The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial

A Multi-Center, Open-Label, Randomised Clinical Trial Comparing HIV Incidence and Contraceptive Benefits in Women using Depot Medroxyprogesterone Acetate (DMPA), Levonorgestrel (LNG) Implant, and Copper Intrauterine Devices (IUD)

Jared Baeten MD PhD

University of Washington

MTN Regional Meeting, Cape Town

October 2015

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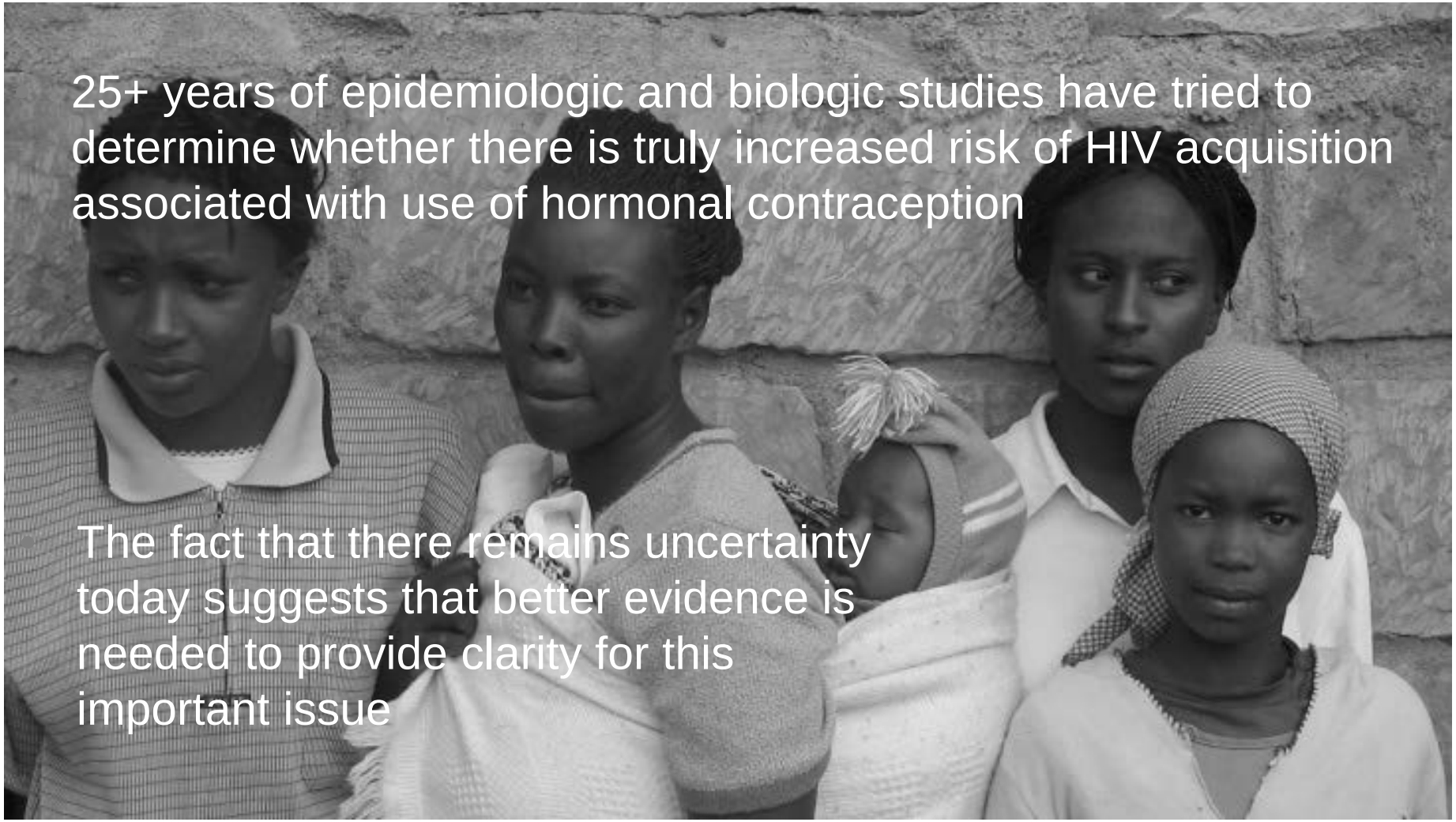
Starting Point



