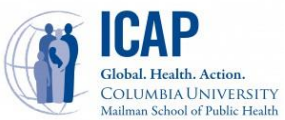
Hormonal contraception and HIV risk

Jared Baeten, MD, PhD
Departments of Global Health, Medicine, and Epidemiology,
University of Washington
On behalf of the ECHO Consortium

HPTN Annual Meeting
Washington DC, April 2017

echo
Evidence for Contraceptive Options & HIV Outcomes

ECHO Team



echo
Evidence for Contraceptive Options & HIV Outcomes

Starting Point

echo
Evidence for Contraceptive Options & HIV Outcomes

Outline

- Contraception and HIV risk: the evidence and the challenge
- Rationale for a randomized trial
- Design and oversight of ECHO
- ECHO status
- Potential outcomes and challenges

echo
Evidence for Contraceptive Options & HIV Outcomes

Evidence

- 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.
- Evidence has included:

Laboratory and non-human primate studies

Progesterone implants enhance SIV vaginal transmission and early virus load

Preston A. Marx[1,2], Alexander I. Spira[1,2], Agegnehu Gettie[1], Peter J. Dailey[3], Ronald S. Veazey[4], Andrew A. Lackner[4], C. James Mahoney[5], Christopher J. Miller[6], Lee E. Claypool[7], David D. Ho[1] & Nancy J. Alexander[8]

Marx et al. Nature Medicine 1996

Evidence

- 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.
- Evidence has included:

Epidemiologic studies, particularly prospective cohort analyses

Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

*Renee Heffron, Deborah Donnell, Helen Rees, Connie Celum, Nelly Mugo, Edwin Were, Guy de Bruyn, Edith Nakku-Joloba, Kenneth Ngure, James Kiarie, Robert W Coombs, Jared M Baeten, for the Partners in Prevention HSV/HIV Transmission Study Team**

Heffron et al. Lancet ID 2012

echo
Evidence for Contraceptive Options & HIV Outcomes

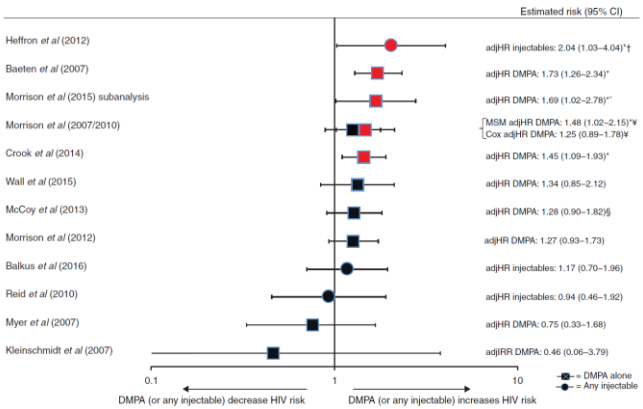
Evidence

- 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.
- Evidence has included:

Meta-analyses

An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women

Chelsea B. Polis[a,b], Kathryn M. Curtis[c], Philip C. Hannaford[d], Sharon J. Phillips[e], Tsungai Chipato[f], James N. Kiarie[g], Daniel J. Westreich[h] and Petrus S. Steyn[g]



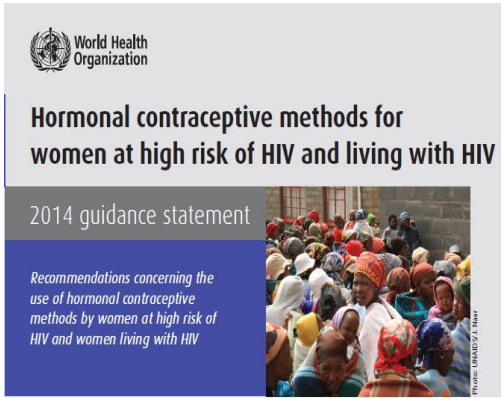
Polis et al. AIDS 2016

echo
Evidence for Contraceptive Options & HIV Outcomes

Evidence

- 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.
- Evidence has included:

