AVAC
Global Advocacy for HIV Prevention

A Cascade of Hope and Questions

Volume 2

Understanding the results of CAPRISA 004

Key messages

- CAPRISA 004 provides the first proof of concept that a microbicide (1% tenofovir gel) can reduce women's risk of HIV via vaginal sex.
- The data from CAPRISA 004 are a milestone in biomedical prevention research. However, more information about effectiveness, adherence strategies and other issues is needed to support widespread introduction of 1% tenofovir gel.
- Tenofovir gel is an experimental product and is only accessible through trials that are currently underway.
- There is an urgent need to implement simultaneous agendas for follow-up research, regulatory preparation and pipeline expansion.
- The South African women participants, along with the trial team, are owed a tremendous debt of gratitude for their dedication to biomedical HIV prevention research.

A Milestone Moment

In July 2010, Dr. Quarraisha Abdool Karim and her husband Dr. Salim Abdool Karim, the South African researchers from the Centre for the AIDS Programme of Research in South Africa (CAPRISA) who led the CAPRISA 004 microbicide trial, announced that the experimental product, 1% tenofovir gel, reduced women's risk of acquiring HIV from their male sexual partners by an estimated 39 percent overall. The data came from a study in which women were asked to follow a specific dosing strategy, known as BAT 24 (see box on p. 2), for vaginal application of the gel. This announcement was an historic moment for the field of microbicide research, which has sought a woman-initiated method of preventing HIV for two decades. It was also of great significance to the field of ARV-based prevention research, which includes trials of oral pre-exposure prophylaxis (PrEP) using tenofovir and tenofovir/emtricitabine in addition to topical ARV-based microbicides like 1% tenofovir gel.

CAPRISA 004 trial design at a glance

Purpose of trial: Assess safety and effectiveness of the vaginal microbicide 1% tenofovir gel for the prevention of HIV infection in women in South Africa

Design: Two-arm, double-blind, randomized, placebo-controlled trial

Dosing strategy: Women were asked to insert one applicator of gel up to 12 hours before sex and to insert one as soon as possible within 12 hours after sex using no more than two doses in a 24-hour period. This dosing regimen is called BAT 24 (see box on p. 2).

Study size and population: 889 sexually active, HIV-uninfected women aged 18 to 40 years who were clients of family planning clinics and/or STI clinics, or reported multiple concurrent partners

Trial implementers/funders: The trial was conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA) in partnership with FHI and CONRAD and was jointly funded by the Governments of South Africa and the United States, through the Technology Innovation Agency (TIA) and the US Agency for International Development (USAID).

In this document:

In this series:

Cascade of Hope and Questions **is planned as a four-part series**

- **Volume 1 (July 2010)** ***Anticipating the Results of ARV-based prevention trials***
- **Volume 2 (August 2010)** ***Understanding the results of CAPRISA 004***
- **Volume 3 (Q4 2010)** ***Anticipating the results of PrEP effectiveness trials***
- **Volume 4 (Q1 2011)** ***Understanding the results of ARV-based prevention trials to date***

All documents available at **www.avac.org.**

As exciting and hopeful as the news from CAPRISA 004 is, 1% tenofovir gel is not likely to be introduced for widespread use on the basis of this single trial. It's highly probable that additional trials to ensure that the results are replicable and generalizable beyond the original trial population will take place before any regulatory decision is made that would lead to introduction of 1% tenofovir as a new, licensed HIV prevention strategy.

This initial positive finding has triggered a range of processes both in South Africa, where CAPRISA 004 took place, and around the world, particularly developing and developed countries with severe epidemics among women. This document is designed for advocates seeking to understand what these processes are and how to track and influence progress along the way.

This document is Volume Two in AVAC's *Cascade of Hope and Questions* series focused on ARV-based prevention. Volume One, released in July 2010 before CAPRISA 004 results were known, provided advocates with the "big picture" of how CAPRISA and other ongoing ARV-based prevention trials relate to one another. Volume Three, to be released in the fourth quarter of 2010, will anticipate upcoming results from oral PrEP trials, including the iPrEx trial in gay men and other men who have sex with men. Early in 2011, Volume Four of this series will look at the developments on all of these fronts.

