MTN-003 VOICE Protocol Overview

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MTN-003

- Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet, and Emtricitabine/ Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

VOICE

- **V**aginal and **O**ral **I**nterventions to **C**ontrol the **E**pidemic

Study Products

Study Products

- Vaginal
  - Tenofovir 1% gel
  - Placebo gel

- Oral
  - Tenofovir disoproxil fumarate (TDF) 300 mg tablet
  - TDF placebo tablet
  - Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) 200 mg/300 mg tablet (Truvada)
  - FTC/TDF placebo tablet

30 tablets per bottle

Study Objectives

Primary Objectives

- To estimate the **effectiveness** of daily Tenofovir gel, daily Tenofovir tablet, and daily Truvada tablet in preventing HIV infection among women at risk for sexually transmitted infection
- To evaluate the **extended safety** of daily Tenofovir gel, daily Tenofovir tablet, and daily Truvada tablet in women at risk for sexually transmitted HIV infection

Secondary Objectives

- Adherence/Behavioral
  - To evaluate **adherence** to daily regimens of vaginal gel and oral tablets
  - To evaluate whether key **behaviors** (sexual activity, condom use, intravaginal practices) **change** over time in women who use either daily vaginal gel or daily oral tablets

Secondary Objectives

- HIV Drug Resistance
  - To assess the frequency of HIV **drug resistance** in women who acquire HIV while using study product

Secondary Objectives

- Pharmacokinetic
  - To evaluate the **pharmacodynamic** relationship between plasma drug concentrations and study outcomes (HIV seroconversion, toxicity, resistance)
- Delayed Seroconversion
  - To assess incidence of HIV **seroconversion** during the approximate 8 weeks of follow-up **off study product** between the Product Use End Visit and the Termination Visit (to identify potential delayed seroconversions due to masked infection)

Exploratory Objectives

- Vaginal Microenvironment
  - To correlate **biomarkers** in the cervicovaginal environment with HIV seroconversion, reported product adherence, stage of menstrual cycle, contraceptive use, intercurrent sexually transmitted infections, and reported adverse events
  - To measure the association between **abnormal vaginal flora** and HIV seroincidence

Exploratory Objectives

- Method of Contraception
  - To explore the potential relationship between method of **contraception** and HIV seroconversion, reported product adherence, and reported adverse events

Study Design

Study Design

- VOICE is a:
  - Multi-site
  - Five-arm
  - Double-blinded
  - Placebo-controlled
  - Randomized trial

Multi-Site

- Blantyre, Malawi (1 clinic)
- Durban, South Africa (4 clinic)
- Harare, Zimbabwe (2 clinic)
- Johannesburg, South Africa (1 clinic)
- Kampala, Uganda (1 clinic)
- Lilongwe, Malawi (1 clinic)
- Lusaka, Zambia (1 clinic)

Multi-Site

Data will be combined across sites for primary analyses

Multiple sites allow for secondary analyses of product safety and effectiveness in diverse geographical, ethnic, and cultural contexts

Five Arms

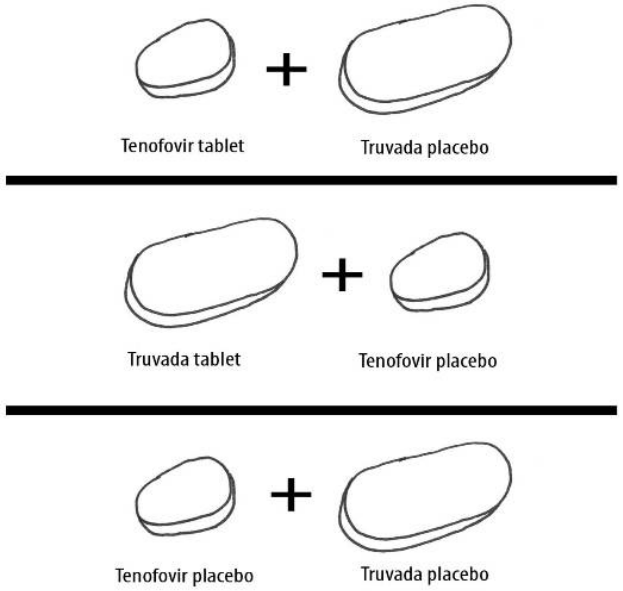
- Participants in all five arms receive risk reduction counseling, condoms, and diagnosis and treatment of sexually transmitted infections

