PHASES
PREGNANCY + HIV/AIDS
SEEKING EQUITABLE STUDY

Evaluating HIV Products in Pregnant Women: Toward an Ethical Framework

Anne Drapkin Lyerly, MD, MA

Professor, Department of Social Medicine

Research Professor, Department of Obstetrics and Gynecology

Associate Director, Center for Bioethics

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

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NIH

Pregnancy Research Ethics
for Vaccines, Epidemics,
and New Technologies
PREVENT

wellcome

pregnancyethics.org

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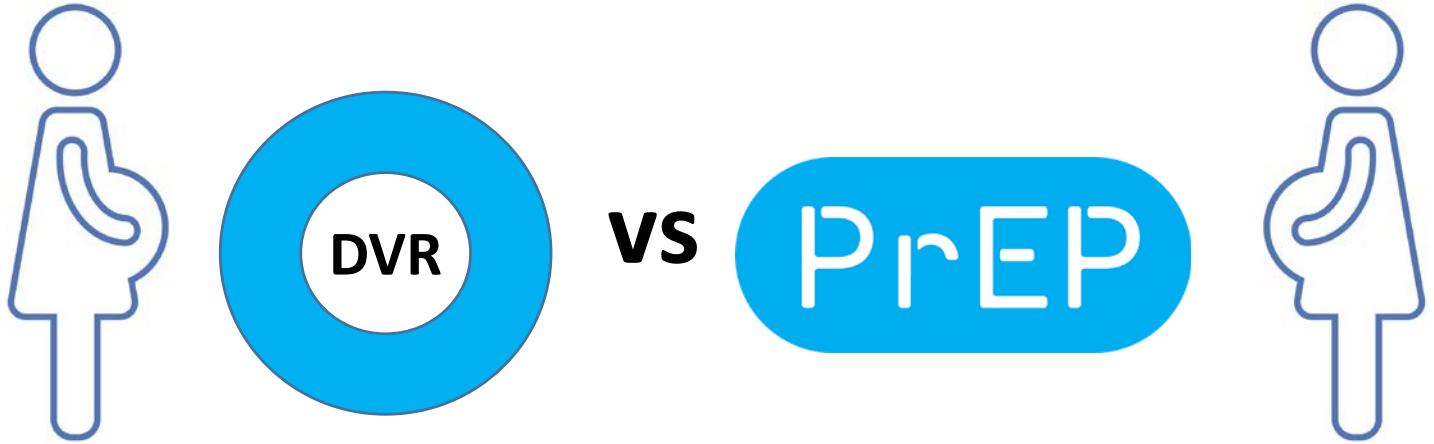
MTN 042

- Phase 3b, Randomized, Open Label Safety and Pharmacokinetic Trial of Dapivirine Vaginal Ring (VR) and Oral FTC/TDF Use in Pregnancy
- 750 pregnant women, randomized 2:1
- 4 cohorts, progressively earlier gestation (36,30,20,12 weeks GA)



Women, pregnant women, and research

- **First wave:**
  - Early 1990s, women and their health interests under-represented in research
  - 1993 NIH Revitalization Act
  - Women now a majority of research participants

