

The Importance of Moving Microbicides into Pregnant & Breastfeeding women

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Why Consider Pregnancy & Lactation?

- **Major challenge in HIV Prevention trials**
 - 2008 IOM – “Major Methodological Challenge to HIV Prevention Research”
 - Safety, Statistical Design, Analysis, etc.
- **HIV Prevention trials enroll sexually active women**
 - Pregnancy natural consequence
 - 85% per year – Non-contraceptive
 - 0.5-15% per year – Typical users
 - Pregnancy rate: 16-64/100 woman-years
 - Lactation: @ 20-50% Exclusive BF 6 mos
- **Microbicides developed to:**
 - Prevent HIV/STI's among sexually-active women
 - Have widespread availability



Darroch. Fam Planning Perspect 1999;31. Trussel Contraception 2004;70.

Ranjit. Fam Planning Perspect 2001;33. Raymond. STD's 2007;34

Lagakos. National Academies Press,2008. www.Unicef.org

Why Important to Study

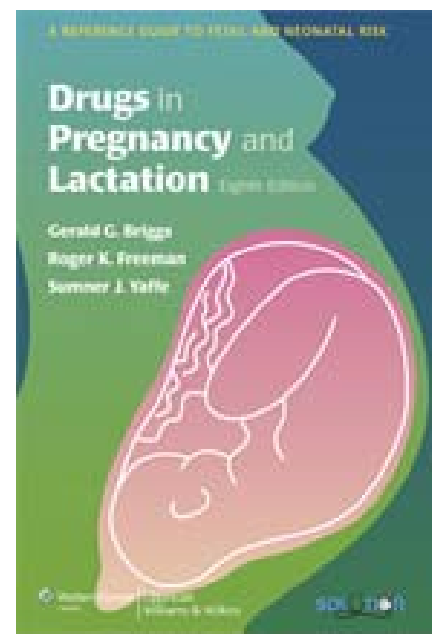
- **Frequent sexual activity in pregnancy & PP**
 - Multiple partners common
- **Pregnant women often use Rx & OTC meds**
 - When microbicides agents available will use
 - (?) urine HcG
- **Pregnancy high-risk**
 - HIV acquisition
 - OR = 15 for MTCT

Incident HIV in pregnancy



Background – Current Approach

- \geq 99% of therapeutics **NEVER** studied during pregnancy (during R&D)
 - If done, late-stage retrospective study
 - Not controlled & variable participation → BIAS
 - Expose more pregnant women
- “Therapeutic orphans”
 - Pregnant women use therapeutics
 - Avg #: 2-5 meds used/pregnancy
 - Major Disconnect



Real life example

- Influenza
 - Well known (> century) pregnant women worse off
 - New class flu drugs
 - Neuraminidase inhibitors
 - Zero testing...Zero data
 - Influenza vaccine
 - Retrospective investigation, marginal public understanding of no risk
- 2009 H1N1 influenza pandemic
 - Late use/no use of oseltamivir during pregnancy
 - Worse outcomes (CDC personal communication)
 - Many sectors → poor vaccine uptake
- Sub-optimal → Change
- Microbicides & MTN:
 - Rare opportunity to breach this disconnect

Why Study

- **1% Tenofovir Gel**
 - **Used with sexual activity**
 - **40% protective for HIV**
 - **50% protective for HSV 2**
 - **Ongoing studies → validate protection**
- **Above + ethics favors controlled study**



MTN-002: Objectives

□ **Primary:**

- Assess term pregnancy maternal single-dose pharmacokinetics (PK) of Tenofovir (TFV) 1% vaginal gel

□ **Secondary:**

- Characterize the systemic safety profile
- Compare 3rd trimester absorption of TFV gel to non-pregnant
- Assess TFV: cord blood, amniotic fluid, endometrial tissue and placental tissue levels

