Critical Issues in Phase 2b and 3 Trials: Special Populations

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Overview

Special Populations

- Pregnant women
  - Participants who become pregnant during microbicide trials
- Adolescents

Introduction

- Historically, clinical trials of microbicides did not allow women who became pregnant to continue to use the investigational microbicide and excluded pregnant women to protect them and their fetuses from research-related risks
- Inclusion of adolescents in biomedical trials has been delayed, awaiting evidence of safety and effectiveness in adults
- Lack of data in these special populations may result in more harm because prescribing information is lacking and clinicians and patients may opt for no treatment or drug use with undefined risks
- Rational and responsible approach to inclusion of pregnant women and adolescents in microbicide trials became necessary for many reasons

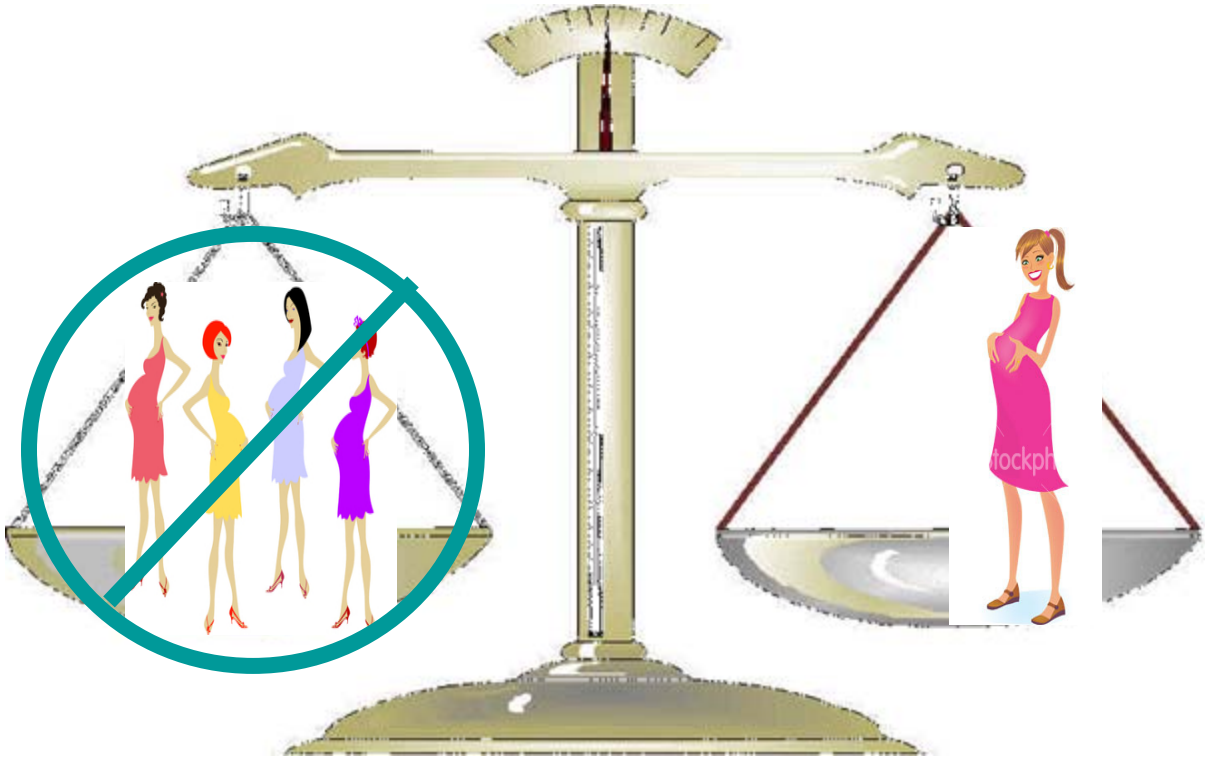
Pregnancy in Microbicide Trials

- Microbicide trials involve women of child bearing potential
- Trial premise relies on sexual acts → pregnancies will result
- Pregnancy rates have major implications for the conduct and interpretation of trials
  - In previous trials of microbicides pregnancy rates up to 22%
  - Resulted in discontinuations
    - Impacted conduct of trial and interpretation of results