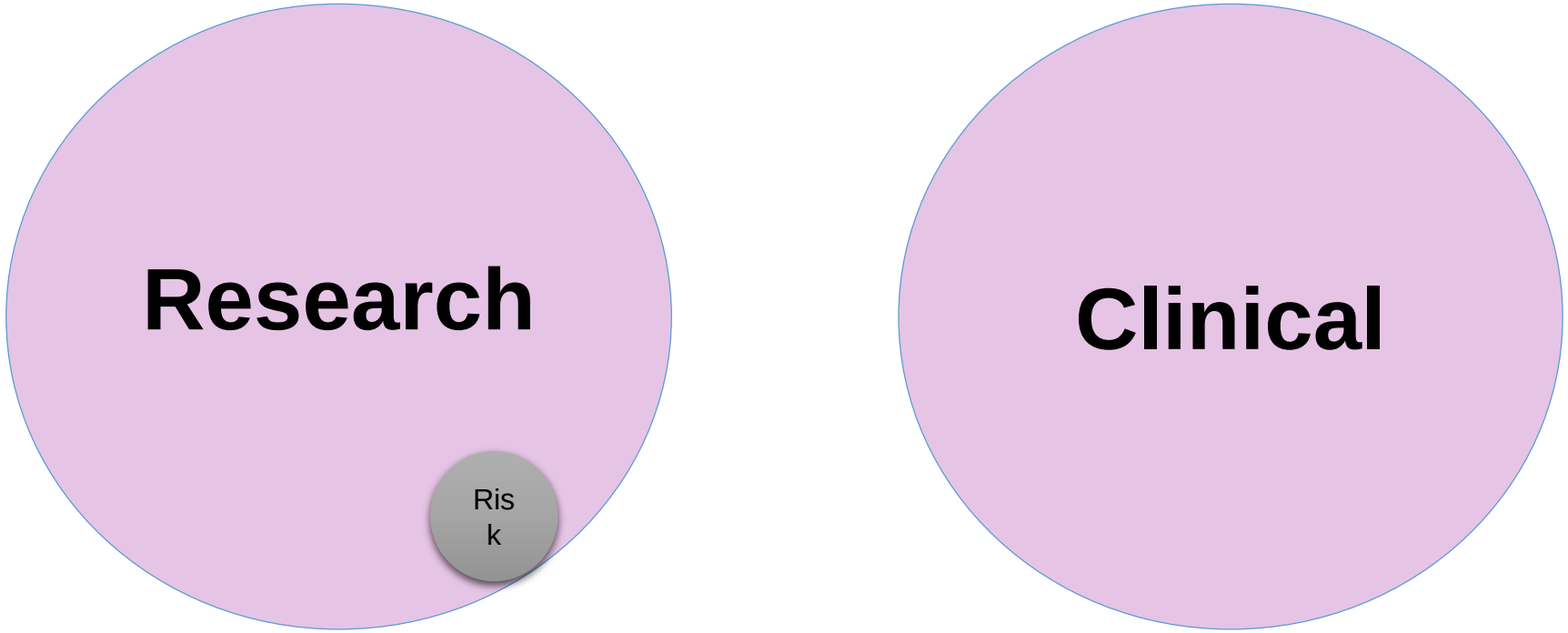
- **Second wave:**
  - Pregnant women and their health interests still under-represented in research
  - Result is a dearth of information to guide treatment and prevention
  - Second Wave Initiative: ethics requires inclusion

Ethics requires inclusion

- Pregnant women need **effective treatment**
- Pregnant women need **information about safety** of treatments and preventives
- Limited data leads to **reticence** to prescribe/take needed meds
- Pregnant women deserve **fair access** to research with prospect of direct benefit

Lyerly, Little and Faden, *IJFAB* 2008

Risk shifting



HIV – an exception, partly

- To some extent, HIV is an exception given success of PMTCT research

- Significant evidence gaps remain:
  - Data on newer ARVs, maternal outcomes
  - Treatment of co-infection (TB, malaria)
  - Prevention of maternal HIV

HIV prevention research & pregnancy

- **Pregnancy has been an exclusion criteria** from all major PrEP trials in Africa
- Women who became pregnant on such trials **required to discontinue** medication

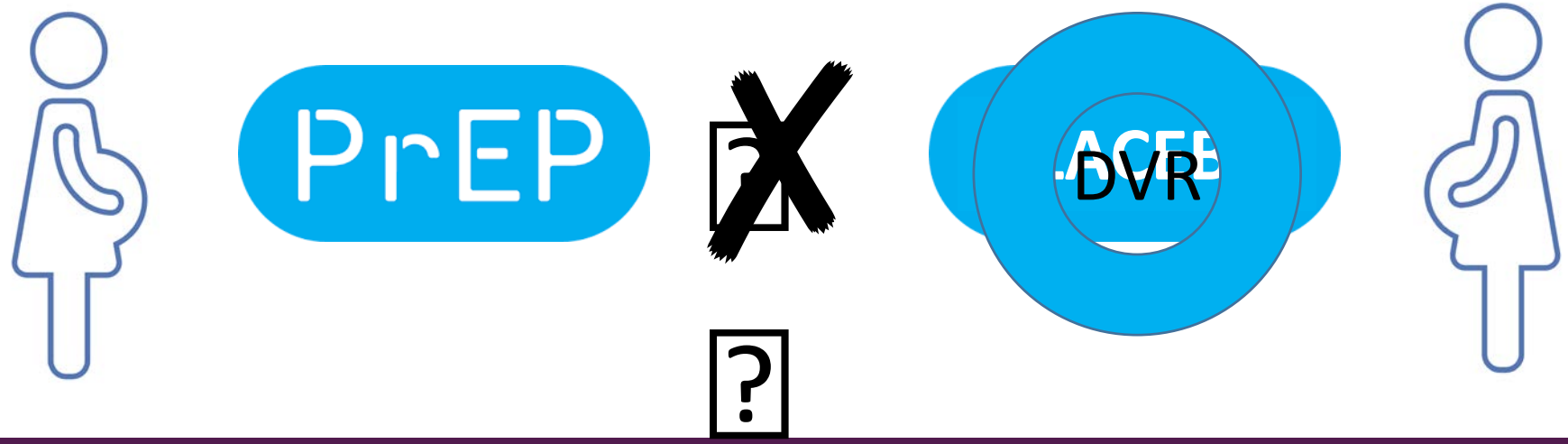
- Evidence of safety from other sources:
  - Outcomes of incident pregnancy on PrEP trials
  - HIV+ women on ARVs
  - HIV- women taking TDF for HBV

