



MTN-016 Regional Meeting 2014

26 October 2014
Cape Town, South Africa

Agenda

- Introductions
- EMBRACE Implementation Update
 - Malawi Activation
 - Protocol V2.0 Implementation
 - Accrual Progress
- MTN-016 Publications Update
 - R4P Poster Summaries
 - Overview of VOICE/MTN-016 Analysis Plan

Implementation Updates

- Activation Progress at Blantyre and Lilongwe:
 - Both sites are making good progress on activation requirements.
 - Activation timeline has been extended due to regulatory delays. Both sites currently waiting on first reviews by NHSRC.
 - Training dates to be set once regulatory timelines are known.

Implementation Updates

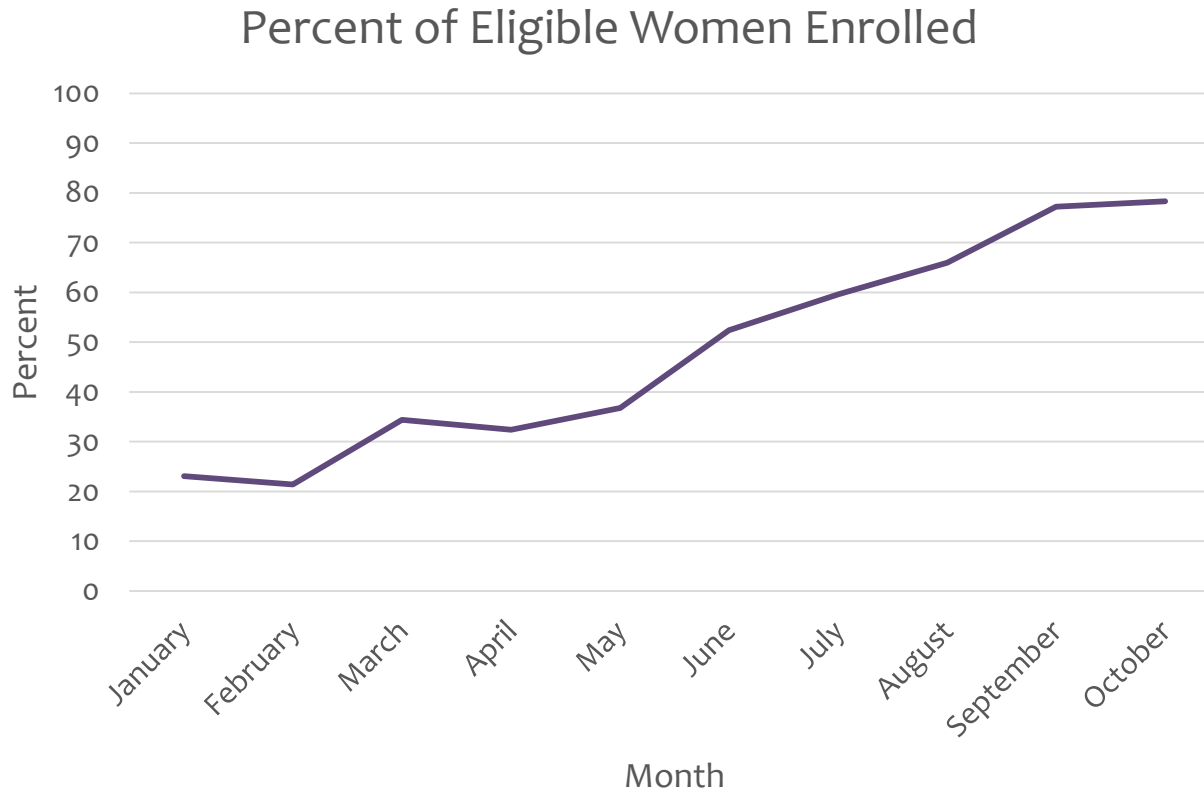
- V2.0 Implementation:
 - All activated MTN-016 sites have completed requirements for V2.0 implementation – Congratulations!
 - Any questions about changes from V1.0 to V2.0?
 - Any implementation challenges so far?
 - Any specific questions/challenges related to the new protocol deviation reporting process for MTN-016?

