



# THE EVIDENCE FOR CONTRACEPTIVE OPTIONS AND HIV OUTCOMES 'ECHO' TRIAL

## Rationale and Proposed Way Forward for the ECHO Trial

8<sup>th</sup> INTEREST Workshop  
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Lusaka, Zambia

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# FULL TITLE

- A Multi Center, Open-Label, Randomised Clinical Trial *Comparing HIV Incidence and Contraceptive Benefits* in Women using Progestin-Only Injectable Contraceptives and Copper Intrauterine Devices (IUDs)



# DISCLOSURE

- Seed funding for proposal development from BMGF
- Proposal still in development, with consultation ECHO consortium, funders, scientific reviewers, community advocates





# The ECHO Consortium

- is composed of multiple organizations providing complementary expertise with wide representation committed to **one team one study**

# Presentation outline

- RCT to be ethical requires a state of equipoise
  - Justification for the Trial
  - What if there is no RCT?
- Outline of study design
- Is the trial feasible and can it be conducted ethically
  - Potential Challenges



# Inconsistent Observational Evidence

- **Ambiguity in current evidence with inconsistency in results**
  - ✓ Majority of studies are secondary analyses, not designed to assess HC/HIV risk<sup>2</sup>
    - *Comparison Groups Have Different HIV Risk Exposure*
    - *Uncertainty In HC Exposure*
    - *Uncertainty In Outcome (HIV Incidence) Relative To HC Exposure*
- **Randomization to contraceptive method and a well conducted clinical trial would take care of these limitations**



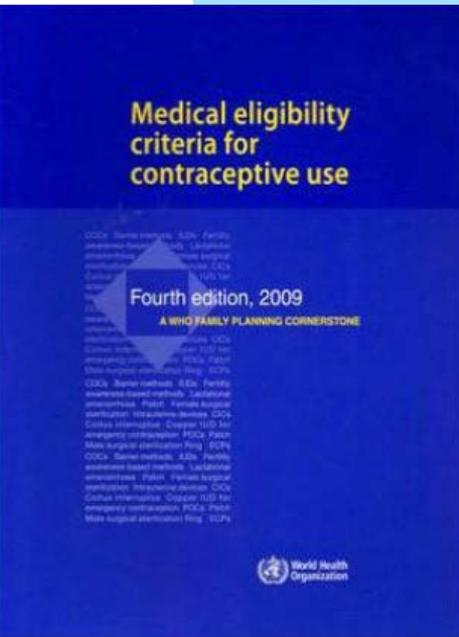
# DMPA Use Across Clinical Trials

Trial	DMPA Use as Percentage of Contraceptive Users
PARTNERS/HSV	73%
CAPRISA 004	93%
MDP 301	71%
FEM-PrEP	69%
VOICE	75%
PARTNERS/PrEP	78%

Minimal data on other contraceptive methods  
& HIV Risk from secondary data analysis



# Why Consider A Randomized Clinical Trial?



- HIV and reproductive health are crucial issues of public health importance
  - Women of reproductive age are in great need for family planning and at highest risk for HIV infection
- The primary reason to consider a randomized clinical trial is to provide evidence for public health practice decisions
- Current global and national policies call for obtaining high-quality evidence



# Feedback From Policy Makers

- **Family Planning Knowledge Sharing Meeting, held in Nairobi Sept 2013**
  - **Participants**
    - ✓ Policy makers mostly government
    - ✓ Family planning NGO
    - ✓ Ethiopia, Zambia, Malawi, South Africa, Eritrea, Sudan, Kenya, DRC, Uganda, Tanzania, Madagascar



# Feedback From Policy Makers

- Family Planning Knowledge Sharing Meeting, held in Nairobi Sept 2013
- **General Consensus**
- On review of systemic review of data
  - ✓ None of the countries felt there was sufficient evidence to change guidelines
  - ✓ General concern regarding risk on fragile family planning programs already challenged with low usage
- There was a general sense of protecting methods and preserving vulnerable young programs

# The Voice Of Civil Society

- ECHO civil society consultation meeting:  
Jo-burg Sept 2013 & AVAC Meeting Kampala
- ✓ Is it ethical to conduct this study with current evidence of risk?
  - Should women be randomized to DMPA? (equipoise)
  - Why not expand method mix and remove DMPA from our shelves?