Conflicting guidelines

World Health Organization[8]	South Africa[9]
Permissive of PrEP in pregnancy: PrEP is recommended as, “an additional prevention choice for people **at substantial risk of HIV infection”** PrEP “**should not be discontinued** during pregnancy and breastfeeding for women who continue to be at substantial risk [and] can also be considered as **additional prevention choice for HIV-negative pregnant women at substantial of HIV infection**. and … “**further research is needed** to fully evaluate PrEP use during pregnancy and breastfeeding”	PrEP is contraindicated in pregnancy: “…**PrEP in pregnant or breastfeeding women is contra-indicated**. However, as the risk of seroconversion during pregnancy is high, the risks and benefits of PrEP should be discussed with potential PrEP users, **allowing these women at high risk of HIV acquisition to make an informed decision** regarding PrEP use."

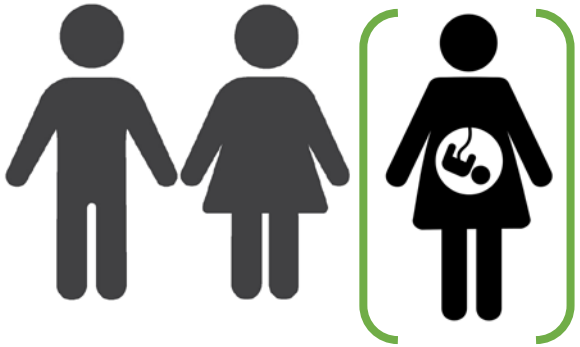
Finding equipoise

- Ethically important in randomized controlled trials
- Genuine **uncertainty or conflicting expert opinion** about relative therapeutic, preventive or diagnostic merits of interventions
- Relevant to interests of science **AND** respect for research participants

