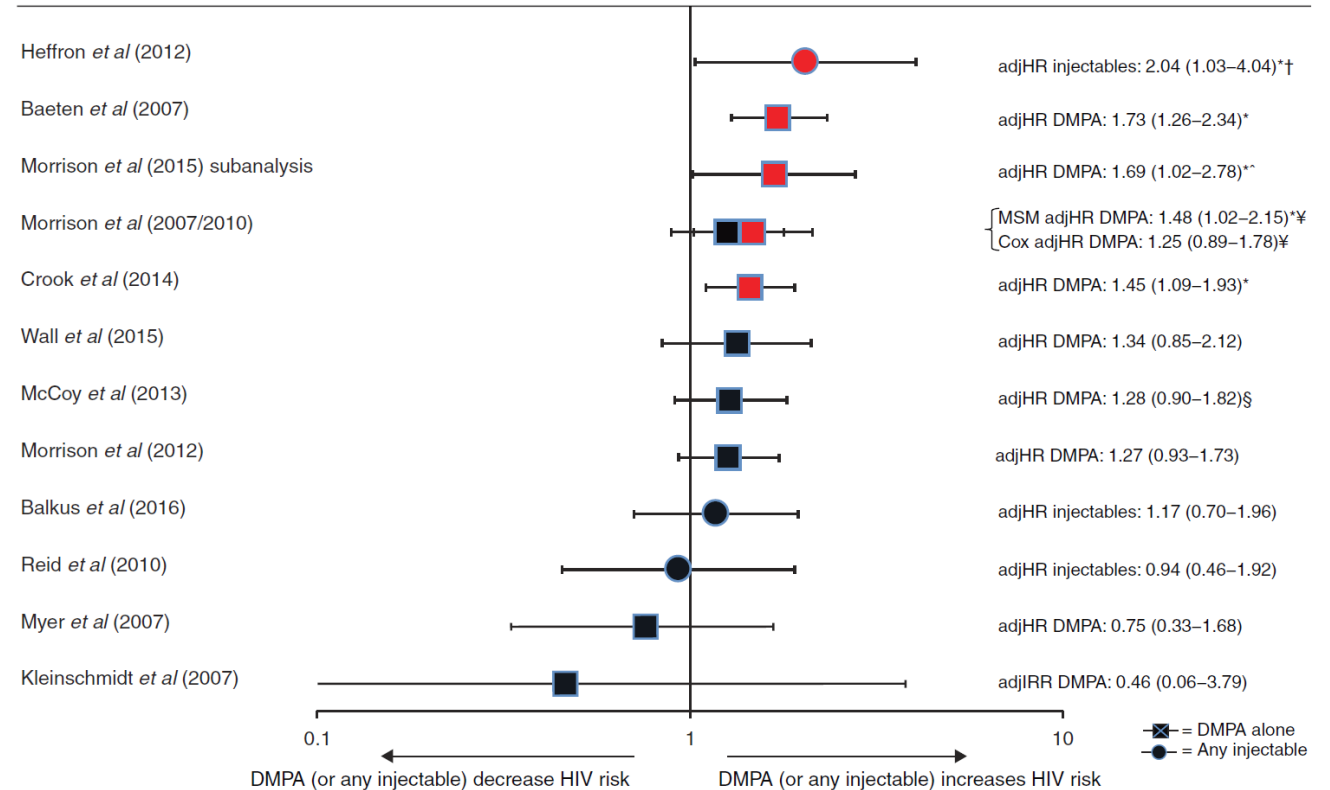
Statement on the Heffron et al study on the safety of using hormonal contraceptives for women at risk of HIV infection

October 2011



# Prior evidence

- 30 years of epidemiologic and laboratory studies have tried to determine whether there is truly increased risk of HIV acquisition associated with use of hormonal contraception.
- Some studies showed that progestin-only injectables, particularly the intramuscular injectable depot medroxyprogesterone acetate (DMPA-IM), were linked to increased HIV risk, but other studies did not show this result.
  - Some studies showed a doubling of HIV risk; in meta-analyses, the magnitude was approximately 40-50% (i.e., hazard ratios of 1.4-1.5)



