CONTACT: Lisa Rossi
+1- 412-641-8940
+1- 412- 916-3315 (mobile)
rossil@upmc.edu

QUESTIONS AND ANSWERS
VOICE B: Bone Mineral Density Sub-study of VOICE

1. What was the aim of VOICE B, or the Bone Mineral Density Sub-study?

VOICE B, also known as the Bone Mineral Density Sub-study, was an observational study within a major HIV prevention trial called VOICE – Vaginal and Oral Interventions to Control the Epidemic. VOICE tested two antiretroviral (ARV)-based approaches for preventing the sexual transmission of HIV in women – daily use of an ARV tablet (tenofovir or Truvada®) or of a vaginal gel (tenofovir gel). Oral tenofovir, known by the brand name Viread®, and Truvada, an oral tablet that contains both tenofovir and emtricitabine, are ARVs commonly used in the treatment of HIV. Although they are considered safe and effective for treating people with HIV as part of combination drug therapy, modest decreases in bone mineral density (thinning of bone) have been observed in HIV-infected people during treatment with these drugs. The aim of VOICE B was to explore the potential effects, if any, that daily use of oral ARVs may have on bone health in pre-menopausal, HIV-negative women in Africa. While African women generally have higher bone mass density than women elsewhere in the world, there may be other factors that could put them at risk for bone loss.

2. Who conducted the VOICE B sub-study?

As a sub-study of VOICE, VOICE B was conducted by a team of researchers working in the Microbicide Trials Network (MTN). The MTN is an HIV/AIDS clinical trials network established and funded in 2006 by the National Institute of Allergy and Infectious Diseases 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). As a co-sponsor of VOICE, Gilead Sciences Inc., of Foster City, Calif., provided the oral study products free of charge. VOICE B was led by Sharon Riddler, M.D., M.P.H., of the University of Pittsburgh School of Medicine.

3. When and where was VOICE B conducted?

VOICE B was conducted between November 2009 and May 2013 – in parallel with the VOICE parent study – at two VOICE study sites: the Makerere University-Johns Hopkins University Research HIV Clinical Trial Unit in Kampala, Uganda; and the University of Zimbabwe-University of California-San Francisco HIV Prevention Trials Unit in Harare, Zimbabwe. A total of 518 women were enrolled from among participants who had been randomly assigned to the oral tablet regimens (oral tenofovir, oral Truvada or oral placebo) in VOICE.

4. How was VOICE B designed?

In the VOICE parent study, participants were randomly assigned to use either a vaginal gel (tenofovir gel or a placebo gel with no active ingredient) or to take an oral tablet (tenofovir, Truvada or a placebo tablet). At the Uganda and Zimbabwe sites, women in the oral tablet groups were then given the opportunity also to enroll in VOICE B.

VOICE B involved the use of DXA scans (short for dual energy x-ray absorptiometry), a specialized test that assesses bone strength in the spine and hips and helps predict risk of bone fracture due to progressive bone loss, otherwise known as osteoporosis. Women had a DXA scan every six months during the time they were using study product in VOICE, as well as six months and one year after stopping study product and exiting VOICE. Women's height and weight measurements were taken at each study visit as were assessments of their diet and nutrition. They were also asked about their level of physical activity, use of contraception and breast feeding, all of which can influence overall bone health. Blood and urine samples were taken so that researchers could assess changes in bone-related minerals, such as calcium and phosphate, if needed based on the overall results.

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Both VOICE and VOICE B were blinded studies, meaning that neither the researchers nor the participants knew which of the three oral products being tested they were actually using during the time the studies were being conducted: (In September 2011, VOICE stopped testing oral tenofovir after a review by the trial's independent data safety and monitoring board, or DSMB, determined that while safe, tenofovir was not effective in preventing HIV compared to its matched placebo. Women in the oral tenofovir group were able to continue their participation in VOICE B)

5. What were the results of VOICE, the parent study?

All three products tested in VOICE (tenofovir gel, tenofovir tablets and Truvada tablets) were found to be safe, but none was effective in preventing HIV among the women in the study. Moreover, the study's results indicate that most participants had not used their assigned product daily as recommended. In a cohort of 647 participants randomly selected from among those assigned to use an active product, drug was detected in 29 percent of blood samples from women in the Truvada group, 30 percent of samples in the oral tenofovir group and 25 percent among those in the tenofovir gel group. The results were first reported at the 20th Conference on Retroviruses and Opportunistic Infections (CROI) 4 March 2013 in Atlanta and reported in greater detail in the 5 February 2015 issue of the *New England Journal of Medicine*.