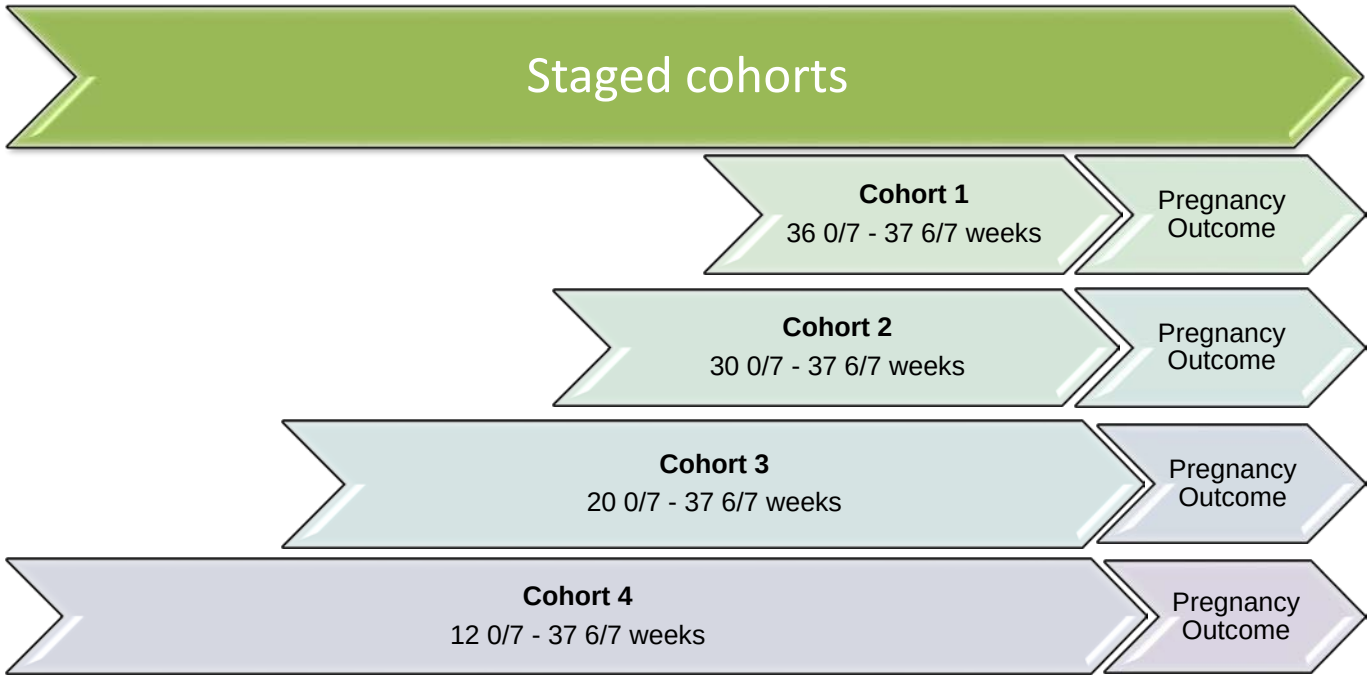


Minimizing risk

reprotox



Studies in non-pregnant people (incident pregnancy data)



Risks and benefits

Prospect of direct benefit (PDB)?

Either

woman or fetus (or both)

Reasonable ratio of risk to benefit

e.g. Phase III efficacy trials

Neither

woman nor fetus

Fetal RRR capped at ~~minimal risk~~

e.g. Phase I/II PK studies

Little, PRGLAC 2017

The “either” challenge: trade-off scenarios

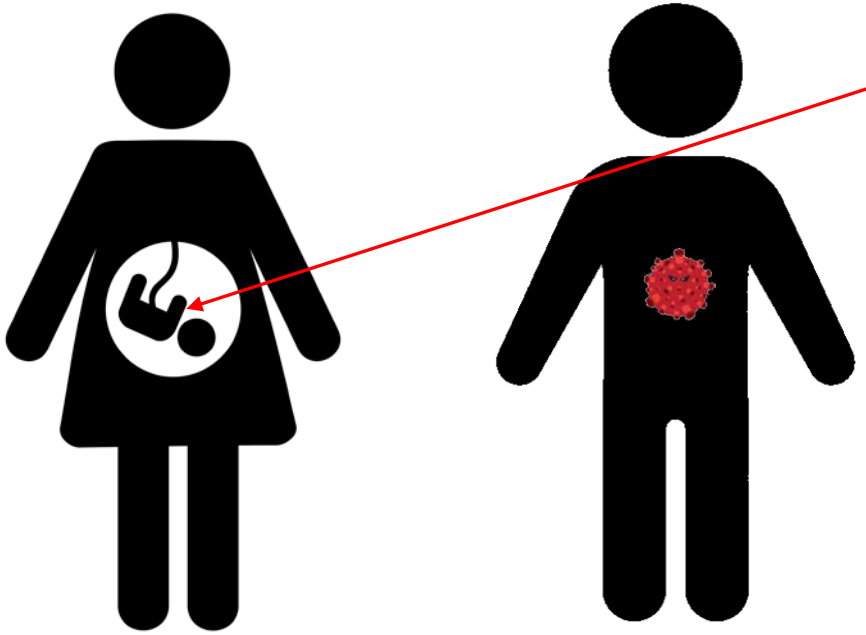
Maternal risk/ fetal benefit	• Like other competent agents, a pregnant woman can altruistically volunteer to participate in clinical research with minimized risk and no PDB to her
Fetal risk/ Maternal benefit	• The decision to continue a pregnancy should not require a pregnant woman to forfeit rights to all important medical benefits
Fetal risk/ Future child benefit	• Pregnant women reasonably differ in the priority they place on avoiding fetal loss versus improving future child benefit

