Regulatory Considerations for Microbicide Development

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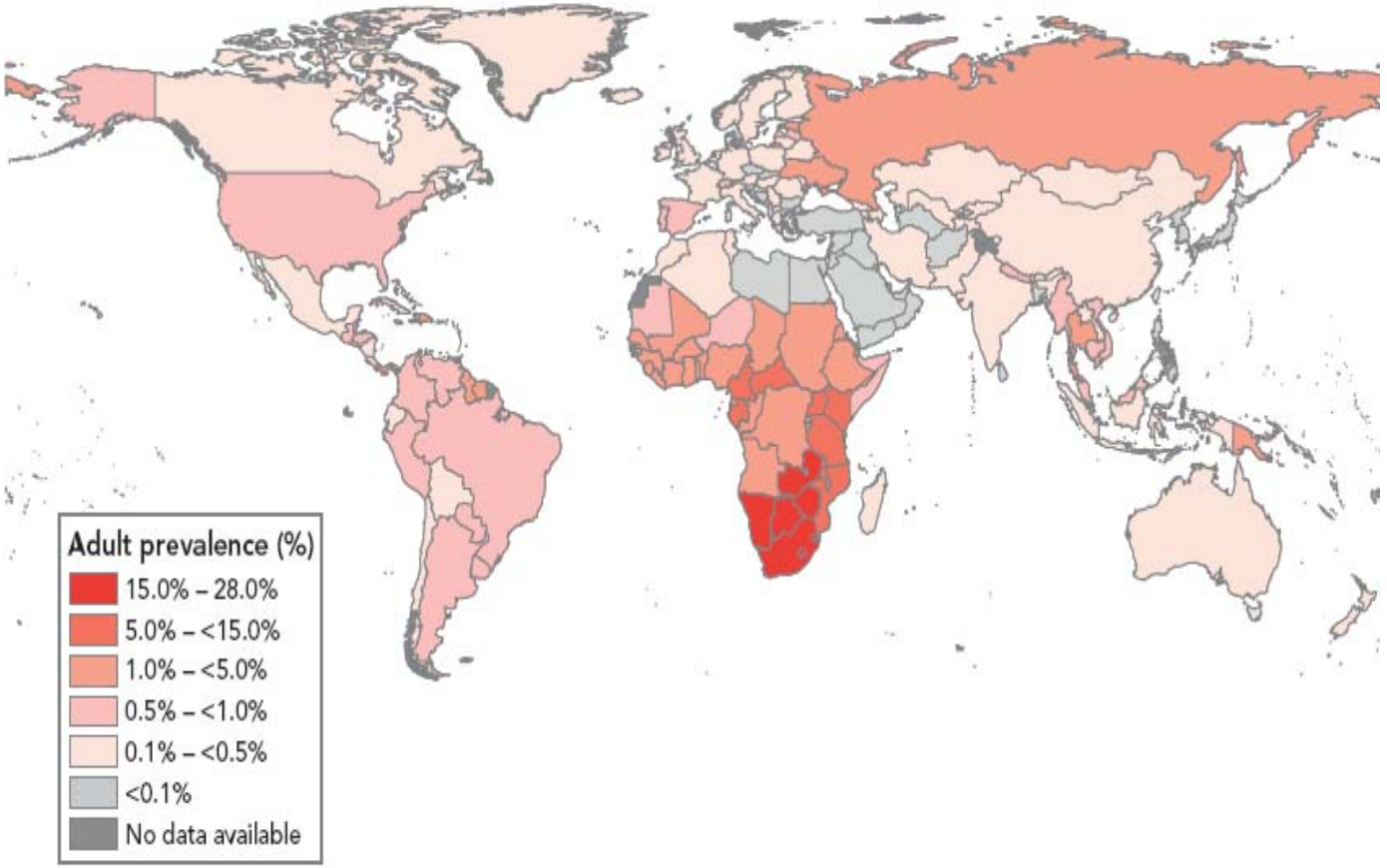
Outline of the talk

- The HIV epidemic
  - Need for prevention of HIV transmission
- Introduction to Prevention
  - Precedents for prophylaxis or prevention
  - Modalities for HIV prevention
  - Vaginal microbicides
- Regulatory perspectives in microbicide development
  - Non-clinical considerations
  - Clinical considerations