Current Thinking

- Lack of data in pregnant women may result in more harm
  - Potential fetal exposure may occur before a woman knows she is pregnant
  - Microbicides will likely be used off-label in pregnant women post-approval
  - Rigorous data collection only possible in the clinical trial setting
  - Post-approval reporting of adverse events is voluntary and difficult to interpret

Contraception vs Pregnancy: need balance



on-site contraception counseling to prevent pregnancies

If sufficient nonclinical/clinical data available, then women who become pregnant make informed decisions

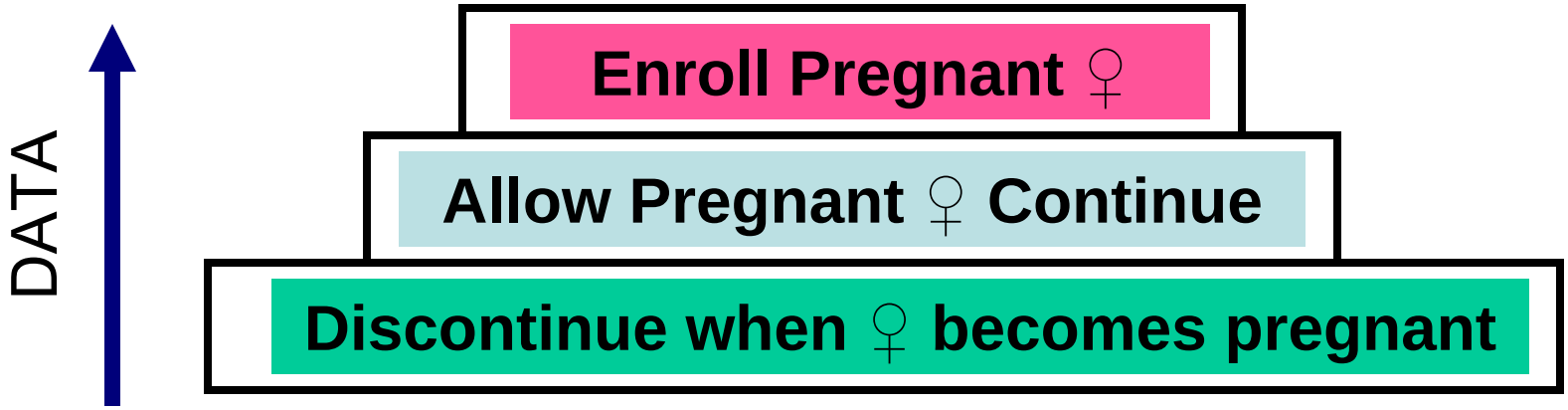
Regulatory Approach Evolving

To allow women who become pregnant while on study to continue depends on:

- Completed reproductive toxicology (Segment I, II, III) and genotoxicity nonclinical studies
- Chronic toxicity studies (2 species) to support duration in human trials
- Determination of systemic absorption in non-pregnant female subjects
- Carcinogenicity studies should be initiated concurrently with phase 3 clinical studies or before
- Decision made on a case-by-case basis depending on type of abnormality, background rate, safety factors, etc.

