Microbicides and Clinical Trials 101: An introduction

Manju Chatani-Gada, AVAC
Thesla Palanee, Wits Reproductive Health and HIV Institute

6 August, 2014
Presentation Overview

- The basics of clinical research and randomized controlled trials
- What is a microbicide?
- How might a microbicide work?
- Rectal microbicides
- Where are we in the search for microbicides?
- Future directions
The research process pathway

Basic science
Translational research
Clinical (human) trials
License
Post-effectiveness

Basic research
Preclinical research

Concept studies
Lab studies
Animal studies

Phase I
Smaller safety studies
Phase II
Larger, longer look at safety and immunogenicity
Phase IIb
Even larger look at safety and efficacy
Phase III
Even larger look at safety and efficacy
Open-label extension (OLE)/Post-trial access

Safety and efficacy
Real-world effectiveness

Often a product/intervention does not progress in a linear fashion, and can require multiple studies in each of the following phases:

Post licensure activities vary with each product/intervention, but likely include some combination of the following:

Demonstration Project
Phase IV Marketing studies
Product introduction

Quarter I, 2013. For more information visit www.avac.org.
Open-label, IIIb, post-licensure Phase IV marketing studies
Highlighted in darker blue are the areas where biomedical HIV prevention research has the most experience to date. The “gap” between positive effectiveness data and access for trial participants and their communities is less familiar territory – as are the steps in lighter blue.
How are clinical trials conducted?

The “gold standard” in research is a randomized and controlled study.

3 key concepts
- Controlled
- Randomized
- Double-blind
Goal is to assess if the active study product really works, by comparing to the control.

1. **Intervention or Active Arm**
   - Intervention Group (active product)
   - New HIV infections

2. **Control Arm**
   - Control Group (placebo)
   - New HIV infections

I find this slide a bit confusing. The next slide does a much better job in illustrating what randomization looks like. I guess it’s fine to keep because it covers basic, important topics, and next slide will help reinforce.
Why a placebo controlled trial?

• The gold standard
  – Best way to determine if a new drug or product is safe and effective

• Important for licensure

• Conducted when there is not already an approved product widely available and/or no clear evidence supporting a new indication
  – When warranted, trials are designed to compare one proven intervention with another proven method.

I pulled this slide from one of our presentations. The first bullet is a repeat of what is said in the slide just before, but perhaps you want to incorporate the other two bullets somewhere?
Measuring effectiveness

Randomized Controlled Trial

Random assignment

Control group

Placebo & prevention package

Follow-up

Compare results

Intervention group

Microbicide & prevention package

Follow-up

KEY

HIV uninfected women

Women who seroconverted during the trial

Women who are lost to follow-up or withdraw from the trial

Quarter I, 2013. For more information visit www.avac.org.
How do we determine efficacy?

- At the end of a study, the number of HIV infections that occurred among women who received an active product is compared with the number of HIV infections that occurred among women in the matched placebo group.
- We hope there are fewer HIV infections in the active drug group than in the placebo group and the difference is statistically significant.
- In this example, there are 55% fewer women who acquired HIV in the active product group.
- Can also say:
  - Active product reduced HIV risk by 55%
  - Active product 55% more effective compared to placebo
  - Active product 55% effective.

It would be nice to use/explain this way of looking at effectiveness since we use in other presentations.
Safeguards in clinical trials

- International Ethical Standards
- National Regulatory Bodies
- Institutional Review Boards (IRBs)/Ethics Review Committees
- Community/stakeholder input – governed by Good Participatory Practice (GPP) guidelines
- Informed Consent
- Adverse event monitoring
- Data Safety and Monitoring Boards (DSMBs/IDMC)
- Community Involvement
What is a microbicide?

- An effective microbicide could be used in the vagina or rectum to reduce the risk of HIV transmission during sex.

- Microbicides are being tested in various forms – creams, foams, gels, slow release vaginal rings, films, injectables, enemas and suppositories/pessaries.

- Microbicides being explored in clinical trials incorporate a single ARV or a combination of two ARVs.

- Work also focused on non-ARVs and dual-purpose products (with contraception).
Why do we need microbicides?

- To put something in women’s (and men’s) hands
- Increase options from which to choose
- Easier to negotiate than condoms
- Increased pleasure (like lube)
- Not systemic like a drug or vaccine
- Giving drug topically delivers drug:
  - where it is needed in genital tissue
  - closer to when it is needed as absorption is local
  - at a much higher level (10-100x) than a tablet

Source: Prof Sheena McCormack, MRC UK
An ideal microbicide

- **Safe** – no localized toxicity, no damage to vaginal epithelium, no localized inflammatory responses
- **Effective** – in the ‘real world’
- **Cost effective** – affordable to individual; sustainable by donors
- **User friendly** – usable during sex
- **Appropriate delivery** – at viral entry portals
- **High barrier for resistance**
- **Limited impact on therapy**
How might a microbicide work?

