

**MTN-003B**

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

**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**

**Microbicide Trials Network**

**Sponsored by:  
Division of AIDS, US National Institute of Allergy and Infectious Diseases  
US National Institutes of Health**

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**Protocol Chair:**

**Sharon Riddler, MD, MPH**

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**MTN-003B**

**Bone Mineral Density Substudy**

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## MTN-003B

### Bone Mineral Density Substudy

#### LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
AUC	area under curve
BMD	bone mineral density
BMI	body mass index
BSAP	bone-specific alkaline phosphatase
CTX	C-terminal telopeptide of type 1 collagen
CWG	Community Working Group
DAIDS	Division of AIDS
DAIDS PRO	DAIDS Protocol Registration Office
DXA	dual energy x-ray absorptiometry
DMPA	depot medroxyprogesterone acetate
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event
EC	Ethics Committee
ETV	Early Termination Visit
FDA	(United States) Food and Drug Administration
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GEE	generalized estimating equation
HIV	human immunodeficiency virus
IND	investigational new drug
IoR	Investigator of Record
IRB	Institutional Review Board
LDMS	Laboratory Data Management System
mSv	millisievert
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NL	network laboratory
P1NP	N-propeptide of type 1 collagen
PSRT	Protocol Safety Review Team
PrEP	pre-exposure prophylaxis
PTH	parathyroid hormone
PUEV	Product Use End Visit
RSC	Regulatory Support Center
SD	standard deviation
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SSP	study specific procedures

STI sexually transmitted infection  
TDF tenofovir disoproxil fumarate  
VOICE Vaginal and Oral Interventions to Control the Epidemic

**MTN-003B**

**Bone Mineral Density Substudy**

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**MTN-003B**

**Bone Mineral Density Substudy to MTN-003 (VOICE)**

**INVESTIGATOR SIGNATURE FORM**

**Version 2.0**  
**August 29, 2011**

**A Study of the Microbicide Trials Network (MTN)**

**Sponsored by:**

Division of AIDS, US National Institute of Allergy and Infectious Diseases  
US National Institutes of Health

**Co-Sponsored by:**

Gilead Sciences, Inc.

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for each of the two oral VOICE Study products for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, and Gilead Sciences, Inc. for review prior to submission.

I have read and understand the information in the Package Inserts including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

\_\_\_\_\_  
Name of Investigator of Record

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

## MTN-003B

### Bone Mineral Density Substudy to MTN-003 (VOICE)

#### PROTOCOL SUMMARY

- Short Title:** BMD Substudy
- IND Sponsor:** Division of AIDS, NIAID, US NIH
- Chair:** Sharon Riddler, MD, MPH
- Sample Size:** All eligible participants
- Study Population:** Sexually active, HIV-uninfected women 18 to 45 years old who have been randomized to oral study product in MTN-003 [VOICE (Vaginal and Oral Interventions to Control the Epidemic)], and elect participation in the Bone Mineral Density (BMD) Substudy.
- Study Sites:** VOICE Study sites selected by the MTN Executive Committee
- Study Design:** Observational substudy of VOICE
- Study Duration:** Approximately 48 months total. Accrual will require approximately 21 months. Follow-up will continue 12 months after the VOICE Product Use End Visit (PUEV).
- 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 Endpoints:**
- Total hip and lumbar spine BMD via dual energy x-ray absorptiometry (DXA).



**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 the BMD Substudy among participants receiving oral TDF and FTC/TDF compared with placebo.
- To evaluate changes in BMD in the 12 months following the discontinuation of an oral study product in VOICE.

**Secondary Endpoints:**

- Nutritional assessment components, including height, weight, body mass index (BMI), clinical findings, and dietary history.
- Total hip and lumbar spine BMD via dual energy x-ray absorptiometry (DXA).

**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.

**Exploratory Endpoints:**

- Markers of bone turnover and metabolism.
- Ratio of the maximal tubular reabsorption rate of phosphate and the glomerular filtration rate ( $TmPO_4/GFR$ ).<sup>1</sup>

# 1 KEY ROLES

## 1.1 Protocol Identification

Protocol Title: Bone Mineral Density Substudy

Protocol Number: MTN-003B

Short Title: BMD Substudy

Date: August 29, 2011

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## **2 INTRODUCTION**

### **2.1 Vaginal and Oral Interventions to Control the Epidemic (VOICE)**

The VOICE Study will simultaneously assess the safety and efficacy of daily dose oral and vaginal formulations of tenofovir (TDF) and oral FTC/TDF in preventing HIV acquisition. The study design of VOICE also allows limited comparisons of effectiveness, safety, adherence, and associated frequency of viral resistance among HIV seroconverters across formulations.

VOICE is a Phase 2B, five-arm, multi-site, randomized, placebo-controlled trial that is double-blinded within each mode of administration, but open-label with respect to the randomly assigned mode of administration (vaginal or oral). Approximately 5000 participants will be randomized to the five study arms in a 1:1:1:1:1 ratio.

While investigators and participants will be aware of randomization to either the oral or vaginal administration of study product, they will be blinded to the specific study products randomly assigned. All participants will complete monthly follow-up visits for a period of 12 to 36 months, and will receive ongoing HIV risk reduction counseling, condoms, and diagnosis and treatment of sexually transmitted infections (STIs) throughout the course of study participation. Participants will also be scheduled for a Termination Visit approximately 8 weeks following completion of their scheduled end-of-study product use.

The BMD Substudy will explore the potential effects of oral study products on BMD in a subset of VOICE participants.

### **2.2 BMD Considerations in VOICE**

#### **2.2.1 Expected BMD of VOICE Participants**

Based on the cross-sectional study of steroidal hormonal contraception and BMD by Petitti et al.—a study that included the UZ-UCSF site participating in the VOICE Study—it is expected that the baseline BMD of VOICE Study participants will be normal, if not higher than average.<sup>2</sup> This study, conducted among women 30 to 34 years of age who were attending family planning clinics in Brazil, China, Egypt, Mexico, Thailand, and Zimbabwe from 1994-1997, indicated that mean BMD (g/cm<sup>2</sup>) values ranged from 0.488 at the midshaft ulna and 0.409 at the distal radius in African women to an average of

0.462 at the midshaft ulna and 0.360 at the distal radius in Asian women (values adjusted for study site, age, BMI, years of lactation, years since last lactation stopped, and occupation of partner, except entry itself and colinear variables).