Five Arms

- Participants in each arm use one product, either vaginal or oral
  - Arm 1 = Tenofovir gel
  - Arm 2 = Placebo gel
  - Arm 3 = Tenofovir tablet
  - Arm 4 = Truvada tablet
  - Arm 5 = Placebo tablet

Five Arms

- But things are more complicated in the oral arms
- Participants in the oral arms use one product, but take two tablets daily
  - Arm 3 = Tenofovir tablet + Truvada placebo
  - Arm 4 = Truvada tablet + Tenofovir placebo
  - Arm 5 = Tenofovir placebo +Truvada placebo



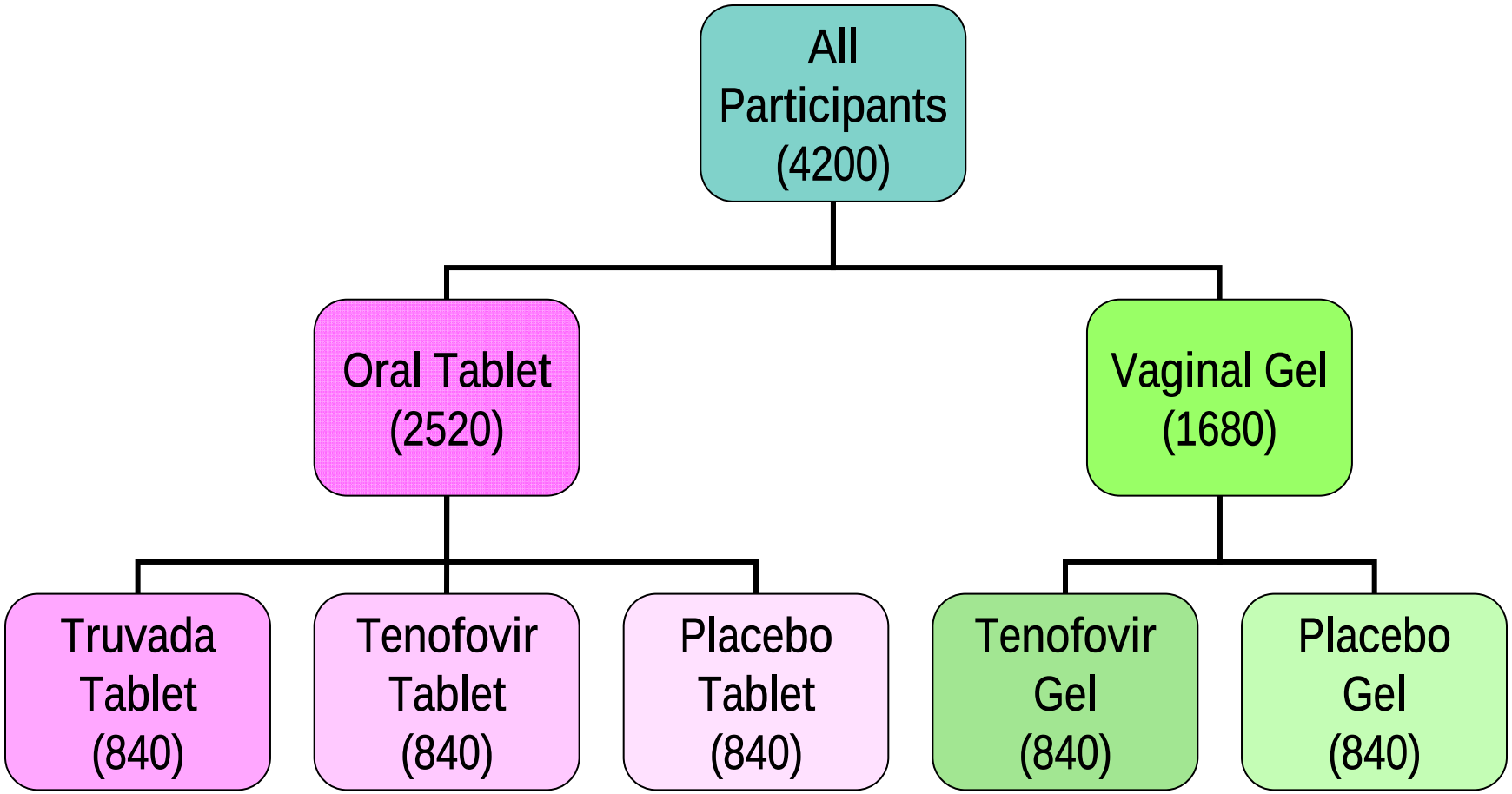
Double-Blinded & Placebo-Controlled

- Study participants and study staff will know whether participants are using oral product or a vaginal product
- Neither participants nor study staff will know whether participants are using a candidate active product or a placebo
- The oral arms are further blinded such that neither participants nor study staff will know whether participants are receiving Tenofovir (or placebo) or Truvada (or placebo)

