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BACKGROUNDER

VOICE B

Bone Mineral Density Sub-study of VOICE -- Vaginal and Oral Interventions to Control the Epidemic

Overview

VOICE B, also known as the Bone Mineral Density Sub-study, is an observational study within a larger trial called VOICE – Vaginal and Oral Interventions to Control the Epidemic, which is looking at whether some of the same antiretroviral (ARV) medicines used successfully for treatment of HIV are safe and effective for HIV prevention, as either a vaginal microbicide or an oral tablet. The ARV tablets being tested in VOICE are called tenofovir (also known as Viread[®]) and Truvada[®]. Although they are considered safe and effective for treating people with HIV as part of combination drug therapy, researchers have observed modest decreases in bone mineral density (thinning of bone) in HIV-infected people during treatment with tenofovir. As such, researchers are conducting VOICE B to determine the potential effects, if any, these oral drugs may have on bone health in HIV-negative women, and in particular, pre-menopausal women in Africa. VOICE B will provide valuable data that will help inform a field looking at the promise of ARV-based approaches for prevention of HIV.

As a sub-study of VOICE, VOICE B is funded by the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID). Both studies are being conducted by a team of researchers associated with the Microbicide Trials Network (MTN). The MTN was established and funded in 2006 by DAIDS/NIAID with co-funding from the National Institute of Mental Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, all components of the U.S. National Institutes of Health (NIH). VOICE B is taking place at two VOICE Study sites: Makerere University-Johns Hopkins University Research HIV Clinical Trial Unit in Kampala, Uganda; and University of Zimbabwe-University of California-San Francisco HIV Prevention Trials Unit in Harare, Zimbabwe. Sharon Riddler, M.D., M.P.H., of the University of Pittsburgh School of Medicine, is the protocol chair leading the VOICE B sub-study.

Why this Study is Important

If a trial like VOICE finds daily use of either tenofovir or Truvada effective for preventing HIV, and the approach becomes more widely available, it will be important to understand the effects, if any, on bone in women who are otherwise in good health. It is especially important to gain understanding of the potential effects on women in sub-Saharan Africa who are among those at highest risk for acquiring HIV. Although data are limited, African women seem to have comparatively higher bone mass density than women elsewhere in the world. But other factors could contribute to changes in bone health if coupled with a daily regimen of tenofovir or Truvada. For instance, Depo-Provera, a contraceptive popular in many African countries, can result in gradual loss of bone-mineral density that usually returns to baseline once Depo-Provera is discontinued. VOICE researchers anticipate about half of its participants will be using Depo-Provera based on experience from the recently completed HPTN 035 study of PRO 2000 gel. Breastfeeding is another potential risk factor for bone loss, although any effects on bone are usually reversed when breastfeeding is stopped. Women who are pregnant or are breast feeding are not eligible to participate in VOICE, but it will still be important to fully evaluate the impact of prior breastfeeding on bone density changes during the course of the study. VOICE B will track bone density as a means of evaluating product safety and improving understanding of the effects of such drugs in healthy pre-menopausal, HIV-negative women.

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How the Study is Being Conducted

VOICE B will involve about 300 sexually active, HIV-negative women who are participating in the VOICE Study and who have been randomly assigned to one of the trial's three groups testing the oral tablet regimen. Each study participant who is randomized to the tablet regimen takes two tablets once a day, one that looks like tenofovir and one that looks like Truvada, although one contains the oral dose of the drug to which the participant was assigned (tenofovir, Truvada or placebo) and the second is an inactive placebo tablet. Neither the participants nor the researchers know who is in which tablet group because the study is "blinded." Two other groups in VOICE apply a vaginal gel daily – either tenofovir gel or a placebo gel. Women in the gel groups will not be enrolled in VOICE B.

In order to determine if there are changes in bone health associated with use of the study tablets, participants in VOICE B undergo a specialized test called a DXA scan (short for dual energy x-ray absorptiometry) every six months. The DXA test assesses bone strength in the spine and hips and helps predict risk of bone fracture due to progressive bone loss, a condition called osteoporosis. In addition to the DXA scans, women in VOICE B have tests of their blood and urine to look for changes of bone-related minerals, such as calcium and phosphate; measurements of height and weight; and assessments of diet and nutrition. Women also are asked about their use of contraception, history breast feeding and physical activity, all of which can influence overall bone health.

Participant Safety

As part of the VOICE Study, VOICE B is being conducted according to rigorous standards to protect the safety and well-being of its participants. VOICE incorporates a multi-tiered safety review process, which begins at the site level, and includes strict national and international procedures for monitoring and reporting. Safety data collected in the Bone Mineral Density Sub-study will be reviewed by the VOICE Protocol Safety Review Team and the NIAID Vaccine and Prevention Data Safety Monitoring Board (DSMB), together with all other VOICE Study safety data. The DXA scan is a safe and painless diagnostic procedure considered the most reliable way to assess bone strength and predict fracture risk.

The Oral Products Being Studied in VOICE

The full name for tenofovir is tenofovir disoproxil fumarate (TDF) and is also known by the brand name Viread. Truvada is the brand name for a combination drug that contains tenofovir and another active ingredient called emtricitabine. Both drugs are manufactured by Gilead Sciences, Inc., of Foster City, California. Participants in VOICE are given the same daily doses of tenofovir and Truvada used for treating HIV as part of a regimen called antiretroviral therapy (ART). Both drugs have extensive safety profiles and are well tolerated by most HIV-infected people. In some, occasional minor side effects may be upset stomach, dizziness, headache, joint pain or fever. Serious side effects are rare, but can include liver function problems and kidney damage or failure. HIV-positive women who are treated with an ART regimen that includes either tenofovir or Truvada can sometimes experience moderate bone loss. According to an ongoing Gilead-sponsored study following both men and women receiving tenofovir as part of ART, changes in bone mineral density have not been associated with increased risk of bone fracture. The effects of tenofovir and Truvada on bone health in HIV-negative individuals has not been studied.

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About the MTN

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases 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. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners who are devoted to preventing or reducing the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally. More information about the VOICE Study can be found at <http://www.mtnstopshiv.org/news/studies/mtn003>