Protocol

□ Enrollment

■ Screening visit \leq 4 weeks before planned Cesarean (C/S) Delivery

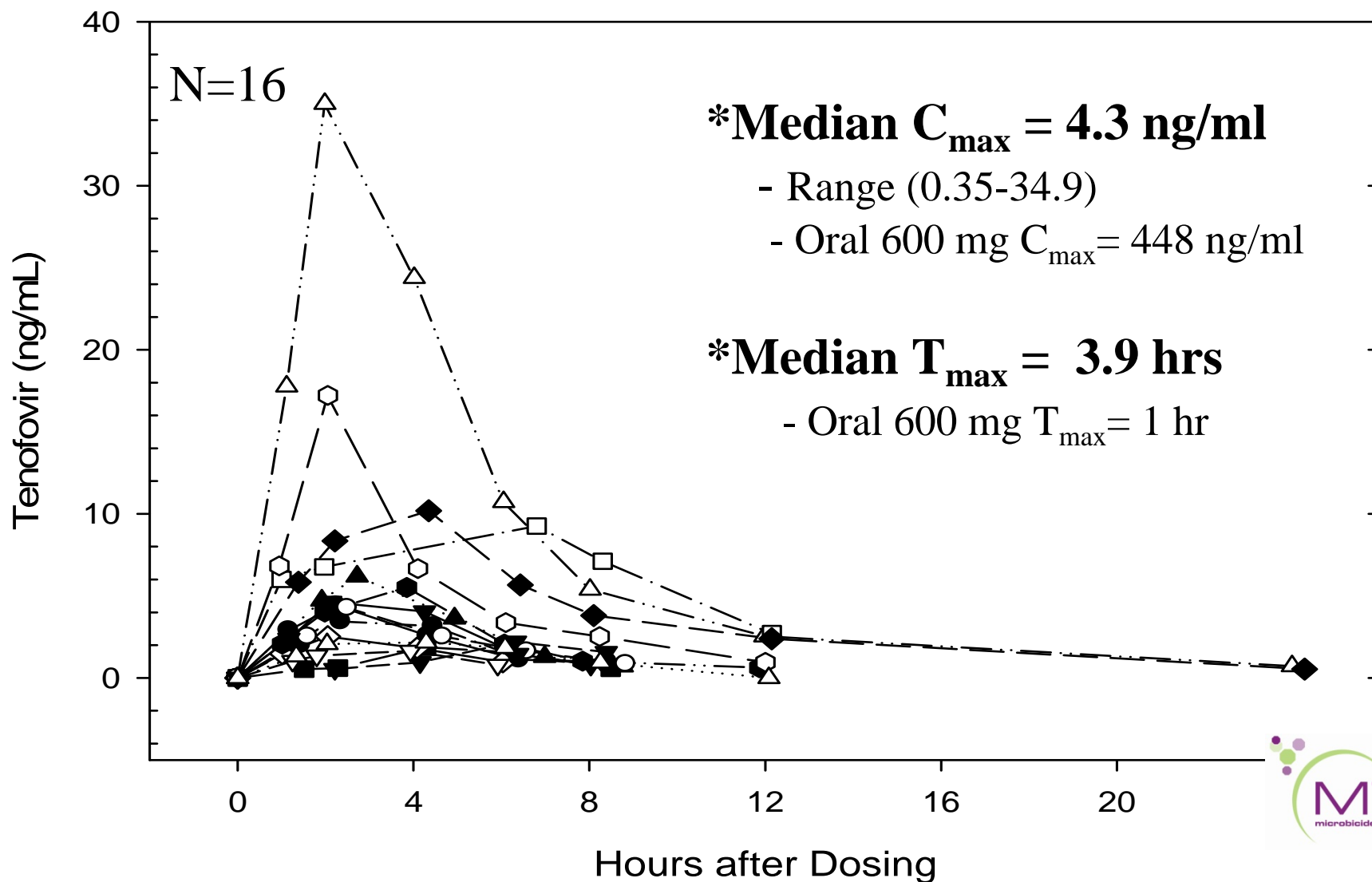
□ Healthy term, aged 18-45, singleton pregnancy, no co-morbidities

- Demographic data, confirm eligibility criteria, undergo informed consent
- Targeted pelvic: Trichomonas Culture, GC/CT by SDA
- Blood:
 - Serum creatinine, AST/ALT, Rapid HIV test with counseling
 - *Confirmatory Testing for HIV, *HBsAg, *RPR, *Confirmatory Testing for Syphilis (* When needed)

□ Single-dose Tenofovir (TFV) 1% gel (40 mg)