25+ years of epidemiologic and biologic studies have tried to determine whether there is truly increased risk of HIV acquisition associated with use of hormonal contraception

- The fact that there remains uncertainty today suggests that better evidence is needed to provide clarity for this important issue

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Outline

- Rationale for the ECHO trial
- Design and objectives
- Contraceptive methods to be evaluated
- Study population and follow-up
- Potential outcomes and challenges

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Rationale for a randomized trial

- 25+ years of epidemiologic and biologic studies have attempted to determine whether there is truly increased risk of HIV acquisition associated with use of hormonal contraception. But, there is still uncertainty. A randomized trial, if done well, provides the highest-quality evidence.

- Such high-quality evidence is needed to resolve the uncertainty in the field:
  - Providing clear guidance for policymakers and programs
  - Helping to formulate clear counselling messages for clinicians
  - Permitting women to make fully informed choices

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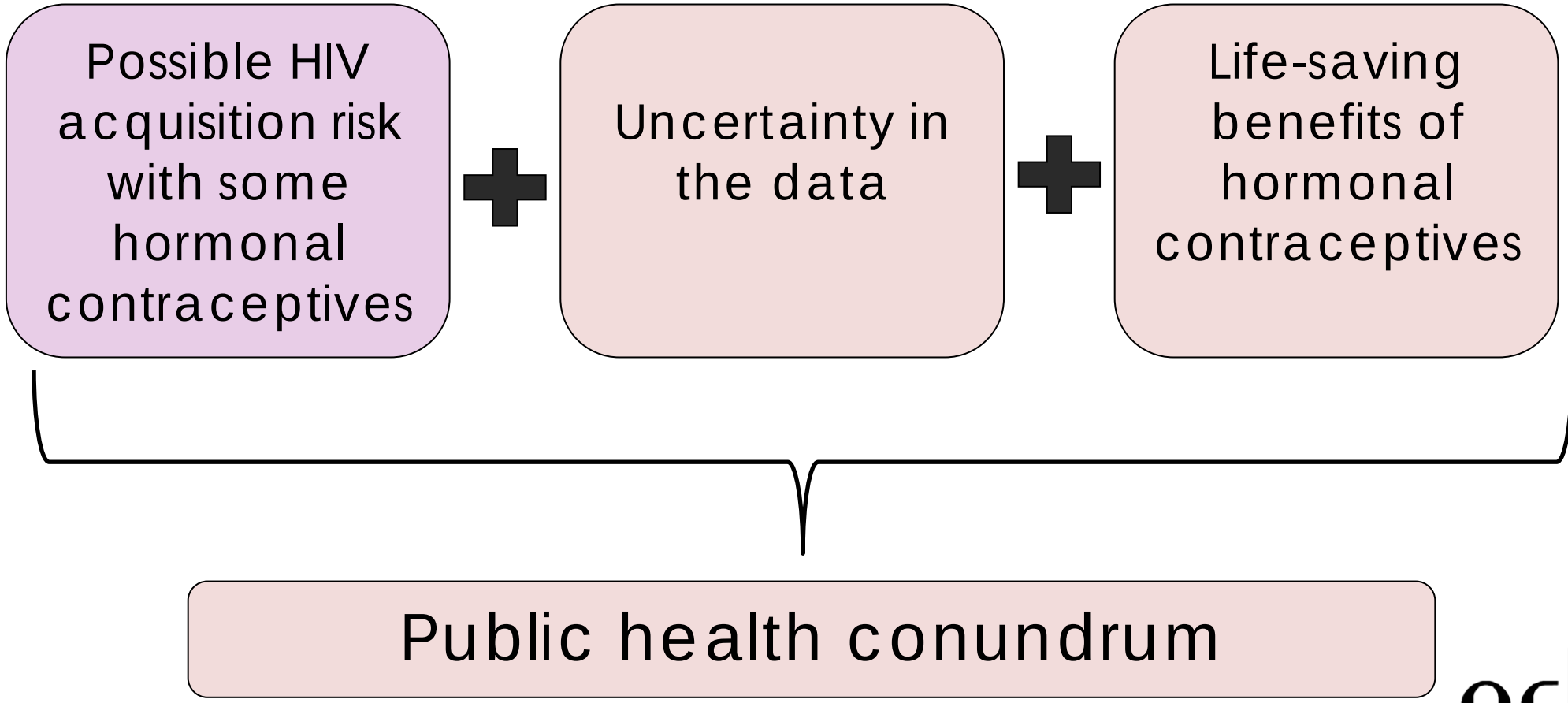
The challenge