A global view of HIV infection

33 million people living with HIV

UNAIDS report 2007

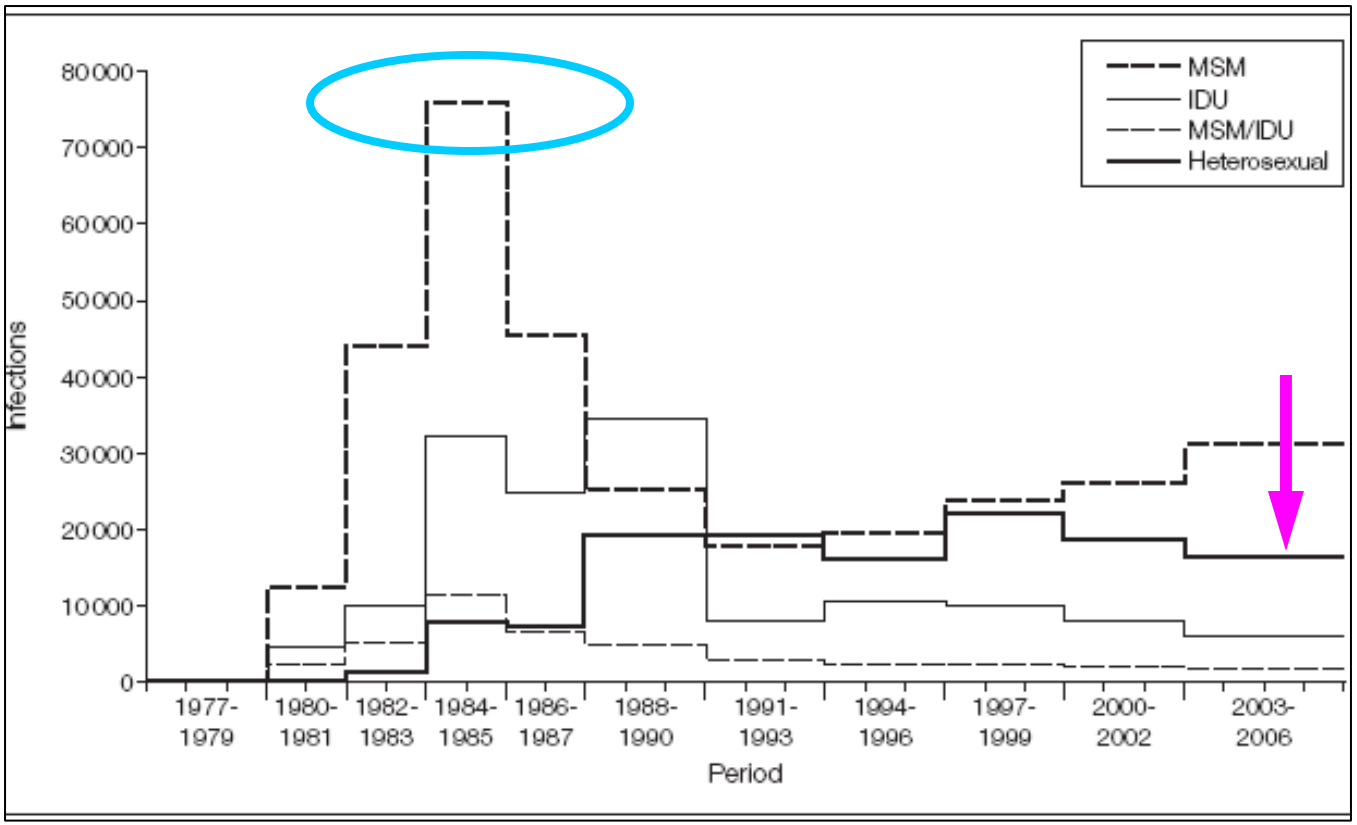


The HIV Burden

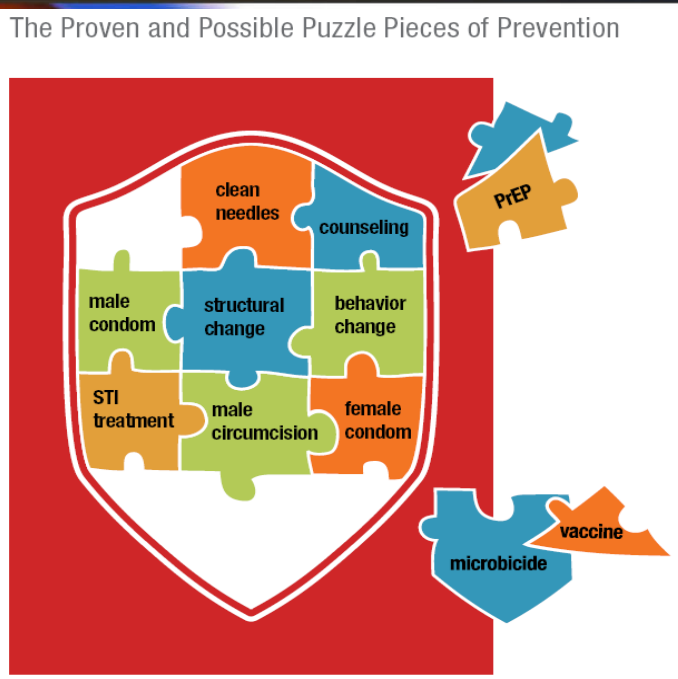
- Worldwide
  - Number of annual AIDS deaths has declined due to increased access to HIV treatment
  - 2.7 million new HIV infections in 2007
  - Globally, women account for 50% of people living with HIV
  - Sub Saharan Africa with the highest rates
    - Accounts for 67% of global HIV infection
    - 15-28% HIV prevalence in the adult population
- United States
  - HIV prevalence: CDC estimates 1,106,400 persons infected in 2006
  - HIV incidence: 56,300 people were newly infected in the year 2006