BAT 24: CAPRISA 004's dosing strategy

The CAPRISA 004 dosing strategy is known as BAT 24. This stands for:

- Insert one applicator of gel up to 12 hours Before sex
- Insert one applicator of gel as soon as possible within 12 hours After sex
- No more than Two doses in 24 hours

It's important to note that this series focuses on ARV-based prevention trials in HIV-negative people. There is also ongoing exploration of how ARVs, which play an essential role in preserving the health of HIV-positive people, could also be used to reduce their risk of transmitting the virus to sexual and needle-sharing partners. (ARVs are already used in this way in prevention of parent-to-child transmission.) Terms used to refer to such strategies include "test and treat", "treatment as prevention" and "TLC-Plus" (enhanced Test, Link to Care, Plus Treat). The guiding principle being explored in these approaches is that initiating ARVs early—i.e., before the treatment thresholds of most clinical guidelines used in developing countries—would reduce an individual's viral load and, therefore, his or her risk of transmitting HIV. While this document focuses on ARV-based prevention in HIV-negative people, AVAC

How did CAPRISA 004 measure protection against HIV infection?

In CAPRISA 004, as in all ARV-based prevention trials that enroll HIV-negative volunteers, participants received a standard HIV prevention package. In the case of CAPRISA 004, this included HIV counseling and testing, free broad-based STI treatment for participants and their partners who had symptoms of sexually transmitted infections (syndromic treatment) and condoms. This package was provided at every monthly study visit; participants could also come to the site at other times if they had any concerns or questions. Half of the participants also received the active product, 1% tenofovir gel, while the other half received a placebo gel (an inert gel with no antiretroviral that was indistinguishable from 1% tenofovir gel). Neither the participants nor the research team knew who received which gel. At monthly visits, participants received HIV testing and risk reduction counseling and were reminded they should not assume that they had received the experimental product or that the product had any benefit. Participants were followed over time (a minimum of 12 months and a maximum of 30 months). Participants who tested positive for HIV were immediately taken off the study product and asked to return all used and unused gel applicators. At the end of the trial, rates of HIV infections in the group of participants who received the experimental product were compared to HIV rates in those who received the placebo. There were lower rates of infection among participants using 1% tenofovir gel, and statistical analysis led scientists to conclude that the product reduced risk of HIV.

Some of the unanswered research questions about 1% tenofovir gel

- Can the level of effectiveness against HIV observed in CAPRISA 004 be repeated or improved upon using the same or different regimen in similar and different populations, both in South Africa and in other countries where women are at high risk of HIV?
- Is the gel safe and effective for adolescents, pregnant women and women with different patterns of sexual behavior from CAPRISA 004 participants?
- Is it safe and effective for dosing strategies other than BAT 24 (see box on p. 2)?
- What is the risk of HIV drug resistance among women who acquire HIV while using 1% tenofovir gel and are receiving less frequent monitoring than CAPRISA 004 participants did?
- Is it safe and effective for rectal use?

is also monitoring treatment as prevention. Please visit our website at *www.avac.org* for more resources on these topics as well as information on our work on the full range of biomedical prevention strategies.

What are CAPRISA data on HIV prevention?

Effectiveness in reducing risk of HIV infection

At the end of the CAPRISA 004 trial, 38 new HIV infections occurred among women who received 1% tenofovir gel plus the standard prevention package, and 60 new HIV infections occurred among women who received the placebo gel (which was indistinguishable from 1% tenofovir gel but did not contain tenofovir) plus the standard prevention package. This translates into 39 percent fewer infections among women assigned to the 1% tenofovir gel arm of the study.

This point estimate of 39 percent is one element of the data that advocates need to consider. To fully interpret the results from CAPRISA 004 or any similar trial, it is important to consider additional aspects of the finding including whether or not the result is statistically significant, the confidence level and the confidence interval. For CAPRISA 004, the 95 percent confidence interval associated with the point estimate of 39 percent effectiveness was 6 to 60, and the p-value was 0.017. The 95 percent confidence interval reflects a plausible range for the true effectiveness of 1% tenofovir gel in the study population. Based on the CAPRISA 004 data, the true effectiveness could be as high as 60 percent or as low as 6 percent. The p-value of 0.017 is the chance that CAPRISA 004 would have obtained an estimate of effectiveness equal to or larger than 39 percent if 1% tenofovir gel were not actually effective. P-values less than 0.05 are generally taken to be significant statistical evidence that an effect exists.