Implementation Updates

- Accrual Progress:
 - Overall Accrual into MTN-016:
 - Total Women Enrolled: 364 (83.5% of eligible ppts)
 - Total Infants Enrolled: 314 (93.5% of live births)
 - ASPIRE-specific Accrual into MTN-016:
 - Women Enrolled: 47 (78.3% of eligible ppts)
 - Infants Enrolled: 31 (88.6% of live births)

Implementation Updates

- ASPIRE 2014 Accrual Improvements:



Obstetric and Infant Outcomes Following Maternal Third Trimester Exposure to Tenofovir 1% Vaginal Gel

Lisa M. Noguchi, Joseph Biggio, Katherine Bunge, James Dai, Karen Isaacs, Kristine Torjesen, Samuel Kabwigu, Jill Schwartz, Juan Vargas, Cindy Jacobson, D. Heather Watts, Jeanna M. Piper, & Richard H. Beigi, for the MTN-002, MTN-008 & MTN-016 (EMBRACE) Study Teams

MTN-016 Protocol Team Meeting, 2014 MTN Regional Meeting

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Introduction

- Drug safety evaluation in pregnancy:
assess potential impact of drug exposure
 - Obstetric (OB) outcomes
 - Infant outcomes
- Evaluated OB and infant outcomes,
including infant malformations
 - Registrants enrolled in planned 3rd trimester
TFV gel studies

Design

Planned third trimester exposures

- MTN-002
- MTN-008

Unplanned first trimester exposures

- Phase 2B & 3 trials

MTN-016
Pregnancy
Registry

Methods

- Restricted to planned 3rd trimester exposure, comparisons using Fisher's exact test
 - MTN-002: open label, single dose, 1% TFV gel prior to cesarean
 - MTN-008: 2:1 placebo-controlled, 7 daily doses, 1% TFV gel
- Outcomes
 - OB: preterm birth, postpartum hemorrhage, non-reassuring fetal status, chorioamnionitis, gestational diabetes (MTN-008)
 - Infant : any visit with variation from normal physical exam (PE) (MTN-008)

Malformation outcomes

- Two consultant geneticists determined endpoints via independent review of PE data, pregnancy and medication history, genetic screening data, and photo data (MTN-002 & MTN-008)

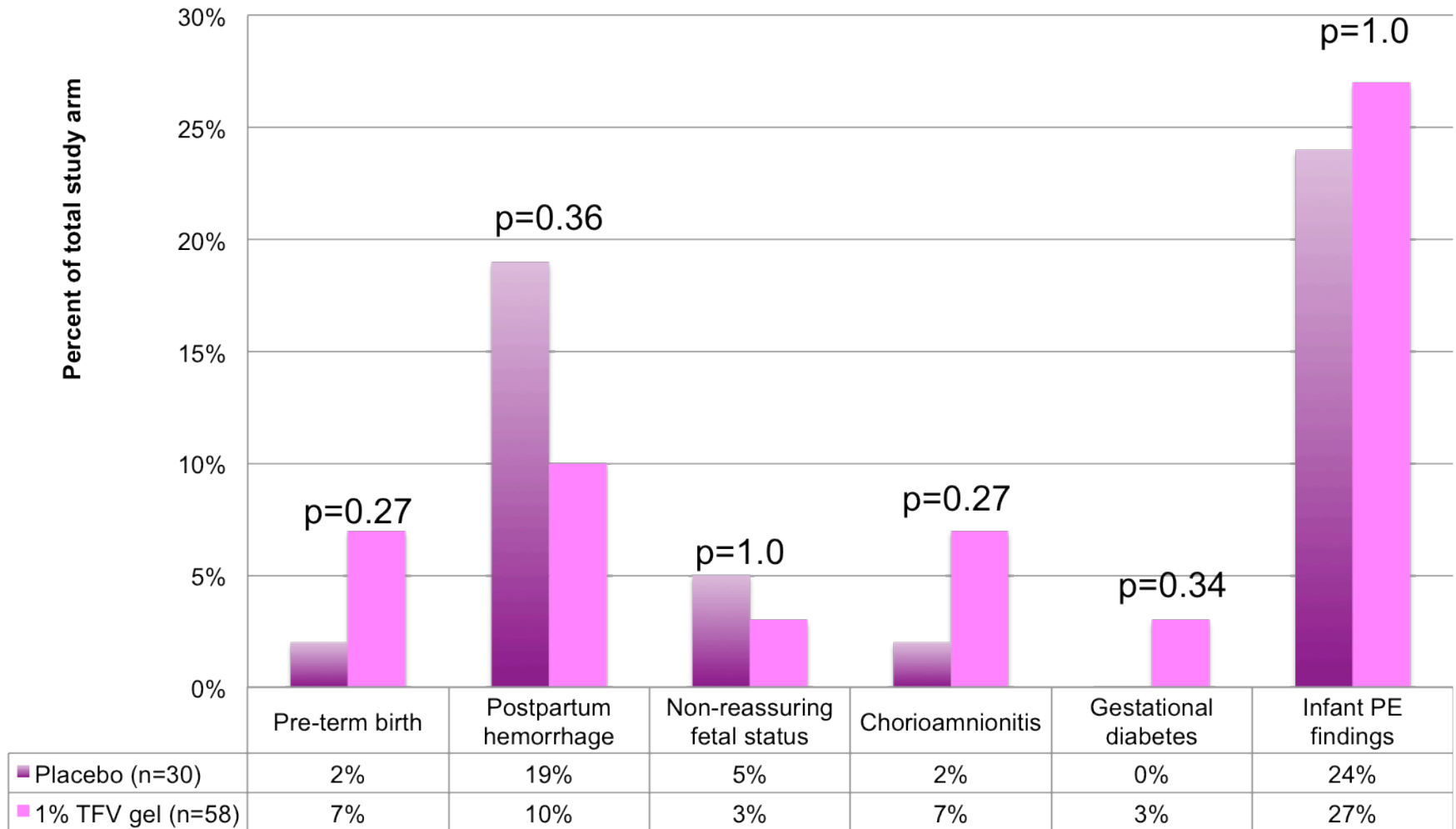
The screenshot displays the ATLAS (AIDS Treatment and Learning) and SCHARP (Statistical Center for HIV/AIDS Research & Prevention) Atlas web interface. The page is titled "Results" and shows "Photographic Documentation Results" for a specific participant. The participant ID is redacted. The results are for "Visit 1, Exam Date: 23-Apr-12". The "Infant Malformation Assessment Form" is identified as "MTN-016 Mjor Malformation Assessment Worksheet3.doc". The "Site Comments" section notes "Umbilical hernia". The "Site Images" section is redacted. The "CRF Images" section lists two forms: "Infant: contains the following CRF (if present)... -Infant Physical Exam" and "Mother: contains the following CRFs (if present)... -Woman Concomitant Medications Log -Genetic Screening History -Pregnancy Report and History". At the bottom, the "Consultant 1 Status" and "Consultant 2 Status" are both "Completed (on null)". The "Overall Assessment" is "AGREE".