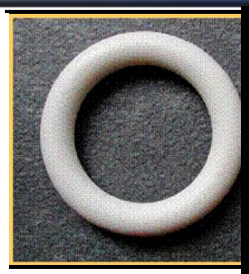
New HIV Infections in the United States

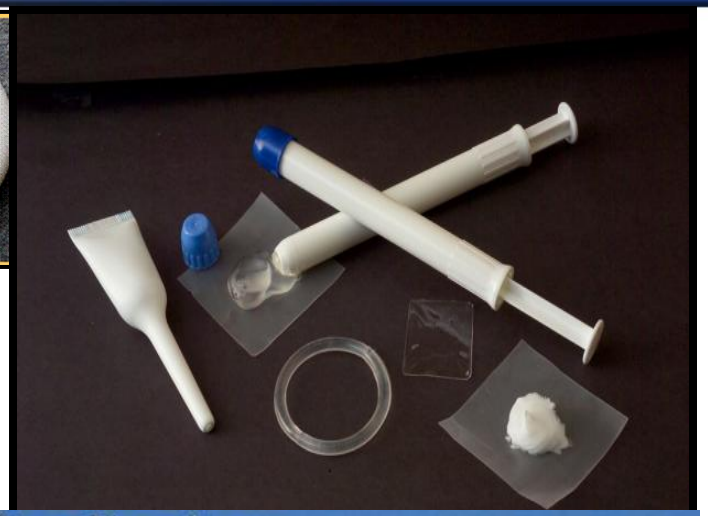
1977-2006

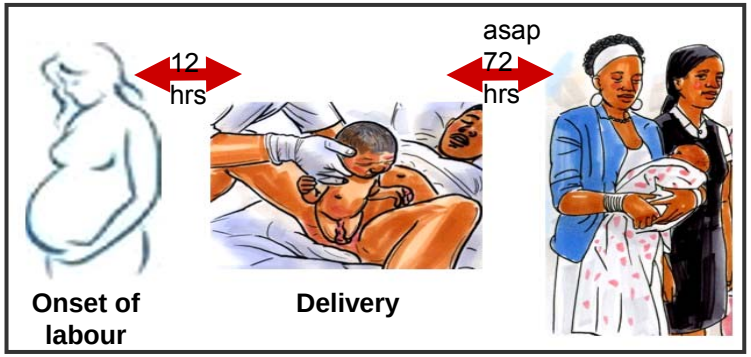


Hall et al. JAMA 2008









Different approaches to HIV prevention

Approaches to HIV Prevention

- Behaviorally-focused
  - Condoms
  - Risk-reduction counseling
  - HIV testing
- Medically-focused
  - Prevention of mother-to-child transmission (MTCT)
  - Post-exposure prophylaxis
  - Male circumcision
  - Oral Pre-exposure prophylaxis (oral PrEP)
  - Vaginal microbicides
  - ART for HIV-infected individuals
  - HIV Vaccine

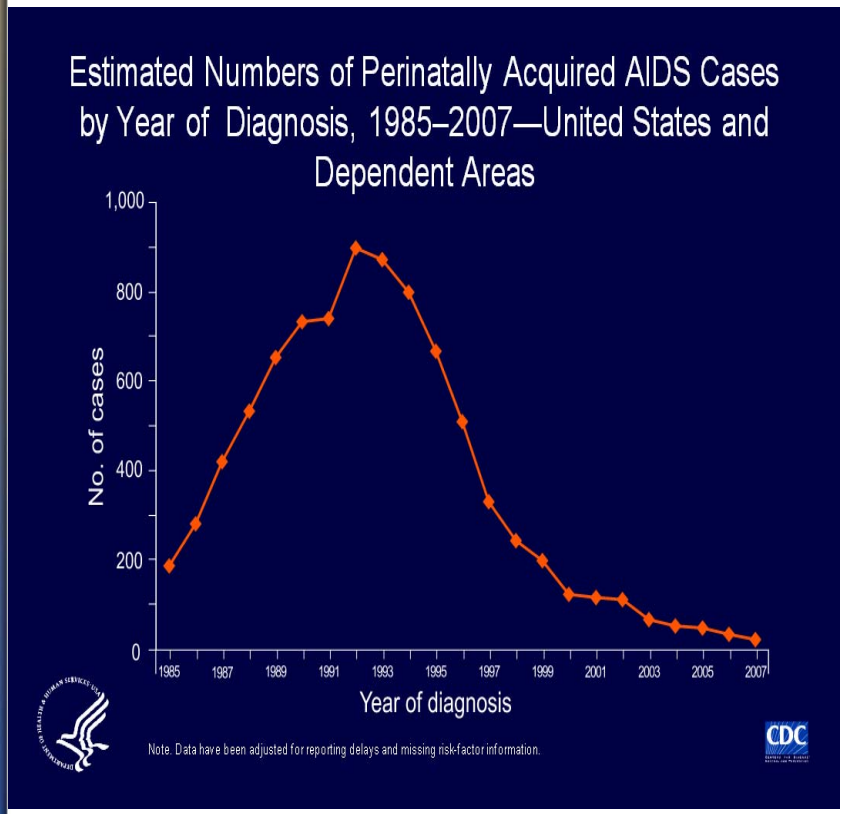
Precedents for Prevention or Prophylaxis of Infection

- Trimethoprim-sulfamethoxazole prophylaxis to prevent *Pneumocystis* pneumonia
- Endocarditis prophylaxis for abnormal heart valves
- Isoniazid for latent tuberculosis

- HIV prophylaxis examples
  - Prevention of mother-to-child transmission
  - Post-exposure prophylaxis
  - Male circumcision

Precedence for HIV Prophylaxis (1)

Prevention of Perinatal Transmission



- HIV testing in pregnancy
  - When pregnancy is detected
  - Repeat testing in 3rd trimester
  - Rapid HIV test at time of labor for those with unknown status
- Elective C-section if HIV VL > 1000 copies/ml
- ART during pregnancy; labor and delivery; ART for newborn

Precedence for HIV Prophylaxis (2)

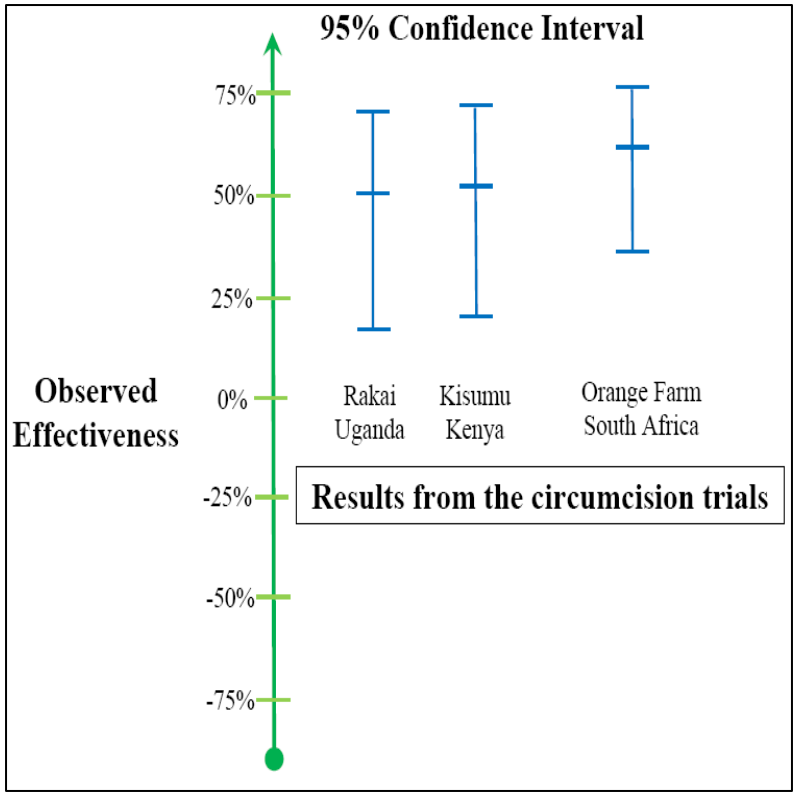
Post-exposure prophylaxis for HIV

1. Occupational Exposure to HIV:
   - Antiretroviral PEP reduces HIV transmission
     - Recommend 2- or 3-drug PEP based on type of exposure and infection status of source
     - 81% decrease in incidence of HIV was observed with prompt zidovudine administration following needlestick injuries