The possible contributory effect of two other modifiers on BMD also requires attention. First, some data indicate a small decrease in BMD from the use of the hormonal contraceptive, depot medroxyprogesterone acetate (DMPA).<sup>3</sup> The difference in BMD among the DMPA users was less than one SD of the mean of the group who never used hormonal contraceptives. In the study by Petitti et al., use of DMPA was associated with a significantly lower adjusted mean BMD at the distal radius as measured by single x-ray absorptiometry. The BMD (g/cm<sup>2</sup>) values among women in the DMPA group in the Petitti et al. study, measured 0.465 at the midshaft ulna and 0.369 at the distal radius (adjusted for study site, age, BMI, years of lactation, years since last lactation stopped, and occupation of partner, except entry itself and colinear variables), which is still higher than the BMD values for Asian women. Thus, the observed natural differences between different populations (African versus Asian) were apparently much greater than the differences due to contraceptive method used. It is important to note that data from the HPTN 035 study indicate that approximately 48% of study participants used DMPA and a similar proportion might be expected in the VOICE Study.

Second, breastfeeding may also adversely impact BMD.<sup>4</sup> Given the high frequency of breastfeeding among sub-Saharan African women, VOICE participants might expect a relatively increased risk for BMD loss through this mechanism. However, there are data to indicate that the impact of both DMPA and breastfeeding on bone density, though measurable, is likely to be small and reversible.<sup>3,4</sup> This is particularly true in women with good baseline bone density, as is the case with this population, thus, the cumulative lifetime risk of BMD loss in such individuals may not be appreciable.

### **2.2.2 Tenofovir**

All three active study products in VOICE contain a form of tenofovir, though only two of the active products (oral TDF and oral FTC/TDF) are expected to have significant and consistent systemic absorption of tenofovir. The effects of tenofovir on BMD have been studied in animals and humans. Although clinically significant bone toxicity has not been observed in human trials of tenofovir performed to date, the effects of this drug on bone health in young, pre-menopausal women has not yet been studied and remains of potential concern.

Tenofovir and TDF administered orally in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs [areas under curves])  $\geq$  6-fold those observed in humans caused bone toxicity.<sup>5</sup> In monkeys bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in some monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, bone toxicity manifested as reduced BMD. The mechanism(s) underlying bone toxicity is unknown. However, data in humans have been reassuring. Gilead Study 903, which continues to follow men and

women receiving tenofovir as part of an antiretroviral regimen, has reported on bone monitoring for up to six years in this cohort.<sup>6</sup> Observed decreases in spine BMD were statistically significant at week 144 with a mean percentage decrease at the lumbar spine in patients receiving TDF + lamivudine + efavirenz ( $-2.2 \pm 3.9$ ) compared with patients receiving stavudine + lamivudine + efavirenz ( $-1.0 \pm 4.6$ ). Although observed decreases in spine and hip BMD were statistically significant, these percent changes from baseline are not clinically relevant, and no bone fractures related to TDF have been observed.

#### Clinical Monitoring for Bone Health in VOICE

Given the current limitations in our understanding of the effects of oral TDF and FTC/TDF on BMD in healthy women, the VOICE Study team solicited recommendations from an independent consultant with expertise in the area of bone metabolism and measurement of bone loss. These discussions prompted us to undertake standardized clinical monitoring related to impact on bone, including biannual height measurement and active surveillance for fractures in all participants in VOICE. These outcomes are feasible for all sites to monitor and will provide exceedingly valuable data to inform future studies of longer-term tenofovir use in the setting of both PrEP and antiretroviral therapy.

### **2.3 Study Hypothesis**

It is hypothesized that use of the VOICE oral study products will not cause a clinically significant decrease in BMD in substudy participants.

### **2.4 Rationale for Study Design**

The BMD Substudy will explore the impact of TDF and FTC/TDF on BMD. To measure and interpret this potential impact, participants in the BMD Substudy will undergo measurement of BMD at the spine and hip throughout their participation in the substudy. They will also have blood drawn and stored for possible future testing to evaluate bone turnover (bone resorption and formation) and bone mineral metabolism, and have urine collected and stored for possible future testing of phosphorus and creatinine. The results of these tests will inform our understanding of BMD outcomes. Possible analyses include those listed in Section 7.5, as well as other assays related to bone resorption, formation, and/or metabolism.

#### BMD

In a clinical setting, BMD test results are typically compared to the average bone density of young, healthy adult peak bone mass (T-score) and to the average bone density of other people of the same age, sex, and race (Z-score). For women, the classification of osteoporosis using DXA measurements of BMD is currently based on the T-score if they are age 30 or older. For women under age 30, the Z-score is used (comparison to age-matched) since peak bone mass has not yet been reached. In the BMD Substudy, we will look for changes in BMD in women taking the oral study products used in VOICE.

### Bone turnover

Previous investigators have demonstrated that high bone turnover is an independent risk factor for hip fractures in older women.<sup>7</sup> Although it is unlikely that young women will experience fractures, they may experience bone loss, a major endpoint in the substudy. Greenspan and others have previously demonstrated that bone turnover (bone resorption coupled with bone formation) is associated with the rate of bone loss in women.<sup>8,9,10</sup> Markers of bone resorption include CTX (C-terminal telopeptide of type 1 collagen). Markers of bone formation/growth include P1NP (N-propeptide of type 1 collagen) and BSAP (bone-specific alkaline phosphatase). The major objective of the substudy is to examine potential changes in bone mass in women taking the oral study drugs. If there are significant decreases in BMD, it will be important to determine whether this is due to an increase in bone resorption (increase in CTX), a decrease in bone formation (decreased P1NP and BSAP), or possibly an increase in all markers characterized by greater resorption than formation, leading to the loss of bone.

### Bone mineral metabolism

Persons with vitamin D insufficiency may also demonstrate increased bone resorption.<sup>11</sup> Vitamin D insufficiency and deficiency are more common in those with dark skin (i.e., African Americans compared to Caucasians).<sup>11</sup> It will be critical to examine vitamin D status in these participants to understand the pathophysiology of bone turnover and bone loss. Vitamin D status is assessed by examining levels of 25-hydroxy vitamin D, serum calcium, and parathyroid hormone (PTH). In participants with vitamin D deficiency, PTH levels may be elevated (secondary hyperparathyroidism) with low to normal levels of serum calcium. The BMD Substudy will allow for levels of 25-hydroxy vitamin D to be analyzed in conjunction with parathyroid hormone, permitting the exploration of the pathophysiology of bone mineral metabolism among African women, for whom data are very limited. Storage of samples from baseline and longitudinally will provide the opportunity to document changes in bone mineral metabolism that may result from the oral study medication. Additionally, phosphorus levels (which can be affected in vitamin D deficient states) will be measured on all participants in the VOICE Study; these levels will be available for analysis for the BMD Substudy as well.