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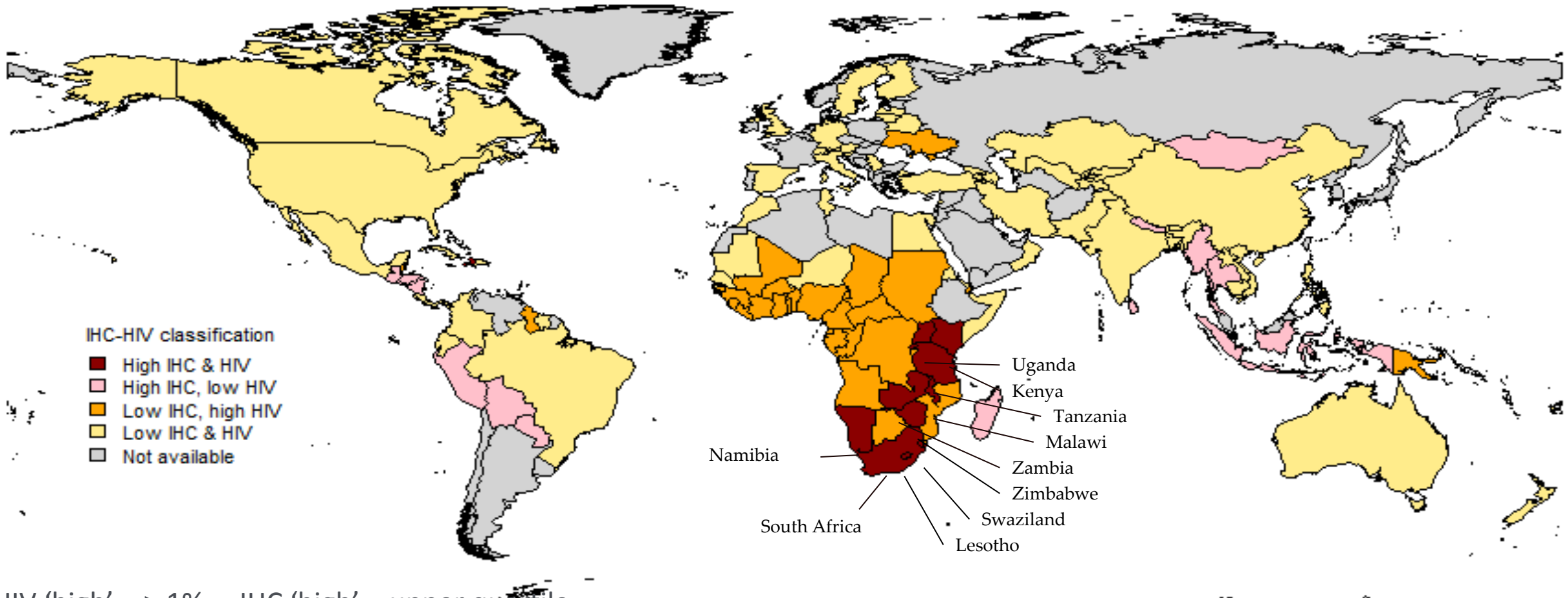
HIV prevalence and injectable use