Simply put, what the CAPRISA statistics say is that it is highly likely that the trial conclusion that 1% tenofovir gel provides some protection against HIV is correct. However, the level of protection could be anywhere from 6 to 60 percent. This is one reason why there is an urgent need to conduct additional trials. (For more on statistical terms, visit *www.avac.org/statsguide*.)

Adherence

The trial team highlighted two main findings from the initial analyses of adherence data:

- One percent tenofovir gel had greater effectiveness in women who had high rates of consistent gel use following the BAT 24 dosing strategy (see next page for details on how levels of adherence were estimated).
- Overall rates of adherence declined over the course of the trial. The trial team suggested this was perhaps due to the consistent counseling at monthly study visits, which stressed that the

women should not assume they had the active product; that there was no evidence that the product provided protection; and that they should still use condoms and other risk-reduction strategies. The trial team also discussed "study fatigue"—participants tiring of following trial protocol—as another possible factor. The decline in adherence might help explain why the effectiveness also declined from approximately 50 percent at 12 months to 39 percent at 30 months when the trial ended.

The research team gathered information on adherence through a counseling technique called Information, Motivation and Behavior change (IMB). Participants were asked about when they used the gel and how many sex acts they had had since the last study visit. They were also asked what their challenges to gel use had been and were provided with assistance in planning their own strategies for following BAT 24. Women were also asked to return all of their used and unused gel applicators at every monthly study visit. (Overall, nearly 95 percent of applicators dispensed were returned.)

Adherence was calculated by looking at the number of used applicators each woman returned at a study visit and the number of sex acts she reported having had since the last study visit. Based on this information, the trial team placed the participants into three categories and analyzed levels of protection in each of these subgroups.

Advocates' Watch List: Tracking follow-up research

- Will protocols for additional trials be developed swiftly and through a consultative process that prioritizes key questions?
- Is there adequate funding for an optimal suite of additional trials?
- Is the correct balance being struck between gathering additional information and ensuring timely access to the product, should it be warranted?

High adherers: Women who returned used applicators corresponding to BAT 24 coverage for more than 80 percent of their reported sex acts. There were 54 percent fewer infections among high adherers who received 1% tenofovir gel, compared to high adherers who received the placebo. This difference was statistically significant.

Intermediate adherers: Women who returned applicators corresponding to BAT 24 coverage for 50–80 percent of sex acts. There were 38 percent fewer infections among intermediate adherers who received 1% tenofovir gel, compared to intermediate adherers who received the placebo. This difference was not statistically significant.

Low adherers: Women who returned applicators corresponding to BAT 24 coverage for less than 50 percent of reported sex acts. There were 28 percent fewer infections among low adherers who received 1% tenofovir gel, compared to low adherers who received the placebo. This difference was not statistically significant.

HIV drug resistance

CAPRISA 004 enrolled women who were HIV-negative. If someone becomes infected with HIV while using an ARV-based prevention strategy, then her virus will be exposed to whatever ARV drug or drugs are being used in that strategy and resistance could emerge. (Use of an antiretroviral cannot cause resistance in someone who is not infected with HIV.) CAPRISA 004 trial participants underwent HIV tests at every monthly study visit. Any participant who tested positive for HIV was asked to immediately stop using the gel she had been given and to return all used and unused gel applicators (neither participants nor trial staff knew who was using active versus placebo gel). This approach minimized the time that any participant was exposed to 1% tenofovir gel after becoming HIV infected, in order to minimize the risk of acquiring resistance. Women who did become HIV-infected during the trial received HIV drug resistance testing. The research team has analyzed HIV isolated from 36 of the 38 women who became HIV infected while using 1%

tenofovir gel. None of these women had tenofovir resistant virus in the tests completed to date. (Two additional women who became infected while using 1% tenofovir gel did not have detectable virus that could be isolated for resistance testing.) Additional viral sequencing is ongoing.