TDF has been associated with proximal renal tubular dysfunction and urinary loss of phosphorus. These changes may be mild and not associated with hypophosphatemia since the bone phosphate will compensate for the urinary losses. Collection of urine will allow for the calculation of the ratio of the maximal tubular reabsorption rate of phosphate and the glomerular filtration rate ( $TmPO_4/GFR$ ) as a more sensitive measure of renal tubular dysfunction related to TDF, and may provide additional information about the physiology of any change in BMD.

As nutritional status may have a significant impact on BMD, a nutritional assessment, comprised of anthropometrics (height, weight, and BMI), clinical findings, and dietary history, will also be used to assist in interpretation of the BMD results.

### Bone Mineral Density Changes Over Time

Two studies have reported on the changes in bone mineral density in healthy HIV negative adult men. In both the iPrEx<sup>12</sup> and CDC MSM PrEP<sup>13</sup> studies, healthy men taking tenofovir DF 300 mg daily had a statistically significant loss of bone mineral density of approximately 1% after 24 to 48 weeks compared to placebo. In the iPrEx study, 503 geographically diverse (5 countries) men participated in the BMD substudy. The loss of bone mineral density among participants in the FTC/TDF arm of the iPrEx study was not associated with any clinical harm, as the FTC/TDF (247 randomized to FTC/TDF) and placebo (256 randomized to placebo) participants reported comparable rates of bone fractures. Although these results are reassuring it is important to closely examine the effect of tenofovir in HIV-negative women, who, as previously stated, are exposed to the differential effects on bone density of contraception, breastfeeding, pregnancy, etc., all known to impact bone mineral density.

Limited data suggest that the bone mineral density changes related to tenofovir are reversible after discontinuation of drug in HIV-positive individuals. This has not been studied in HIV-uninfected persons and is critical information for determining the long term effect of a period of oral PrEP, especially for women. MTN-003B is well structured to obtain BMD data after study drug discontinuation, and to compare changes among active drug and placebo participants.

## **3 OBJECTIVES**

### **Primary Objective:**

- To compare changes in BMD after one year among VOICE participants receiving oral TDF and FTC/TDF compared with oral placebo.

### **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 the BMD Substudy among participants receiving oral TDF and FTC/TDF compared with placebo.
- To evaluate changes in BMD in the 12 months following the discontinuation of an oral study product in VOICE.

### **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 study products.

## **4 STUDY DESIGN**

### **4.1 Identification of Study Design**

The BMD Substudy will be a substudy of VOICE. All VOICE participants randomized to oral study product at selected sites will be offered participation in the BMD Substudy and will be accrued, until all eligible participants have been enrolled. Substudy assessments (detailed in Section 7) will be completed at enrollment in the substudy and semiannually thereafter. These assessments will also be completed at the VOICE Product Use End Visit (PUEV) or the BMD Substudy Early Termination Visit (ETV) if either occurs at least 30 days after the last semiannual BMD Substudy visit.

### **4.2 Summary of Major Endpoints**

- Total hip and lumbar spine bone density via DXA

### **4.3 Description of Study Population**

The study population will be comprised of sexually active, HIV-uninfected women 18 to 45 years old who have been randomized to oral study product in VOICE, elect participation in the BMD Substudy, and meet criteria outlined in Section 5.

### **4.4 Time to Complete Accrual**

Accrual is expected to be completed in approximately 21 months.

### **4.5 Study Groups**

The three study groups included in the BMD Substudy are as follows:

- TDF group (TDF 300 mg and FTC/TDF placebo)
- FTC/TDF group (TDF placebo and FTC/TDF 200 mg/300 mg)
- Oral placebo group (TDF placebo and FTC/TDF placebo)

### **4.6 Expected Duration of Participation**

The expected duration of participation in the BMD Substudy is approximately 48 months total. Accrual will require approximately 21 months. Follow-up will continue for 12 months after the VOICE PUEV.

### **4.7 Sites**

This study is open to VOICE Study sites selected by the MTN Executive Committee.



## **5 STUDY POPULATION**

### **5.1 Selection of the Study Population**

In addition to the inclusion and exclusion criteria of VOICE, participants must meet criteria below specific to participation in the BMD Substudy.

### **5.2 Inclusion Criteria**

Women must meet all of the following criteria to be eligible for inclusion in the BMD Substudy:

1. Randomized to oral study product in VOICE within the past 14 days
2. Able and willing to provide written informed consent for participation in the BMD Substudy

### **5.3 Exclusion Criteria**

Women who meet any of the following criteria will be excluded from the BMD Substudy:

1. Pregnant at Screening and Enrollment Visit
2. Has a medical condition known to affect bone (e.g., hyperparathyroidism, bone cancer) or taking any medication known to affect bone (e.g., glucocorticoids, heparin, warfarin, cyclosporine, cancer drugs, and thyroid hormone).
3. Permanently discontinued from oral study product in VOICE prior to the BMD Substudy Screening and Enrollment Visit.
4. At enrollment, any other condition that, in the investigator's opinion, would preclude informed consent, make substudy participation unsafe, complicate interpretation of substudy outcome data, or otherwise interfere with achievement of the substudy objectives.

## **6 STUDY PRODUCT**

No additional study product considerations are applicable for the BMD Substudy

## 7 STUDY PROCEDURES

VOICE participants at BMD Substudy sites will be offered participation in the BMD Substudy via a separate informed consent process following random assignment in VOICE to oral study product. Eligibility determination and enrollment may take place on the day of random assignment in VOICE or any time up to 13 days after the date of random assignment in VOICE. In addition to study procedures outlined in Section 7 of the VOICE protocol, participants in the BMD Substudy will have the following evaluations and procedures related to the assessment of bone density and bone turnover/metabolism:

- BMD of spine and hip by DXA
- Serum and urine collection and storage for markers of bone turnover, bone mineral metabolism, and urinary phosphorus and creatinine measurements
- Collection of medical history (if not done in VOICE or other study)
- Collection of concomitant medications (if not done in VOICE or other study)
- Collection of contraception history
- Collection of lactation history
- Collection of physical activity history
- Nutrition assessment
  1. Anthropometric
    - Measurement of weight
    - Measurement of height
  2. Clinical, including assessment of physical signs of malnutrition
  3. Dietary, including a food frequency questionnaire that will capture intake of common local foods

Detailed instructions to guide and standardize all study procedures across sites will be provided in the VOICE Study Specific Procedures (SSP) Manual, available at [www.mtnstopshiv.org](http://www.mtnstopshiv.org).