High rates of HIV coincide with high use of injectables in E. & S. Africa

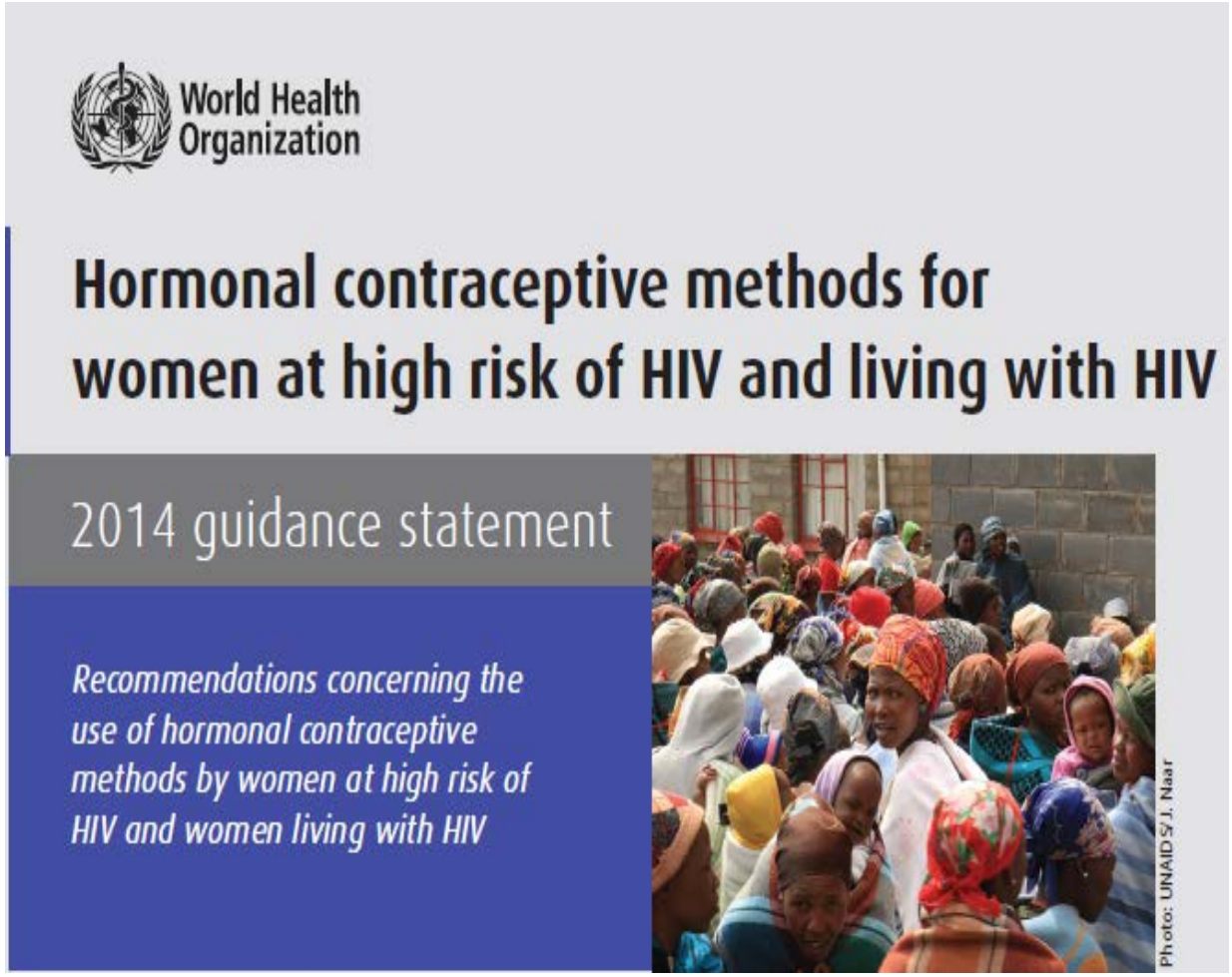
Butler AR 2013;27(1):105-13.