Policy statements



"Women at high risk of acquiring HIV should be informed that progestin-only injectables ***may or may not increase*** their risk of HIV acquisition"

echo
Evidence for Contraceptive Options & HIV Outcomes

Evidence

- Summary:
  - The greatest potential concern has centered on the use of the injectable progestin **depot medroxyprogesterone acetate (DMPA)** – in a recent meta-analysis, the magnitude of effect was 1.40 (95% CI 1.23-1.59)
  - **Oral contraceptive pills** appear not to increase HIV risk
  - **Norethisterone enanthate (NET-EN),** another injectable may have less HIV risk than DMPA but data are somewhat limited
  - Limited data are available for **hormonal implants** and **hormonal and non-hormonal IUDs** with respect to HIV risk

Polis et al. AIDS 2016

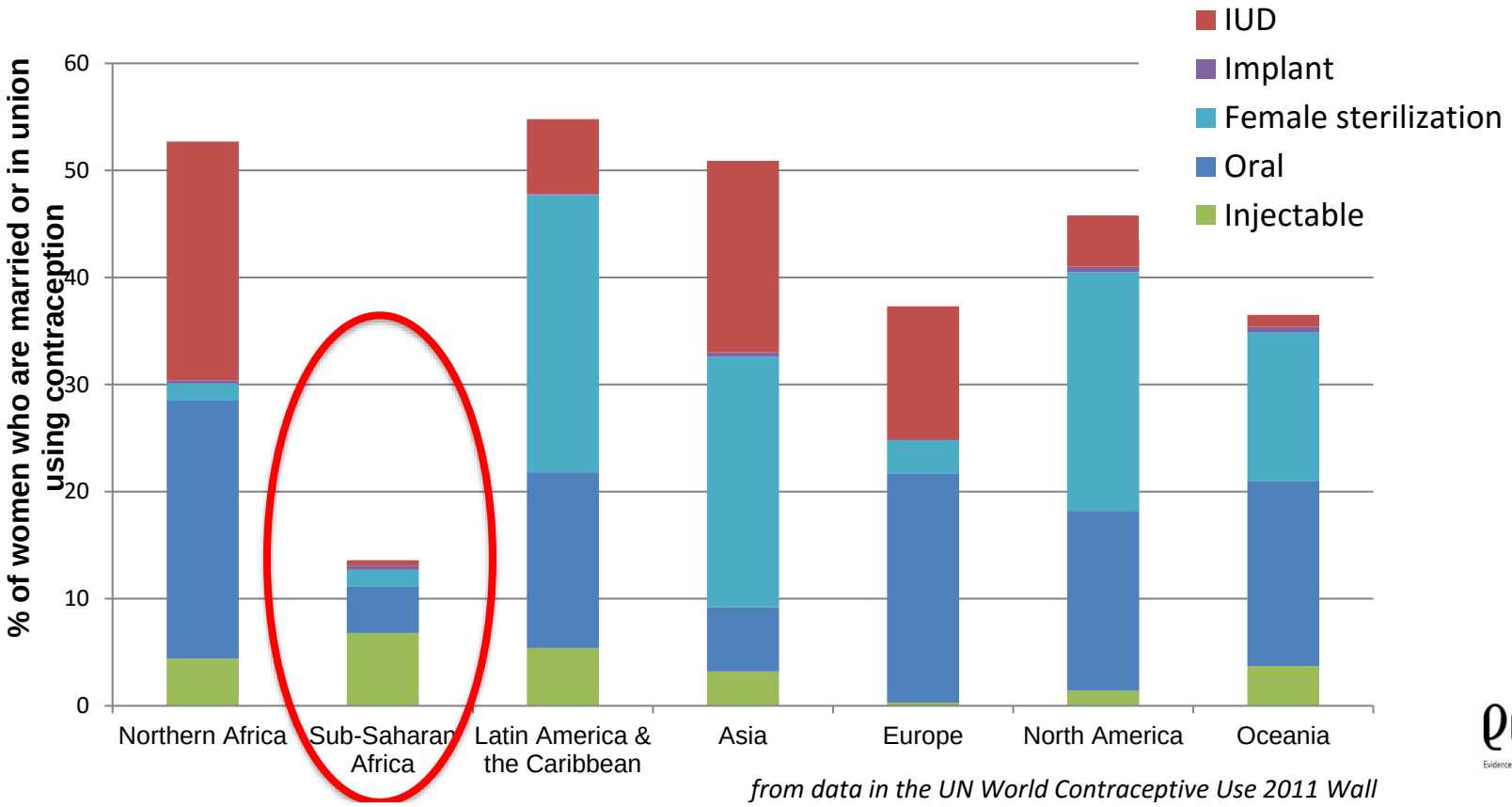
echo
Evidence for Contraceptive Options & HIV Outcomes

