Antiretroviral based microbicides: an overview

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What are antiretroviral (ARV)-based microbicides?

Antiretrovirals (ARVs) are chemical compounds that disrupt the molecular interactions essential and specific to HIV-1 replication at the cellular level.

Microbicides are vaginally and/or rectally applied gels, creams, films, rings, and/or suppositories that prevent the sexual transmission of HIV-1.

ARV-based microbicides contain a chemical compound(s) that disrupt molecular interactions specific to HIV-1 *infection* at the cellular level and are formulated as vaginally applied gels, creams, films, rings and/or suppositories to prevent the sexual transmission of HIV-1.
Early Generation Microbicides

- Gel products that non-specifically block HIV from interacting with target cells or are directly virucidal
  - Surfactants
  - Multiple poly-anions

- Short-acting (used just prior to or just after sex)

- Efficacy trials complete
  - Partial, low or no effectiveness
Next Generation Microbicides

• Based on successful HIV treatment drugs (IPM’s microbicide candidates fall in this category)

• Once a day or monthly use offering longer term protection

• Trial of tenofovir gel initiated May 2007
  The CAPRISA trial demonstrated 45% protection against HIV transmission
Microbicidies in product development

Free virus

Attachment

BufferGel
- PRO2000
- SPL7013 (VivaGel)
- RANTES analogs
- Cyanovirin-N
- DS003 (BMS 793)
- DS001 (Merck 167)
- Maraviroc (Pfizer)

Next-generation compounds

Early-generation compounds

Lactin-V
Invisible Condom
NCp7’s
GM Biotics (Osel)

Fusion

Reverse Transcription

Integration

Protein synthesis and assembly

Budding

Maturation

DS007 (Merck L’644)

S-DABO
Dapivirine
UC781
Tenofovir
PC-815

Pyrimidinediones (Samjin)

Integration

DS007 (Merck L’644)
ARV-Based Microbicides

• Advantages
  ▪ Highly potent and HIV-specific
  ▪ Established safety & efficacy in AIDS treatment
  ▪ Developed as single drugs and in combination
  ▪ Multiple mechanisms of action against HIV
  ▪ Can be formulated for sustained protection
    • Once a day / once a month (or less frequent)
    • Gels / rings / tablets / films (increased options)

• Disadvantages
  ▪ Potential to select for resistant virus in HIV+ persons is unknown
  ▪ Lack of activity against other STDs
  ▪ Likely to be prescription only
ARV-based microbicide development: TMC120/Dapivirine

Tissue culture - cervical explants - PBMC replication assays

Formulation - vaginal ring, gel, and film

Animal model - toxicity

HIV negative women - safety, pharmacokinetics
Global distribution of HIV-1 subtype variability
Do candidate microbicide ARVs protect against HIV-1 infection from different subtypes?

Entry inhibitors protected against HIV-1 infection better in combination over single compound treatment.
The scale of HIV-1 variation

Original analysis from Bette Korber, Los Alamos National Labs
Is ARV resistance a concern in microbicide development?

- HIV-1 mutation rate is high
- Incidence of drug resistant virus is increasing worldwide
- Some drug resistant HIV-1 variants are as ‘fit’ as drug susceptible HIV-1 variants and are transmitted just as easily
- ARVs that are similar to those used in treatment regimens may not be as efficacious against drug resistant HIV-1 in the context of microbicides

Question: Could ARV-based microbicides ‘select’ for drug resistant HIV-1?
incoming viral swarm is diverse and may include drug resistant variants

which variant establishes infection is unknown

Vaginal/Rectal Intercourse

Initial Infection/Transmission Event

Primary Infection

Systemic Infection

Progression of Infection

ARVs

HIV-1 variability/diversity
Why combine candidate microbicide ARVs?

**Advantages**
- Different mechanisms of virus-centered inhibition
- Block different steps of the replication cycle (safety net)
- Better blocks a variety of subtypes
- Better blocks a variety of resistant strains of HIV
- **Lower toxic effects**
- Possibility of synergy

**Challenges**
- Possibility for antagonism
- Difficult to demonstrate true/robust combination effect due to complex nature of HIV replication, lack of a standard protocol that accounts for HIV diversity, and ‘tricky’ data analysis
Microbicide development: pre-clinical evaluation of ARVs in combination

McGill AIDS Center
Mark A. Wainberg laboratory
ARV-based microbicide research supported by IPM

What we do
- test candidate microbicide ARVs in combination: tenofovir, dapivirine, DS001 & DS003
- test combination candidate ARVs against ‘wild type’ and drug resistant HIV-1 from multiple subtypes
- evaluate combined effect and the ‘robustness’ of this effect in increasingly more sophisticated in vitro systems

Key Findings
1. DS001 + DS003 is additive against HIV-1 infection
2. Tenofovir + dapivirine demonstrate synergy against wild type and drug resistant HIV-1 infection from multiple subtypes
3. Tenofovir + dapivirine synergy is stronger against dapivirine resistant ‘transmission fit’ HIV-1 infection (Y181C)

Key Question
What is the nature of the protective advantage demonstrated by combinations of candidate microbicide ARVs over single ARVs?
Microbicide development: Canadian contributions
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Phase III Clinical Trials
(CONRAD study & FHI study)

First analysis (2007)

HIV+ individuals

Conclusions

1. increased risk of HIV seroconversion was not statistically significant
2. no clear benefit as an HIV microbicide

Toronto, ON

Cellulose sulphate
USHERCELL (6% gel)
Microbicide development: Canadian contributions

Centre de recherche en infectiologie du CHUL
Dr. Michel Bergeron and team

A brief history

2000
Sodium lauryl sulphate (SLS) protects non-specifically against HIV-1 and HSV infections, surfactant
SLS a potential candidate for and microbicide development

2001
SLS abrogates HIV-1 infection by interfering with viral attachment to cells

2007
Safe, tolerable and acceptable to healthy women and their male sexual partners when gel formulation applied once or twice daily for 14 days

2008
SLS in gel formulation (ethylene oxide/propylene oxide gel, 2% SLS w/w) safe for most tissues that could be exposed under normal use when evaluated in rats and male/female rabbits
Novel applicator design distributes Invisible condom® throughout vaginal and cervical mucosae before and after simulated intercourse
Thank you.