Limitations of observational data

- Disagreement across studies
- Potential risk for bias and confounding by factors that are difficult to measure
- Imperfect data: marginal contraceptive measurement, modest/high loss to follow-up or missing visits, sometimes long intervals between visits
- Contraceptive use often self-reported or otherwise unverified
- Laboratory studies in disagreement about mechanisms, or unclear what the key mechanisms even are

World Health Organization perspective

- Women at high risk of acquiring HIV:
  - can use all hormonal methods without restriction
  - who are using progestogen-only injectables should be informed that available studies have important limitations hindering interpretation
  - should be informed that progestogen-only injectables ***may or may not increase their risk of HIV acquisition***



Example: Kenya

Wednesday, July 30, 2014 / The Standard

Popular birth control injection linked to HIV

Kenyan researchers say Depo Provera, a prophylactic jab, doubles the risk of HIV infection in women

By GATONYE GATHURA

The locally popular injectable birth control method, Depo Provera, has yet again been linked to higher HIV infections in women.

FINDINGS PRESENTED BY KENYAN TEAM AT FORUM

- Results presented at Aids conference show Depo Provera increases the risk of HIV acquisition compared to women not using this contraceptive or not using any at all. But in this study it was also indicated that another injectable NET-EN, also increases the risk of HIV infection
- Team had looked at 18 studies involving 37,124 women from eastern and southern Africa. They

same presentation, WHO maintained the injectables are safe and women should continue using them. Dr Mary Lyn Gaffield of the global health agency said reviews they had done earlier this year did not warrant a change of WHO guidelines on the use of the two products.

"We are strongly advising women using progestogen-only injectable contraception to also always use condoms, and other HIV preventive measures," say the current WHO guidelines which are also in use in Kenya.

But Kenya scientists did not take the WHO opinion kindly writing a rejoined in the scientific journal The Lancet, saying they stood by their findings and called for more studies

Los Angeles Times

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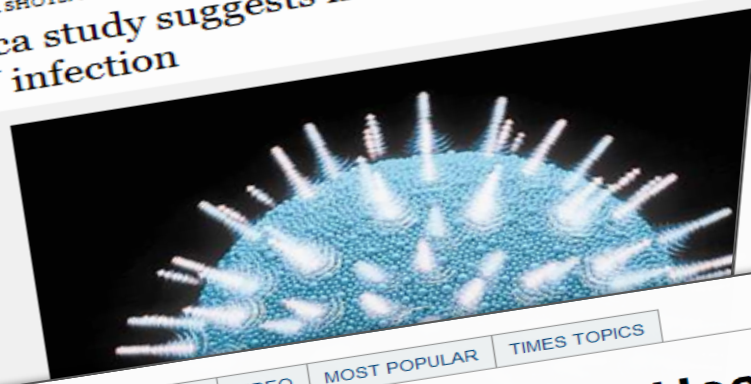
Africa study suggests hormonal contraceptiv HIV infection



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Female hormonal contrac linked to higher HIV risk

Women who use control are rough likely to become HIV or pass on t their partner, ac

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NEWS

Birth control method blamed for HIV risk

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Photo/FILE Last week, the US Federal Drug Administration warned over the potentially high risk of blood clots in women using birth control pills containing the hormonal chemical called drosplrenone. It is marketed under various brand names. In Kenya, such a product is registered with the Pharmacy and Poisons Board as Yasmin, and is sold in the form of tablets.