# **Biological Plausibility for Increased HIV Risk with use of Hormonal Contraceptives**

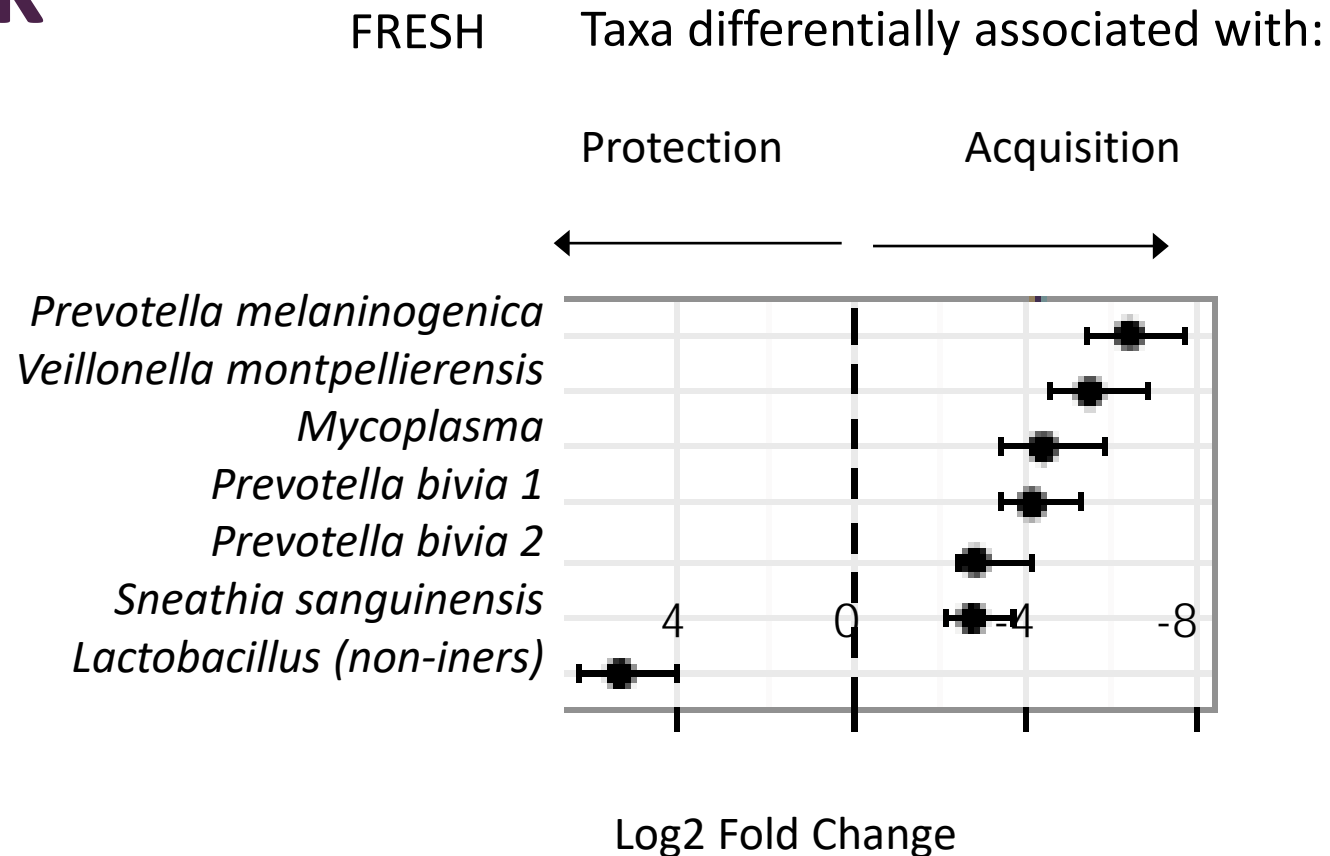
Slides courtesy Renee Heffron



# Possible biological mechanisms through which DMPA increases HIV risk

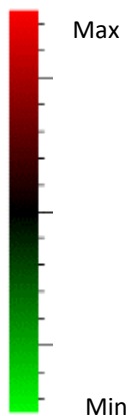
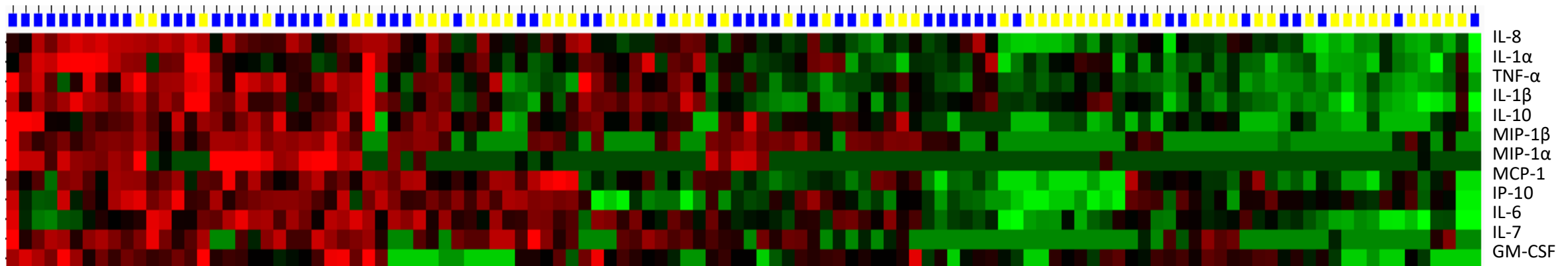
- Alterations in microbiota
- Increasing inflammation
- Alterations in frequency and activation status of HIV target cells
- Alterations in mucosal barrier integrity
- Decreased antiviral immunity
- Glucocorticoid receptor related immune changes