In addition to blood samples, the trial team took samples from women's genital tract (including cervicovaginal fluid and tissue biopsies) and compared levels of tenofovir in these samples with blood levels. As would be expected, levels were higher in the genital tract, where the gel was used, compared to the blood. Overall, there were very low levels of tenofovir (less than 1 nanogram per milliliter) detected in the blood in both HIV-positive and -negative participants who used 1% tenofovir gel. Very low blood levels of tenofovir mean that HIV is exposed to minimal amounts of the drug if infection is established. This could translate into a lower risk of resistance even among women who receive less frequent monitoring than the CAPRISA 004 participants. However, this is one of many questions that need to be further explored in follow-up studies.

What did CAPRISA 004 data show about effectiveness against HSV-2?

One unexpected and exciting finding from CAPRISA 004 was that, among women who were uninfected with herpes simplex virus type 2 (HSV-2) at the start of the trial, those who used 1% tenofovir gel were at significantly lower risk of acquiring HSV-2, compared to HSV-2 negative women using placebo.

Twenty-nine out of 202 HSV-2 negative women using 1% tenofovir gel acquired HSV-2 during the trial, compared to 58 out of 224 HSV-2 negative women using placebo gel. This translated to a point estimate of effectiveness of 51 percent protection against HSV-2 by 1% tenofovir gel. The 95 percent confidence interval for this result was 21 to 70. This result was statistically significant.

What would the price be for 1% tenofovir gel?

At this point, it's not possible to say with certainty what the price would be for 1% tenofovir gel.

The price per dosage of 1% tenofovir gel will be determined by the component costs of the applicator, the gel and the active pharmaceutical ingredient (in this case tenofovir). Estimates of the cost per dose of the gel used in CAPRISA 004 and VOICE (see next page for trial details) have not included tenofovir, since the drug was donated for the experimental product.

An accurate estimate of cost must also take into account the programs that will need to be developed to deliver the product effectively and sustainably to the people who need it. Operational research, pilot programs and monitoring of initial rollout efforts will help guide program design over the long term.

Reduction in risk of HSV-2 infection could be an additional benefit of using the gel. This effect could also enhance the HIV prevention benefit of 1% tenofovir gel, since HSV-2 increases the risk of HIV infection among HIV-negative people.

What happens next?

The positive result from CAPRISA 004 has triggered calls for the development of three simultaneous agendas:

- Follow-up research;
- Regulatory preparation; and
- Pipeline expansion.

These parallel agendas involve distinct steps and timelines, and can be pursued simultaneously. At the same time, developments in one agenda can impact the other. In the best-case scenario, there would be clear leadership providing guidance, mobilizing resources and acting on developments in each of these three agendas. This leadership could come from any number of entities—a funding agency, research organization or manufacturer.

At this point, while there is significant activity on many fronts, there is no clear leader driving all of the CAPRISA 004 follow-up agendas. Advocates have an essential role to play in ensuring that such leadership emerges, incorporates concerns and priorities from civil society and stays on track with agreed-upon timelines over the coming months. Below are some components of each agenda.

Follow-up research

CAPRISA 004 showed that 1% tenofovir gel reduced women's risk of HIV acquisition during vaginal sex, but there are still additional questions whose answers will help guide regulatory decisions and potential introduction. Some of these questions are listed in the box on p. 3. As this document went to press, the follow-up research agenda was still under discussion, but here are some of the main trials or types of trials being discussed—and what each can answer.

Open-label trial

What it is: In this type of trial both the participants and the research team know what product each woman is using.

What it means for CAPRISA 004 follow-up: There are plans being considered for an open-label trial of 1% tenofovir gel in which all CAPRISA 004 participants who have remained HIV-negative would receive the experimental gel. Since 1% tenofovir gel is still an experimental product, it can be made available only under a research protocol. This open-label trial design would allow CAPRISA 004 participants (from both the placebo and active gel arms) to access 1% tenofovir gel before regulatory decisions are taken. An open-label trial would not have a placebo arm.

What data could it provide: Different types of open-label trial designs exist and could be explored for CAPRISA 004 follow-up. In general, such a trial could provide additional information on product safety and effectiveness over time. It could also gather more information on adherence, including indications of whether women in this population use the product more consistently and/or change their patterns of sexual behavior with the knowledge that the product reduces risk of HIV infection.

