An Update on FACTS 001

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FACTS 001

A Phase III, Multi-Centre, Randomised Controlled Trial to Assess the Safety and Effectiveness of the Vaginal Microbicide 1% Tenofovir Gel in the Prevention of HIV-1 Infection in Women, and to Examine Effects of the Microbicide on the Incidence of HSV-2 Infection
## Rationale for confirmatory study

### HIV Protection
- Confirm CAPRISA 004 results i.e. 39% (CI: 6.60), p=0.017

### Safety
- Safety of tenofovir gel when used as BAT 24 regimen.

### Generalizability
- CAPRISA 004 included 899 women in KZN. Effectiveness in diverse populations required.

### HSV-2
- Confirm CAPRISA data on effectiveness for prevention of HSV-2
Primary objective

• To evaluate the safety and effectiveness of 1% tenofovir gel applied intravaginally in preventing sexually transmitted HIV-1 infection in women.
Secondary objectives

• To evaluate the effectiveness of 1% tenofovir gel applied intravaginally in preventing sexually transmitted HSV-2 infection in women
• To ascertain the impact of 1% tenofovir gel on pregnancy outcomes
• To investigate the effectiveness of 1% tenofovir gel according to levels of gel and condom use
• To seek evidence of incident HIV-1 infections unmasked by product withdrawal
• In women who become infected with HIV-1 during the trial:
  – To assess the impact, if any, of 1% tenofovir gel on HIV-1 viral load set point
  – To assess tenofovir resistance
Protocol changes V3 to V4

- 2200 women aged 18-30 years enrolled at 6 sites in South Africa
- 88 endpoints
- Minimum 15 months on product maximum 24 months

- 2900 women aged 18 – 40 years (approx. 300 women aged 31-40 for safety)
- 118 endpoints
- This will increase the power of the study to detect an effect, at 1-sided alpha=0.025, of 90% for a 45% reduction in risk for active gel relative to placebo gel
- Minimum 16 months on product maximum 27 months
Version 4 approval

• Submitted to MCC April 2012
  – Responded to queries July 2012
  – Further responses submitted
  – Approval pending

• Submitted to all EC
  – All approved
Achievements to date

• Rapid initiation of 9 South African sites
  – 295 staff across all sites
  – 18 staff in CORE
• Accrual initiated October 2011
• Version 4 training complete
• Additional training: social science, VIRA, adherence, adherence IDI, GPP
• Adherence focus
# Accrual

Data provided by ACRO from sites 21 September 2012

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<th>Site Name</th>
<th>Number Screened</th>
<th>Number Enrolled</th>
<th>Screen failures</th>
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<td>MATCH</td>
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<tr>
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<td>WRHI</td>
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<td><strong>3265</strong></td>
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</table>

Accrual expected to complete March-April 2013
Enhancing and Measuring Adherence in FACTS001
Focus on Adherence

• Optimise gel use and gel use assessment

• Reduce factors which dilute adherence viz. pregnancy, missed visits
As the number of applicators used decreases so does the effectiveness. After 18 months of study participation – participants who remained HIV negative still used more than 4 gels a month but the usage of those who seroconverted dropped to less than 2 gels a month.
What is our approach informed by?

• CAPRISA: Visual inspection of returned applicators (VIRA)
• MDP301: Coital Diaries, gel returns, CRFs,
• VOICE C: serial in depth interviews on adherence and barriers to use
FACTS 001 Adherence Measurements

1. Pharmacy: Visual Inspection of Return Applicator
2. Sex Diaries
3. Triangulation Interview
Adherence checks

• Coital Diary
  – Sex, Gel and Condom use and timing
  – Reviewed at monthly visits
  – Assists in the Sexual Behavior and Gel Use CRF

• IDI
  – Purpose: Explore adherence, barriers and facilitators, experiences of clinical trial and gel use, partnerships
  – Random sample of 145 participants
  – Interviewed 3 x during the trial (M3, M6, Exit)

• All administered by social science interviewers
Supporting Adherence

- **Client-Centred Counseling (motivational interviewing)**
  - Participant-centred, counsellor directed approach with feedback loop to support adherence to product use

- **Waiting Room Observations**
  - Identify issues, rumours and concerns of participants—to facilitate development of messages and responses as needed