**ECHO**

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  - Should women be randomized to DMPA? (equipoise)
  - Why not expand method mix and remove DMPA from our shelves?
- ✓ Is this study feasible?
  - Will women accept randomization to contraceptive methods?
- ✓ One HIV infection is one too many



**ECHO**

# What If No RCT?

- Observational evidence might remain inconclusive
- Counseling messaging could continue to be challenging for providers, policymakers, and family planning clients
- If HIV risk exists, unnecessary infections will occur
- If HIV risk does not exist, DMPA use (and possibly other hormonal methods) may be discontinued in some settings with negative consequences for maternal and infant morbidity/mortality

# HC-HIV RT: Overall ECHO Study Goal

To answer the public health question of the relative **risks** (HIV acquisition) and **benefits** (pregnancy prevention) of 3 commonly-used, highly effective contraceptive methods among women seeking family planning services



# HC-HIV RT: Primary Objective

To compare the relative risks of HIV acquisition between women randomised to DMPA, copper IUDs and *NET-EN or Implants\**



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Discussion on going whether to include NET-EN or Implants

# Secondary Objectives

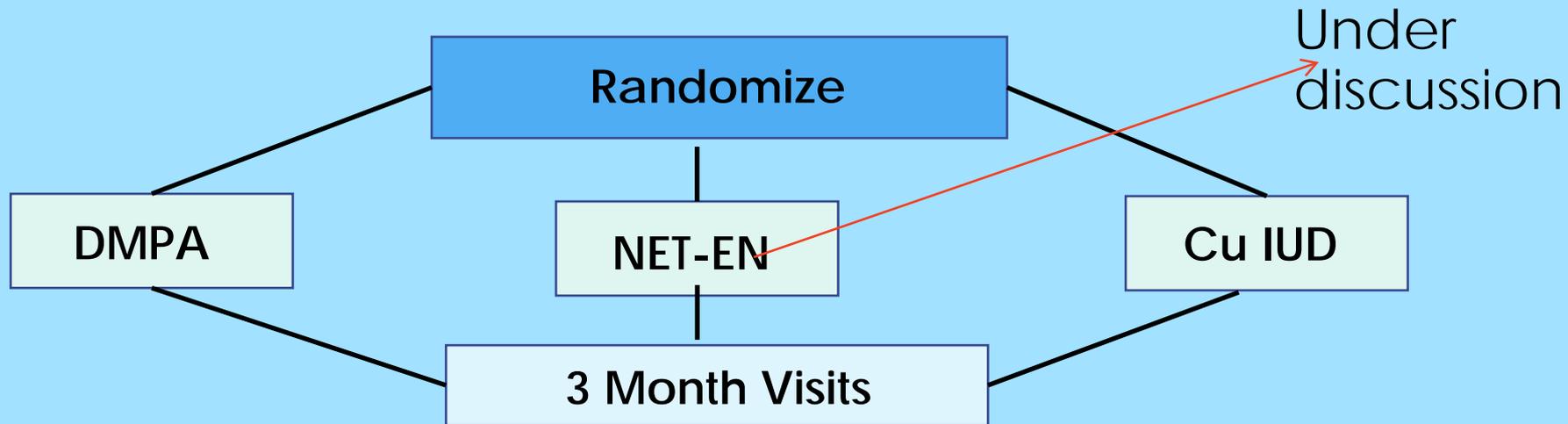
- Among women randomised to DMPA, \*NET-En and copper IUDs to compare
  - ✓ pregnancy rates
  - ✓ rates of method-related serious adverse events
  - ✓ rates of method-related adverse events that result in method discontinuation
  - ✓ contraceptive method continuation rates

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  - ✓ pregnancy rates
  - ✓ rates of method-related serious adverse events
  - ✓ rates of method-related serious adverse events that impact method discontinuation
  - ✓ contraceptive method continuation rates
- Evaluate
  - ✓ whether age modifies the hormonal contraception and HIV acquisition relationship
  - ✓ early HIV disease progression among seroconverters

# ECHO - An RT of HC/HIV

8600 Women Not Wanting to Conceive  
Willing to be randomized



1° Endpoint: HIV Infection

Other Endpoints: Pregnancy,  
Method Continuation, Method related SAE

# Proposed Study Design

- Design            Multi-center, open-label randomized clinical trial
- Study arms        Random allocation in a 1:1:1 ratio to DMPA, \*NET-EN or copper IUD
- Sample size      • ~ 8600 women
- Sites              **~14 sites in Eastern and Southern Africa**
- Study              • **Enrollment of 15-18 months**
- Duration          • **Total duration ~36 months**



