VOICE Study Update

Jeanne Marrazzo, MD, MPH

Mike Chirenje, MD

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Introduction

- Protocol update
- Sites
- Accrual plan
- Implementation timeline
- CWG issues
- VOICE B & VOICE C

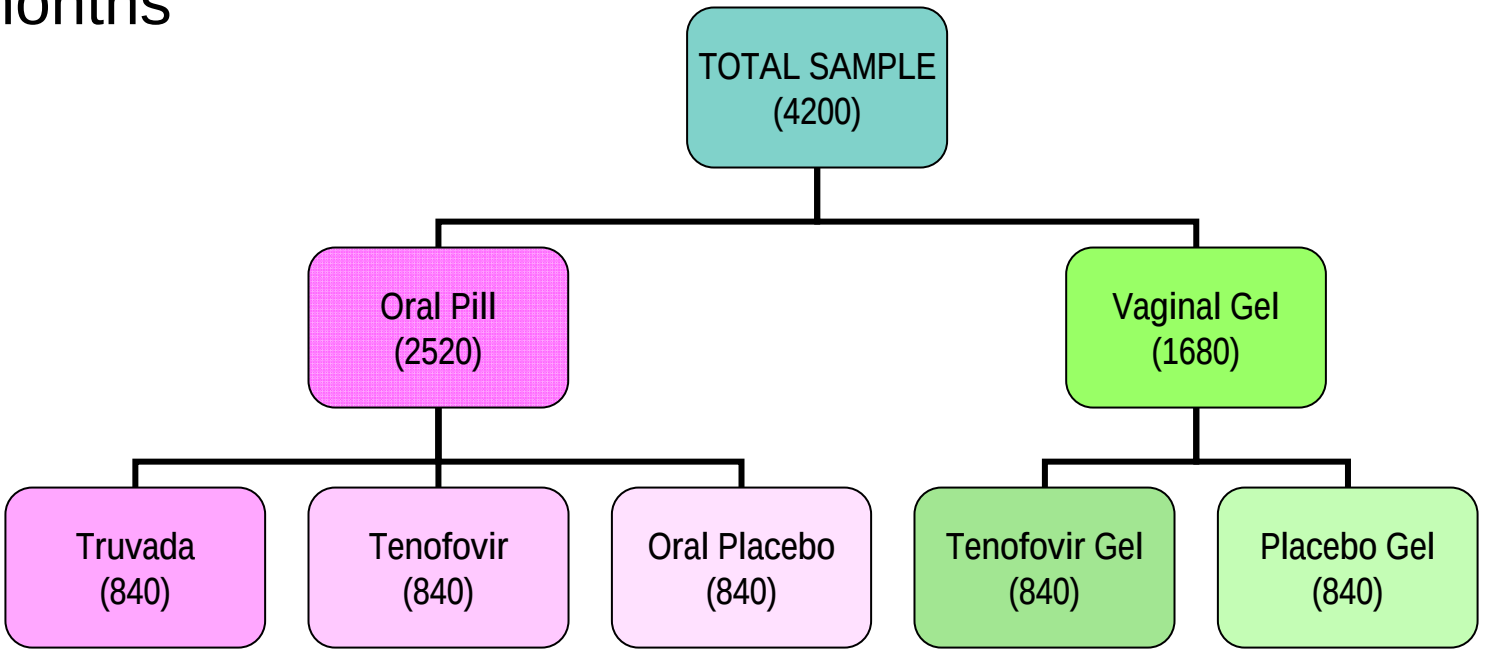
The VOICE Study:

Vaginal and Oral Interventions to Control the Epidemic

- Phase IIb trial with five study groups testing two different HIV prevention approaches in women:
  - A once-a-day antiretroviral tablet (PrEP)
    TDF or TDF/FTC
  - A once-a-day application of a vaginal gel
- 4,200 women to be enrolled at 10 centers in Africa
- Target start date January 2009

The VOICE Study

- Safety and effectiveness study of tenofovir gel, tenofovir tablet and Truvada tablet for prevention of HIV infection in 4,200 women
- Randomized trial with 5 study groups. Two sequential randomizations. Women will use product for average of 21 months



Protocol Update

- Exclusion criteria for dipstick results and addition of periodic dipsticks
- More detail on evaluation of lactic acidosis
  - Modification of clinical management plans (section 9)
- Community consultations regarding interim analysis of efficacy
- Version 1.0 in April pending RAB review

Protocol Update

- Exclusion criteria for urine dipstick results and addition of periodic dipsticks
  - 1+ proteinuria on 2 sequential screenings excluded
  - Quarterly dipstick added; detailed algorithm for responding to new proteinuria / euglycemic glycosuria
  - Background data on urinary abnormalities in target population reassuring (WHIS unpublished data; Wools-Kaloustian 2007)

Sites

- Milestone letters sent to all early April
  - Malawi: Blantyre, Lilongwe
  - S. Africa: MRC sites (3 + Overport); CAPRISA
  - Zambia
  - Zimbabwe: Harare 035 sites (+ Zengeza)
- Protocol submission at sites pending receipt of v 1.0

Accrual Plan

- No. of participants: 4200
- Expected baseline HIV incidence: 4.76%
- Accrual period: 21 months (from 18)
- Expected average follow-up: 22.5 months
- Total follow-up: 7088 person-years
- Endpoints: 228

CWG Issues

- Regular teleconferences continue
- Critical input into
  - Consultation with Network Pharmacist regarding study product packaging and dispensation
  - PSRC response
  - BRC development of strategies for assessing study product adherence and for VOICE-C objectives

Bone Mineral Density Substudy

- Rationale:
  - Bone toxicity observed in animal studies at high dose
  - Statistically significant, but not clinically significant, decreases in bone density have been observed in TDF treated HIV-infected individuals
  - Effects of TDF on bone have not been studied in healthy premenopausal women who may also be receiving DMPA (which itself may reversibly decrease bone density)

- Hypothesis: The use of oral study products (TDF, FTC/TDF) in VOICE will not cause clinically significant decrease in BMD

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Substudy Design

- Primary Objective: To compare changes in BMD over time among VOICE participants receiving oral TDF and TDF/FTC compared to oral placebo
- N=300 (3 sites) from VOICE oral arm
- BMD by DXA at baseline, annually
- Serum for markers of bone turnover and metabolism
- Dietary questionnaire (calcium intake)

BMD Substudy Statistical Considerations

- Primary endpoint: Total hip and spine bone density by DXA
- Sample size of 100 women per oral arm (300 total) provides 90% power to detect a difference of 2.2% between arms

- Current status: PSRC review completed; responses pending; sites being identified

VOICE C

- Objective: measure community and individual factors that might be associated with product adherence
- Rationale: contribute to understanding levels of product adherence during trial participation, and determine whether they differ between women in the vaginal gel and oral tablet arms
- Specifically, these will focus on sexual behavior practices, partnership characteristics, and community perceptions of microbicide trials, in addition to sociodemographic characteristics

VOICE C

- Monitor social, and community-level factors influencing product use and visit completion rate, **in real time,** through quarterly assessments among a random subset of participants from 4 study sites attending visits. This would assess those that regularly visit the clinics as well as participants who have missed 2 subsequent monthly visits.
- Involve community as true stakeholders by working with key site staff, CABs and community members to quickly identify and respond to emerging issues/problems, and implement strategies identified by site and coordinating team to overcome challenges