- Placed in Pre-operative < 8 hrs prior to C/S

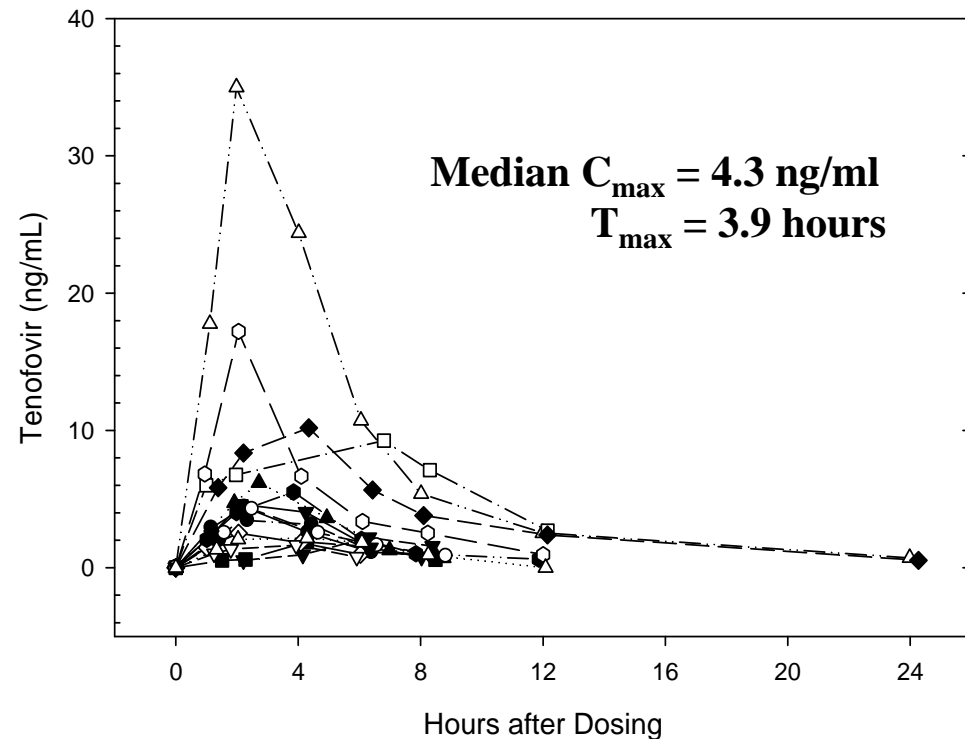
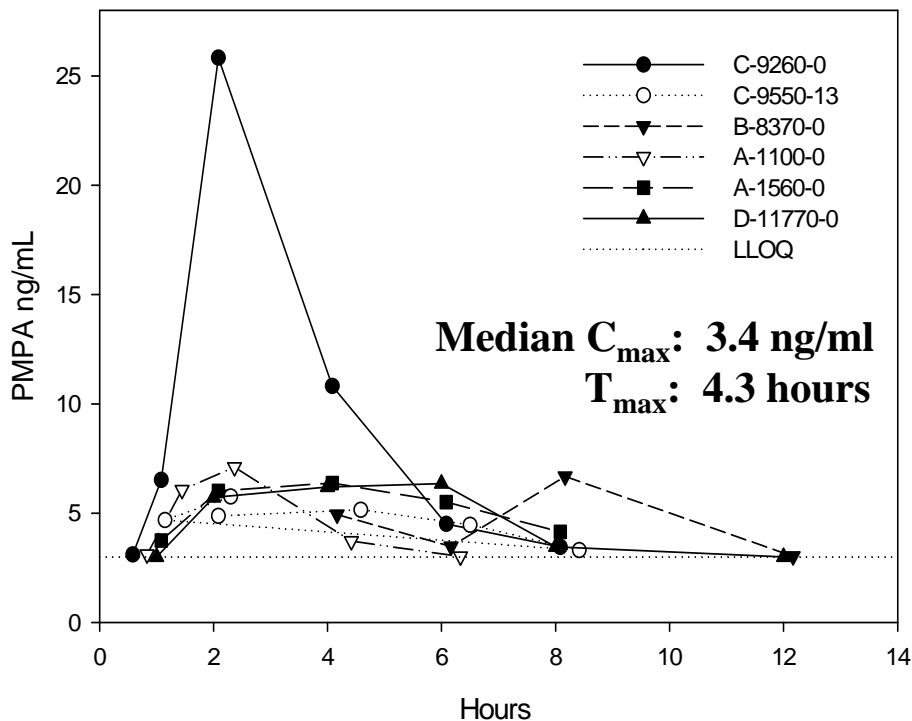
Results – Maternal TFV levels