# Relative abundance of vaginal microbiota and HIV risk



# Inflammation and HIV risk

CAPRISA 004: KZN South Africa

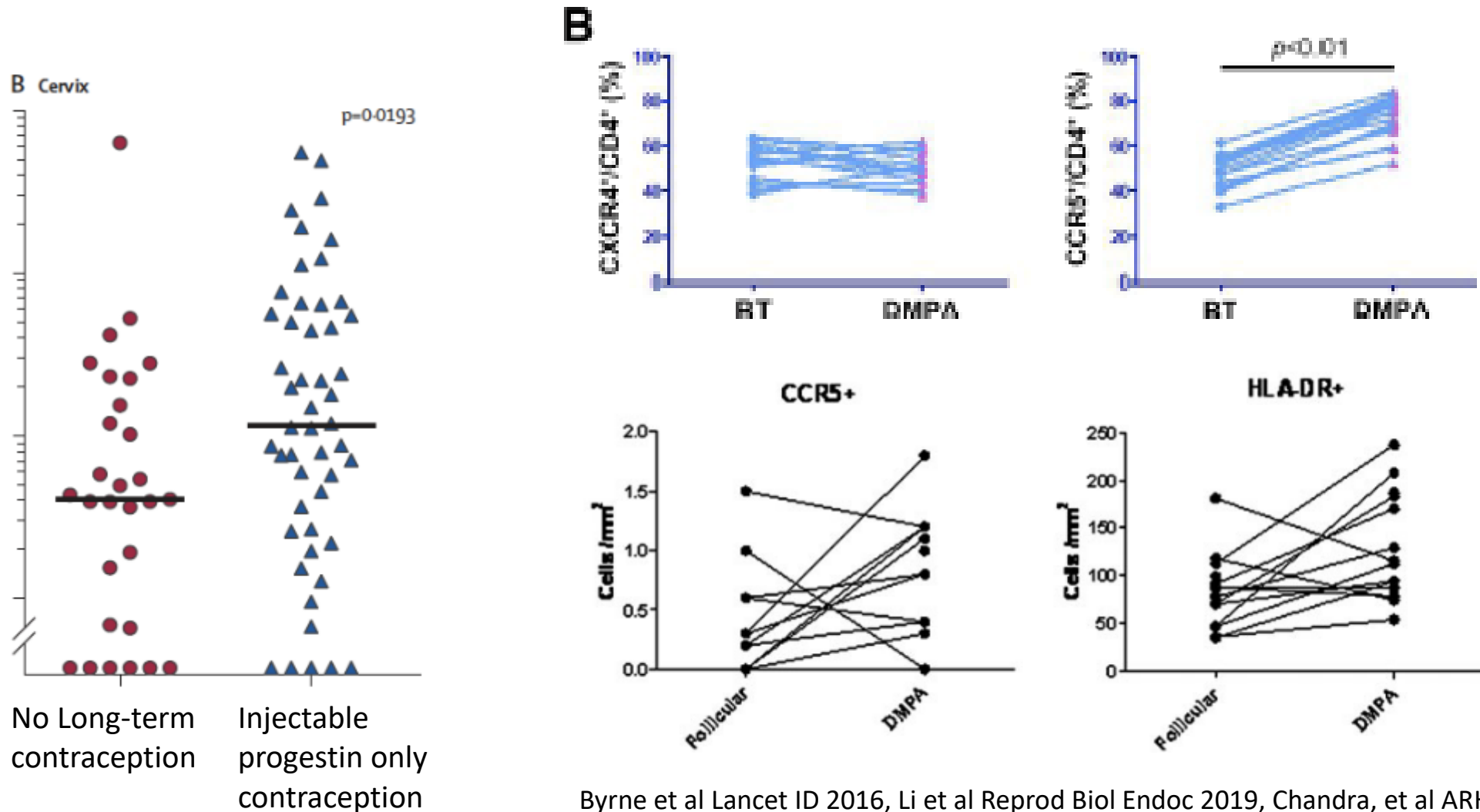


■ Later became HIV-infected (n=58)

■ Remained HIV-uninfected (n=58)

**Women who later became HIV-infected had pre-infection genital inflammation**

# Data from cross-sectional or observational studies exploring mechanisms through which HC may increase HIV risk: target cells



# Women's right to know

- Women need to know whether certain contraceptives increase their chances of getting HIV. This information will help them make informed choices about which contraceptive they want to use and which HIV prevention methods they need.



**A randomised trial provides the highest quality evidence to enable women to make fully informed choices, inform clear counselling messages for clinicians, and offer guidance for policymakers and programs.**

# ECHO

- ECHO was a multicentre, open-label, randomised clinical trial comparing HIV incidence and contraceptive benefits in women living in areas of high HIV incidence and using one of three highly-effective, licensed contraceptive methods:
  - intramuscularly-delivered depot medroxyprogesterone acetate (DMPA-IM)
  - a copper intrauterine device (IUD)
  - and a levonorgestrel (LNG) implant



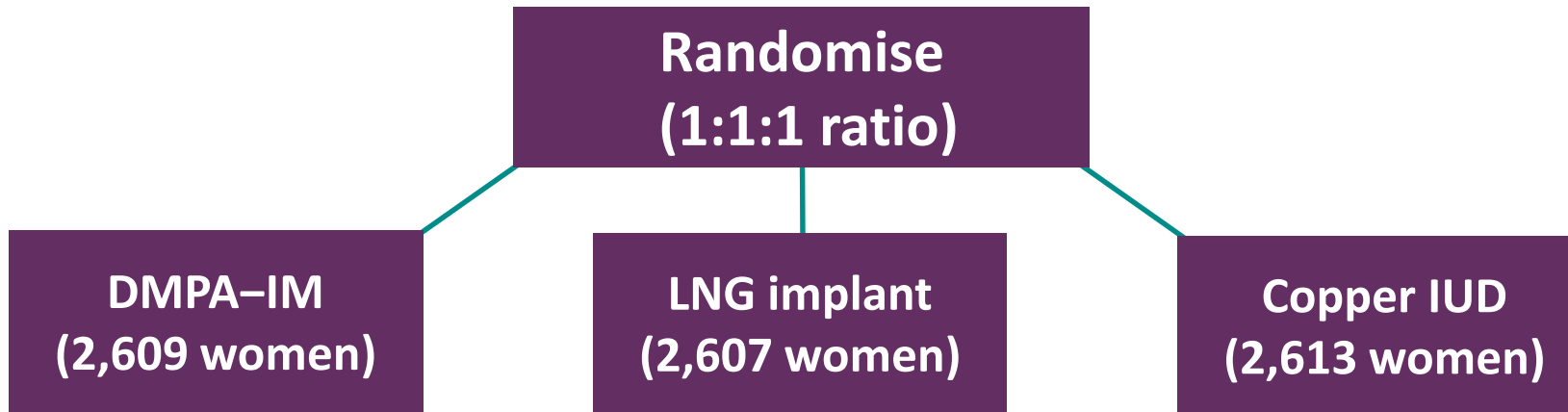
# ECHO

- **The primary objective was to compare HIV incidence among women randomised to DMPA-IM, a copper IUD, or an LNG implant.**
- Secondary objectives included comparison by randomised method of rates of pregnancy, contraceptive method continuation, and serious adverse events and adverse events leading to method discontinuation.
- The trial began in December 2015 and concluded in October 2018.