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

Additional Evidence

- In Africa, there is significant unmet need for contraception and injectables are the most used method



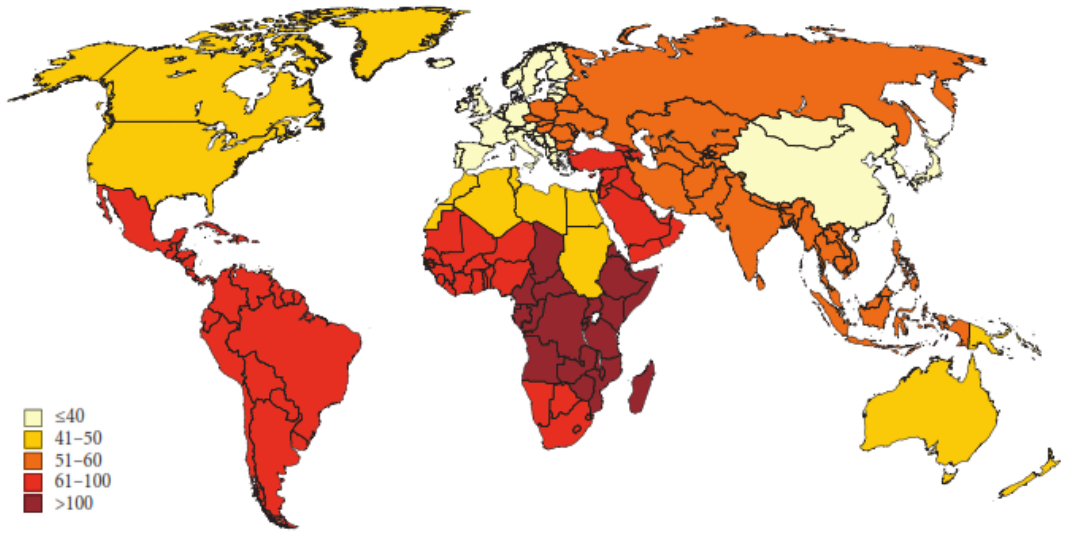
from data in the UN World Contraceptive Use 2011 Wall