# Sample Size and Power Assumptions

- Expected to yield 280 HIV endpoints for each of three comparison
  - Yielding 80% power to detect 50% increases in risk of HIV between any two methods
    - no presumed control arm
- Assuming:
  - HIV incidence: 3.5 per 100 w-y
  - Average of 15 months follow-up per participant
  - Up to 10% of woman-years lost to follow-up
  - up to 15% differential method switch or discontinuation rate
- Actual enrollment/events could be larger or smaller, depending on stopping rules and HIV incidence



# Trial Integrity

- In general, randomized clinical trials maintain their integrity only if they are done well:
  - High retention, protocol and product adherence
  - Post-randomization changes non-differential across study arms (usually protected by blinding)
  - Ethical conduct
- One reason no trial has been initiated to date has been questions about feasibility challenges to a potential trial.

(Ralph et al., Lancet 2013)



# Potential Challenges

Selection of study arms

Will women be willing to randomized (and remain on assigned method for study duration?)

Selection of sites with women with high HIV incidence

Generalizability of results

Geographic representation

How much data to collect vs cost and time

What level of HC HIV risk would lead to change in policy?

Rate of method switch/discontinuation; and will it be differential?



# Selection of Study Arms

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This would provide evidence on DMPA risk for HIV acquisition but the study would leave women, providers and policy makers with no information on the safety of other progesterone only contraceptives

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**Why not 4/5/6/7 arms and include NET EN, Implants, DMPA, Cu T IUD**

Sample size estimated at  $\geq 11500$ , may provide more information in increase in risk if there is a risk, may be more complex and increase risk of differential method switch

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Sample size estimated at 11500, more complex, increase risk of differential method switch

**Recognize placebo arm would create ethical and scientific challenges**

- ✓ Condoms would not be an acceptable control
  - Study design proposes multiple comparisons between arms

# Is Randomization Feasible

- Dissonance between principle of choice of family planning methods and random allocation



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- Dissonance between principle of choice of family planning methods and random allocation
- Three studies have shown large proportions of women requesting family planning do consent to be randomly allocated to HC vs. copper IUD
  - ✓ Multi-country pilot study by FHI 360 <sup>1</sup>
  - ✓ Zambian study of HIV+ women <sup>2</sup>
  - ✓ Injectable progestin versus IUD study in Eastern Cape <sup>3</sup>



<sup>1</sup>Feldblum 2006, <sup>2</sup>Stringer 2009, <sup>3</sup>Hofmyer-ongoing

# Other Potential Challenges

- **Cost and value for money, funds better used to expand method mix**
  - This trial will expand provider training and expansion of method mix
  - There is no evidence that other progestins, not DMPA do not have increased HIV risk
  - RCT will provide public health data on overall clinical and biological risk for HIV acquisition
  - Injectable remain popular in sSA and



# Generalizability of Results

- Policy directive will be most relevant to populations most impacted by the HIV epidemic
- Study has geographic representation
- Expanded age for participants to include women age 16-18 years- high risk for HIV infection
- Community engagement will include training of other local family providers outside the trial settings on contraceptive methods with an aim to increase method mix at population level



# Study Limitations

- **Lack of blinding may influence sexual behaviour and use of condoms**
  - Not observed in the male circumcision clinical trials
  - intention to treat analysis
- **Women could switch or stop use of contraceptive** -would undermine randomization design
  - ✓ Women have the right to stop use of contraceptive-  
personal desire, experience adverse event
    - Continuous monitoring, training of providers and counseling of clients

# Strict Operational Metrics & Monitoring

- Timely enrollment
- Method continuation (improves with careful planning and counseling)
- Differential method switch
- Retention
- HIV Incidence
- Adequate training study staff and local providers on different contraceptive methods



# Good Participatory Practice (GPP)

- ECHO Study Team is committed to conducting meaningful community consultation,
  - from protocol development and implementation to results dissemination and policy development
- Resources and technical support for GPP activities to facilitate meaningful stakeholder engagement



# Summary

- Both HIV and unintended pregnancy remain global health priorities
- Increased visibility/uncertainty about risks of hormonal contraception and HIV acquisition
- An RCT is our best hope to determine the most effective contraceptive method with lowest HIV risk and provide meaningful evidence for
  - Policy
  - Program
  - Clinical care
- Women need accurate information to exercise informed contraceptive choices



# Conclusion

- **ECHO study follows a quarter century of uncertainty**
- An opportunity for a “win-win-win”
  - Conduct an ethical randomized trial
  - Obtain higher quality evidence
  - Model of expanded mix of highly effective contraceptive options





## CONSORTIUM GROUP TEAM MEMBERS

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