# ECHO study design

7 829 women ages 16-35 desiring contraception and willing to be randomised



3-monthly visits for up to 18 months



# Number of women who took part in the study per country

<b>Eswatini</b> <b>502</b>	<b>Kenya</b> <b>901</b>	<b>South Africa</b> <b>5 768</b>	<b>Zambia</b> <b>658</b>
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# Who enrolled in ECHO?



Average age 23 (range 16-35)



Most (81%) were not married

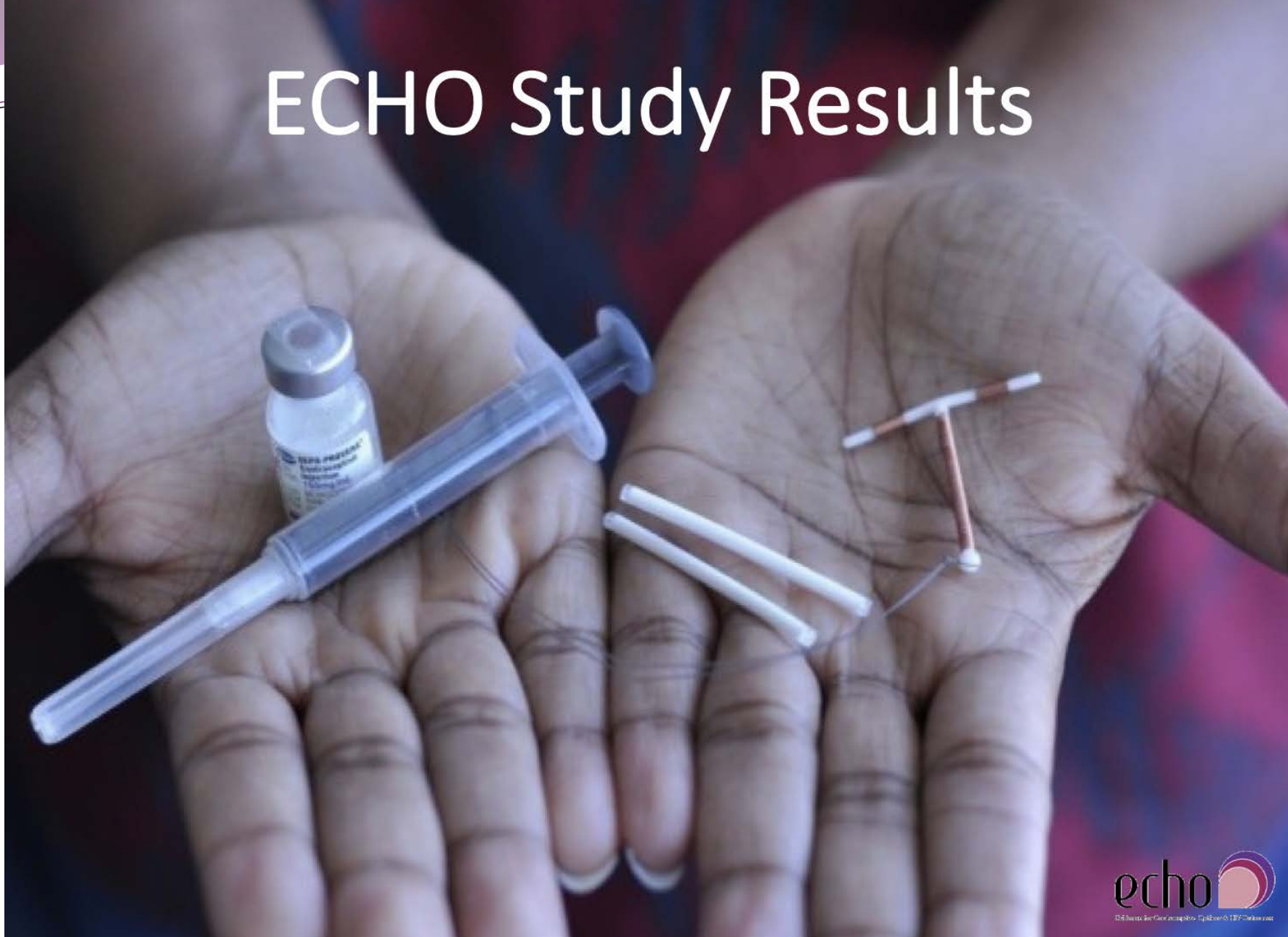


Only about 7% reported >1 partner in the prior 3 months



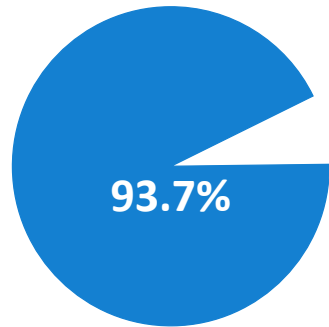
Nearly half did not use a condom with their last sex act

# ECHO Study Results

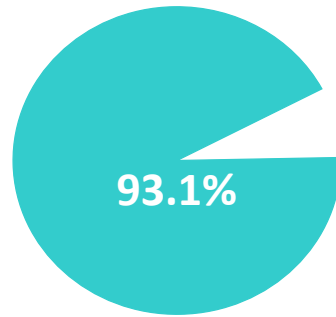


# How well did women use their contraceptives ?

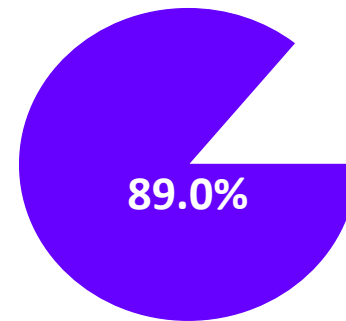
- Participants used their methods for 92% of the time they were in the study
- The percentage of time spent using an assigned method was high for all three contraceptives