echo
Evidence for Contraceptive Options & HIV Outcomes

Additional Evidence

- Unintended pregnancy rates are high, and high in areas where HIV is prevalent

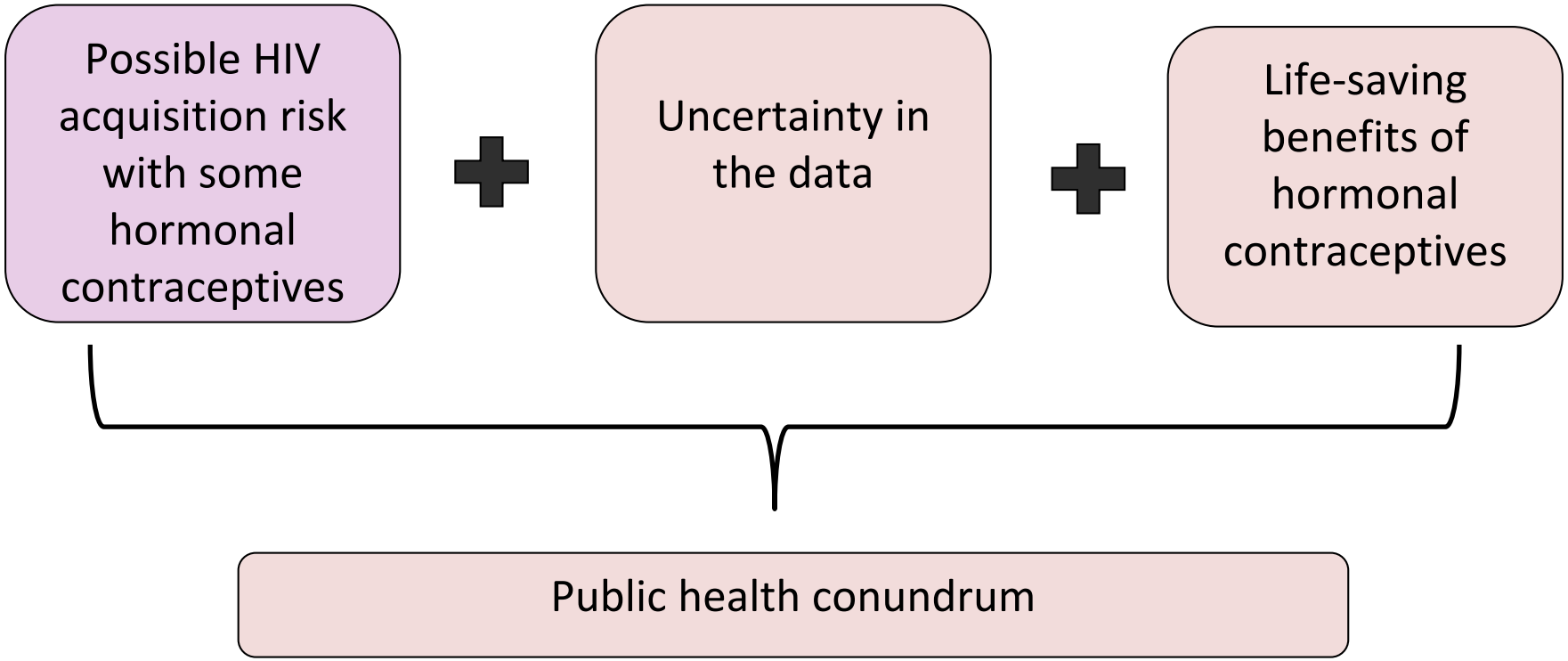
FIGURE 1 Unintended pregnancies per 1,000 women aged 15–44, by subregion, 2012