### 7.1 Schedule of Study Visits

An overview of the study visit and evaluations schedule is presented in Table 1. Detailed instructions to guide and standardize procedures across sites are provided in the VOICE SSP Manual available at [www.mtnstopshiv.org](http://www.mtnstopshiv.org). As indicated in the SSP Manual, all MTN-003B visits may be conducted as split visits.

**Table 1: Schedule of BMD Substudy Visits and Evaluations**

Procedure	Screening and Enrollment Visit	Semiannual Follow-up Visit (every 6 mo during VOICE participation and for 12 months after the VOICE PUEV)	VOICE PUEV / BMD Substudy ETV *
Informed Consent for BMD Substudy	X		
Eligibility Determination	X		
Reimbursement	X	X	▲
Schedule Next Visit	X	▲	▲
Collect Contraception History	X		
Collect/Update Lactation History	X	▲	▲
Collection of medical history (if not done in VOICE or other study)		▲	▲
Collect concomitant medications (if not done in VOICE or other study)		▲	▲
Nutrition Assessment – Anthropometric (height and weight)**	X	X	X
Nutrition Assessment – Clinical (physical signs of malnutrition)	X	X	X
Nutrition Assessment – Dietary (food frequency questionnaire)	X	X	X
Collect/Update Physical Activity History	X	X	X
Urine Collection for Pregnancy Test (may be omitted if already performed as part of VOICE procedures on same day)	▲	▲	▲
Urine Collection and Storage for Exploratory Objective Testing of Excreted Phosphorus and Creatinine	X	X	X
DXA of Spine and Hip	X	X	X
Blood Collection and Serum Storage for Exploratory Objective Testing of Markers of Bone Turnover and Bone Mineral Metabolism	X	X	X

*X required*

*▲ if indicated*

*\*These procedures are performed at the VOICE PUEV or BMD Substudy ETV if either occurs at least 30 days after the last semiannual BMD Substudy follow-up visit*

*\*\* Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B*

## **7.2 Screening and Enrollment Visit**

Eligibility determination and enrollment may take place on the day of random assignment in VOICE, or up to 13 days after the date of random assignment in VOICE.

### **7.2.1 Administrative and Regulatory Procedures**

- Informed consent for screening and enrollment

- Eligibility determination
- Reimbursement
- Schedule next visit (if applicable)

### **7.2.2 Anthropometric and Clinical Procedures**

- Contraception history
- Lactation history
- Nutrition assessment - anthropometric (height and weight) *Note: Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B*
- Nutrition assessment – clinical (physical signs of malnutrition)
- Nutrition assessment – dietary (food frequency questionnaire)
- Physical activity history
- Blood collection
- Urine collection

### **7.2.3 Laboratory and DXA Procedures**

- Urine pregnancy test (may be omitted if already performed as part of VOICE Study procedures on same day)
- Urine storage for possible testing for levels of phosphorus and creatinine
- Serum storage for possible testing of markers of bone turnover and bone mineral metabolism
- DXA of spine and hip

## **7.3 Follow-up Visits**

Follow-up visits will occur on a semiannual basis (approximately every 6 months) and may be completed on the same day as VOICE Study visits. The follow-up visits will occur at 6 months and 12 months following the VOICE PUEV. The semiannual follow-up visit procedures listed below will also be completed at either the VOICE PUEV or the BMD Substudy ETV if at least 30 days have passed since the last semiannual follow-up visit.

### **7.3.1 Administrative and Regulatory Procedures**

- Reimbursement
- Schedule next visit, if indicated

### **7.3.2 Anthropometric and Clinical Procedures**

- Update lactation history, if indicated

- Nutrition assessment - anthropometric (height and weight) *Note: Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B*
- Nutrition assessment – clinical (physical signs of malnutrition)
- Nutrition assessment – dietary (food frequency questionnaire)
- Collection of medical history (if not done in VOICE or other study)
- Collection of concomitant medications (if not done in VOICE or other study)
- Physical activity history
- Urine collection
- Blood collection

### 7.3.3 Laboratory and DXA Procedures

- Urine pregnancy test (may be omitted if already performed as part of VOICE Study procedures on same day)
- Urine storage for possible testing for levels of phosphorus and creatinine
- Serum storage for possible testing for markers of bone turnover and bone mineral metabolism
- DXA of spine and hip

### 7.4 DXA Scan

The most widely recognized test for measuring BMD is a quick, painless, noninvasive technology known as DXA. This technique, which uses low levels of x-rays, involves passing a scanner over the body while the individual lies on a cushioned table. DXA can be used to determine BMD of the entire skeleton and at various sites that are prone to fracture, such as the hip, spine, or wrist. BMD by DXA at the hip and spine is generally considered the most reliable way to classify osteoporosis, assess changes in BMD, and predict fracture risk.

To reduce measurement error, all DXA scans of the hip (total hip, femoral neck) and PA spine (L1-L4) will be performed in duplicate at each visit, and results will be recorded on case report forms. The SDMC will use this data to calculate the average of the two scans for a given visit. Use of the DXA scanner will follow standard protocols provided by the manufacturer.

Detailed instructions to guide and standardize all study procedures across sites will be provided in the VOICE SSP Manual, available at [www.mtnstopshiv.org](http://www.mtnstopshiv.org). The MTN will purchase identical scanners for each site, and appropriate training will be provided prior to implementation of the study according to International Densitometry Standards available at [www.iscd.org/](http://www.iscd.org/). The sites will follow routine daily QA protocols for the machine using a phantom and standard protocols. One of the study site phantoms will be sent to the second site for scanning to assess comparability of the two sites scans. The sites will routinely send (electronically) scans to the University of Pittsburgh Osteoporosis Center for QC.

## 7.5 Laboratory Evaluations

Evaluations will be conducted at local, regional, network, or approved reference laboratories according to guidelines outlined in the VOICE SSP Manual.

- Urine pregnancy test (done at local laboratories)
- Serum and urine will be collected and stored; these samples may be used for future measurement of markers of bone turnover and bone mineral metabolism and levels of excreted phosphorus and creatinine, respectively, if significant changes in BMD from baseline are observed following review of DXA scan results. The markers of bone turnover and bone mineral metabolism may include but are not limited to the following:
  - Bone turnover:
    - Bone resorption (CTX)
    - Bone formation (P1NP, BSAP)
  - Bone mineral metabolism:
    - Calcium
    - Albumin
    - PTH
    - 25-hydroxy vitamin D
    - Urine phosphorus and creatinine

## 7.6 Follow-up Procedures for Participants who Temporarily Hold or Permanently Discontinue Study Product

Participants who temporarily hold or permanently discontinue use of study product will not routinely be withdrawn from this substudy. Rather, every effort will be made to complete all protocol-specified visits and procedures with these participants, except as noted below.

