Regulatory Considerations for Microbicide Development

Charu Mullick, M.D.
Division of Antiviral Products
U.S. Food and Drug Administration

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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

Prevention of Perinatal Transmission

- HIV testing in pregnancy
  - When pregnancy is detected
  - Repeat testing in 3\textsuperscript{rd} 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
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
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

Male Circumcision

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?

- Gel/cream:
  - Physical barrier
  - Lubrication

- Maintenance of normal microflora

- Prevention of other STDs

- Viral disruption

- Inhibition of HIV uptake by dendritic cells (e.g. anti-DC-SIGN)

- Inhibition of reverse transcriptase

- Fusion/absorption inhibition (e.g. polyanions, co-receptor antagonists)
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](http://www.natap.org) and [www.avac.org](http://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 impregnated 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

• 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

- 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)

Lack of effectiveness of Cellulose Sulfate Gel for Prevention of HIV transmission NEJM 359;5;463-473
HIV prevention gel PRO2000 proven ineffective. Insciences.org/article
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
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.
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

Chemistry, Manufacturing
Pharmacology/Toxicology
Microbiology
Clinical Pharmacology
Statistics
In-FDA consult e.g. CDRH
## Pharmacology/Toxicology Considerations

<table>
<thead>
<tr>
<th>Prior to Human Exposure</th>
<th>During Clinical Trials</th>
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<tr>
<td>• Rabbit vaginal irritation test</td>
<td>• Repeat-dose toxicology studies (longer term)</td>
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<tr>
<td>• PK studies to determine systemic absorption</td>
<td>• Segment III reproductive toxicology study</td>
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<tr>
<td>• Repeat-dose general toxicology</td>
<td>• Genetic toxicology studies completed prior to Phase 2</td>
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<tr>
<td>• Safety pharmacology studies</td>
<td>• Initiation of carcinogenicity studies prior to or concurrent with Phase 3</td>
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<tr>
<td>• Genetic toxicology studies (≥ 2)</td>
<td></td>
</tr>
<tr>
<td>• Segment I and II reproductive toxicology studies</td>
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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$_2$O$_2$-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.
Selected References

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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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