2. Non-Occupational Exposure (IVDU, sexual):
   - No definitive evidence for risk reduction, however, observational studies appear supportive

Precedence for HIV Prophylaxis (3)

Male Circumcision



- Three clinical trials demonstrate reduction in HIV infection rates by 50%-60%
- No evidence of reduction of HIV transmission from men to women
- Mechanism unclear

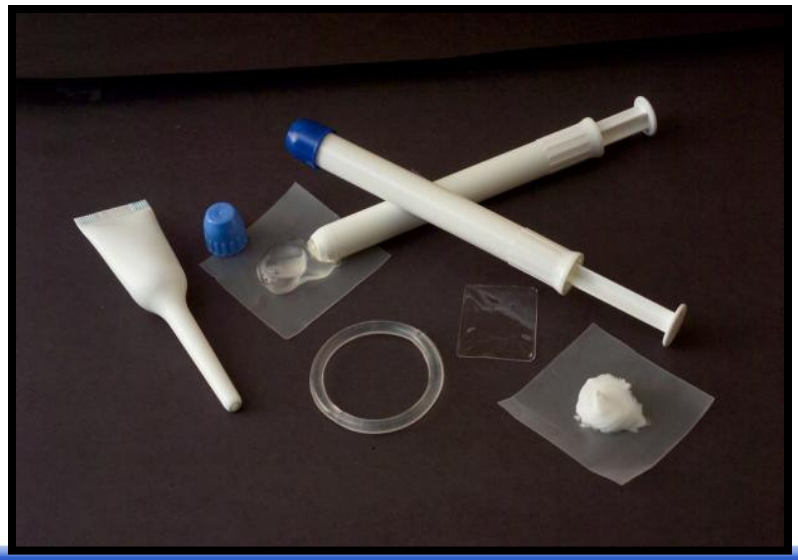
Bailey RC et al Lancet 2007; 369:643-56

Vaginal Microbicides

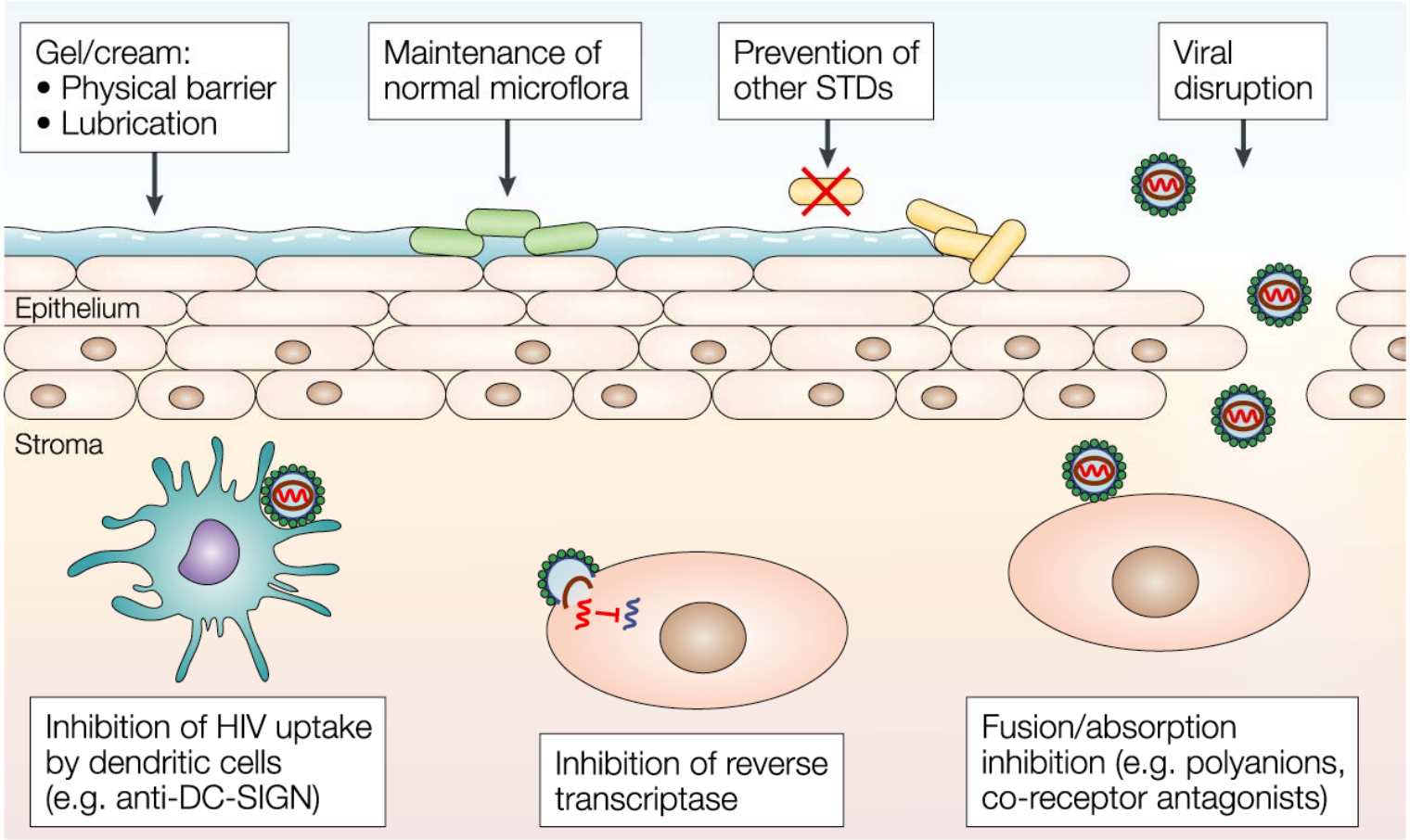
What are microbicides?

