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VOICE trial changes are disappointing, says AVAC
Calls for continued research to find new prevention options for women

New York, NY, 25 November 2011 — The announcement today that the 1% tenofovir gel arm of a large-scale HIV prevention trial known as VOICE will stop early is disappointing but is not the end of the road for tenofovir gel or antiretroviral (ARV)-based microbicides.

"This is a blow to the HIV prevention field but is not the definitive answer about whether 1% tenofovir gel is an effective HIV prevention product for women," said Mitchell Warren, AVAC Executive Director. "New interventions are studied in multiple effectiveness trials for exactly this reason. CAPRISA 004, the first trial of 1% tenofovir gel, found effectiveness in women. VOICE found no effect. The FACTS 001 safety and effectiveness trial of tenofovir gel, which has just begun in South Africa and uses a different dosing strategy from VOICE, will provide additional information and hopefully clarity about the effectiveness of tenofovir gel."

"One immediate priority is ensuring that communities directly connected to planned and ongoing trials of tenofovir gel are informed and engaged with discussions about the way forward. Finding prevention options that work for women must remain a top priority, and there is still crucial investigation of tenofovir gel as both a rectal and a vaginal microbicide, which must continue," Warren said.

After a recent, scheduled interim review of trial data, the independent Data Safety and Monitoring Board (DSMB) for VOICE—a five-arm proof-of-concept trial that has enrolled more than 5,000 women in South Africa, Uganda and Zimbabwe—recommended that the 1% tenofovir gel arm of the study be stopped and that the women in that arm exit the trial in a structured process. The DSMB concluded that there was no possibility that daily use of tenofovir gel would show efficacy in preventing HIV in the context of the VOICE trial. Importantly, the DSMB found no safety issues in any arm of the trial. No other data from the trial have been released at this time.

In September, the VOICE trial DSMB met and recommended stopping the oral tenofovir (TDF, brand-name Viread) arm of the trial after it was determined that oral TDF could not be shown effective in the context of this trial.

VOICE will continue to evaluate oral TDF/FTC (a combination of TDF and emtricitabine (FTC), brand-name Truvada) with final results expected in late 2012.

In July 2010, results from the CAPRISA 004 trial showed that 1% tenofovir gel reduced the risk of HIV infection by 39 percent overall among the women in that trial. At this time, it is impossible to know why the results of VOICE and CAPRISA 004 were different. The differences could be related to the dosing schedule—women in CAPRISA 004 were counseled to use the gel before and after sex, while women in VOICE were counseled to use it daily—or it could be related to how frequently women used the gel or other variables. VOICE launched in 2009 with a five-arm trial design to evaluate the safety and effectiveness of oral TDF, oral TDF/FTC and 1% tenofovir gel, each used daily, compared to a placebo gel or placebo pill.

"Based on the limited information available at this time, we simply don't know whether the lack of effect was due to biology, adherence, both, or something else. This is one reason why the ongoing FACTS 001 trial, which is evaluating a different dosing strategy, with different adherence requirements, should continue," Warren said. "The concept of ARV-based prevention has been proven, but to meet the prevention needs of different populations we need the right drug at the right time in the right place. We hope that further research

with tenofovir- and other ARV-based options will provide a range of new prevention options."

The FACTS 001 trial of 1% tenofovir gel, which began enrolling in October and will include 2,200 HIV-negative women in South Africa counseled to follow the same dosing schedule as CAPRISA 004, should provide more information about how and if tenofovir gel might reduce risk of HIV infection in women. Results from FACTS 001 are expected in 2014. In addition, follow-on studies among women who participated in the CAPRISA 004 study will provide more critical information about the effectiveness and acceptability of tenofovir gel under different circumstances.

"We commend the VOICE trial team, the members of the DSMB and especially the more than 5,000 women who are participating in the trial," said Warren. "VOICE has and will continue to provide critical information about both tenofovir-based PrEP and microbicides that will help move the HIV prevention research agenda forward," Warren said.

The disappointing news from the VOICE trial is the latest development in a complex picture of what ARV-based prevention means for HIV-negative women. The Partners PrEP trial provided evidence of benefit that both daily oral TDF/FTC or daily oral TDF reduced HIV-negative women's risk of acquiring HIV from an HIV-positive male spouse or stable partner. (The same benefit was observed for HIV-negative men with HIV-positive female partners.) The trial enrolled serodiscordant couples, in which one partner was HIV-negative and one was HIV-positive. The smaller TDF2 expanded safety study, which enrolled young men and women, also showed a reduction in risk for both men and women who took daily TDF/FTC. However, the VOICE oral TDF arm and the FEM-PrEP study of oral TDF/FTC in women found flat results.