Sedgh, Singh, Hussain. *Studies in Family Planning* 2014

echo
Evidence for Contraceptive Options & HIV Outcomes

The Challenge




Los Angeles Times
BOOSTER SHOTS
LOCAL U.S. WORLD BUSINESS SPORTS ENTERTAINMENT HEALTH LIVING
BOOSTER SHOTS | MEDICINE | FITNESS & NUTRITION | MENTAL HEALTH | COLON CANCER | CAFFEINE & WOMEN'S DEPRESSION
HEALTH TOPICS: TAINTED CANTALOUPES
BOOSTER SHOTS: ODDITIES, MUSINGS AND NEWS FROM THE HEALTH WORLD
Africa study suggests hormonal contraceptive tie to HIV infection
HIV transmission rat
HOME PAGE | TODAY'S PAPER | VIDEO | MOST POPULAR | TIMES TOPICS
The New York Times
WORLD | U.S. | N.Y. / REGION | BUSINESS | TECHNOLOGY
Contraceptive Used in Africa May
By PAM BELLUCK
Published: October 3, 2011
The most popular contraceptive for women in eas
Africa, a hormone shot given every three months
the risk the women will become infected with H.I.V.,
large
published Monday. And when it is used by H.I.
ir male partners are twice as likely to become i
h had used no contraception.
FRANCE 24 INTERNATIONAL NEWS 24/7
FR - EN - AR
04 October 2011 12:20 PM GMT
NEWS | WIRES
13 hours 44 min ago - health
Female hormonal contraception linked to higher HIV risk
Women who use hormonal birth control are roughly twice as likely to become infected with HIV or pass on the AIDS virus to their partner, according to a study published on Tuesday.
The research was carried out among 3,790 heterosexual couples in Africa where one partner had the human immunodeficiency virus (HIV) whi
the other was uninfected.
The findings, if confi
repercuss
prevention
DAILY NATION
Mobile Site | Nation Media Group | Nation Careers | Africa Review | The Easterner | Business Daily | NTV | NTV
News | Business | Op/Ed | Blogs | Technology | Features | Sports | Transitions | Counties | Sunday Echo
Politics | Africa | World
ONLINE REAL ESTATE FAIR
Exhibitors: DAYKIO Housing Finance
Home | News
Birth control method blamed for HIV risk
SHARE | BOOKMARK | PRINT | EMAIL | RATING
Most P
I'd ha
Damn
John
I won
Odam
Raila
Lawy
Muthe
Birth
Kibak
Mitara
Ocam
NTV A
the potentially high risk of blood clots in women using birth
marketed under various brand names. in Kenya, such a product is
Miguna Miguna
Uhuru won propaganda war but lost legal battle
Comment: Page 24
Building online
Nairobi Council starts e-Construction permits
Property: Page 38
FRESH, INDEPENDENT, DIFFERENT
theSTAR
NO. 1287
WEDNESDAY, OCTOBER 5, 2011
www.the-star.co.ke
Ksh40/00
CONTRACEPTIVES DOUBLE HIV RISK
BY JOHN MUCHANGI
THE most popular contraceptive in Kenya doubles the risk of women becoming infected with HIV, a new study shows.
Use of the injectable contraceptive also increases the risk of HIV-positive women infecting their male partners.
The results present a predicament for
women because injectables and the pill are Kenya's most popular contraceptives, in part because women can keep them secret.
The study was published in the respected Lancet Infectious Diseases journal on Monday and involved 3,800 couples from Kenya, Uganda, Tanzania, Botswana, Rwanda, South Africa and Zambia.
It was led by University of Washington
but also included researchers from Kenyatta National Hospital, University of Nairobi and Moi University.
The study has prompted the World Health Organisation to convene a meeting next January to consider if evidence is now strong enough to advise women against injectable contraceptives.
Two past studies showed similar results
but researchers yesterday said the current study is the strongest.
"We want to make sure that we warn when there is a real need to warn, but at the same time we don't want to come up with a hasty judgement that would have far-reaching severe consequences for the
CONTINUED ON PAGE 6
traceptives double HIV risk
ductive
said
an
World
's
ductive
jected in
Public
aiting
WHO.
a
hormonal contraception causes biological changes, such as changes to the cells that line the vagina or cervix and that influence susceptibility to HIV
Renee Heardron, an epidemiologist and co-author of the study, however, said research examining whether the hormone changes genital tissue or vaginal mucous had been inconclusive.
"It could be that progestin in injectables causes immunologic changes in the vagina and cervix or could increase the HIV's ability to replicate," Charles Morrison, senior director of clinical sciences at FHI 360, an NGO whose work includes researching the intersection of family planning and HIV told the US media.
Researchers also found that there was more HIV in the genital fluid of those using hormonal contraception than those who were not, which could explain why men might have increased risk of infection from women using injectables.
The researchers also found that oral contraceptives increased risk of HIV infection and transmission, but the number of pill users in the study was too small.
Others suggested that women on birth control often are careless in using condoms for protection.
The study however recorded condom use, thus excluding the possibility that increased infection occurred because couples using contraceptives were less likely to use condoms.
Injectable contraceptives in Kenya include Depo Provera. Pfizer, the US-based manufacturer of the branded version of Depo-Provera, declined to comment to the New York Times on the study saying officials had not yet read it.
The study's authors however said the injectables used by the African women were probably generic versions.
Depo Provera has never been approved for use as a contraceptive in the US. It is controversial because it reportedly can cause heavy bleeding, weight gain
RISKY: A nurse shows one of the most widely used contraceptives
theguardian
04.10.11
Updated 13.23
Sections | Favourites | Search
World news
HIV could spread if birth control injections increase, warn scientists
Researchers call for new guidelines for women using family planning service
Aids-hit areas
THE NEW YORKER
FREE TOTE
SUBSCRIBE
$1 A WEEK
NEW YORKER
NEWS | CULTURE | BOOKS | SCIENCE & TECH | MAGAZINE | AUDIO
OCTOBER 4, 2011
AIDS AND CONTRACEPTIVES: BAD CHOICES IN AFRICA
BY MICHAEL SPECTER

Rationale for a Randomized Trial

- A randomized trial, if done well, provides the highest-quality evidence:
  - Providing clear guidance for policymakers and programs
  - Helping to formulate clear counselling messages for clinicians
  - Permitting women to make fully informed choices