Consultant 1 Status:	Completed (on null)	Overall Assessment:	AGREE
Consultant 2 Status:	Completed (on null)		

Results

- Enrollment into registry
 - 100% (16/16) of MTN-002 mothers, 25% (n=4) of whom enrolled prior to pregnancy outcome
 - 90% (88/98) of MTN-008 mothers, 97% (n=86) of whom enrolled prior to pregnancy outcome
- Infant retention at 12 months
 - 88% (MTN-002) and 80% (MTN-008)
- Infant malformations
 - One defect (ear canal) in MTN-002: prevalence (6%) comparable to US background prevalence (3%) for malformations ($p=0.51$)
 - No defects noted among infants from MTN-008

Obstetric and newborn outcomes following 7-day third trimester exposure to TFV gel



Conclusions

- First report from a novel pregnancy registry
 - Suggests single-dose and 7-day repeat dose TFV 1% gel exposure in 3rd trimester do not impact several important OB/infant outcomes
- Pregnancy registries can provide valuable data for evaluating maternal and infant safety associated with third trimester microbicide use

Acknowledgements

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- MTN-002 and MTN-008 study site teams and participants
- Jennifer Balkus, PhD, MPH
- Jason Pan, MS



The MTN-016 Pregnancy Registry: Baseline Characteristics of Enrollees from the VOICE Study and Reasons for Non- enrollment of Eligible Women

MTN REGIONAL MEETING 2014 CAPETOWN
26 OCT 14

Samuel Kabwigu, Lisa Noguchi, Jayajothi Moodley, Thesla Palanee-Phillips, Kenneth Kintu, Gonasagrie Nair, Ravindre Panchia, Pearl Selepe, Jennifer E. Balkus, Kristine Torjesen, Jeanna Piper, Rachel Scheckter, Rohan Hazra, and Richard Beigi for the MTN-016 Study Team

Outline

- Background
- Methods
- Results
- Conclusion

Background

- Many HIV prevention trials target reproductive age women. If HIV prevention agents come to market, women of reproductive age will use them, highlighting the importance of safety assessments before licensure in both non-pregnant and pregnant women.
- The Microbicide Trials Network (MTN) initiated the MTN-016 study, a prospective observational cohort enrolling participants who became pregnant during MTN effectiveness studies or those with planned exposures in pregnancy safety studies.

Background cont'd

- MTN-016 collected data on exposure to investigational HIV prevention agents during pregnancy, potential confounding and/or relevant factors such as maternal age, disease status during pregnancy, gestational age at exposure, pregnancy outcomes, genetic history and infant outcomes during the first year of life
- Our abstract describes participant enrollment in MTN-016 from MTN-003 (VOICE), a phase 2B double-blinded, placebo-controlled, five arm safety and effectiveness trial of daily use of tenofovir 1% vaginal gel, oral emtricitabine/tenofovir disoproxil fumarate for prevention of HIV acquisition in women.