### 7.6.1 Participants Who Become Pregnant

All protocol-specified study procedures will continue except for the following:

- DXA scan
- Collection and storage of urine and serum

These procedures may be resumed according to original schedule following completion of the pregnancy.

## **7.7 Specimen Collection and Processing**

Each study site will adhere to the standards of good clinical laboratory practice, the HPTN-MTN Network Laboratory Manual ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)), DAIDS Laboratory Requirements ([www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/labs/LabPolicy.pdf](http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/labs/LabPolicy.pdf)), VOICE SSP Manual ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

## **7.8 Specimen Handling**

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/labs/LabPolicy.pdf>)

## **7.9 Biohazard Containment**

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by CFR 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

# **8 ASSESSMENT OF SAFETY**

The BMD Substudy is an observational study involving no investigational products (beyond those in VOICE) or procedures associated with significant risk to participants. Therefore, few safety concerns are expected as a result of study participation. Safety monitoring specific to participation in this substudy includes reportable occurrences (as defined below) related to study participation and procedures, as well as results of DXA scanning.

## **8.1 Safety Monitoring**

Site Investigators of Record (IoRs) are responsible for continuous close safety monitoring of all study participants, and for alerting the VOICE Protocol Team if

unexpected concerns arise. Safety data collected in the BMD Substudy will be reviewed by the VOICE Protocol Safety Review Team (PSRT) and the NIAID Vaccine and Prevention Data Safety Monitoring Board (DSMB), together with all other VOICE Study safety data, as outlined in Section 8.1 of the VOICE Protocol.

Following completion of VOICE, the site IoRs will notify the MTN-003B Protocol Team with any unexpected safety concerns. No DSMB oversight or MTN Study Monitoring Review is planned for this study following completion of VOICE. The protocol team will conduct periodic internal reviews of study progress, including rates of participant retention. These reviews will take place every 3 months.

## 8.2 Adverse Events Definitions and Reporting Requirements

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not this sign is considered product related. AEs will be identified, documented, reported, and managed in the VOICE Study as outlined in Section 8.2 of the VOICE Protocol. In addition, for VOICE participants who take part in the BMD Substudy, bone mineral loss (grade 2 or higher) will be reported as an AE. The severity of AEs involving bone mineral loss will be graded according to Table 2 below. The relationship of AEs involving bone mineral loss will be assessed based on the Manual for Expedited Reporting of Adverse Events to DAIDS, dated January 2010 (DAIDS EAE [expedited adverse event] Manual), the VOICE Study oral product Package Inserts and the clinical judgment of the IoR designee. The study products that must be considered when AE relationships are specified are the TDF tablet and the FTC/TDF tablet.

**Table 2: Protocol-specific Grading Table for Bone Mineral Loss**

<b>Bone Mineral Loss</b>			
<b>GRADE 1 MILD</b>	<b>GRADE 2 MODERATE</b>	<b>GRADE 3 SEVERE</b>	<b>GRADE 4 POTENTIALLY LIFE-THREATENING</b>
BMD T-score -2.5 to -1.0	BMD T-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
BMD Z-score -2.0 to -1.0	BMD Z-score < -2.0	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences

Following participant completion of the VOICE PUEV, any AEs identified during an MTN-003B visit, including bone mineral loss of any grade, will not be reportable (unless the participant is co-enrolled in another MTN trial, in which case the other trial's AE reporting guidelines apply).



### **8.3 Expedited Adverse Event Reporting Requirements**

The EAE reporting requirements and definitions for this substudy are the same as those outlined in Section 8.3 of the VOICE protocol, except that the study agents considered in determining relationships of AEs requiring expedited reporting are the TDF tablet and FTC/TDF tablet.

### **8.4 Regulatory Requirements**

Information on all reported AEs will be included in reports to the US Food and Drug Administration (FDA) and other applicable government and regulatory authorities. Site IoRs/designees will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. Site IoRs/designees will also submit AE information and any other relevant safety information to their Institutional Review Boards (IRBs)/Ethics Committees (ECs) in accordance with IRB/EC requirements.

### **8.5 Social Harms Reporting**

The social harms reporting requirements and definitions for this substudy are the same as those outlined in the VOICE protocol.

## **9 CLINICAL MANAGEMENT**

In addition to those listed in Section 9 of the VOICE protocol, guidelines for clinical management and product temporary hold/permanent discontinuation for the BMD Substudy are outlined in this section.

### **9.1 BMD Status: Baseline**

- For participants with a baseline BMD < -2.0 SD Z-score (ages 18 to 29 years) or T-score < -2.0 SD (ages 30 and older), the IoR/designee will be required to do the following:
  - Discuss options for treatment or prevention of osteoporosis with the study participant. The study will provide calcium supplementation if recommended by the IoR/designee.

### **9.2 BMD Status: During Follow-up**

For participants with more than a 1 SD reduction in BMD compared to baseline, the IoR/designee should repeat the DXA scan as soon as possible and consult the PSRT.

For participants with Z-scores (ages 18-29) or T-scores (age  $\geq 30$ ) less than -2.0 SD during follow-up the IoR/designee will be required to do the following:

- Discuss options for treatment or prevention of osteoporosis with the study participant. The study will provide calcium supplementation if recommended by the IoR/designee.

### **9.3 BMD Status: Following Participant Completion of the VOICE PUEV**

For participants with more than a 1 SD reduction in BMD compared to baseline, the IoR/designee should repeat the DXA scan, if not previously done.

For participants with Z-scores (ages 18-29) or T-scores (age  $\geq 30$ ) less than -2.0 SD compared to baseline, the IoR/designee will be required to do the following:

- Discuss options for treatment or prevention of osteoporosis with the study participant. The study will provide calcium supplementation if recommended by the IoR/designee.

### **9.4 Malnutrition**

Participants identified as malnourished according to the clinical judgment of the IoR/designee will be counseled regarding locally available treatment options and sources for nutrition support.

### **9.5 Clinical Management of Pregnancy**

Participants who become pregnant will discontinue DXA scans and collection and storage of urine and serum, but will resume these procedures per their original substudy follow-up schedule after completion of the pregnancy.

## **10 STATISTICAL CONSIDERATIONS**

### **10.1 Overview and Summary of Design**

This is a substudy conducted in an ancillary fashion to VOICE. All eligible participants randomized to oral study product will be enrolled at selected substudy sites. Follow-up assessments will occur semiannually throughout participation; follow-up assessments will also be completed at the VOICE PUEV or the BMD Substudy ETV if at least 30 days have passed since the last BMD Substudy semiannual follow-up visit.