6. What were the results of VOICE B?

VOICE B found no significant changes in bone mineral density among women assigned to use the tenofovir and Truvada tablets compared to those in the placebo group, most likely because adherence to product use in the VOICE parent study was low overall. However, a secondary analysis involving 81 participants for whom plasma samples indicated more regular use, daily use of tenofovir or Truvada was associated with small decreases in bone mineral density (about 1 percent). Importantly, bone mineral density returned to base-line levels after women stopped using the products, according to the study's results published online ahead of print in *JAIDS, Journal of Acquired Immune Deficiency Syndrome* in September 2015.

7. How do VOICE B results compare to other trials?

VOICE B results are very similar to results of other HIV prevention trials that evaluated daily use of Truvada, an approach called oral pre-exposure prophylaxis (PrEP). The iPrEx trial involving men who have sex with men found that participants receiving Truvada had about 1 percent greater decrease in bone density over one year compared to placebo. Besides VOICE B, only one other study tested bone density in women. In the TDF2 study in Botswana, which involved both heterosexual men and women, Truvada was associated with a greater decrease in bone density but the change was quite small.

8. How is VOICE B important?

Both tenofovir and Truvada are mainstay drugs approved for use in the treatment of HIV in combination with other ARVs. In July 2011, the U.S. Food and Drug Administration approved the use of Truvada also for PrEP, largely based on the results of the iPrEx study in MSM and the Partners PrEP Study of heterosexual couples with an infected partner. In 2015, Truvada was approved as PrEP in both South Africa and Kenya and provisionally approval in France. Gilead Sciences, which makes both tenofovir and Truvada, has applications for approval and licensure of Truvada in other countries as well. Meanwhile, the World Health Organization (WHO) announced in September 2015 its recommendation that PrEP be offered as an additional prevention option to all people at substantial risk of HIV infection worldwide. Results of VOICE B are particularly relevant as the use of Truvada for HIV prevention gains momentum, with demonstration projects and PrEP rollout offering opportunities to more closely track the longer-term impact of Truvada on bone health in larger numbers of young African women.

9. What does a DXA scan involve? Is it safe?

The DXA scan is a safe and painless diagnostic procedure considered the most reliable way to assess bone strength and predict fracture risk. As the individual being tested lies on a table, a scanner passes over the body, capturing specialized images of bone. The DXA scan uses low-level x-rays, so the risk of radiation exposure is minimal. The test takes about 10 minutes. DXA scanners were installed at both VOICE B study sites and staff

were trained in its operation and how to read results. As part of routine quality control, sites sent scans electronically to the University of Pittsburgh Osteoporosis Center, where they were reviewed a second time by a team of specialists in the field.

10. How was safety monitored in VOICE B?

As a sub-study of VOICE, VOICE B was conducted according to rigorous standards to protect the safety and well-being of its participants. VOICE incorporated a multi-tiered safety review process, beginning at the site level, and with strict national and international procedures for monitoring and reporting. Safety data collected in VOICE B was reviewed by the VOICE Protocol Safety Review Team. In addition, the Prevention Trials DSMB conducted routine reviews of safety for both VOICE and VOICE B, none of which raised any concerns about safety in either study.

11. Were special approvals required to conduct VOICE B?

VOICE B and VOICE were reviewed as separate studies by NIAID, the U.S. FDA, government and regulatory authorities in trial-site countries and by each trial site's Institutional Review Board (IRB) or Ethics Committee (EC). IRBs and ECs ensure that studies are scientifically valid and ethically sound and provide oversight throughout the duration of the trial.

12. Did women participating in VOICE B provide informed consent?

VOICE B was for women who had already agreed to participate in the VOICE parent study, and who had been randomly assigned to the oral tablets regimen. Participation in VOICE B was voluntary, and women who decided not to join VOICE B could still be in VOICE. Separate written consent was obtained prior to screening and enrollment using forms translated into local languages. An extensive education process was employed to ensure that women understood the procedures, as well as possible risks and benefits of the study.

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Additional information about VOICE and the VOICE B sub-study can be found at http://www.mtnstopshiv.org/news/studies/mtn003

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 whose work is focused on the rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use. More information about the MTN is available at www.mtnstopshiv.org.

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