- Microbicides are products that are applied to genital or rectal mucosa for HIV prevention

- Block HIV at the portal of entry, and directly at the mucosal level through delivery of high drug concentrations locally



How would microbicides work?



Nature Reviews | Microbiology

Mechanism of Action

- Antiretroviral (ARV)-based
  - Active ingredient is an ARV
    - Specific target is HIV
    - Tenofovir gel: NRTI
      - Oral tenofovir tablet is approved for HIV treatment
      - Animal studies show topical tenofovir gel can prevent vaginal transmission of SIV
    - Maraviroc gel: CCR5 co-receptor inhibitor
    - Dapivirine ring, UC 781 gel: NNRTI
- Non-ARV based
  - E.g. Buffering agent: Buffergel, Acidform

From public sources: www.natap.org and www.avac.org

Delivering Vaginal Microbicide

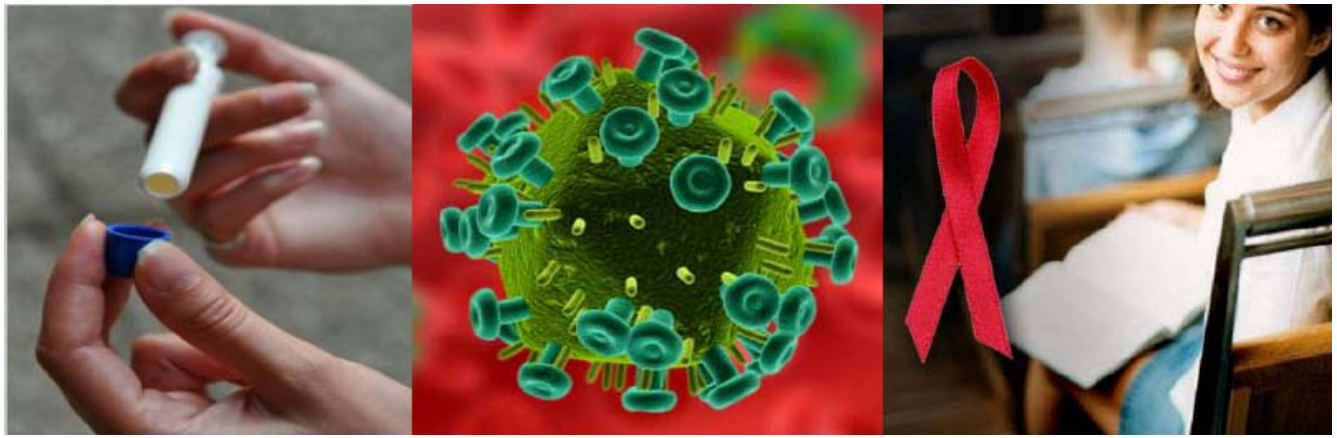
- Different ways of delivering active product to the vaginal surface
  - Gel
  - Intravaginal ring impregnated with active product
  - Vaginal cream or film
  - Cervical barrier impregnated with active product
  - Condom impregnated with active product

Vaginal applicator for gel

Vaginal ring impreganted with drug

Advantage of Vaginal Microbicide

- An effective vaginal microbicide will offer a female-controlled option for HIV prevention
  - Important issue in settings where women are unable to persuade their spouses or sex partners to use a condom



Microbicide Trials Outcome (1)

- Nonoxynol-9 gel (N-9)
  - N-9 approved for vaginal use as a spermicidal contraceptive
    - Surfactant – damages the spermatozoa lipid membrane
  - Was evaluated in phase 3 trials as a vaginal microbicide
    - Significantly lower incidence of HIV in the placebo arm compared to N-9 arm (2000)
    - N-9 users were more likely to develop vaginal ulcers
  - Conclusion: N-9 increased HIV transmission

Van Damme L et al. Lancet 2002;360(9338)971-7

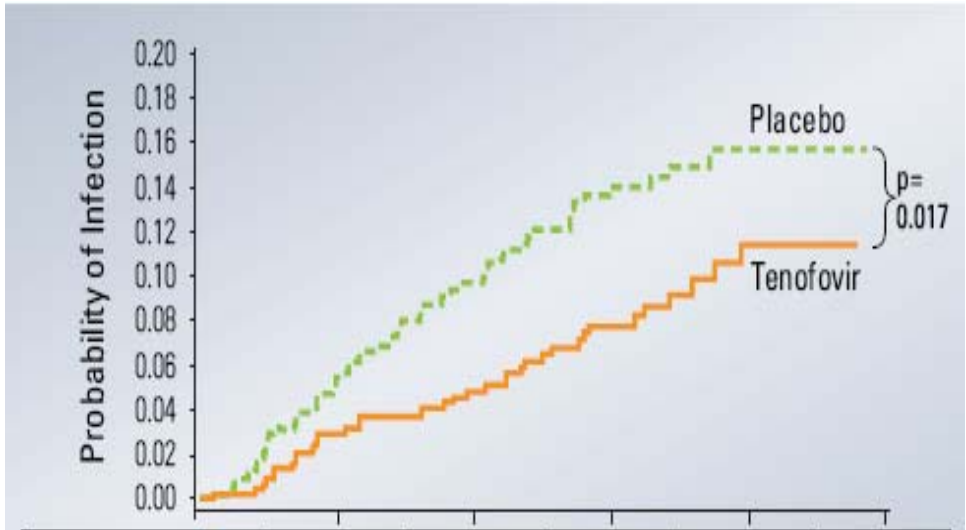
Microbicide Trials Outcome (2)

- Savvy gel
  - Phase 3 trials unable to detect a difference between treatment arms (2006)
  - Lower-than-estimated HIV incidence in Ghana
- Cellulose Sulfate gel
  - Higher rate of HIV infections in CS arm than placebo (2007)
- Carraguard gel
  - Failed to show effectiveness (2008)
- PRO 2000 gel
  - Failed to show effectiveness (2009)