## 10.2 Study Endpoints

### Primary endpoints

Consistent with the substudy objective to explore changes in BMD among VOICE participants using oral study products, the following primary endpoints will be assessed:

- Total hip and lumbar spine bone density via DXA

Note that these endpoints will be used also for the secondary objective to explore changes in BMD among VOICE participants using oral study products after discontinuation of product use.

Consistent with the substudy secondary objective to describe changes over time in nutritional status among VOICE participants receiving oral study products, the following secondary endpoints will be assessed:

- Nutritional assessment components, including height, weight, BMI, clinical findings, and dietary history

## 10.3 Primary Study Hypotheses

### Primary endpoints

The protocol team hypothesizes that oral TDF and FTC/TDF will not cause a clinically significant decrease in BMD in substudy participants. Therefore, the null hypothesis is that there will be no difference in the safety profile between daily regimens of oral active products and oral placebo after one year of product use.

## 10.4 Sample Size and Power Calculations

For the VOICE Study population, the estimated range of baseline means for single measurements of total hip and lumbar spine BMD at a given time point are between 1.0 and 1.2 g/cm<sup>2</sup> with standard deviation (SD) between 0.1 and 0.2 g/cm<sup>2</sup>. Longitudinal measurements of BMD are highly correlated when correlation coefficients are in the range of 0.85 to 0.95, which translates to SD estimates in the range of 3.5% and 5.5% for the percentage change in BMD from baseline to a time point 12 months after initiation of follow-up. Through 144 weeks in Gilead Study 903, for example, the observed SDs for the percentage change in BMD from baseline for hip and lumbar spine was between 3.5% and 4.6%. Therefore, for sample size calculations in this substudy, we will assume that the SD for the percentage change in BMD from baseline to a time point 12 months after initiation of follow-up for the hip and lumbar spine is 4.5%. Duplicate measurements will be made at each time point since the variability associated with the instrument/operator is relatively high in comparison to between-subject variability.

For the purpose of sample size determination, we are conservatively assuming that a minimum of 300 women will be enrolled in the study (i.e. 100 women per oral arm). Given that at the selected sites all women enrolled into oral arms will be asked to participate in this study, the total enrollment will be between 300 and 540 women.

At each assessment time point during the expected product use period, the arithmetic mean of the duplicate measurements will be used for the following primary analysis. Two Student t-tests (two-sided) will be used to compare the percentage reduction in BMD between the TDF active arm, FTC/TDF active arm, and placebo arm. Analyses for hip and lumbar spine measurements will be done separately. Based on the above SD estimates, a sample size of 100 women per oral arm allows the detection of a difference as small as 2.1% with 90% power with a type one error rate of 5%. Note that this is a conservative estimate of power since the duplication of measurements at each time point will reduce the SD and thus provide power to detect lower differences (i.e., <2.1%). However, the reduction in SD is difficult to quantify since no data are currently available on the measurement error that could be anticipated at each of the proposed sites.

Similarly, the percentage change in BMD between the TDF active arm, FTC/TDF active arm, and placebo arm observed during the year after product use was discontinued will be compared. Based on similar assumptions as above, 100 women per oral arms will allow the detection of a difference as small as 2.1% with 90% power with a type one error rate of 5%.

## **10.5 Data and Safety Monitoring and Analysis**

When the use of descriptive statistics to assess group or site characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). To assess the differences between the three oral arms, participants will be compared for baseline characteristics including demographics using descriptive statistics.

For the primary analysis, two Student t-tests will be used to compare the percentage reduction after one year of follow-up in BMD between each of the following: (1) the TDF active arm and placebo oral arm; and, (2) FTC/TDF active arm and placebo oral arm. Analysis for hip and lumbar spine measurements will be done separately.

BMD hip and lumbar assessments are done every 6 months, but a substantial number of women will have terminated the VOICE trial before reaching their year-2 BMD assessments. Assuming uniform recruitment over 21 months, about 130 of the 300 women will have a year-2 BMD assessment. This reduction in participant numbers will result in a reduction of the statistical power in comparison to that observed following year-1. However, to explore possible trends over the entire follow-up time, GEE models for repeated measures will be used where BMD from all time points are included in the analysis.

Similar methods will be used to compare changes after one/two year(s) of follow-up in bone turnover, bone mineral metabolism, and nutritional assessment components. Distribution of some of these endpoints may not allow the use of the Student t-test (e.g., height is expected to have very little variation over a year), in which case a McNemar's test approach might be used, or the proportion of women with an observed percentage change might be compared across arms using a Fisher exact test.

For evaluating changes in BMD after product use was discontinued, two Student t-tests will be used to compare the percentage change over the year of follow-up without product use in BMD between each of the following: (1) the TDF active arm and placebo oral arm; and, (2) FTC/TDF active arm and placebo oral arm. Analysis for hip and lumbar spine measurements will be done separately. Note that this analysis is more relevant in the case where at least one effect from the use the active oral products on BMD is observed. In that case, it would be worthwhile to investigate if the effect on the BMD is waning after product use is discontinued and eventually returns to its baseline values (i.e. prior to initiation of product use).

### **10.5.1 Data and Safety Monitoring Board (DSMB)**

DSMB reviews of VOICE Study data will be conducted approximately every eight to twelve months. Safety data from the BMD Substudy will be included in these reviews. While not limited to the following review parameters, the DSMB will monitor for the onset of osteoporosis and adult non-traumatic fragility fractures in women >30 years of age, and for the development of Z-scores < -2.0 or non-traumatic fractures in women aged 18 to 29.

In addition to safety data presentations, analyses will be performed to assess substudy conduct operational characteristics (e.g., accrual and retention), which will be compared to protocol substudy assumptions. If necessary, alterations will be made to the study design (e.g., increased or decreased accrual and/or follow-up and/or number of sites) if recommended by the DSMB. Study conduct operational characteristics are also reviewed by the MTN Study Monitoring Committee (SMC) more frequently. Recommendations of the SMC are forwarded to the DSMB.

No DSMB oversight or MTN Study Monitoring Review is planned for this study following completion of VOICE as there will be no further product exposure, thus no deleterious effect of study participation is anticipated.

# 11 DATA HANDLING AND RECORDKEEPING

## 11.1 Data Management Responsibilities

Study case report forms will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries will routinely be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all case report forms to be used as source documents. Study data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

## 11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch>).

Each IoR/designee will maintain, and store securely, complete, accurate, and current study records throughout the study. In accordance with US regulations, for each of the three investigational products tested, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval for each of the three study products for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US FDA is notified.