Randomized

- Participants are assigned at random to each of the five study arms
- Participants are assigned in equal numbers to each arm at each site
- Random assignment ensures equal distribution of participant characteristics across arms (e.g., age, sexual activity, condom use, STI history)

Random Assignment



Study Population

Participant Accrual

- 4200 women
- Enrolled across sites
- Over approximately 21 months

Key Eligibility Criteria

- Able and willing to provide informed consent
- Able and willing to provide adequate locator information
- Sexually active
- HIV-uninfected
- In general good health, with normal liver and kidney function
- Not pregnant, planning to become pregnant, or breastfeeding
- Using effective contraception and intending to continue using an effective method for the next 24 months
- Not planning to re-locate for the next 24 months
- Agrees not to participate in other studies involving drugs, medical devices, or vaginal products for the next 24 months

Eligibility Criteria

- Rationale is to select participants who are
  - At risk for HIV infection
  - Likely to be retained
  - Likely to be adherent to product use
  - At low risk for safety problems potentially associated with product use
- Specific inclusion and exclusion criteria will be reviewed in detail on Day 2

Participant Follow-up

- Participants will complete monthly follow-up visits, with target dates every 28 days
- Follow-up visit procedures will be reviewed in detail on Day 3

Participant Follow-up

- Follow-up in the study overall will continue until 217 HIV seroconversions are identified
- Each participant will be followed for 14-35 months
  - 12-33 months of product use
  - Followed by approximately 8 weeks off product
- Based on sample size assumptions and calculations, follow-up should end about 14 months after the last participant is enrolled
- Assumptions and calculations will be monitored closely during the study, and adjusted if needed

Study Outcomes

Primary Outcomes

- **Effectiveness:** HIV infection, as measured by seroconversion, per the algorithm in protocol Appendix III, at the end of the study product use period
- **Safety:** Grades 2, 3, and 4 clinical and laboratory adverse events

Secondary Outcomes

- **Adherence/Behavioral:** Self-reported use of study product, sexual activity, condom use, and intravaginal practices, study product counts
- **HIV Drug Resistance:** HIV drug resistance mutations among participants who acquire HIV, as measured by genotypic methods

Secondary Outcomes

- **Pharmacokinetic:** Area under the curve, maximum serum concentrations, and minimum serum concentrations
- **Delayed Seroconversion:** HIV infection, as measured by seroconversion, according to the algorithm in protocol Appendix III, during the approximate 8 weeks off-product between the Product Use End Visit and the Termination Visit

Exploratory Objectives

- **Vaginal Microenvironment:**
  - Biomarkers, including measures of intrinsic immunity and functional immunity against HIV, STIs, and cervicovaginal inflammation
  - Abnormal vaginal flora as assessed by Gram stain and bacterium-specific PCR testing applied to vaginal fluid

Exploratory Outcomes

- **Method of Contraception:**
  - Methods of contraception used by participants

Expected Study Results

Primary Safety Results

- **Safety** data analyses will compare each candidate product group with its own control group with respect to rates of Grade 2, 3, and 4 **adverse events**
- Candidate products will be considered “safe” if rates of adverse events in the candidate product groups are similar to rates in the respective control groups

Primary Effectiveness Results

- Primary **effectiveness** data analyses will compare each candidate product group with its own control group with respect to rates of **HIV seroconversion**
- Candidate products will be considered “effective” if rates of HIV seroconversion are lower in the candidate product groups than in the respective control groups

Secondary & Exploratory Analyses

- Will assess each of the secondary and exploratory outcomes
- Will explore the safety and effectiveness of the candidate products compared to each other, e.g., Tenofovir gel compared to Tenofovir tablet, Tenofovir tablet compared to Truvada tablet

Let's Discuss Your Questions