By GATONYE GATHURA gathurae@ke.nationmedia.com AAN | nationmedia.com

Posted Tuesday, October 4 2011 at 19:30

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The New York Times

Health

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Contraceptive Used in Africa May Double Risk of H.I.V.

By PAM BELLUCK
Published: October 3, 2011

The most popular contraceptive for women in eastern and southern Africa, a hormone shot given every three months, appears to double the risk the women will become infected with H.I.V., according to a large study published Monday. And when it is used by H.I.V.-positive women, their male partners are twice as likely to become infected than if the women had used no contraception.

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World news

HIV could spread if birth control injections increase, warn scientists

Researchers call for new guidelines for women using family planning services in Aids-hit areas

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ECHO: Overarching goal

To answer the pressing public health question of the relative risks (HIV acquisition) and benefits (pregnancy prevention) of three commonly-used, effective contraceptive methods among women who desire contraception

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ECHO Trial Study Schema

Design	Multi-center, open-label randomized clinical trial
Study arms	Random allocation to one of three study arms: DMPA, levonorgestrel (LNG) implant, copper IUD
Population	Sexually active HIV-uninfected women, ages 16-35 years seeking highly effective contraception, willing to be randomized to any study arm
Sample size	7800 women (~2600 per study group)
Study Sites	12 sites in East and southern Africa
Study Duration	• Follow-up: 18 months per woman • Total study duration of ~36 months

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ECHO Trial Design

7,800 women wanting not to conceive and willing to be randomized

Randomize (1:1:1 ratio)

- **DMPA (2,600 women)**
- **LNG implant (2,600 women)**
- **Copper IUD (2,600 women)**

3-monthly visits for up to 18 months

Primary Endpoint: HIV Infection.

Secondary Endpoints: Pregnancy, SAEs, Method Continuation,

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Primary Objective

Primary objective

- To compare the risks of HIV acquisition between women randomised to DMPA, levonorgestrel (LNG) implants, and copper IUDs

Study power

- 80% statistical power to observe a 50% increase in HIV risk between any of the contraceptive methods tested in the trial

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Secondary & Tertiary Objectives

- To compare pregnancy rates, rates of serious adverse events, rates of adverse events that lead to method discontinuation, and rates of contraceptive method continuation rates among women randomised to DMPA, LNG implants, and copper IUDs

- To explore the effect of age (<25 vs. ≥25 years) and HSV-2 infection status on the relationship between contraception and HIV, as well as the effect of different contraceptive methods on early HIV disease progression

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ECHO contraceptive methods

DMPA

- Most commonly used reversible contraception in Africa
- Highly effective when used consistently (0.2% failure rate)
- Easy to administer, can be used covertly

Jadelle implant

- Highly effective and user-independent
- Failure rates of <1% for both perfect and typical use

Copper IUD

- Extremely safe, non-hormonal, highly effective, and reversible
- Approved for 10 years of use
- Failure rates of <1% in both perfect and typical use if inserted properly

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Study Population

To participate in the study, women must be:

- Sexually active, HIV negative
- Seeking effective contraception
- Willing to be randomised to any of the study arms
- Ages 16-35 years old (16-17 if previously pregnant and at sites where adolescent participation in research is allowed by national regulations and ethics review approval)
- Able and willing to provide written informed consent
- Not having any medical condition that would make use of the contraceptive methods unsafe

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Study Setting

12 potential sites:

- South Africa (9 sites)
- Kenya
- Swaziland
- Zambia

Study products (DMPA, Jadelle implant and copper IUD) are registered and available in all these countries

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Study Visits

Study visits will be quarterly for up to 18 months and will include:

- HIV testing and contraceptive counseling
- Brief questionnaires on behavior, symptoms, and related factors

All participants will be provided a comprehensive contraceptive, HIV prevention, and HIV care package:

- Risk-reduction counselling, condoms, offer of partner testing
- STI screening and treatment
- Other prevention options (like PrEP and microbicides), as they become part of regular care
- HIV care plans for seroconverters
- Linkage to contraceptive care at the end of follow-up

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Key Metrics

- To do this study well, it has to be done right. The study team has defined key metrics that will be monitored in real-time:
  - Accrual rate
  - Refusal of contraceptive method assigned just after randomization
  - Retention
  - Rate of contraceptive discontinuation
  - HIV incidence
  - Quality of study performance (timeliness, data quality, etc)

An independent DSMB will review data on participant safety, study conduct, and scientific validity and integrity of the trial approximately every 6 months

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Implications of some possible outcomes

- **No difference in HIV risk** (DMPA=LNG=IUD): Reassurance to continue these methods in use.
- **Difference in HIV risk (possible scenarios):**
  - LNG lowest risk: Strengthen access to LNG
  - IUD lowest risk: Strengthen access to IUD
  - DMPA highest risk: Weigh how to use less DMPA, including messaging, delivery, alternatives

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Differing opinions

- Some scientists, advocates and policy makers disagree on whether there should be a randomized controlled trial of this question.
- Some issues that have been raised include:
  - **Evidence** → Is the question already answered?
  - **Ethics** → Is it ethical to randomize? Is it ethical to randomize to DMPA?
  - **Feasibility** → Will women agree to randomization? Will they continue their assigned method?

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Evidence

- While there are important studies suggesting that some contraception, particularly DMPA, may be associated with increased HIV risk, the evidence is not consistent across studies nor is it definitive. Moreover, it is not clear if alternatives would be better.

- WHO expert panels have reviewed the evidence twice in the last three years and found it inconclusive for a causal relationship between DMPA and HIV
  - Thus, from the point of view of "is the question answered," independent scientific and policy review is saying "no"

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Ethics

- Careful consideration of the ethics of randomization in general and randomization specifically to DMPA must be given
- The evidence points to balance (=equipoise) for the question of the relative risk of HIV across the proposed contraceptive methods, which allows randomization to be done ethically, with informed consent.
- The three proposed contraceptive methods are all highly effective for pregnancy prevention.

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Feasibility

- Other studies have randomized women at risk for HIV to different contraceptive methods, with high success for randomization.
  - Pre-consent counseling will anticipate acceptance of assignment
- As detailed earlier, the study team will be carefully optimizing study performance.

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What If No Trial

- The observational evidence base is unlikely to improve

- Without a trial, messaging will be continue to be challenging for providers, policymakers, and patients. Essentially:
  - If HIV risk exists *in truth*, unnecessary infections will continue to occur.
  - If HIV risk does not exist *in truth*, policies and/or individual women's choices may alter, with potentially serious negative consequences for maternal morbidity/mortality

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Upon conclusion, ECHO will provide

- Results from a study of the highest quality, and as a result:
  - Women will have accurate information to make informed choices
  - Providers will have accurate information for contraceptive counseling
  - Policymakers will have accurate information about which contraceptive methods to offer
  - Contraceptive method mix will be enhanced

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Summary

- HIV and unintended pregnancy are global health priorities
- There is increased visibility & uncertainty about the risks of hormonal contraception as related to HIV acquisition
- A 3-arm RCT with both hormonal and non-hormonal methods provides best option to provide meaningful evidence:
  - Policy
  - Program
  - Clinical care
- Women need accurate information to exercise informed contraceptive choices

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ECHO Team


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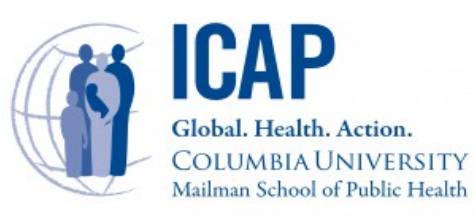
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