The 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 (IUDs)

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

echo
Evidence for Contraceptive Options & HIV Outcomes

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

echo
Evidence for Contraceptive Options & HIV Outcomes

ECHO Trial Design

7,800 women ages 16-35 wanting to prevent pregnancy and willing to be randomized

Randomize (1:1:1 ratio)

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

echo
Evidence for Contraceptive Options & HIV Outcomes

ECHO Overview

Design	Multi-center, open-label randomized trial
Arms	Random allocation to: DMPA, levonorgestrel (LNG) implant, *or* 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	7,800 women (~2,600 per study group)
Outcomes	Primary = HIV (80% power to rule out 50% increases across the 3 methods) Secondary = pregnancy, SAEs, method continuation
Duration	Up to 18 months per woman; study will last ~36 months
Sites	12 sites in Kenya, South Africa (9), Swaziland, Zambia

echo
Evidence for Contraceptive Options & HIV Outcomes

ECHO Contraceptive Methods

DMPA

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

Jadelle (LNG) 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

echo
Evidence for Contraceptive Options & HIV Outcomes

Study Visits

Study visits are quarterly for up to 18 months and include:

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

All participants are 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 services at the end of follow-up

Oversight

- An **independent DSMB** reviews data on participant safety, study conduct, and scientific validity and integrity of the trial approximately every 6 months
- **Ethical review** of protocol conducted prior to study start and annually IRBs/ECs at FHI 360, WHO, and each study site
- A **safety oversight committee** reviews safety data from all sites monthly and has 24/7 availability for clinical advice.
- A **Global Community Advisory Group** and **CABs** at each site meet regularly. Each site has an active **Good Participatory Practice** plan.
- To assure the trial meets all **regulatory requirements** (both US and each country), the study is conducting quality control and assurance activities, and being reviewed by qualified independent clinical monitors

echo
Evidence for Contraceptive Options & HIV Outcomes

Evidence, Ethics, and Feasibility of ECHO

Prior to ECHO's initiation, many people (including members of the ECHO consortium) questioned whether the trial needed to be done and could be done well. Key questions included:

- **Evidence** → Is the question already answered?
  - While studies suggest some contraception, particularly DMPA, may be associated with enhancing HIV risk, the evidence has not shifted policy and data from a trial may be clarifying. Importantly, it is not clear if alternatives to DMPA would be better.

- **Ethics** → Is it ethical to randomize?
  - Randomization can done ethically, with informed consent.

- **Feasibility** → Will women agree to randomization, method continuation, etc.?
  - Assessable only by doing the trial itself.

echo
Evidence for Contraceptive Options & HIV Outcomes

ECHO Performance Standards

To do the ECHO trial well, the team, funders, and DSMB agreed prior to initiation that a key operational metrics would be reviewed continually during the study and if not met would trigger careful reevaluation of whether to stop the trial:

ECHO Performance Standard	Target (*=overall and at each site)
#1 Accrual	Achieve target sample within ~18 months
#2 Method refusal	<5% of subjects*
#3 Retention	Per-visit completion of ≥90% and ≤10% of expected person-years lost*
#4 Method discontinuation	≤10% of all person-time off assigned method*
#5 HIV incidence	sufficient to meet the study objectives (≥3.5%/year)
#6 Ineligible enrollments	<1-2% of total*
#7 HIV endpoint adjudication	up-to-date for each DSMB review*
#8 Data quality	current for each DSMB, QC ≤5/100 CRFs, fax time ≤7d*

echo
Evidence for Contraceptive Options & HIV Outcomes

Implications of some possible outcomes

- **No difference in HIV risk** (DMPA=implant=IUD): Evidence that all methods can be continued in use.
- **Difference in HIV risk (example possible scenarios):**
  - Implant lowest risk: Strengthen access to implant
  - IUD lowest risk: Strengthen access to IUD
  - DMPA highest risk: Help women/programs shift to less use of DMPA and greater use of alternative highly-effective methods, including messaging, delivery, alternatives