Study records must be maintained on site for the entire period of study implementation. Thereafter, instructions for record storage will be provided by DAIDS. No study records may be moved to an off-site location or destroyed prior to receiving approval from DAIDS.

## 11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites (<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gmppolicy.pdf>).

Staff training and quality control/calibration procedures for DXA scanning will be standardized across study sites.

## **12 CLINICAL SITE MONITORING**

Study monitoring will be carried out by PPD (Wilmington, NC) in accordance with all applicable DAIDS guidance for monitoring of substudies. Please refer to the VOICE (DAIDS Protocol# 10622) Clinical Site Monitoring Section (Section 12) for additional applicable details.

## **13 HUMAN SUBJECTS PROTECTIONS**

Section 13 of the VOICE protocol provides information on human subjects protections applicable to the BMD Substudy, with additional guidance provided below.

### **13.1 Risk Benefit Statement**

#### **13.1.1 Risks**

Exposure to radiation has been associated with increased risk of cancer. However, the effective radiation dose from this procedure is about 0.01 mSv (millisievert), which is about the same dose the average person receives from background radiation in one day or an amount similar to that received during a 5 hour airplane flight.

Exposure to radiation in pregnancy has been associated with fetal malformations. The effects of DXA testing on a developing fetus are unknown. However, the very low dose of radiation associated with DXA is not expected to be a risk to undetected early pregnancy. Participants will be instructed to inform study staff if there is any possibility that they are pregnant, and will have a pregnancy test performed prior to each DXA test.

No complications are expected with the DXA procedure. Care is taken during DXA testing to use the lowest radiation dose possible while producing the best images for evaluation. National and international radiology protection councils continually review and update the technique standards used in DXA testing. DXA systems have tightly controlled x-ray beams with significant filtration and dose control methods to minimize stray or scatter radiation. This ensures those parts of a participant's body not being imaged receive minimal radiation exposure.

Participants may become worried while waiting for test results. Every effort will be made to protect privacy and confidentiality. Participant visits will take place in private. It is possible that others may learn of participant study involvement, and participants may be treated unfairly as a result. BMD Substudy counselors will be trained to counsel participants subjected to this.

No additional risks to participants are anticipated from the collection of nutrition history, contraception history, lactation history, physical activity history, the measurement of

weight or height, or the collection of urine. Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling, and/or infection.

### **13.1.2 Benefits**

Participants may benefit from information obtained about their nutritional status, BMD, and associated information on estimates of their risk of fracture. Participants also may benefit from nutritional counseling and calcium supplements provided by the study, if needed.

## **13.2 Protocol Registration**

Prior to implementation of this protocol, sites must have the protocol and protocol consent form approved by their local institutional review board (IRB). Protocol documents must be registered with and approved by the DAIDS Regulatory Support Center (RSC) Protocol Registration Office. Protocol registration must occur before the site can enroll any subjects into the study. Protocol registration material can be sent electronically to [epr@tech-res.com](mailto:epr@tech-res.com). For questions regarding protocol registration, contact the Protocol Registration Office via e-mail at [protocol@tech-res.com](mailto:protocol@tech-res.com), fax 800-418-3544 or 301-897-1701, or phone 301-897-1707.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS Protocol Registration Office (DAIDS PRO) and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

## **13.3 Informed Consent Process**

Separate written informed consent for the BMD Substudy will be obtained from study participants prior to enrollment.

# **14 PUBLICATION POLICY**

DAIDS/NIAID and MTN policies and Clinical Trial Agreements between CONRAD and NIAID, and between Gilead Sciences, Inc. and NIAID will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, NICHD, NIMH, CONRAD, and Gilead Sciences, Inc., for review prior to submission.



# APPENDIX I: SAMPLE INFORMED CONSENT (BONE MINERAL DENSITY)

## SAMPLE INFORMED CONSENT FORM DAIDS, NIAID, NIH

### Bone Mineral Density Substudy, Ancillary Study to MTN-003 (VOICE)

Version 2.0  
August 29, 2011

**PRINCIPAL INVESTIGATOR:** [insert name]

**PHONE:** [insert number]

**Short Title for the Study:** Vaginal and Oral Interventions to Control the Epidemic (VOICE) Bone Mineral Density (BMD) Substudy

#### INFORMED CONSENT

You are being asked to volunteer for the research study named above. This Bone Mineral Density (BMD) Substudy is for women who have already agreed to be in the VOICE Study at this site, and who will be taking oral tablets in the VOICE Study. Before you decide whether to be in the Bone Mineral Density Substudy, we would like to explain its purpose, and outline your risks and benefits, what is expected of you, and what you can expect from us. The United States National Institutes of Health is funding this BMD.

#### YOUR PARTICIPATION IS VOLUNTARY

Before you decide whether to be in this BMD Substudy, we would like to explain the purpose of the BMD Substudy, the risks and benefits, what is expected of you, and what you can expect from us. This consent form might contain some words that are unfamiliar. Please ask questions about anything you do not understand or want to learn more about. Once you understand the BMD Substudy, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the BMD Substudy, it is important to know the following:

- It is up to you whether or not you join the BMD Substudy. If you decide not to join this BMD Substudy, you can still be in the VOICE Study.
- You may decide not to join this BMD Substudy, or you may choose to leave this BMD Substudy at any time, without losing the benefits of your regular medical care. If you choose to leave this BMD Substudy, you can still stay in the VOICE Study. Also, if you choose to leave this BMD Substudy, you will be asked to come in to the clinic for a final set of tests.
- If you decide not to join this BMD Substudy, you can still join another study later, if one is available and you qualify.

## **PURPOSE OF THE STUDY**

The main purpose of the Bone Mineral Density Substudy is to find out if women who take oral tablets in the VOICE Study have changes in the thickness of the bones in their spine and hips. The US Food and Drug Administration (FDA) has been informed of this BMD Substudy and has permitted it to be conducted. [The [local authority] also has permitted the BMD Substudy to be conducted.] The United States National Institutes of Health is funding this BMD Substudy.

Women who take oral tablets in the VOICE study will be offered enrollment into the BMD Substudy. Up to 540 women will join this study. Each woman will be in the BMD Substudy for up to 4 years; the substudy will continue for about 1 year longer than the VOICE study. Results and other medical information collected during your participation in the VOICE Study may be used to help researchers understand the results of this BMD Substudy.