SAVVY (C31G) gel for prevention of HIV infection in women. Peterson L et al PLoS One. 2007;2(12):1312
Lack of effectiveness of Cellulose Sulfate Gel for Prevention of HIV transmission NEJM 359;5;463-473
Efficacy of Carraguard for prevention of HIV infection in women in South Africa. Skoler-Karpoff et al. Lancet Vol 372;9654;1997-1987
HIV prevention gel PRO2000 proven ineffective. Insciences.org/article

Outcome: Tenofovir Gel CAPRISA 004

- Oral Tenofovir – approved for treatment of HIV
- CAPRISA 004: tenofovir vaginal gel compared to placebo vaginal gel
- 38 new HIV infections in TFV gel arm compared to 60 infections in placebo gel arm
- Proof-of-concept that topically applied ARVs can interrupt HIV transmission in women



Months of follow-up	6	12	18	24	30
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 10.2	5.6 vs 9.1
Effectiveness (p-value)	**47%** (0.064)	**50%** (0.007)	**47%** (0.004)	**40%** (0.013)	**39%** (0.017)

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Tenofovir Gel CAPRISA 004

- Reduction in HSV-2 seroconversion rate by 51% in the TFV gel arm compared to placebo gel arm
- Among women with high gel adherence (used gel > 80%), 54% reduction in HIV infection observed
- Safety findings
  - No increase in the overall rate of side effects
  - No increase in renal, hepatic, hematologic and bone adverse events
  - Inadequate safety data in persons with compromised renal function and those with HBV infection

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Regulatory Considerations for Vaginal Microbicides

Phases of Typical Drug Development

- Phase 1
  - Dose escalation, Drug-Drug interaction
  - Safety, PK
  - Generally healthy subjects

End of Phase 1 Meeting

- Phase 2
  - Proof of efficacy, dose-finding, safety
  - In target population

End of Phase 2 Meeting

- Phase 3
  - Efficacy and safety
  - Single large trial or two trials
  - Designed to support FDA approval

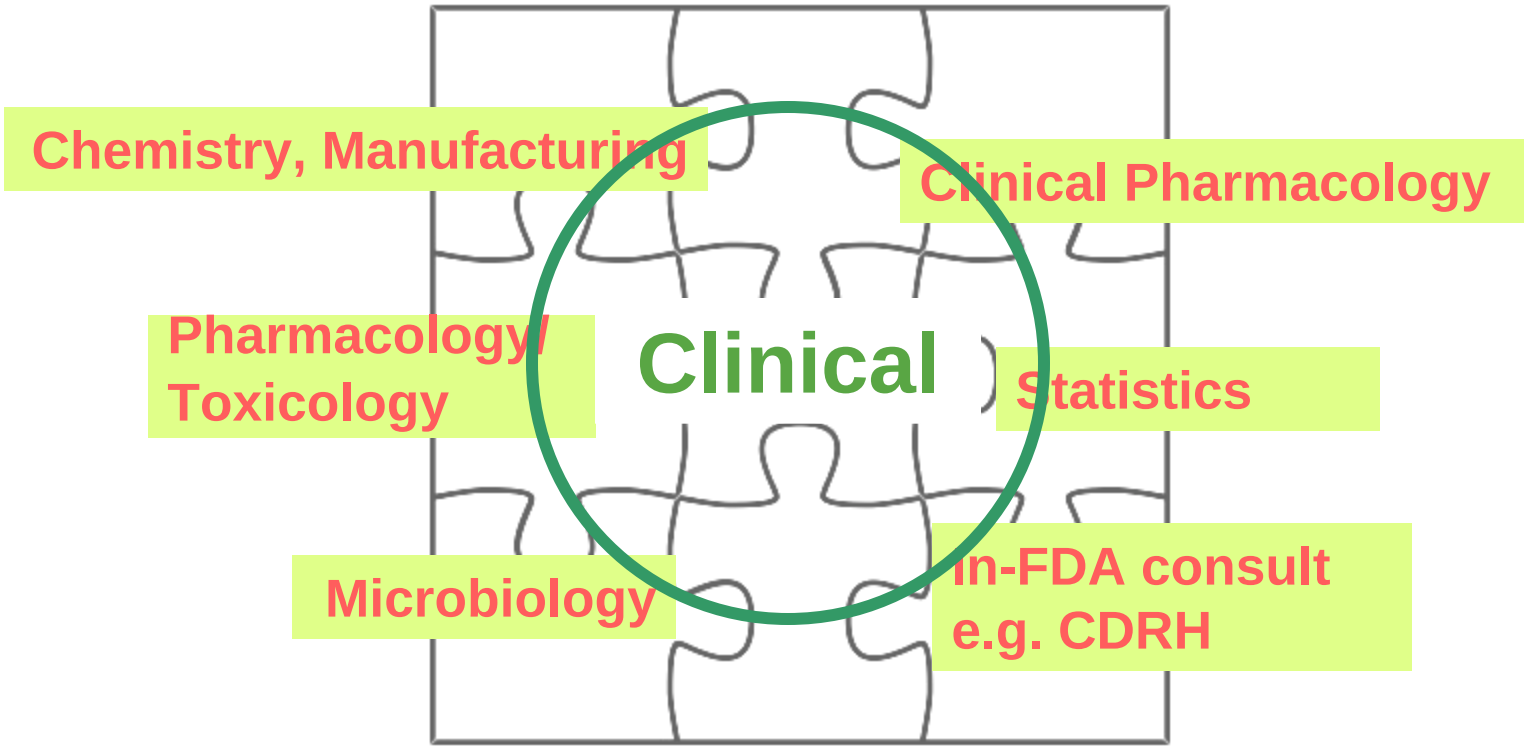
Pre-NDA Meeting

Approach to Microbicide Development

- Microbicide development differs from typical antiviral drug development
- Focus on important regulatory issues specific to development of topical vaginal microbicides
  - Nonclinical
  - Clinical

