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Transparency, accountabilty and feminist science — **what next for microbicide trials?**

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Transparency, accountabilty and feminist science - what next for microbicide trials?

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The success of the first microbicide ever shown convincingly to prevent HIV/ AIDS in women was announced in Vienna at the International AIDS Conference, 2010.

A vaginal gel, applied by a woman at any time in the 12 hours before sexual intercourse and then again at any time within 12 hours after intercourse, was found to significantly reduce the risk of HIV infection in women.

On the basis of the argument outlined below, we propose that this gel (1% Tenofovir) is both safe enough and effective enough to be made immediately available, under controlled conditions, to women in high risk populations. The gel, if widely distributed, could be expected to reduce the number of infections without harm to those who choose to use it. It has been estimated that in South Africa alone in the next five years wide use of this gel could avert thousands of infections. One must bear in mind that every woman who does become infected will in time require treatment for the rest of her life. Prevention is not only humane, it is also sensible health policy.

The effectiveness of the Tenofovir gel was tested among 889 women in KwaZulu-Natal and the results published in Science. Over 30 months, the incidence of new HIV infections was compared, among those using a 1% vaginal gel containing Tenofovir, against a placebo gel with similar appearance, taste and consistency. Among those using the gel, the overall result was 39% protection (with the rate of infection reduced from 9.1% among placebo users, to 5.6% among Tenofovir users) certainly significant (0.017). Among the 336 participants who used the gel consistently, 80% of the time, protection was 54%, (with the rate of infection reduced from 9.3% among consistent placebo users to 4.2% among consistent Tenofovir users) also significant (0.025).

Given this result, we may ask, where do we go next?

As one senior researcher wrote us before attending the 85 member conference held on this topic in Johannesburg in August: "As you know, for drug regulators the standard for licensing is TWO independent studies with P less than .05 and we have landed in the dreaded no-man's land where a new placebo-controlled trial will be difficult to implement – politically, practically and ethically."

Indeed this high level conference, attended by WHO, UNAIDS, USAID, South African governmental bodies, funders, researchers and other stake holders surprisingly recommended further randomized control trials (using placebos) one ongoing and one to be newly launched in South Africa. These further trials involve the dilemma of assigning thousands of women to a known inferior treatment, raising serious ethical challenges. Such further trials will almost certainly delay the roll-out of a source of protection for women for 3 years or longer.

The first question for women across the world especially for those at high risk of HIV infection, and for the men who join with us in our concern, then becomes "What is the standard that drug regulators should require?"

A close reading of the current USA FDA Code of Federal Regulations for the approval of new drugs does not demand two randomized controlled trials.

In fact it carefully specifies the criteria required before a planned study can be judged adequately designed and well controlled. The current trial included large numbers of women involved, careful monitoring of all the women's behavior in diverse ways, significant risk reduction and a key finding of a dose response relationship between use of the gel and prevention. Some people have called the published trial only a test of concept or a preliminary study. However, in fact, the KwaZulu-Natal trial satisfies the requirements to be judged an adequately designed and well-controlled trial. Hence, there is every reason for the FDA and other regulatory bodies to release this gel for general use. Nonetheless, prudence calls for the distribution of the gel to be monitored and only provided to women under certain conditions, for instance prior testing for renal or liver disease. Under an open trial both confirmatory evidence and respect for ethical principles should now follow.

For every new drug, including Tenofovir, there is always a possibility of harm. However, Tenofovir is an antiretroviral drug that has been safely used as a pill by many thousands if not millions of HIV infected women and men all over the world. Thus, the likely side effects for taking the drug by mouth are few and well known. However, far fewer women have used Tenofovir as a vaginal gel. Among the over 400 participants in the trial who did use Tenofovir gel, adverse events were few and carefully studied. No Tenofovir-related resistant mutations have been detected among the 35 women tested among the 38 who acquired HIV infection while using the gel. The study showed no adverse effect of use of the gel on pregnancy outcomes although, again, numbers were few. It is always possible that after thousands more women have used the gel in a roll- out (which should be monitored) some adverse effect might appear, for instance in relation to renal dysfunction, or hepatitis, or as mentioned above, pregnancy. These and other adverse events are unlikely to occur in sufficient numbers in a repeat randomized controlled trial, as again too few women will be included for such rare occurrences to be discerned. So drug regulators and public health advocates should certainly emphasize open trials and post-marketing studies for further possible findings about harm from Tenofovir gel.