## **STUDY PROCEDURES**

If you decide to join the Bone Mineral Density Substudy, your first visit will start today, after you read, discuss, and sign or make your mark on this form. BMD Substudy staff will help you understand the form and answer your questions before you sign or mark this form. If you decide to join this BMD Substudy, the following will be done:

- Urine pregnancy test
- Measurement of your height and weight
- A DXA test, which is a type of X-ray test that checks the thickness of your bones in the spine and hips. This test does not hurt. You will lie on a table and have a special photograph taken of your bones. You will get the results of your DXA test when they are available, which is usually right after the test. However, if the doctor needs to review your results again, it may take a little longer to get them.
- Collection of blood (about 30 mL [insert local equivalent]) and urine that will be stored and may be tested later to help the BMD Substudy doctors better understand the DXA results. The BMD Substudy doctors will decide which blood and urine samples will be tested during or after the BMD Substudy based on results of the DXA tests. If any tests are done, the BMD Substudy doctors do not plan to give you the results of the tests unless they feel the results are important to your health. If you wish the BMD Substudy doctors to contact you with this type of result, you must give the BMD Substudy staff any changes to your contact information. If these tests are done on your blood samples, you will get results of blood tests that can be used by you or your health care provider to make decisions about your health when they are available.
- Measurement of your height and weight.

You will also answer questions about the following:

- The foods you eat and whether you have had problems with nutrition in the past. If you might benefit from changing your diet, the BMD Substudy staff will talk with you about ways to make your diet better.
- Breastfeeding.
- Contraception.
- Physical activity.
- Medical history and any medicines you may be taking.

After today you will be in the BMD Substudy for up to 4 years. You will have the procedures listed above today and every 6 months while you are in this BMD Substudy. If needed, you will also have a visit when you stop taking the oral product for VOICE. These procedures will continue for approximately 12 months after you finish taking your VOICE Study tablets. These procedures will take about 60 to 90 minutes. These procedures may be done on the same day as your regular VOICE Study visits, when possible. [BMD Substudy site to insert if applicable: A BMD Substudy staff member will take you to a different clinic for the DXA test]

**Before each DXA test and at any time in the BMD Substudy**, if you or the BMD Substudy staff thinks you might be pregnant, you will give urine for a pregnancy test. The DXA test should not be done if you are pregnant, but can be performed after you are no longer pregnant.

If at any time in the BMD Substudy your DXA test results show that you might benefit from taking a calcium vitamin, the BMD Substudy will give you this vitamin.

### **POSSIBLE FUTURE TESTS**

Storage of your blood and urine for future testing is required for participation in this BMD Substudy . Your blood and urine may be stored here in [insert country] or in the United States until all testing has been done. Some tests may be done outside of [insert country]. After all tests have been done, and the results reviewed, all samples will be destroyed.

### **RISKS AND/OR DISCOMFORTS**

**Risks of Blood Draws:** You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, small clot, or infection where the needle goes into your arm.

**Risks of DXA Test:** There is a risk from being near x-rays, also known as radiation. High levels of x-rays have been associated with cancer. However, the level of x-rays used in a DXA test is much lower than the level that may cause cancer. The BMD Substudy staff members have been trained to do the DXA test using the smallest amount of x-ray possible.

**Other Possible Risks:** You may become worried while waiting for your test results. We will make every effort to protect your privacy and confidentiality while you are in the

BMD Substudy. Your visits here will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. If you have any problems like this, BMD Substudy counselors will talk with you to try to help resolve them.

### Pregnancy

It is not known if the DXA test has effects on pregnancy or on the fetuses of women who have a DXA test when pregnant. Because of this, pregnant women may not join this BMD Substudy. This also is why BMD Substudy participants must have pregnancy tests while in the BMD Substudy. However, you will not have extra pregnancy tests if you have procedures done for this BMD Substudy on the same day as a VOICE Study visit.

All VOICE Study participants should use effective contraception. Effective contraception includes hormonal methods (such as the birth control pill or shot), intrauterine contraceptive device (IUCD); and sterilization of you or your partner. You should not use spermicides as a method of contraception while participating in the VOICE Study. After completion of the VOICE study, contraception will not be required but the study staff will ask whether or not you are using contraception and will discuss contraceptive options with you if you wish.

If you become pregnant during the BMD Substudy, the study staff will refer you to available sources of medical care and other services you or your baby may need. You will stop having DXA tests and giving blood and urine samples, but keep coming here for substudy visits as originally planned. Depending on when you become pregnant, you may be able to have the DXA tests again after your pregnancy. The BMD Substudy staff will talk more with you about this after your pregnancy.

### **NEW INFORMATION**

You will be told about new information from this or other studies that may affect your health, welfare or willingness to stay in this BMD Substudy.

### **BENEFITS**

You may get no direct benefit from being in this BMD Substudy. You will learn if your bone thickness is normal. You may benefit from hearing about ways to make your diet better. You may be given calcium vitamins if you need them. You and other people may benefit in the future from information learned in this BMD Substudy.

## **REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT**

You may be removed from this BMD Substudy without your consent for the following reasons:

- The BMD Substudy and/or the VOICE Study is stopped or canceled.
- The BMD Substudy staff feels that staying in the BMD Substudy would be harmful to you.
- You are not able to attend BMD Substudy visits or complete the BMD Substudy procedures.
- Other administrative reasons.

## **ALTERNATIVES TO PARTICIPATION**

There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places you can go for the types of tests and counseling used in this BMD Substudy. We will tell you about those places if you wish.

## **COSTS TO YOU**

There is no cost to you for being in this substudy.

## **REIMBURSEMENT**

*[Sites to insert information about local reimbursement:]*

You will receive [\$xx] for your time, effort, and travel at each scheduled BMD Substudy visit. This is in addition to any reimbursement you receive for the VOICE Study.

## **CONFIDENTIALITY**

Efforts will be made to keep your personal information confidential. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this substudy will not use your name or identify you personally.

Your records may be reviewed by any or all of the following:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the organization that supplies tenofovir gel
- the company that makes tenofovir tablets and Truvada<sup>®</sup> tablets

## **RESEARCH-RELATED INJURY**

*[Sites to specify institutional policy:]* It is unlikely that you will be injured as a result of participation. If you are injured as a result of being in this BMD Substudy, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to

pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

### **PROBLEMS OR QUESTIONS**

If you ever have any questions about this BMD Substudy, or if you have a research-related injury, you should contact [insert name of the investigator or other BMD Substudy staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert telephone number and/or physical address].

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the BMD Substudy, please sign your name or make your mark below. All other information that is contained in the main (VOICE) study consent that you signed also applies to this BMD Substudy consent.

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Participant Name (print)	Participant Signature	Date
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Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
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Witness Name	Witness Signature	Date
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## REFERENCES

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