**LNG implant**



**DMPA-IM**



**Copper IUD**



# Results: Rate of new HIV infections

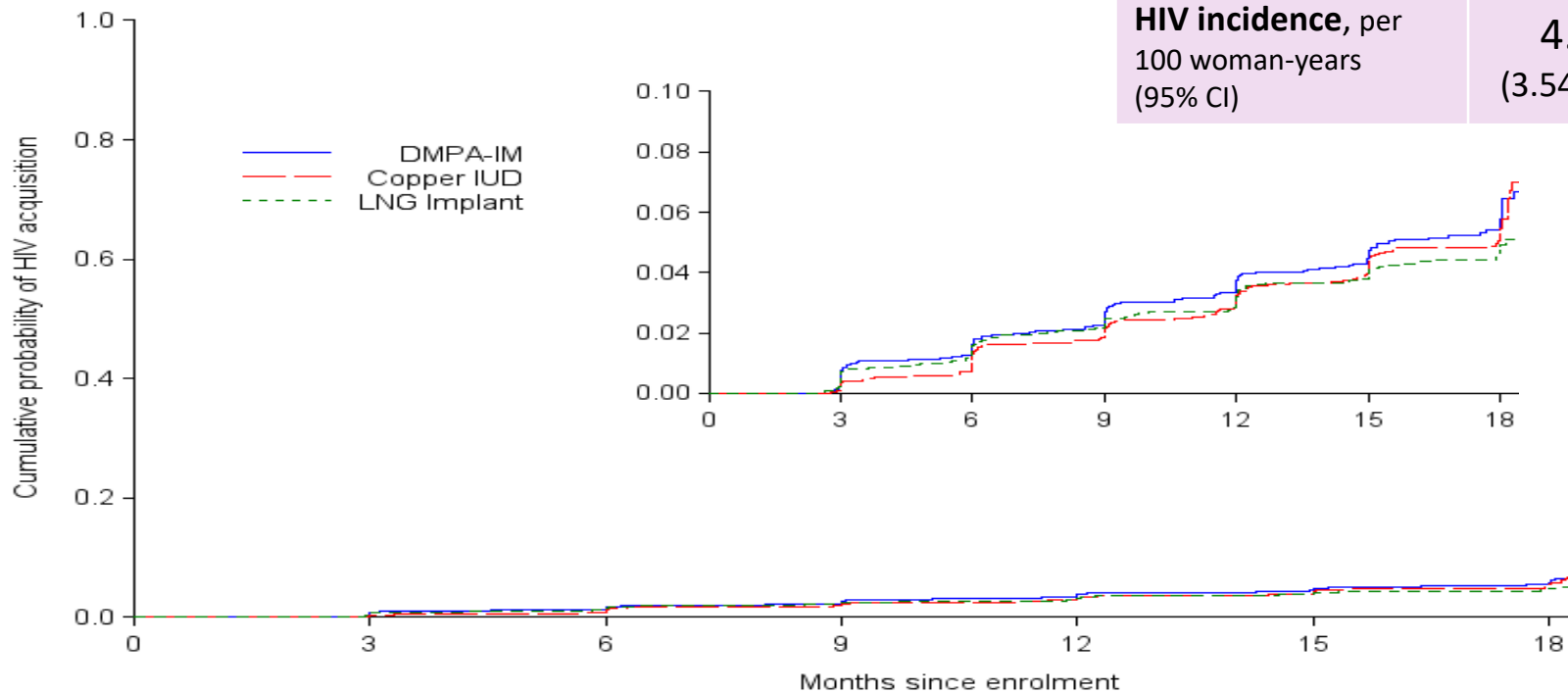


- The overall rate of new HIV infections per year was high: 3.8%.
- In total, **397 of the 7 829** women became HIV positive during the study

# HIV incidence

## Intention-to-treat analysis

	DMPA-IM	Copper IUD	LNG Implant
# HIV infections	143	138	116
HIV incidence, per 100 woman-years (95% CI)	4.19 (3.54-4.94)	3.94 (3.31-4.66)	3.31 (2.74-3.98)



No. at risk	0	3	6	9	12	15	18
DMPA-IM	2556	2555	2478	2412	2341	2077	1595
Copper IUD	2571	2571	2539	2492	2440	2158	1656
LNG Implant	2588	2587	2534	2484	2442	2166	1670

# HIV incidence – South Africa (post hoc)

Intention-to-treat analysis			
	DMPA-IM	Copper IUD	LNG Implant
# HIV infections	124	118	103
HIV incidence, per 100 woman-years (95% CI)	4.94 (4.11-5.89)	4.58 (3.79-5.49)	4.02 (3.28-4.87)

DMPA-IM vs. Copper IUD	DMPA-IM vs. LNG Implant	Copper IUD vs. LNG Implant
HR = 1.05	HR = 1.19	HR = 1.13
96% CI = 0.82-1.36	96% CI = 0.91-1.55	96% CI = 0.87-1.47
p = 0.69	p = 0.20	p = 0.37

# Pregnancy

## Primary intention-to-treat analysis

	DMPA-IM	Copper IUD	LNG Implant
# Pregnancies	61	116	78
Pregnancy incidence, per 100 woman-years	1.75	3.27	2.19

## Continuous use analysis

	DMPA-IM	Copper IUD	LNG Implant
# Pregnancies	18	35	21
Pregnancy incidence, per 100 woman-years	0.61	1.11	0.63

- Pregnancy rates were low, in all three groups, and most pregnancies (71%) occurred among women who had previously discontinued their randomised method.
- All methods had high contraceptive effectiveness – the two hormonal methods had lower pregnancy rates than the IUD.