Current Thinking

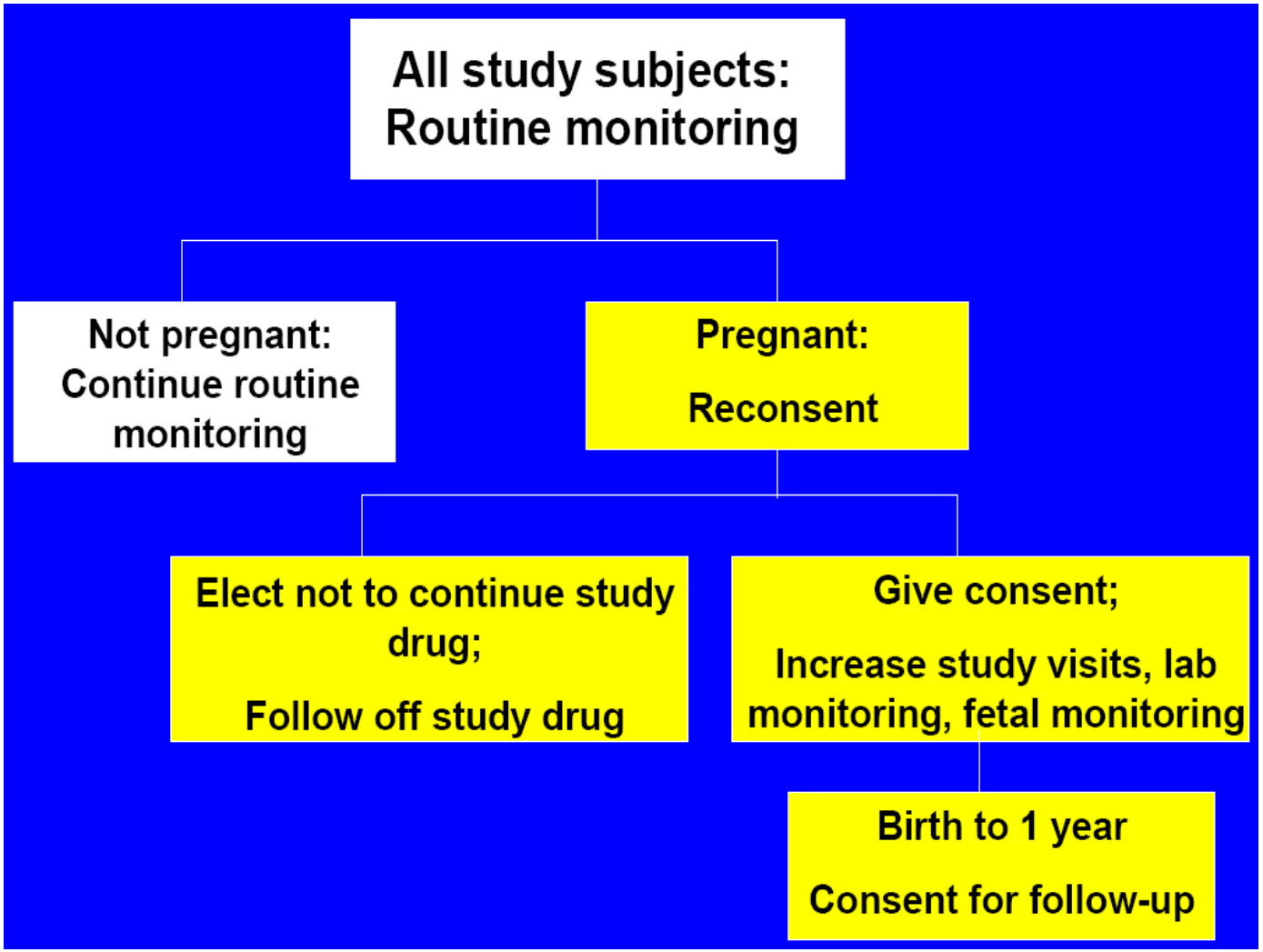
Decisions on the study of a particular microbicide during pregnancy must be made on a case-by-case basis



Regulatory Approach Evolving

- **But additional data are needed if a woman who becomes pregnant continues in the trial:**
  - Increased monitoring of the pregnant woman and the fetus/infant
  - Pharmacokinetic(PK) data during pregnancy, the postpartum period, and possibly lactation if product is absorbed

Rigorous Safety Monitoring



Monitoring of Pregnant Women: FDA Guidances

- Collection of pharmacokinetic data during pregnancy
  - PK Studies in Pregnancy - draft guidance
- Collection of safety data for fetus / infant - two guidances:
  - Evaluating the Risks of Drug Exposure in Human Pregnancies
  - Pregnancy Exposure Registries

Collection of Pharmacokinetic Data During Pregnancy

- Why collect more PK data?
  - Physiologic changes in pregnancy such as change in total body weight and fat composition, increased extracellular fluid, changes in blood flow etc.
  - Potential for increase in local absorption
- Recommendations in FDA Guidance
  - Study design
    - Longitudinal study with subject as own control and PK in all 3 trimesters