"We must, without any delay, accelerate the development of prevention strategies for HIV-negative women that address possible adherence issues. While we do not yet know the role that adherence to the drug regimen might have played in the FEM-PrEP and VOICE trial data to-date, we know that, for some women, strategies that require less-frequent dosing, such as a vaginal ring inserted monthly, and long-acting injectables, will be simpler to use from an adherence stand point," Warren said.

"Simultaneously, we must make good on the promise made to all trial participants to extract every bit of valuable data that we can from the ongoing trials. We have much to learn from analyses of FEM-PrEP and VOICE as well as from FACTS 001 and the ongoing Partners PrEP trial. The prevention field must be prepared to act on emerging findings from these trials with clear plans and processes for accelerating or shelving approaches."

"Medical research is often complicated, and we know to expect setbacks along the way. But with 2.7 million new HIV infections every year, it is imperative that we continue to look for new ways to curb the epidemic," Warren added. "It is especially important that we focus on interventions that will help young women—who so often bear the brunt of the epidemic—protect themselves."

"There will never be a silver bullet for HIV prevention, so we must continue to rapidly expand testing, treatment and voluntary medical male circumcision, amongst the array of evidence-based interventions, while also accelerating the research and development of additional new options, notably a range of ARV- and non-ARV-based prevention methods and vaccines to protect against HIV."

A table of ongoing and planned ARV-based microbicide and PrEP trials is attached. For more information visit *www.avac.org*.

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About AVAC: Founded in 1995, AVAC is a non-profit organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of AIDS vaccines, male circumcision, microbicides, PrEP and other emerging HIV prevention options as part of a comprehensive response to the pandemic. More information at www.avac.org.

PrEP and ARV-Based Microbicide Trials
As of November 2011

Trial	Phase	Product tested	Population	Status/Findings
CAPRISA 004	Phase IIB	1% tenofovir gel	889 women in South Africa	Results reported July 2010. Tenofovir gel reduced risk of HIV infection by 39%.
iPrEx	Phase III	Oral TDF/FTC	2,499 gay men and other men who have sex with men and transgender women in Brazil, Ecuador, Peru, South Africa, Thailand and the US	Results reported November 2010. TDF/FTC reduced risk of HIV by an average of 42%.
FEM-PrEP	Phase III	Oral TDF/FTC	1,951 heterosexual women in Kenya, South Africa and Tanzania	Stopped for futility in April 2011, with 28 HIV infections in each arm. Full results expected early 2012.
Partners PrEP	Phase III	Oral TDF and oral TDF/FTC	4,758 serodiscordant heterosexual couples in Kenya and Uganda	DSMB review in July 2011 showed daily TDF reduced risk of HIV by an average of 62%; daily TDF/FTC reduced risk of HIV by an average of 73%. As a result, placebo arms discontinued but the trial is ongoing. Additional data expected 2013.
TDF2	Phase II	Oral TDF/FTC	1,219 heterosexual men and women in Botswana	Results released July 2011. TDF/FTC reduced risk of HIV infection by an average of 63%.
VOICE	Phase IIB	Oral TDF, oral TDF/FTC and 1% tenofovir gel	5,029 women in South Africa, Uganda and Zimbabwe	Oral TDF and 1% topical tenofovir arms dropped for futility based on data from DSMB reviews. Oral TDF/FTC continuing. Full results expected late 2012.
Bangkok Tenofovir	Phase II/III	Oral TDF	2,400 injecting drug users in Bangkok, Thailand	Results expected 2012.
iPrEx OLE	Open-label extension	Oral TDF/FTC	Enrolling participants from iPrEx and ATN 082	Results expected 2013.
FACTS 001	Phase III	1% tenofovir gel	Enrolling 2,200 women in South Africa	Launched October 2011. Results expected 2014.
ASPIRE	Phase III	Dapivirine vaginal ring	Expected to enroll 3,475 women in in Malawi, Uganda, South Africa, Zambia and Zimbabwe	Expected to launch in mid-2012 with results in 2014 or 2015.
TMC278LA	Phase I	TMC278LA injected intramuscularly	Enrolling 66 men and women in the United Kingdom	Launched January 2011. Results expected 2012.