- **Practical tools to support gel use and dosing understanding**
  - Eg. Paper plate 24-hour clocks made by participants to use at home and reinforce understanding of BAT 24 dosing

- **Motivational Text Messages (In planning phase)**
Visual Inspection of Returned Applicators (VIRA)

• **Why visual Inspection of Applicators ?**
  – Participants return used and unused applicators
  – May feel an obligation to show use even if not used
  – Visual inspection will contribute to verifying use

• **How?**
  – Used applicators counted and entered onto the Study Product Returns Inventory Log
  – Returned used product immediately sent for visual inspection and documentation of visual inspections procedures by trained inspector
  – Counts from the visual inspection
  – QC checks by pharmacist
What’s appears used?
Challenges

- Wiping and washing
- Sniff test
- Blood stained
- Gel only at tip of applicators
Feedback Loop

VIRA

- Pharmacist inspects Gel Applicator Returns
- Pharmacist completes log and flags for the attention of the adherence coordinator

Adherence Checklist

- AC reviews VIRA log, chart notes and previous counseling notes, and visit schedule and fills in appropriately
- Interview is conducted

SITE PI

- The Site PI is informed of PPTs who have repeated adherence difficulties to take further steps.
UVL: The Concept

‘UV light inspection of applicators had the highest accuracy in correctly assessing applicator insertion status’.


*Figure 3.* Sham-inserted applicators alternating with vaginally inserted applicators obtained during consecutive daily applications of HEC gel. A, Visible light illumination. B, Ultraviolet light illumination.
How does it work?

• Body fluids fluoresce when viewed using ultraviolet light (cervicovaginal secretions, semen, blood)
Summary of FACTS 001 adherence activities

• Strategies for enhancing adherence
  – Motivational Interviewing (counselling)
  – Checklist and feedback loop integrating VIRA

• Strategies for measurement and monitoring
  – All participants CRF monthly
  – All participants VIRA monthly
    • UVL pending – start date 2013 (?)
  – Coital diaries monthly as additional detailed check measure
  – IDI on a sample
Pregnancy and Contraception in FACTS 001
Limited method mix – implications for trials

<table>
<thead>
<tr>
<th>Total no. of pregnancies</th>
<th>COC</th>
<th>Injectable</th>
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</thead>
<tbody>
<tr>
<td>37</td>
<td>35</td>
<td>2</td>
</tr>
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</table>

**CSC report 21/09/2012**

- Suggestion that women are being offered COC because of concerns of HIV risk with injectable, but consequence is increased pregnancies on COC

- Did participants understand the requirement not to fall pregnant – many are choosing to keep baby
  - 19 currently ongoing (51%)
Impact on trial

• Pregnancy incidence 7% currently

• Time off study product
  – Mean 50 days off product for those that have resumed following pregnancy (n=10)
  – Mean 104 days for those continuing their pregnancy (n=21)
Expanding contraception options

1. Sites provided with contraception counselling guidelines
2. Sites asked to update pregnancy prevention SOP to define strategies beyond contraception for reducing pregnancy in the trial
   - Take into account screening assessments, fertility intentions, as well as contraceptive methods
3. IUCD training for all sites
   - Start with sites with large number of pregnancies and/or high numbers of COC
   - Educate participants on IUCDs
   - Offer IUCDs to all eligible participants
   - Train all clinical staff
Last Reflection

Original FACTS 001 timeline

- Protocol submitted to MCC: Oct 2010
- Site initiation trainings: Nov 2010
- Begin enrolling participants: March 2011
- Complete enrolment by mid-2012: June/July 2011
- Database lock by Sept: June 2012
- Complete follow-up by mid-2013: June 2013
- Analysis: Nov/Dec 2013
- Unblind in Nov
- Results Dissemination By Dec 2013

- Revise and finalize protocol
- Investigator Meeting
- Develop Consortium
- Protocol submitted to MCC
- Site initiation trainings
- Begin enrolling participants
- Complete enrolment by mid-2012
- Database lock by Sept
- Analysis
- Unblind in Nov
- Results Dissemination By Dec 2013
Thank you

To all participants and the whole FACTS team, ACRO, CONRAD and our donors (DST, USAID, BMGF, DoH)