PK Comparison to Non-pregnant Women

*HPTN 050

MTN-002



****Similar absorption to non-pregnant women****



Summary

- **PK of single-dose TFV gel in term pregnancy:**
 - Similar to non-pregnant
 - Serum TFV 50-100X < standard oral dosing
- **TFV gets to fetal compartment**
 - Low overall cord levels (40X lower than oral dosing)
 - Similar Cord:Maternal ratio (.53) as oral dosing
- **Single dose TFV 1% Gel safe in term pregnancy**
- **Findings + efficacy data justify more research**

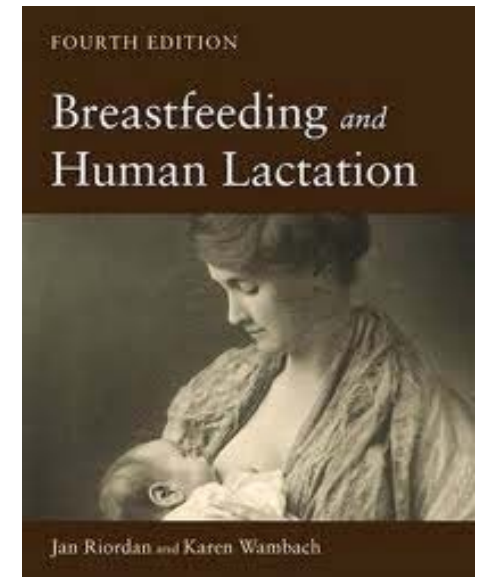


MTN-008

- **Expanded Safety Investigation of Tenofovir 1% Gel in Pregnancy and Lactation**

- **Primary Objectives:**
 - Safety & tolerability of TFV gel for 7 days
 - PK of TFV gel for 7 days

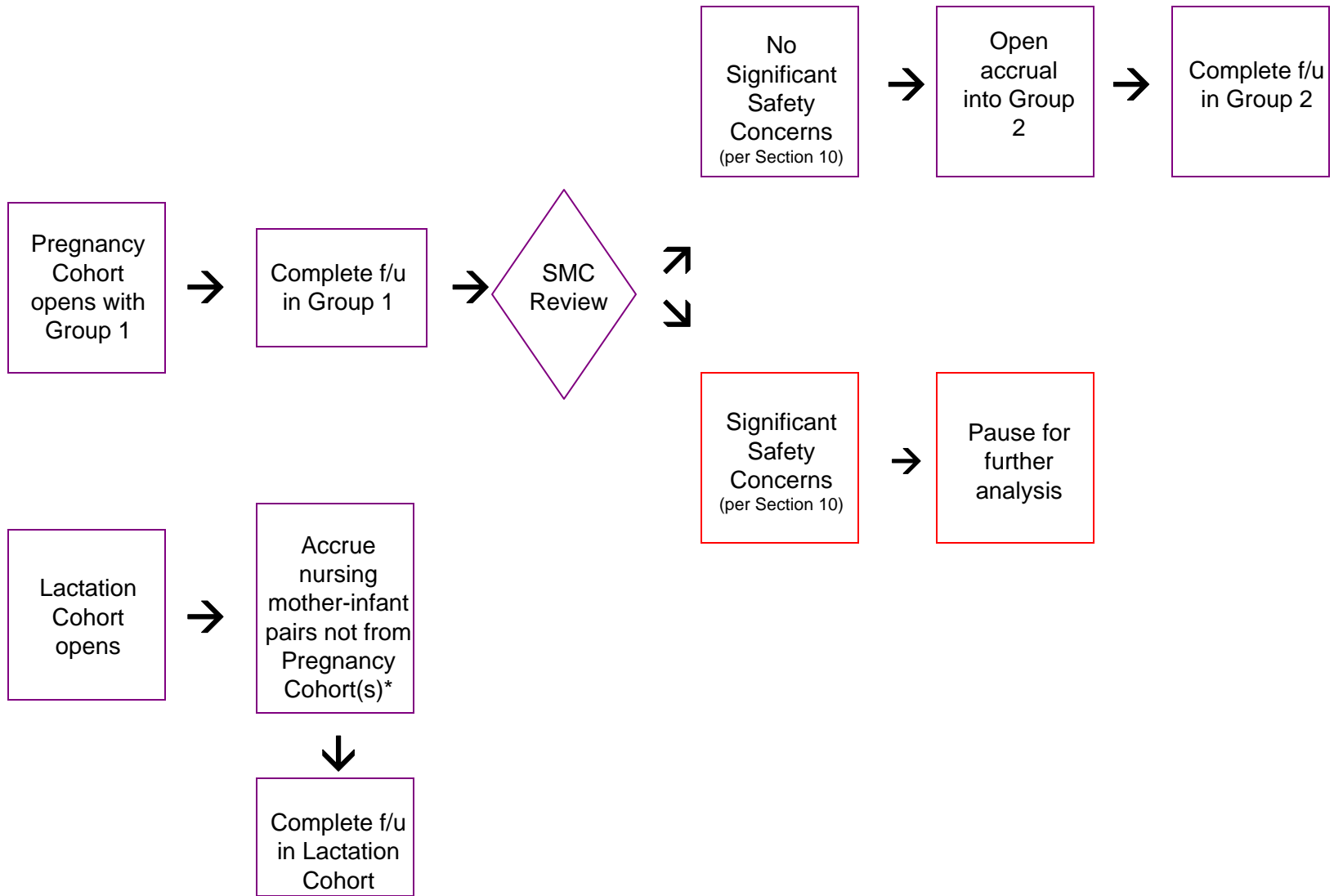
- **Secondary Objectives:**
 - Test for TFV in blood of infants
 - Impact of TFV gel on select organisms associated with neonatal sepsis → Pregnancy Cohort, (e.g., GBS, *E. coli*)
 - Adherence & acceptability TFV gel