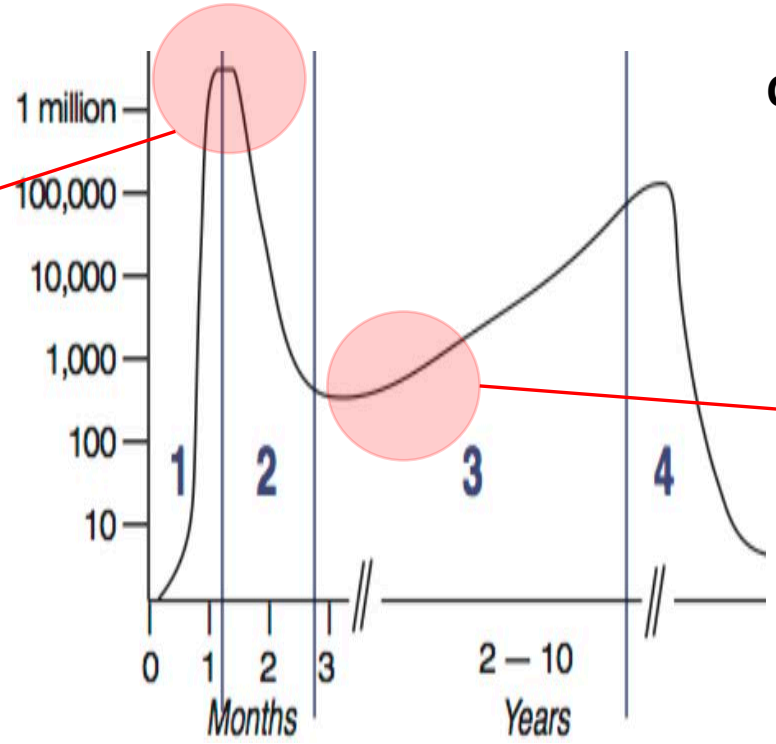
Little, Wikremsinhe, Lyerly, ACOG 2017

➢ **But in the case of DVR, maternal and fetal interests are largely aligned**

HIV-, PrEP/DVR

MOTHER ACUTELY INFECTED WHILE PREGNANT

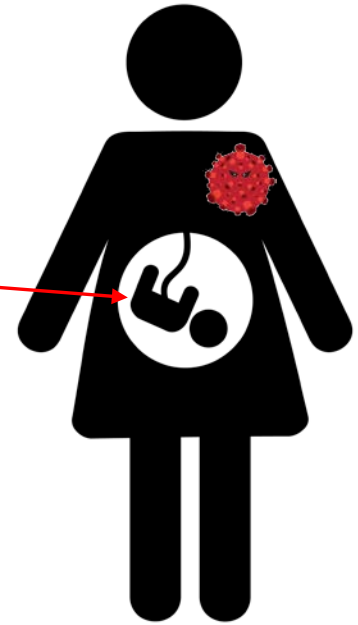




HIV VIRUS IN BLOOD OF MOTHER

HIV+, PMTCT

CHRONICALLY INFECTED MOTHER



"a child who is born to the mother who is HIV negative at the booking visit is more likely to have HIV infection compared to a mother who is HIV positive in the booking"

-HIV researcher, Southern Africa

Beyond vessels and vectors

- Pregnancy as a “marker” for unprotected sex
- *“Although we’re worried about the baby,* ***you still want to worry about the fact that the pregnant woman should not be getting HIV****. Whether she’s pregnant or not HIV acquisition is going to remain with her. Pregnancy won’t remain with her all the time, but the status will remain, and you want to avoid that.”*

-HIV researcher, Southern Africa

Conclusions

- MTN – 042 reflects an important global paradigm shift toward prospective evidence-gathering in pregnant women
- Risk is minimized by step-wise approach
- Given prospect of direct benefit, not necessary to engage with minimal risk standard
- Trade-offs are ethical; even so, maternal and fetal interests are aligned in this case
- Comparison to PMTCT presents a promising opportunity
- Maternal health interests important in their own right

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With gratitude to the PHASES team

hivpregnancyethics.org

UNAIDS/WHO 2012

- Women throughout the life span, **including those who are sexually active and may become pregnant, be pregnant or be breastfeeding, should be recipients of future safe and effective biomedical HIV prevention products** and therefore **should be eligible for enrollment in biomedical HIV prevention trials**, both as a matter of equity and because in many communities throughout the world women, particularly young women, are at higher risk of HIV exposure.