Advocates' Watch List: Tracking regulatory preparation

- Is there clear leadership in South Africa and on an international level around establishing and meeting requirements for a regulatory dossier for 1% tenofovir gel?
- Are other developing countries taking necessary steps to determine their regulatory requirements for 1% tenofovir gel?
- Is scaled-up manufacturing capacity identified and validated for the regulatory dossier?

Confirmatory/bridging trial

What it is: This type of trial seeks to replicate or expand on the result from an initial trial, perhaps involving other populations in the research or modifying the dosing strategy or counseling messages associated with the intervention.

What it means for CAPRISA 004 follow-up: A range of different trial designs could be considered. Confirmatory and/or bridging trials might enroll populations such as adolescents, or women with more frequent sexual contacts or more partners than the original CAPRISA 004 participants. Such a trial would likely use the same BAT 24 dosing regimen and could also compare it to other regimens. One such study would likely take place in South Africa. Confirmatory or bridging trials could also involve sites in other countries.

What data could it provide: A confirmatory study would increase the level of precision and certainty about the effectiveness of 1% tenofovir gel when used in a coitally-related dosing regimen. A bridging trial that enrolled additional populations would provide data that could guide regulatory decision-making about how the product would be licensed (i.e., for use in women in certain age ranges, with different patterns of sexual behavior or in different countries).

VOICE—Vaginal and Oral Interventions to Control the Epidemic (also known as MTN 003)

What it is: VOICE is an ongoing effectiveness trial with five arms or groups of participants that is being conducted by the US NIH Microbicide Trials Network (MTN). One group is receiving 1% tenofovir gel and another group is receiving a placebo gel, identical in appearance to 1% tenofovir gel. Both groups are instructed to use the gel once daily. Two other groups are receiving either oral tenofovir (TDF) or oral tenofovir plus emitricitabine (TDF/FTC) to be taken once daily, and the fifth group is receiving a placebo tablet. Approximately 5,000 women will be enrolled, roughly 1,000 in each group.

What it means for CAPRISA 004 follow-up: Launched in 2009, VOICE is not a follow-up study to CAPRISA 004. VOICE is included here because it is part of ongoing discussions about gathering additional data on 1% tenofovir gel. The VOICE trial is scheduled to release results in 2013. At the moment, VOICE is enrolling at 11 sites in South Africa (including the eThekwini CAPRISA site, one of the two sites where CAPRISA 004 was conducted) and at sites in Zimbabwe and Uganda. VOICE will soon begin enrolling women in Malawi as well.

What data will it provide: VOICE will provide additional data on the effectiveness of 1% tenofovir gel—when used once daily.

Regulatory preparation

As the previous section describes, additional research is needed to follow up and expand on the results from CAPRISA 004. This research will help guide final decision-making about if and how 1% tenofovir gel would be licensed and made widely available. Even as these data are being collected, simultaneous work is needed to map out and implement a pathway to licensure by regulatory authorities both in South Africa and in other settings such as other developing countries where women are bearing the burden of new HIV infections. This section reviews the regulatory process in general and summarizes some of the CAPRISA 004 context.

Regulatory process in brief

When the results in a trial or several trials show strong evidence that the experimental product is safe and significantly reduces the risk of HIV transmission in people who use the product, the data can be submitted to a regulatory agency for approval. Every country has a governmental body that determines which drugs can be licensed and made available within its borders. Some countries, including South Africa, rely solely on their own regulatory agencies. Some developing countries also look to recommendations from the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) as well as the World Health Organization (WHO). South Africa's regulatory body is the Medicines Control Council (MCC).

Regulatory agencies review comprehensive information about the experimental intervention, including preclinical and clinical trial data on safety and effectiveness and information on the manufacturing processes that will be used to make large quantities of the product. This compilation of information is known as the regulatory dossier or package. Regulatory agencies review these dossiers and make decisions about whether the product should be licensed for use. (Regulatory agencies are also often consulted when trials are being designed, for guidance about what strength of evidence would be sufficient for a licensure application.)

Regulatory context surrounding CAPRISA 004 and 1% tenofovir gel

When a product is being developed by a single entity, such as a drug company, that company usually develops and follows a product development pathway that covers every step from initial testing through manufacturing process development and preparation of the regulatory dossier.