- Active ingredient (e.g. ARV) might block HIV activity directly – OR –

- Physical barrier at the site of exposure might block infection
Rectal microbicides

- In earlier research stages than vaginal microbicides
- Barriers: Stigma, denial, homophobia, anal sex Scientific and biological challenges
- First Phase II study – MTN 017
  - Reformulated tenofovir gel for anal use
  - Safety and acceptability
  - 186 MSM and transgender women in Peru, South Africa, Thailand and the United States; Start 2013
- More info at http://www.rectalmicrobicides.org/
- Watch Rectal Revolution is here at http://www.youtube.com/watch?v=ulqFQ87dIfo
A single product, configured for at least two SRH prevention indications: Pregnancy, STI, and/or HIV
Could be different combinations: Drug:Drug      Drug:Device      Vaccine

• Greater efficiency in terms of cost, access and delivery of SRH prevention products
• Capitalize on the demand in populations using one product type to achieve uptake and use of a second “product”

http://www.cami-health.org

Can you replace the scrawny rings with this one?
Ongoing & Planned Microbicide Trials & Participants

Please do not use this map – it’s out of date

United States
2,270
MTN 017
MTN 005
IPM 020
CONRAD 122
NNRTI Microbicide Gel Formulation
CONRAD 121
MTN 014
MTN 011
CONRAD 120
CONRAD 118
CONRAD 117
CONRAD 114
MTN 013/IPM 026
MTN 008
MTN 012/IPM 010
Project Gel
AF020
Vaginal Microbicide Adherence
EMBRACE (MTN 016)
MTN 009

Dominican Republic
36
CONRAD 114

Puerto Rico
120
Project Gel

Uganda
4,530
CHOICE (MTN 018)
ASPIRE (MTN 020)
VOICE (MTN 003)
EMBRACE (MTN 016)
MTN 003B
MTN 015

Rwanda
620
The Ring Study (IPM 027)
IPM 014A

Zambia
928
ASPIRE (MTN 020)

South Africa
8,357
CHOICE (MTN 018)
CAPRISA 008
ASPIRE (MTN 020)
The Ring Study (IPM 027)
FACTS 001
MTN 017

Voice (MTN 003)
FACTS 002
IPM 015
IPM 014A
IPM 014B
MTN 014
EMBRACE (MTN 016)
MTN 003C
MTN 015

Kenya
140
IPM 015
IPM 014A

Zimbabwe
4,529
CHOICE (MTN 018)
ASPIRE (MTN 020)
VOICE (MTN 003)
EMBRACE (MTN 016)
MTN 003B
MTN 015

China
Data collection ongoing

Pakistan
Sex Workers Study

Dominican Republic
36
CONRAD 114

Puerto Rico
120
Project Gel

Uganda
4,530
CHOICE (MTN 018)
ASPIRE (MTN 020)
VOICE (MTN 003)
EMBRACE (MTN 016)
MTN 003B
MTN 015

Rwanda
620
The Ring Study (IPM 027)
IPM 014A

Zambia
928
ASPIRE (MTN 020)

South Africa
8,357
CHOICE (MTN 018)
CAPRISA 008
ASPIRE (MTN 020)
The Ring Study (IPM 027)
FACTS 001
MTN 017

Voice (MTN 003)
FACTS 002
IPM 015
IPM 014A
IPM 014B
MTN 014
EMBRACE (MTN 016)
MTN 003C
MTN 015

Kenya
140
IPM 015
IPM 014A

Zimbabwe
4,529
CHOICE (MTN 018)
ASPIRE (MTN 020)
VOICE (MTN 003)
EMBRACE (MTN 016)
MTN 003B
MTN 015

Pakistan
Sex Workers Study

Peru
46
MTN 017

Total Microbicide Trial Participants

- United States: 2,270
- Dominican Republic: 36
- Puerto Rico: 120
- Uganda: 4,530
- Rwanda: 620
- Zambia: 928
- South Africa: 8,357
- Kenya: 140
- Zimbabwe: 4,529
- Peru: 46

Microbicide Trial Participants by Region

- North America
- Asia & SE Asia
- Africa
- South America
Quick status update...

- Proof of concept in July 2010; CAPRISA 004 trial of 1% tenofovir gel used before and after sex (“BAT-24” dosing) safe and reduce HIV risk by 39% in heterosexual women
  - There were 39% fewer HIV infections among women using tenofovir gel than among women using a placebo gel

- Confirmatory study of same product and dose is ongoing (FACTS 001); results early 2015
  - Tenofovir gel not effective in VOICE among women asked to use it daily

- Two efficacy trials of monthly vaginal dapivirine ring – ASPIRE and The Ring Study – ongoing; results late 2015/early 2016
1,950 women in South Africa & Uganda