MTN-008

□ **Exploratory Objectives**

- Measure vaginal flora and its changes with daily TFV gel use
- Effects of TFV gel on vaginal and cervical biomarker expression



MTN-016

MTN-016 – HIV Prevention Agent Pregnancy Exposure Registry (EMBRACE)

- Evaluation of Maternal & Baby Outcome Registry After Chemoprophylactic Exposure

- Prospective observational cohort:
 - Inadvertent exposures to microbicides and/or PrEP agents early pregnancy
 - Planned exposures late in gestations (MTN-002, MTN-008, etc.)

- Unique:
 - Real-time, built-in placebo arm, longer fu (1 yr),
 - Less bias



OBJECTIVES

□ **Primary Objectives:**

- Pregnancy loss: mothers exposed/not exposed to an active study agent
- Major malformations: infants exposed/not exposed to active study agent *in utero*

Secondary Objectives

- Adverse pregnancy outcomes
- Growth parameters in the first year of life among infants
- To provide a cohort of infants not exposed to active drug:
 - Represents background incidence of major malformations among babies born to women participating in HIV prevention trials

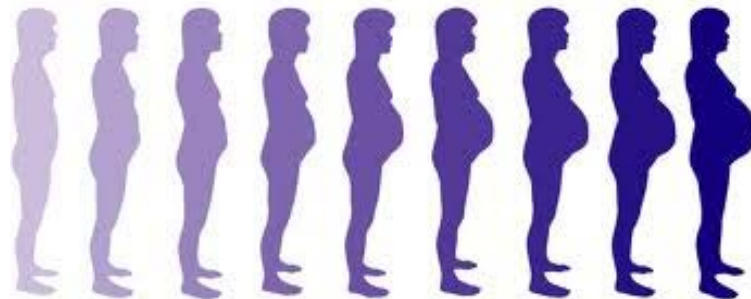


OBJECTIVES

- **Exploratory Objectives**
 - Monitor for select risks of prevention agents
 - Prevalence & persistence of HIV drug resistance mutations in HIV-infected infants
 - Compare infant developmental milestones 1st year

GOALS – MTN & PREGNANCY

- Proactively investigate HIV prevention agents during pregnancy
 - Delineate safety profile in real-time
 - Enable informed global use during pregnancy
 - Delineate a paradigm change for studying therapeutics in pregnancy
 - Challenge status quo
 - Does not serve pregnant women well globally



Acknowledgements

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