Will the gel be beneficial, less so or more so, in other populations?

It is always possible that among a different set of women in different circumstances the protection may be less than half, even among high users, as it was here. However, it's extremely unlikely that there would be no protection at all. The confidence intervals (which indicate the range of likely effects) have been mentioned by some as lowering actual "confidence" in the result; in practice they strengthen inference, because they show that among high users of Tenofovir, 95% of women benefited so that their infection rate lay between 2.1% and 7.6%, whereas for 95% of high placebo users, the infection rate lay between 6.0% and 13.7%. The highest rate of infection for high tenofovir users was 7.6%, well below the rate of 9.2% for all placebo users.

It is quite clear from these results that the more closely the participants followed instructions for use, the less the HIV infections. This would only be possible if Tenofovir was indeed protective and worked to reduce infection.

We note also that the infection rate of another widespread infection, HSV 2, was halved with the use of Tenofovir. This was unexpexted, but very important, because HSV 2 is widespread, and seems, in those infected, to enhance the risk of contracting HIV.

Once Tenofovir has been licensed, even on a provisional basis, much work can follow in terms of enhancing its effectiveness: operational research, post-marketing monitoring, and Randomized Encouragement Trials. These studies need to be carefully designed and widely implemented, especially among women at high risk, whether in Africa, Haiti, the US or elsewhere. As

in the Science study, ongoing comparisons between high users and others will confirm the level of protection without the need for a placebo group.

Observations based on these studies will have several advantages over Randomized Controlled trials. The first, and most important, is that they do not challenge the equipoise rule, eliminating the serious ethical infringememt of assigning some participants without their knowledge to a known inferior treatment.

Here we need to consider equipoise in more detail.

Equipoise is a term used by ethicists to describe or justify the blind and hence non-manipulative assignment of participants to different treatments. The subjects under study are told at the start of the trial that the experimenters do not know which treatment may help and which may not. Clearly, equipoise cannot be achieved in case control trials in which some women will be given a tenofovir gel, already known to be partially effective, while others will be a placebo gel. It is critical for the future of scientific research whether among South African women, or among those in other countries in which these trials are to be conducted, to maintain the highest ethical standards, both for ongoing trials and for future trials.

We have been told that this question was discussed at the recent Johannesburg meeting but not on what grounds it was resolved.

Following on what we have discussed above, and on many conversations we have pursued with others, both in person and in correspondence, we cannot agree that equipoise can be achieved in current and future randomized controlled trials in which a placebo vaginal gel is to be administered.

One possible way around this problem resides in the way in which the consent to participate is framed. For instance, if we invite women to participate in a trial in which they are informed at the start that one of the gels to which they will be (unknowingly) assigned is not expected to reduce their risk, while the other is likely (or, has already been shown) to do so. Nevertheless, the explanation will have to continue, the current trial will contribute more understanding about how much their risk could be reduced. With this kind of "informed" consent, the number of participants may be slightly less than expected, but to compensate for that, an honest contract could be achieved with trialists.

Institutional Review Boards have been tasked with ensuring equipoise, and both Community Advisory Boards and Data Safety and Monitoring Boards are to some extent also responsible for representing the interests of women recruited to trials. In Africa, trials have been particularly active in explaining

the purposes and theories of randomized controlled trials. After decades of fighting for human rights for women, we cannot risk false steps now, when an effective harm reduction procedure is almost within our grasp. This is the first reason why we suggest that rather than continuing randomized control trials, research proceed with a closely monitored roll out of the gel. In future trials, comparisons can be made between different strengths of the gel, different encouragement strategies or other differential procedures, but without the need for a placebo arm of the study.