# Safety

- Serious adverse events were rare across all groups
- Adverse events that resulted in method discontinuation were relatively uncommon (7% of women overall) and more common among women randomised to the copper IUD or LNG implant compared to DMPA-IM

	DMPA-IM	Copper IUD	LNG Implant
SAE	49 (1.88%)	92 (3.53%)	78 (2.99%)
AE resulting in method discontinuation	109 (4.18%)	218 (8.36%)	226 (8.65%)

# Results: Pregnancy prevention and safety

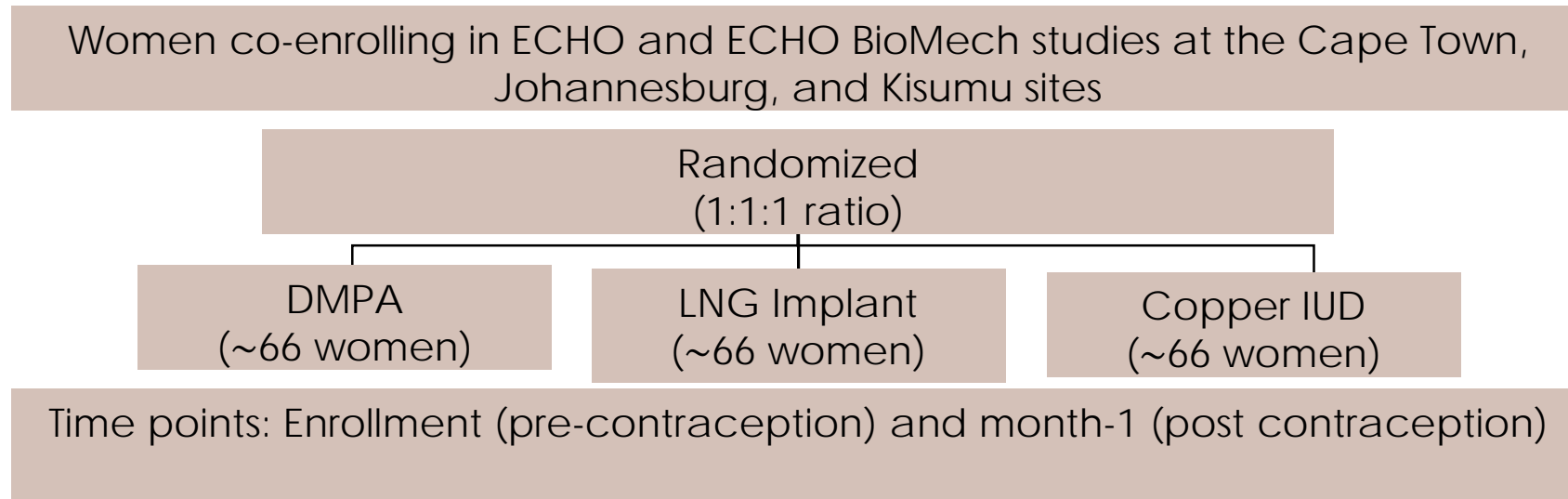
- All three methods were safe and highly effective in preventing pregnancy
- When women were using their contraceptive method, only about 1%, or 255, of 7829 participants became pregnant over one year.
- Most pregnancies (71%) happened after women stopped using their contraceptive method.

# Biological Mechanism Study Data

- Slides presented are courtesy of Renee Heffron and the ECHO Mechanism Study Team