One percent tenofovir gel is not being developed by a pharmaceutical company. Gilead Sciences developed the gel formulation used in CAPRISA 004

and VOICE and donated the active ingredient (tenofovir) used to formulate the gel. If Gilead had been the product developer, it likely would have taken the following steps typical of this role: It would have manufactured the gel needed for the clinical trials, helped to finance and conduct the clinical trials and developed plans for next steps based on initial research findings. Instead, in the case of 1% tenofovir gel, CONRAD arranged for the manufacture of the gel based on the formula that Gilead developed. This included validating manufacturing procedures for both 1% tenofovir gel and the placebo. CONRAD has also modified the product for potential rectal use in the future.

Gilead has also taken steps to allow other entities to manufacture 1% tenofovir gel, should it be licensed for public use. In 2006, Gilead granted royalty-free licenses for 1% tenofovir gel to the International Partnership for Microbicides (IPM) and to CONRAD. These royalty-free licenses grant the holder the right to manufacture and distribute the product without paying any additional fees to the granting entity. CONRAD has, in turn, granted a royalty-free license to the South African parastatal, Technology Innovation Agency (TIA), a step it is allowed to take under the terms of its agreement with Gilead.

While there is no single entity overseeing the product development pathway for 1% tenofovir gel, there is a regulatory working group, which includes CAPRISA, CONRAD, IPM, MTN, the UK Microbicide Development Programme and TIA. This group is working to define regulatory pathways. A new entity, the South African Consortium on Tenofovir Gel, is exploring a South African research agenda to follow up on the results of the CAPRISA 004 study. The larger HIV prevention research agenda for the next five years for South Africa is also being explored in meetings convened by the South African National AIDS Council (SANAC). Given that each country makes its own decisions about product licensure, there may be a need to define more than one pathway.

In order to simplify this complex and evolving picture for advocates, we've broken the process into some of its components.

Mapping and implementing research steps to complete a regulatory dossier

As this document went to press, some stakeholders were calling for accelerated access to 1% tenofovir gel without additional clinical trials, while others were advancing plans for additional research, including at least one additional effectiveness trial, before seeking licensure of 1% tenofovir gel. (It is also important to note that there is a wide range of additional preclinical and clinical trial data available or forthcoming on 1% tenofovir gel. These data would also be critical to preparation of a regulatory package.)

In August 2010, a multi-stakeholder consultation—co-sponsored by WHO and UNAIDS, hosted by the South African Department of Science and Technology with support from USAID—will take place. The goals of this meeting are to identify gaps and develop consensus on priority research to confirm safety, effectiveness and acceptability of 1% tenofovir gel; develop the most efficient pathways for licensure and guideline development, including regulatory dossier development and submission; delineate priorities, next steps and lead responsibilities in clinical research, programmatic research, and regulatory submission and other issues as identified; agree on mechanisms for coordination and execution; and identify funding sources and gaps.

Advocates will need to track outcomes from this meeting and hold relevant stakeholders accountable for next steps. AVAC will provide an update on these issues following the consultation.

Manufacturing capacity

The 1% tenofovir gel used in CAPRISA 004 and currently being used in VOICE was made by CONRAD in relatively small batches sufficient to supply only the clinical trials. Developing large-scale manufacturing processes that can be validated by a regulatory agency is a time-consuming and

multistage endeavor that is a crucial preparatory step for seeking licensure.

The royalty-free licenses held by CONRAD, IPM and TIA lay the groundwork for 1% tenofovir gel to be manufactured and marketed to meet the public-health needs of developing countries. However, there are still many unknowns, in both South Africa and other countries that might seek to license and introduce 1% tenofovir gel as an HIV and/or HSV-2 prevention strategy.

Pipeline expansion

As exciting as the results from CAPRISA 004 are, there is a need to improve on the level of effectiveness observed in CAPRISA 004. As described in the previous pages, there are potential strategies that could achieve higher levels of effectiveness with 1% tenofovir gel. These might include updated adherence counseling based on CAPRISA 004 data and alternative dosing strategies. At the same time, new and additional products, formulations and combination prevention strategies still need to be pursued. Vaginal rings and other novel delivery strategies currently being explored could offer more continuous protection, compared to daily dosing or dosing related to the timing of sex acts. Other antiretroviral agents need to be explored for their safety and effectiveness. Combination prevention strategies using microbicides, standard prevention and new, innovative interventions also need to be explored.