The second advantage of post-marketing strategies, is that they will be carried out in real life situations, so that the experience of all women who opt to use the gel and those who serve them, informed by current understanding of the partial protection which it offers, will add directly to knowledge and experience in the use of the gel. The third advantage of these approaches is that the gel will reach more people more quickly.

Of course, this is where we need input from women and health services from a range of different locales and situations. Early field experiences will pave the way for the roll-out of improved preparations, applicators and procedures, as they become understood and available. The use of this gel will not be dependent on the profits that will accrue to pharmaceutical firms, since it is licensed to the South African government: it can be made available to people in low resource countries at very low cost. This makes it all the more critical that what has been accomplished and the research that is planned for better understanding and improving the gel must be transparent, and the scientific clinical, biological, epidemiological and statistical issues be explained and studied by all who care about harm reduction and prevention.

We very positively appreciate and understand the key role of research in prevention of HIV.

But we urge that the need for research should not delay the use of what we currently have, and that research truly moves us onwards from where we are now. For those who concur with our proposition that a modified consent form would/could meet the ethical dilemma raised by an RCT, it would be important for such a consent form to be transparent, as a guide to others.

The MCC and the FDA should be seen as collaborators who can be convinced of the importance of the release of the gel to the public rather than an inflexible wall. We must devise, together with them, an open trial, that enables women, as fully as we can, and educates them about the pros and cons of use of the gel. We have already been coping with the behavioural issues involving partial protection. For men, following circumcision, this presents one kind of problem. For women, no microbicide likely to appear for years is expected to be more than partial, and yet we see their value...whether 40% or 50% or 60% effective. So an open trial would be meaningful and report of use/non-use would convey to trialists the anticipated reduction in infection rate.

Confidence Limits

We have had many emails questioning our approach to confidence limits and suggesting that we cannot be confident of the results for the microbicide gel. So we asked Professor Bruce Levin, Chairman of Biostatistics, Mailman School of Public Health, Columbia University:

The question really is, what do confidence limits mean to whom?

If I am initiating a health plan, what are the chances I'd reduce the rate of infection, given the statistics on Table 2 of the Karim paper in Science Sept 3 p 1171; (6-60.)? Or, what do they mean to me, a high adherer, if I use the gel and have an expected infection rate of 4.2(.2..1,7.6) versus if I use the placebo 9.5(6.0,13.7)?

Bruce Levin's Answer - Confidence Limits

I think the best way to view a 95% confidence interval is that it tells us what values of the true parameter can be *ruled out* with 95% confidence. Thus in the first example, where the sample effectiveness was 39% with a 95% confidence interval of (6, 60), I would emphasize that that means we can rule out, with 95% confidence, any *true* effectiveness value less than 6%.

Does that mean 6% should be taken as the best estimate of effectiveness? No. The central value of 39% is the most likely true value. (Technically, and literally, the central value is the maximum likelihood estimate, meaning 39% is that value of the true effectiveness which would render the observations most likely to occur.)

In the second example, where the sample HIV incidence rate for high adherers was 4.2 infections per woman per year with a confidence interval of (2.1, 7.6), I would again emphasize that we could rule out, with 95% confidence, an incidence rate greater than 7.6 infections per woman-year, with the maximum likelihood estimate of 4.2 as our best estimate of the truth. You can also state that the upper confidence limit of 7.6 rules out our best estimate of the incidence for the placebo gel group, 9.3 infections per woman-year, as a possible true value for the tenofovir gel group. Similarly, the lower limit of the placebo gel group's 95% confidence interval, 6.0 infections per woman-year, means we can rule out that the placebo group's true incidence rate is as low as our best estimate of the tenofovir group's incidence rate of 4.2 infections per woman-year.

What should be made of the overlapping confidence intervals for the tenofovir gel group (2.1, 7.6) and the placebo gel group (6.0, 13.7)? My answer is: use extreme

caution here! Just because the confidence intervals overlap does NOT mean that there isn't a significant difference between the incidence rates for the two groups. In fact, there IS a significant difference between the groups, with p <0.03.