Monitoring of Pregnancy Outcomes

- Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies
  - Classification of outcomes
  - Background birth defect rates
  - Types of defects - major vs minor, grouping by embryologic origin
  - Timing of exposure
  - At least one year of follow-up

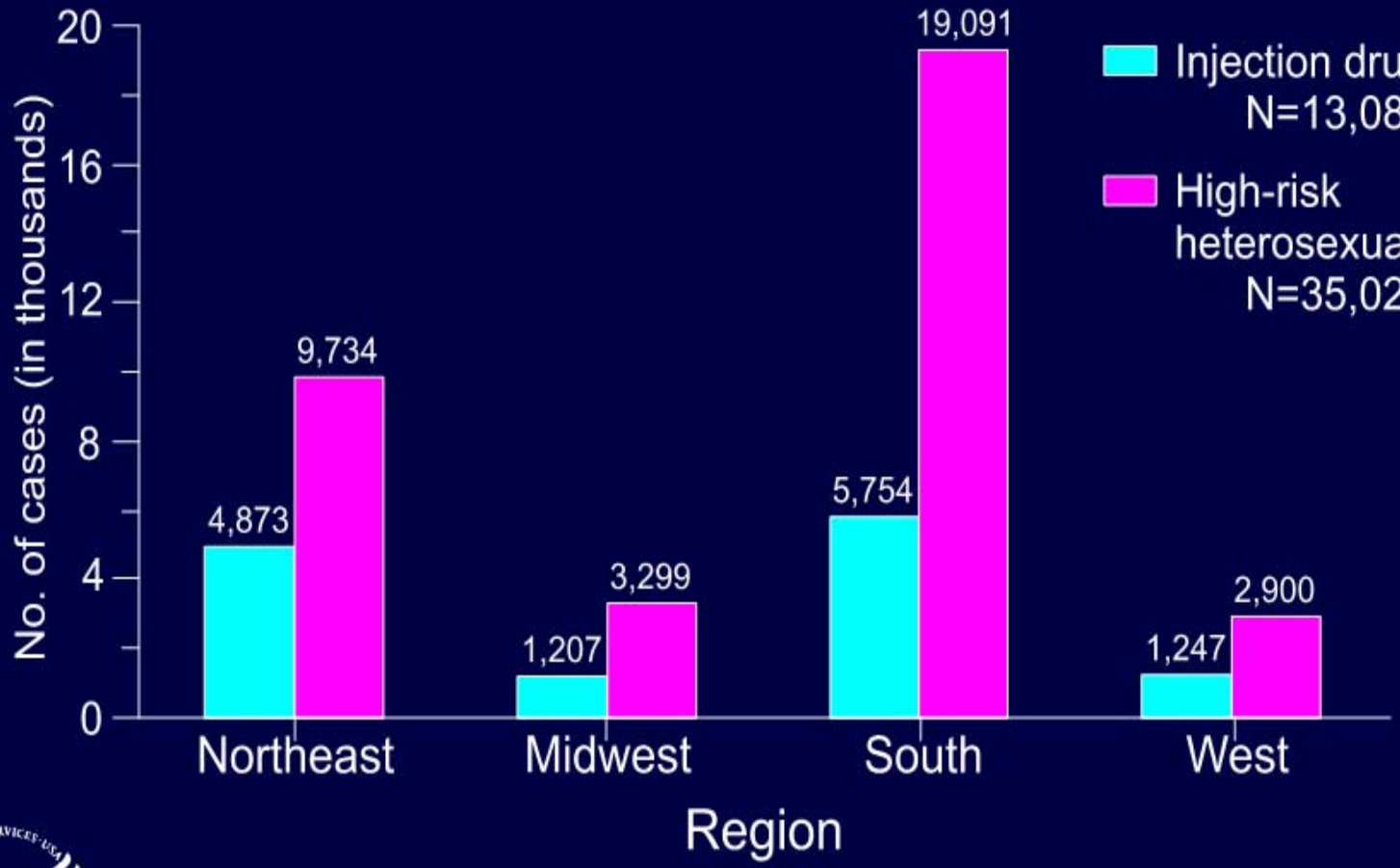
Adolescents and Microbicides

Estimated Numbers of HIV/AIDS Cases among Female Adolescents and Young Adults, by Transmission Category 2004–2007—34 States