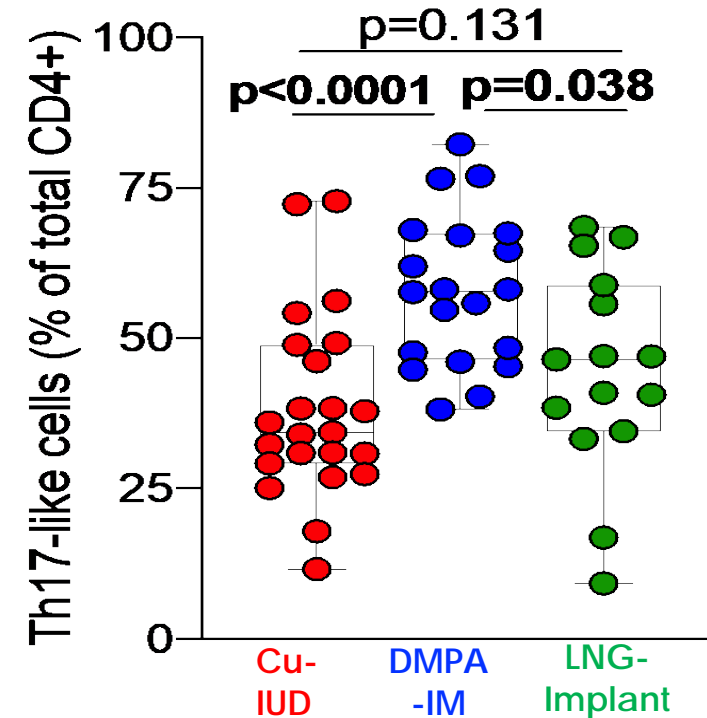
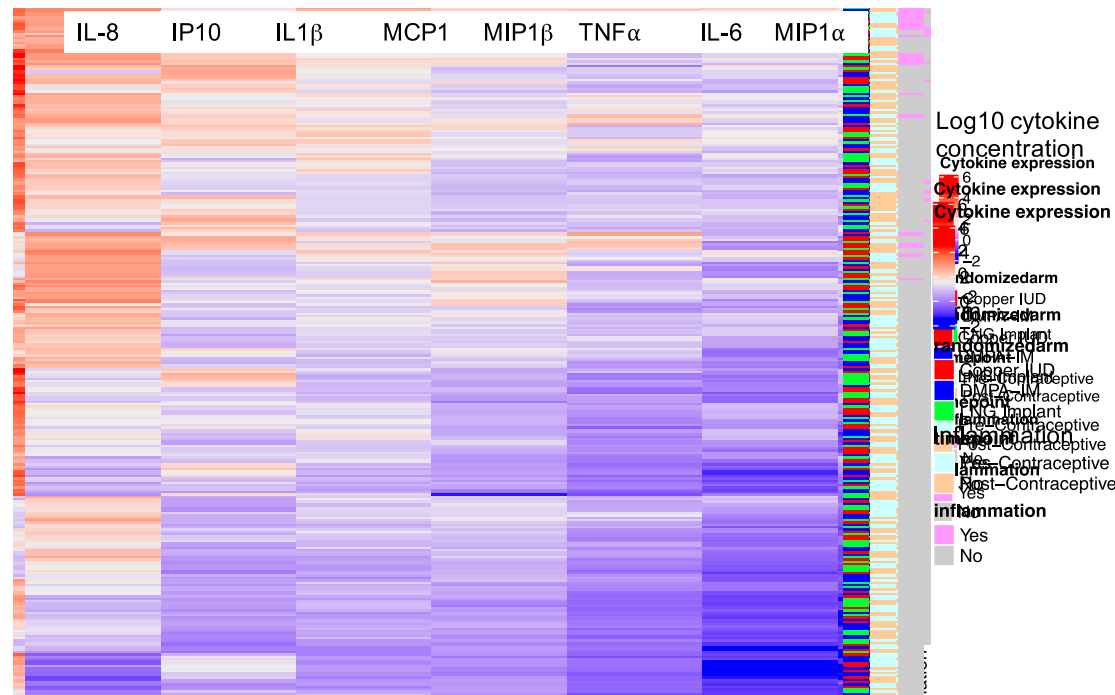
Heather Jaspan, Rubina Bunjun, Bryan Brown, Ramla F Tanko, Maricianah Onono, Gonasagrie Nair, Thesla Palanee-Phillips, Caitlin Scoville, Kate Heller, Shameem Jaumdally, Smritee Dabee, Hoyam Gamiieldien, Jared M. Baeten, Steven E Bosinger, Adam Burgener, Jo-Ann Passmore, Renee Heffron

# Contraceptive-induced changes in genital tract HIV-1 cellular targets and microbiota among women enrolled in the ECHO trial



- **Microbiome** V3-V4 16S rRNA gene sequenced using 300bp PE chemistry on Illumina MiSeq
- **Cytokines** Luminex used to measure concentrations of 27 cytokines (inflammatory, adaptive, chemokines, growth factors, regulatory)
- **HIV cellular targets** Cells from cervical cytobrushes were stained ex vivo for CD4 T cell frequencies, activation, coreceptor expression, including Th17-like cells

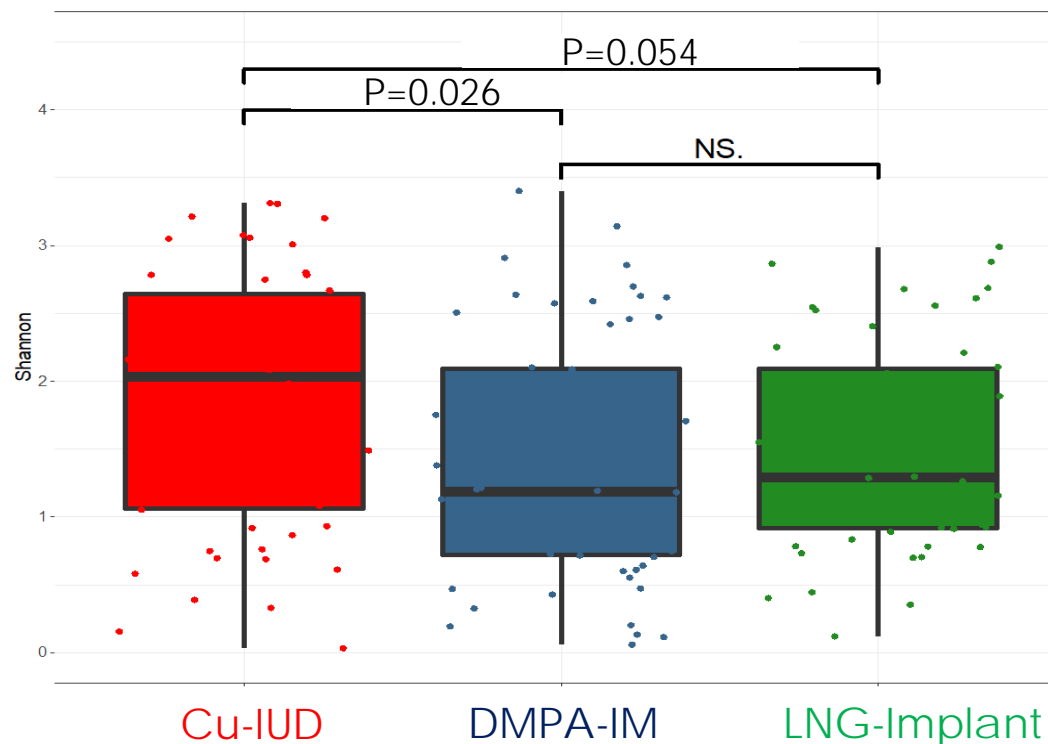
# Changes in HIV cellular targets and inflammation induced by contraceptive initiation