Methods

- The VOICE trial was conducted between 2009-2012 at 15 sites in Uganda, South Africa and Zimbabwe.
- Women who became pregnant while participating in VOICE and met eligibility criteria were invited to enroll in MTN-016
- Pregnant women were eligible to participate if they were able and willing to provide informed consent, provided adequate locator information and had a confirmed pregnancy.

Methods cont'd

- Baseline demographic and behavioral characteristics were captured on standardized case report forms at enrollment in MTN-016 and were summarized using descriptive statistics.
- We collected data monthly on reasons for non-enrollment of potentially eligible women who chose not to participate.

Results

- Among 5,029 VOICE participants with over 5,425 person-years (py) of follow-up, there were 424 pregnancies (7.8/100 py) and 201 live births. The average age of participants who became pregnant during VOICE was 24 years, with 24% of pregnant participants being married at baseline.
- Among women who became pregnant during VOICE, 261 (62%) were eligible to enroll in MTN-016. Of these, 213/261 (82%) women and 185/201 (92%) of their infants enrolled in MTN-016. Baseline characteristics of MTN-016 enrollees from VOICE are summarized in Table 1.

Table 1. Baseline characteristics of women enrolled in MTN-016 from MTN-003

Characteristics	N(%)
Age category	
18-24	115(54.0)
25-34	91(42.7)
35 and above	7(3.3)
Currently married	69(32.6)
Participant earns an income of her own	90(42.3)
Some secondary education or higher	191(89.7)
Participant or relative owns the home the woman lives in	134(62.9)

Results cont'd

- The most common reasons for non-enrollment into MTN-016, as reported to site investigators by potentially eligible pregnant women, included the following:
 - Additional study visit burden associated with participating in two protocols at the same time (co-enrollment in MTN-003 and MTN-016) or continuing obligations to complete MTN-016 study visits after exiting from the parent protocol.
 - Employment considerations/conflicts.
 - Cultural customs related to women's temporary relocation to rural areas/family homes during the perinatal periods.
 - Beliefs that public access to newborns and movements outside of the home should be limited during the postnatal periods.

Conclusion

- Similar to participants in other HIV prevention studies, the majority of women who enrolled in VOICE were young, reproductive age women.
- The majority of eligible women from VOICE and their infants chose to enroll in MTN-016; however, among those who declined enrollment, study visit burden and local cultural customs were common barriers to enrollment that may also impact enrollment of mothers and their infants into other pregnancy-related studies.

Conclusion cont'd

- Efforts to assist women with some of these barriers could foster increased prospective enrollment into MTN-016. Doing so will augment the amount and quality of data gathered in this unique population with early pregnancy exposures to candidate HIV prevention agents.
- Data regarding the impact of early pregnancy exposure to candidate HIV prevention agents is a critically important component of the overall safety profile of HIV prevention agents.

Thanks

- We sincerely thank the women who participated in this study. We gratefully acknowledge all MTN-016 site study teams for their work in data collection and the Statistical Center for data management and analysis.
- The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.



MTN 016 Concept

MTN Regional Meeting

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Background

- Reproductive age women are a primary target population for an effective microbicide
- Early pregnancy exposures will be inevitable once an agent is approved



Purpose

- To compare pregnancy outcome and specific infant outcomes (mortality, growth, and neurodevelopment) between participants randomized to active study agents and their corresponding placebos



Hypothesis

- There will be no difference in rates of adverse pregnancy outcomes (e.g., preterm delivery, stillbirth, ectopic pregnancy, or spontaneous abortion) between active and placebo groups.
- There will be no difference in rates of adverse neonatal outcomes (congenital anomalies or growth restriction at birth) or poor infant outcomes (i.e., neurodevelopmental delay or growth delay at one year).



Data Analysis

- Demographics of study population
 - Entire MTN-016 cohort derived from VOICE
 - Maternal age at enrollment
 - Parity
 - HIV infection
 - Educational status at VOICE enrollment
 - Gestational age at enrollment
 - Gestational age at pregnancy outcome
 - Length of exposure to study product during pregnancy
 - Adherence to study product



Compare

- Rates of pregnancy outcomes across groups
- Rate of poor neonatal outcomes across groups
- Rates of infant death or growth lag across groups



Challenges

- Defining adherence
 - Use the same definition as the primary paper?
 - Based on drug level at time of pregnancy diagnosis
- Defining “groups”
 - Should the two oral products be lumped together?



Importance of Exposed Group

- Add to the data available from HIV seropositive mothers
- Add to the data available from HIV seronegative mothers (Partners)
- Inform prescribing guidelines regarding pregnancy testing



Importance of placebo

- Will provide baseline pregnancy outcome data in this population
 - Partners Prep
 - Challenge of pregnancy studies



Timeline

- Additional blood samples analyzed at JHU- complete
- Data analysis at SCHARP
- 2 month turn around for manuscript