IND review team

- Investigational New Drug (IND)
- IND is reviewed by experts from various disciplines



Pharmacology/Toxicology Considerations

Prior to Human Exposure	During Clinical Trials
•Rabbit vaginal irritation test	•Repeat-dose toxicology studies (longer term)
•PK studies to determine systemic absorption	•Segment III reproductive toxicology study
•Repeat-dose general toxicology	•Genetic toxicology studies completed prior to Phase 2
•Safety pharmacology studies	•Initiation of carcinogenicity studies prior to or concurrent with Phase 3
•Genetic toxicology studies (≥ 2)	
•Segment I and II reproductive toxicology studies	

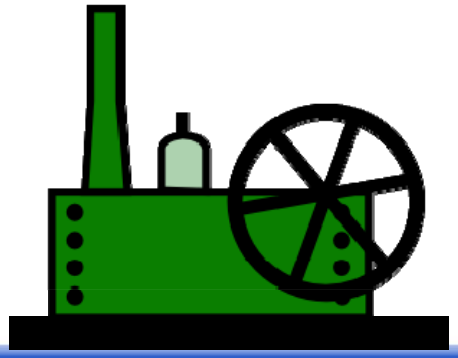
Microbiology/Virology Considerations

- In Nonclinical Studies
  - Antiviral activity
    - With pH adjustment,
    - In the presence of seminal plasma
  - Impact on normal vaginal flora
  - Cross resistance and selection of resistant HIV variants
  - Tests should use relevant clinical isolates of HIV

- In Clinical Trials
  - Effects on normal local flora
  - Sexually transmitted infections other than HIV
  - Diagnostic assays should be sensitive to regional strains
  - Resistance analysis

Formulation Considerations

- Some critical issues related to product chemistry, manufacturing and controls
  - Data assuring quality of drug substance, drug product, and placebo
  - Product consistency across batches
  - “Sameness” of Phase 3 material and commercial product
  - Specification tests, e.g. viscosity, pH, microbial limits
  - Stability across pH and temperature range
  - Adequate packaging/delivery system
  - Assessment of condom compatibility



Clinical Considerations Phase 1 microbicides

- Similar to usual drug development
  - Focus on safety, tolerability and PK
  - Clinical evaluation of systemic absorption
  - Single and multiple doses
  - Exclude pregnant or lactating women, individuals with renal or hepatic abnormalities

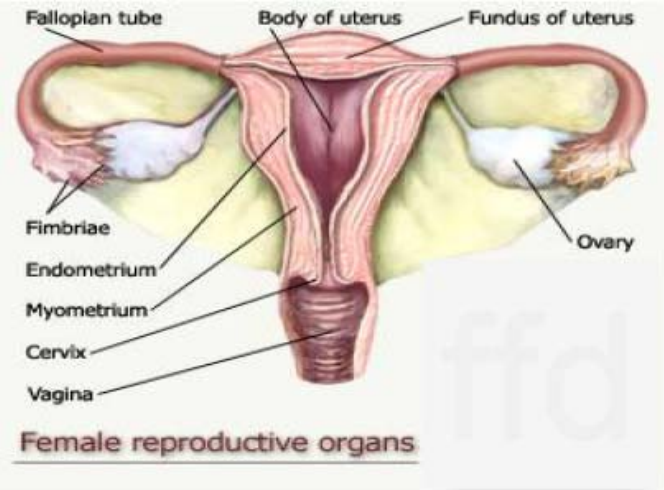
- Specific to microbicides
  - Assess effects related to genital mucosa, surrounding tissue, and local ecology
  - Conduct penile irritation studies
  - Include sexually abstinent or sexually active women (adequate birth control methods)

Clinical Considerations Phase 1 microbicides

- Early microbicide trials should focus on safety
  - Effects on genital mucosa
    - Mucosal irritation
    - Mucosal breakdown
    - Changes in microflora
  - Focus on whether vaginal product is absorbed systemically (systemic side-effects?)
- Acceptability studies (do women and their partners accept the product?)

Safety Considerations

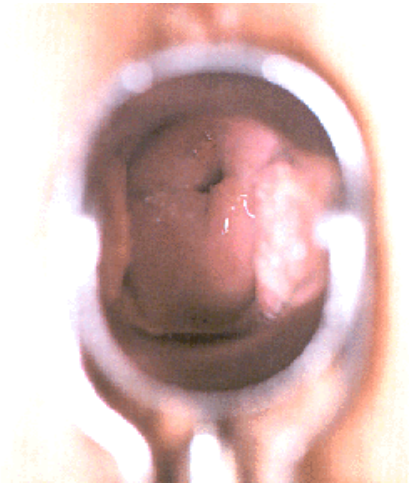
- Safety evaluations to include
  - General physical assessment
  - Gynecologic examination
  - Laboratory testing



- Important that product not cause genital toxicity or increase HIV transmission
  - Nonoxynol-9, a surfactant
  - Shown to increase risk of HIV infection by causing genital epithelial disruption

Genital Toxicity

- Genital toxicity
  - Genitourinary adverse events (AE), e.g. pain, bleeding
  - Visual inspection, speculum exam
  - Signs of epithelial irritation, ulceration, inflammation, or changes in normal vaginal flora
  - Use accepted criteria to grade genital abnormalities, e.g. DAIDS genital toxicity criteria



Genital Toxicity

- Colposcopy
  - Required in at least one Phase 1 trial conducted in sexually active women
  - Focus on findings representing epithelial disruption
  - Utilize standard criteria for technique, e.g. WHO
  - Need for colposcopy in Phase 2 or 3 trials should be based on:
    - Colposcopic findings in Phase 1
    - Overall safety profile of the product
- Vaginal biopsy typically not required
  - Unless indicated by findings of local toxicity