Some key steps to look for include:

- Increased industry involvement in funding and executing research on microbicides. Now that there is proof of concept, industry partners should increase investment of funds and expertise in developing new strategies.

What can advocates do?

- Talk to your community—what do the results mean for them? What are specific questions and concerns? Ensure that there's understanding of the results and that the gel is still an experimental product.
- Seek clarity from your country's regulatory authorities and policy makers about how your country is engaging with the finding. Is there dialogue about whether 1% tenofovir gel should be investigated as a prevention strategy in your country?
- Hold trial sponsors, donors, research teams and governments accountable for developing a comprehensive product development plan for 1% tenofovir gel.
- As a product development plan is formed, look for leadership at global and national levels: Is there clarity about next steps? Are there deadlines in place? Is there adequate funding?
- Ask the hard questions: What is the best way to expand the body of knowledge about 1% tenofovir gel? Are additional placebo-controlled trials essential? What are your community's perspectives on, "How good is good enough?" How might decisions be made about who would get the product first, if licensed and introduced through phased rollout?
- At country and global levels, advocate full funding and continued scale-up of services including HIV counseling and testing, comprehensive prevention programming and ARVs for HIV-positive people who are medically eligible based on current criteria.
- If you are an advocate based in a community where follow-up or related research is planned or ongoing, seek to partner with research teams in developing strategies at a local level.
- Remember that you don't have to do any of this alone—AVAC and many other groups are available to partner in developing strategies, convening dialogues and creating shared visions of what ARV-based prevention means in your context.

- Acceleration of ongoing research into novel compounds, including ARVs that are not licensed for treatment and new delivery strategies such as vaginal rings and injectables.
- Expanded discussion, including extensive community consultation, about the types of trials that could be used to compare "next-generation" PrEP, microbicide and other prevention strategies as data emerge from ongoing trials and as new microbicide candidates and formulations are developed.
- Fieldwide coordination around selection and advancement of new candidates with the goal of minimizing duplication and ensuring that new products move ahead in the context rational drug development plans.

Expansion of the pipeline will require new resources from new and existing donors including governments and industry. Stakeholders must communicate clearly about the goals and plans for each new agent entering development. Advocates can work to ensure that microbicide stakeholders coordinate and put forward clear product development pathways for new agents.

A critical role for advocacy

In the first few weeks following the announcement of the findings, AVAC has heard a range of questions and concerns emerge from civil society stakeholders.

There are questions about the level of partial effectiveness seen in CAPRISA 004. Is 39 percent overall protection "good enough" to warrant licensure? How will it be understood by the products' potential users and their partners? How will it be explained?

Another set of concerns center on the fact that the active ingredient in the gel is, in oral form, a well-tolerated antiretroviral for HIV-positive people. There are questions about how potential use of an ARV-based microbicide using tenofovir or any other ARV might impact potential drug resistance over the long term. What frequency of HIV testing would be acceptable and feasible if the product were to be introduced? Would treatment programs have the resources to identify and treat drug-resistant virus if it emerged?

There are also critical issues being raised regarding treatment access, given that tenofovir is not widely available in many countries, including South Africa. If 1% tenofovir gel were to be licensed, how would issues of treatment needs for HIV-positive people be addressed in these settings? How would spending priorities for ARV-based prevention and treatment be set and balanced?

Many advocates, including HIV-positive women, are continuing to advocate that non-ARV-based products be developed.

These are just some of the complex issues that have emerged in the wake of the CAPRISA 004 result. There are no simple answers. However, these are exactly the types of issues—about how to potentially introduce a new biomedical prevention strategy—that so many advocates have awaited for many years. Working together, sharing ideas, sometimes agreeing to disagree, we can use these findings to change the future of HIV prevention.

For more information, including additional fact sheets and links to CAPRISA 004 publications and presentations, please visit *www.avac.org/CAPRISA004*.

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Advocacy to accelerate ethical research and global delivery of AIDS vaccines and other HIV prevention options