- No change in genital inflammation post-contraception
- DMPA-IM caused a significant increase in Th17-like cells

# Changes in vaginal microbiota induced by contraceptive initiation

- Copper IUD caused an increase in vaginal alpha diversity
  - significant portion of the inter-sample variation, with diverse anaerobic communities being more prevalent among women assigned to Copper IUD



Conclusion: Despite finding no significant differences in HIV-1 incidence across arms, we found differences in HIV-1 target cells and vaginal microbiota that may have implications for women's health globally

# Summary of primary ECHO results

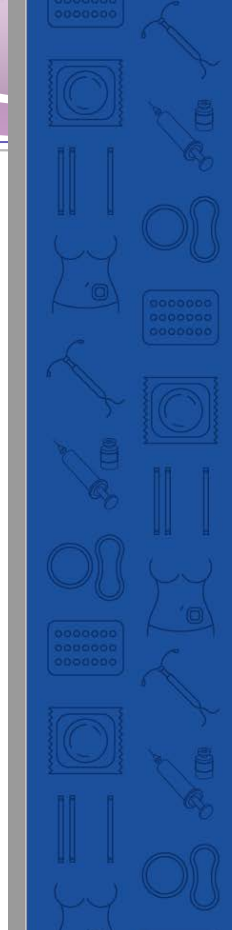
- Evidence on rates of HIV acquisition between the 3 different methods was reassuring
- High level of HIV incidence among study participants
- Contraceptive methods; DMPA-IM, the LNG implant and the copper-IUD are safe and highly effective methods of contraceptive



# WHO guidance statement 2019

## Recommended for women at risk of HIV infection

## Eligible to use DMPA, Cu-IUD and LNG-Implant contraceptive methods without restriction



## Contraceptive eligibility for women at high risk of HIV

Guidance statement

Recommendations on contraceptive methods used by women at high risk of HIV

WHO has released [New Recommendations for Contraception for Women at High Risk of HIV](#). Key messages, the WHO Press Release, and a link to a Webinar outlining the Guideline Review Process and Recommendations can be accessed from the links below.

### Key Messages:

- **A woman's risk of HIV does not restrict her contraceptive choice**
  - **Women at a high risk of HIV infection are eligible to use all progestogen-only contraceptive methods without restriction** (MEC Category 1), including progestogen-only pill (POPs), intramuscular and subcutaneous depot medroxyprogesterone acetate (DMPA-IM and DMPA-SC), norethisterone enanthate (NET-EN), levonorgestrel (LNG) implants and etonogestrel (ETG) implants.
  - **Women at a high risk of HIV infection are eligible to use copper-bearing intrauterine devices (Cu-IUDs) and LNGIUDs without restriction** (MEC Category 1). In considering the use of IUDs, many women at a high risk of HIV are also at risk of other sexually transmitted infections (STIs); for these women, providers should refer to the MEC recommendation on women at an increased risk of STIs, and the [Selected practice recommendations for contraceptive use: third edition](#) on STI screening before IUD insertion.
  - **Women at a high risk of HIV infection are eligible to use all combined hormonal contraceptive methods without restriction** (MEC Category 1), including combined oral contraceptives (COCs), combined injectable contraceptives (CICs), combined contraceptive patches and combined vaginal rings.
- **Efforts to expand contraceptive method options and ensure full and equitable access to family planning services must continue.**
- **A renewed emphasis on HIV/STI testing and prevention services** is urgently needed, including the **integration of family planning and HIV/STI services** as appropriate, along with sexual and reproductive health packages.
  - \*Note: IBP and the SRHR Linkages Group will be hosting a webinar on *Thursday September 12<sup>th</sup> at 9amEST/3pmCEST on Accelerating SRHR and HIV Service Delivery Integration*. [Register here:](#)



# Conclusions

- Women in Africa continue to be at unacceptably high risk of HIV infection and of unplanned pregnancies.
- There is an urgent need to strengthen HIV prevention interventions, including the access to use of PrEP.
- More efforts should be made to integrate HIV prevention and contraceptive services.



# More ECHO results

- **Comparison of pregnancy incidence** in an randomized trial of DMPA-IM, LNG-implant and copper-IUD: Maricianah Onono
- **Contraceptive-induced changes in genital tract HIV-1 cellular targets** and microbiota among women enrolled in the ECHO trial: Heather Jaspan
- **High HIV incidence among young women in South Africa:** data from the ECHO trial: Tesla Palanee-Phillips
- **Integrating oral PrEP delivery** into a large HIV endpoint-driven clinical trial in Eastern and Southern Africa: the ECHO trial experience: : Ivana Beesham
- **Risk of sexually transmitted infections** among women randomized to DMPA-IM, the copper IUD, and levonorgestrel implant in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial: Jen Deese
- **Early relative effects** of intramuscular depot medroxyprogesterone acetate, a copper intrauterine device and the levonorgestrel implant **on HIV disease progression:** results from the ECHO Trial: Charles Morrison

# Acknowledgement



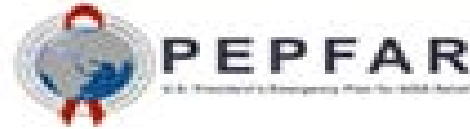
- Each of the 7829 women who participated in the ECHO trial
- 12 amazing clinical trial sites personnel
- Dedicated operations team
- Team of five management committee members
- Global Community Advisory Group
- Donors
- Audience for your attention

# ECHO Trial Consortium



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GATES foundation



Republic of South Africa

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