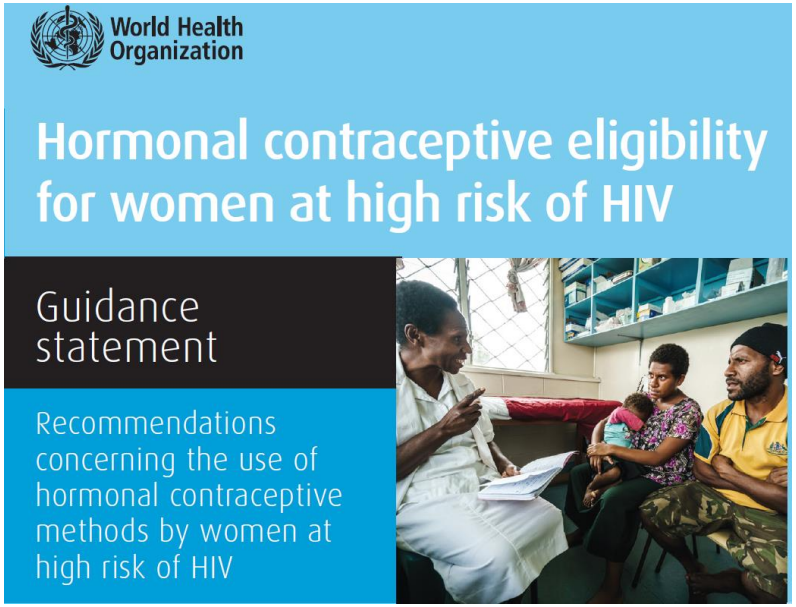
ECHO Current Status

- Started December 2015
- Open at 12 of 12 sites
- DSMB met on 5 August 2016 & 2 March 2017 and strongly endorsed continuation of the study
- Enrollment currently 5,390 (69%) (as of 3 Apr 2017)
- Expect enrollment to be completed in ~Q3 2017 and study visits to be completed in ~Q3 2018
- Performance standards are excellent (no add'l info available while trial ongoing)

echo
Evidence for Contraceptive Options & HIV Outcomes

New WHO Guidance

On 2 Mar 2017, WHO released new guidance regarding injectable progestin contraceptives. The guidance derived from an expert consultation in December 2016 (which members of the ECHO Team did not attend, to avoid conflict of interest) and changed the Medical Eligibility for Contraception (MEC) categorization for injectable progestins from a "1" ("no restriction") to a "2" ("advantages outweigh theoretical or proven risks").



echo
Evidence for Contraceptive Options & HIV Outcomes

WHO recommendations

WHO recommends women considering DMPA/NET-EN be advised:

- There are concerns about a possible increased risk of HIV.
- There is uncertainty about whether injectable contraceptive methods actually cause increased risk.
- There are ways to minimize the risk of becoming infected, such as use of male and female condoms and PrEP, where available.

The WHO guidance also called for data from randomized trials.

Steps Following WHO Announcement

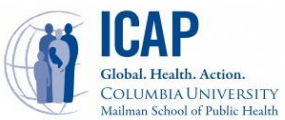
- ECHO statement and updated Q&A posted to ECHO website.
- DSMB met the day WHO released its guidance – endorsed continuing the trial as designed.
- Calls with ECHO Team and CABs were used to discuss the WHO guidance changes and train on the updated counselling guidance.
- Informed consent updated and an information sheet was created in line with WHO recommended counselling.
- ECHO team members participated in participant and stakeholder engagement activities (e.g., AVAC webinar).

ECHO Summary

- The ECHO Study is enrolling in 12 sites in Kenya, South Africa, Swaziland and Zambia
- Accrual is on schedule, performance metrics are excellent, counseling is directly responsive to current WHO guidance, and the DSMB has active oversight
- Results from the trial will be highest quality evidence, and as a result:
  - Women will have highest quality information to make informed choices
  - Providers will have highest quality information for contraceptive counseling
  - Policymakers will have highest quality information about contraceptive risks and benefits for family planning programs

echo
Evidence for Contraceptive Options & HIV Outcomes

ECHO Team



echo
Evidence for Contraceptive Options & HIV Outcomes

ECHO Funders

Contraceptive supplies donated by USAID and the Republic of South Africa

echo
Evidence for Contraceptive Options & HIV Outcomes