Transmission category	13–19 years N	13–19 years %	20–24 years N	20–24 years %
Injection drug use	219	11	555	13
High-risk heterosexual contact*	1,694	88	3,846	87
Other/not identified†	7	<1	16	<1
Total	1,920		4,417	

Note. Data include persons with a diagnosis of HIV infection regardless of their AIDS status at diagnosis.
Data from 34 states with confidential name-based HIV infection reporting since at least 2003.
Data have been adjusted for reporting delays and missing risk-factor information.
*Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
†Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.

AIDS Cases among Female Adults and Adolescents Attributed to Injection Drug Use or High-Risk Heterosexual Contact, by Region, 2003–2007—50 States and DC



Note. Data have been adjusted for reporting delays and missing risk-factor information.
* Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

Rationale for Evaluation of Microbicide in Adolescents

- The majority of HIV/AIDS cases diagnosed among adolescent and young adult females in the US were attributed to high-risk heterosexual contact
  - Inability to negotiate condoms
- An approved microbicide may be used by individuals under age 18
  - No established safety profile in this age group

Basic Ethical Framework

- The basic ethical framework for additional safeguards for children enrolled in research is widely accepted throughout the world.
- An intervention that does not offer a prospect of direct benefit to the enrolled child must be no more than “low” risk.
- The risk of an intervention that is not “low” must offer the enrolled child a sufficient prospect of direct benefit to justify that risk, and the balance of risk and potential benefit must be comparable to available alternatives.

Potential direct benefit must justify risk

- As the experimental intervention likely exceeds a “minor increase over minimal risk”, there must be sufficient data (usually from adult human trials) to establish that the prospect of direct benefit is sufficient to justify the risks.
- Complex quantitative and qualitative judgment
  - Importance of “direct benefit” to subjects
  - Possibility of avoiding greater harm from disease
  - Justification set in context of disease severity (e.g., degree of disability, life-threatening) and availability of alternative treatments.

- This "threshold" for including adolescents in trials (either as a stand-alone or as part of an adult trial) may vary between products, and may shift based on the results of past experience for that product or class.

Considerations in Enrolling Adolescents in Microbicide Trials

- HIV is a serious/life-threatening condition
- Prevalence of HIV among adolescents
- Likelihood of adolescent usage after approval
- Differences in vaginal mucosa between adolescence and adulthood

Enrolling Adolescents in Microbicide Trials

- Approaches
  - Appropriate consent procedures
  - Safe-sex counseling and condoms
  - Small adolescent trial may be initiated if interim safety and possible efficacy data from Phase 3 trials indicate favorable findings to balance risks
  - Initiate trial first in older adolescent group e.g.

    16-18 yrs before < 16 yrs
  - Trial could provide useful safety information prior to approval
    - Extrapolation of adult efficacy data to adolescents may be used to justify approval in adolescents but exposure-response needs further exploration
    - Pediatric safety is never extrapolated

Summary

- Regulatory approach to microbicides in pregnancy is evolving
- Limited information in Federal Regulations or FDA Guidances about studying drugs in pregnant women
- Decisions about microbicide use during pregnancy and in adolescents must be made for each individual drug product (drug and vehicle) based on the safety profile in clinical and nonclinical studies
- There is a unique opportunity to systematically and rigorously collect safety, pharmacokinetic, and activity data on the use of microbicides in pregnancy and in adolescents

FDA Guidances
www.fda.gov/cder/guidance/index

- Guidance for Detection of Toxicity to Reproduction for Medicinal Products, ICH-S58, 1994
- Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals, ICH S2B Genotoxicity, 1997
- Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, ICH M3
- Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, July 1993
- Pharmacokinetics in Pregnancy (Draft), October 2004
- Evaluating Human Pregnancy Outcome Data, April 2005
- Pregnancy Exposure Registries, August 2002
- Clinical Lactation Studies (Draft), February 2005
- Regulations
  - Proposed Rule on Pregnancy Labeling Initiative, May 2008

Acknowledgments

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