Genital Safety

- Effects on sexually transmitted infection (STIs)
  - Concurrent genital ulcer disease due to STI can increase HIV transmission
  - Product may contain components inhibitory to STI assays, e.g. potential interaction between sulfated polysaccharides and PCR assays
- Effects on vaginal microflora
  - Changes in normally protective healthy vaginal microflora, H_20_2-producing *Lactobacillus* levels
- Effects on vaginal pH
- Potential effects on uterus, fallopian tubes, ovaries

Systemic Toxicity

- Systemic toxicity may arise if a product is systemically absorbed
- Routine assessments
  - Hematology and chemistry parameters
- Additional assessments may be required based on preclinical findings
- Non-NMEs approved as an oral formulation
  - Targeted safety assessment plan based on known safety profile; for example, tenofovir gel
- Grading of AE and lab abnormalities should be uniform
  - Commonly accepted toxicity grading schemes (WHO, DAIDS)

Clinical Pharmacology Considerations

- Collection of serial PK plasma samples in early trials to determine extent of systemic absorption
  - Necessary for both new molecular entities and approved agents being incorporated in a vaginal formulation
- Serial assessment of cervicovaginal fluid concentrations should be evaluated in early studies
  - To ensure sufficient local exposure, local distribution and persistence of product
- Determination of protein-binding in vaginal and seminal fluids is important for dose selection
- Consider systemic PK data collection in penile tolerability studies to assess systemic absorption

Acceptability

- Acceptability of product is linked to continued use of the product
  - Physical characteristics of gel
    - Odorless, tasteless, colorless
    - Leakage from vagina – viscosity, volume
  - Effects after Insertion
    - Non-irritating, side-effects
    - Effects on sensation during intercourse
- Assess acceptability in early trials
  - Through questionnaires, interviews

General Approach to Trial Designs for HIV prevention

- Effectiveness trials are randomized, double-blind, multicenter trials
- Comparison between
  - Study agent vs. placebo
  - Background provision of condoms to all subjects
- HIV seroconversion is the primary endpoint
  - Monthly visits for HIV testing
- Safety is the co-primary endpoint
  - Adverse event monitoring (genital, renal, liver side-effects)
  - Quarterly testing for CBC, renal, hepatic parameters
- Provision of intensive prevention services (behavioural counseling)
- HIV referral services for those who seroconvert

From public source: AVAC Global Advocacy for HIV Prevention PrEP Fact Sheet

Clinical Considerations Phase 2/3 microbicides

- Development moves from early studies into large phase 2/3 trials (Phase 2b/3 lead-in trial design)
- No early proof-of-concept microbicide trials
  - Because there is no surrogate marker for HIV infection
- Adherence
  - Markers such as trial pregnancy rates or frequency of STIs can indicate product adherence
  - Compliance with both condom and gel may greatly impact the HIV infection rates and treatment effect sizes

Clinical Considerations: Effectiveness

- Typically require two adequate and well controlled trials
  - Statistical significance (for each trial) based on strength of evidence corresponding to a one-sided p 0.025 or two-sided p < 0.05
- A Single Pivotal Trial: strength of evidence that would be “robust and compelling” p-value < 0.001 (two-sided)
- Future products may need to show efficacy compared to an approved microbicide

Problems with Short Term Trials

- Large short terms trials may not be suitable for the final regulatory decision
- Efficacy conclusions based on short term trials may lead to difficulties in conducting longer-term confirmatory trials
  - Need longer term evaluation for efficacy, safety and impact of behavior
- Shorter-term endpoints in a longer term trial may be used for futility purpose

Follow-up

- Continue study until last subject enrolled completes at least 12 months on study
- Assessment of longer-term efficacy and safety which may differ from short term
  - Adverse events could be due to cumulative exposure and may exacerbate over time
  - Adverse events can impact adherence, thereby impact effectiveness
- If approved, product will be used by subjects for lifetime, therefore the clinical trial needs to be able to describe the long-term safety and efficacy

Overall Risk/Benefit Assessment

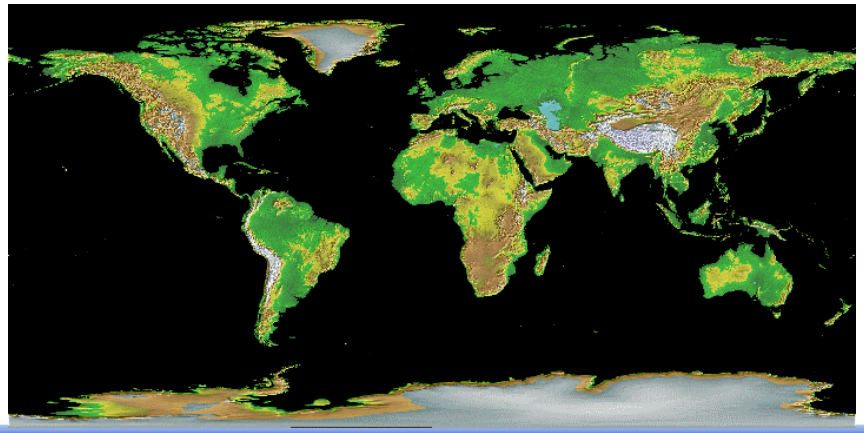
- Benefit as measured by percent reduction in HIV
  - Microbicide studies powered for at least 33% reduction
  - Recognize lower reductions may have large impact on areas with high HIV prevalence
- Totality of the data matters
  - Percent reduction versus side-effect profile
  - Potential issue of condom migration and increase rate of STIs
  - Public advisory committee meeting to discuss efficacy and safety

Foreign Clinical Trial Data

- FDA will accept foreign data
  - Sites must be ready for FDA inspection
- Contact FDA to schedule meeting to discuss data submission

Conclusion

- The FDA recognizes the important role that vaginal microbicides can play in efforts to control the HIV epidemic
- There are several regulatory considerations that are unique to development of vaginal microbicides
- Collaborative efforts among regulatory authorities are important



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- www.mtnstopshiv.org Microbicides Trial Network
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- FDA Guidance for Industry: Chemistry Manufacturing Controls
- FDA Guidance for Industry: Pharmacokinetics in Pregnancy Study design, Data analysis, and Impact on Dosing and Labeling
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