MTN 003B:
Bone Mineral Density Substudy
Ancillary Study to MTN-003 (VOICE)

Sharon Riddler, MD

University of Pittsburgh CRS

MTN CORE

Bone Toxicity with Tenofovir

- In animal studies (~6X human exposure) reduced bone density or osteomalacia observed in rats, dogs, monkeys.
- Statistically significant, but not clinically significant, decreases in bone density have been observed in large clinical trials of TDF treated HIV-infected adults (Gilead 903) (mean percentage decrease in spine BMD after 144 weeks were -2.2 ± 3.9 for TDF versus -1.0 ± 4.6 in controls).
- Significant decreases in bone density and osteomalacia have been reported in HIV-infected children and in case reports of adults on TDF.
- Increased risk of fractures has not been observed in any study to date.

Other Considerations for BMD in VOICE

- DMPA and breastfeeding are associated with reversible decreases in BMD.
- BMD in healthy premenopausal women is higher in African women than those in Asia or South America. BMD is also higher among blacks than caucasians in the United States.
- Effects of TDF on bone have not been studied in healthy premenopausal women who may also be receiving DMPA. Nearly 50% of participants in HPTN 035 used DMPA.

Substudy Design

- Hypothesis: The use of oral study products (TDF, FTC/TDF) in VOICE will not cause clinically significant decreases in bone mineral density (BMD)
- Primary Objective: To compare changes in BMD after one year among VOICE participants receiving oral tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)/TDF compared with oral placebo.
  - Primary Endpoint: Total hip and lumbar spine BMD via dual energy x-ray absorptiometry (DXA)

Secondary Objectives

- **Secondary Objectives:**
  - To describe changes over time in nutritional assessment components among VOICE participants receiving oral study products.
  - To compare changes in BMD over the duration of VOICE among participants receiving oral TDF and FTC/TDF compared with placebo.
- **Exploratory Objectives:**
  - To explore potential mechanisms of BMD changes among VOICE participants receiving oral study products.
  - To explore changes in urinary phosphorus excretion in relation to changes in bone density among VOICE participants receiving oral products.

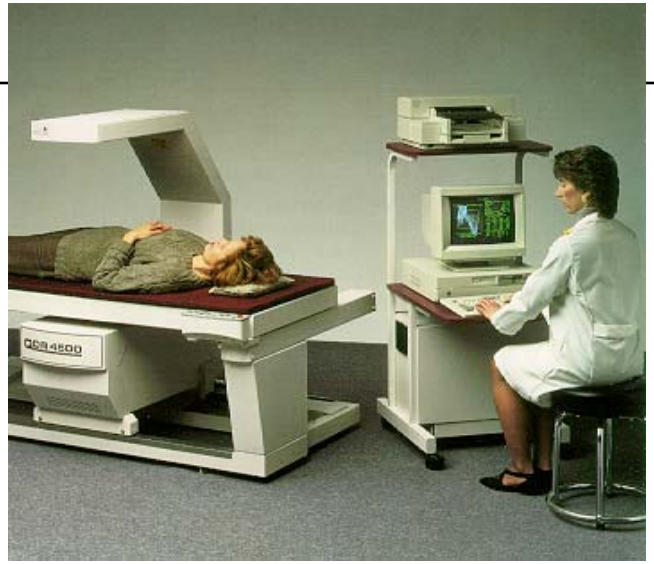
Study Design

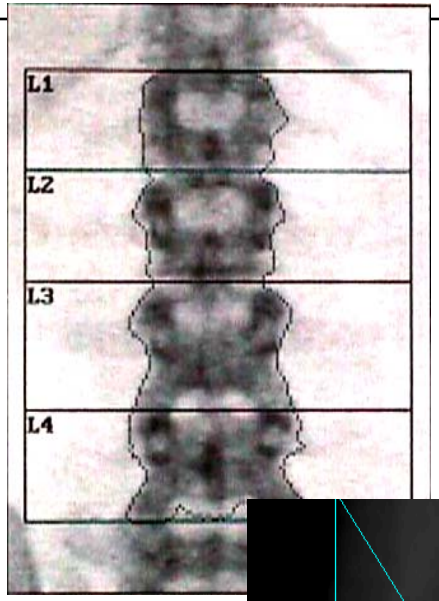
- N=300 (2 sites) from VOICE oral arm
- Visits at baseline and every 6 months
- BMD of hip and lumbar spine by DXA
- Food frequency questionnaire and nutritional assessment
- Collection and storage of:
  - Serum for markers of bone turnover and metabolism
  - Urine for phosphorus/creatinine ratio

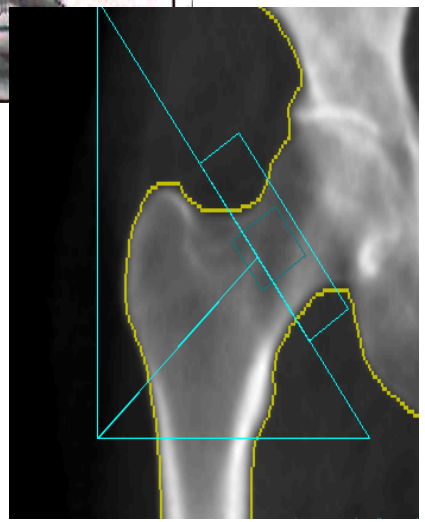
BMD Measurement

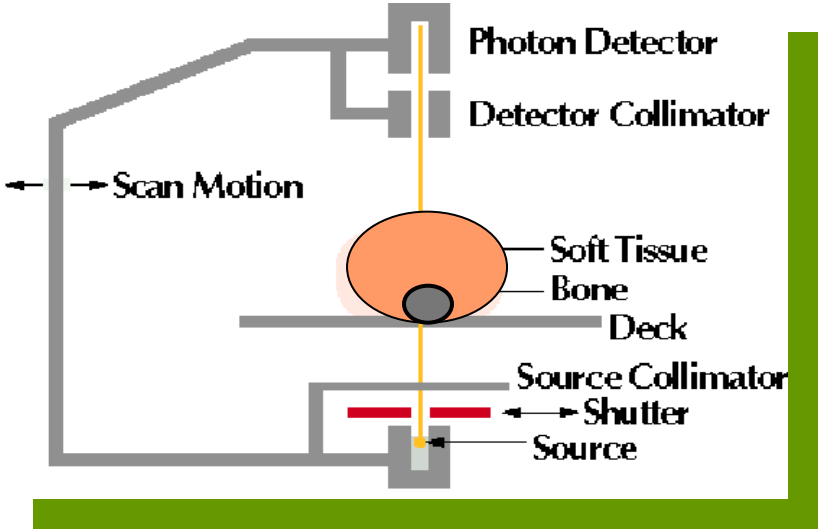
- Primary endpoint: Total hip and spine bone density by DXA
- Identical DXA equipment will be purchased for each site: Hologic Explorer
- Scan will be done in duplicate at each visit
- Sites will perform daily QA using a phantom and standard procedures according to the International Densitometry Standards
- Scans will be sent electronically to the University of Pittsburgh Osteoporosis Research Center for QC

Central DXA Bone Density Measurements









Statistical Considerations

- Assuming SD for the percentage change in BMD from baseline to month 12 of 4.5%
- Sample size of 100 women per oral arm (300 total) provides 90% power to detect a difference of 2.1% between arms

MTN 003B Study Status

- Protocol Version 1.0
- Two sites identified: Kampala, Harare
  - BMD study submitted with VOICE for regulatory review
- BMD equipment order placed (Aug)
- Study specific forms and procedures in development
- Anticipate training early 2009
- On-track to activate concurrently with VOICE