Explanation

Comparing endpoints of two confidence intervals is a conservative way to declare statistical significance. To declare significance by that method requires a separation between the respective midpoint estimates of 1.96 times the sum of the two respective standard errors. But the correct way to declare significance between two estimates at the 95% confidence level is for the difference to exceed 1.96 times the square root of the sum of the squared standard deviations. It can be shown mathematically that the sum of any two positive numbers is always greater than the square root of the sum of their squares. Therefore requiring two confidence intervals not to overlap is too conservative, and sometimes, as in the case of high adherers, the overlapping confidence intervals does not overturn the statistical significance of the difference.

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Should trials proceed as planned without adjusting for the microbicide success?

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The results of CAPRISA 004 represent a major milestone for the HIV prevention field and have brought us to the place that we'd had long hoped and all along believed was possible – proof of concept that a topical microbicide, in this case tenofovir gel, can interrupt HIV transmission in women. But as excited as we all are about these results, proof of concept is not reason enough to declare victory. Evidence about safety and effectiveness must be very strong before any intervention can be considered for widespread use, which is why regulators, including the U.S. Food and Drug Administration, typically require data from more than one rigorously conducted and well-designed trial. Although the CAPRISA 004 study was very well done, it was limited in size and it was not developed as a single trial designed to support licensure. Moreover, while the study's results are compelling, they are simply not strong enough to stand alone. The confidence interval surrounding the estimated effectiveness of 39% is quite broad. In other words, tenofovir gel used at the time of intercourse could be a low as 6% effective or as high as 60% effective. Indeed, the FDA has made clear that a decision about licensure of tenofovir gel will depend on the results of a second pivotal confirmatory trial, namely VOICE. VOICE (Vaginal and Oral Interventions to Control the Epidemic) is a study funded by the U.S. National Institutes of Health that we are conducting in sub-Saharan Africa. We plan to enroll 5,000 women – 1,000 of whom will be randomized to daily use of tenofovir gel. We are already near the halfway mark toward completing enrollment and remain on track for reporting results in early 2013. As researchers and clinicians, we agree with the FDA's requirement for stronger evidence about tenofovir gel. Importantly, the women in the communities where we are conducting VOICE seem to share this sentiment. They, like all women, deserve to have the best possible evidence about the potential benefits and risks of tenofovir gel.

How much protection is enough...?

Erica Gollub and Robert Stempel

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The question, "How much is enough?" has been a central theme in our efforts to provide women with protection against HIV infection for the past two decades.

The idea of promoting a drug or device that is not 100% effective at blocking HIV transmission to a woman – or even close – has been highly contentious. Early studies of 'hierarchical counseling' on traditional female barrier contraceptive methods that might reduce HIV/STI risk for women, were constructed on notions that "something is better than nothing" to give women prevention tools. These studies argued that, in the absence of 100% protection, chipping away at risk must be our goal. Mathematical modeling has borne out this "risk reduction" argument; a substantial number of HIV infections in women could result if even a very partially effective drug or device were used widely in the populations at highest risk.

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After many years of debate, increasingly lower product effectiveness levels (for example, 30%) have come to be accepted in the microbicide research community as the minimally acceptable goal for pursuing approval of a tested formulation. On paper, then, we have moved a good distance, but the consensus is still shaky. There are multiple fears – that the product will not be used correctly (with women and vaginally- inserted products this fear is particularly pronounced with no good evidence to support it); that risk behaviors will change if people believe they are 'protected' (risk compensation); and that women will be subject to future, physical harms that are not apparent with our current, imperfect set of data. There has been a nagging discomfort with the idea that women themselves should be ones to choose in the absence of perfect data and a perfect product.

These fears may explain a large part of the reluctance to move forward with the release of tenofovir gel, now after the entire spectrum of testing has been completed with the first promising results to come from any microbicide trial to date.

Stein and Susser make a compelling argument for releasing tenofovir gel for women on the basis that safety concerns have been already evaluated according to standards that are used for other classes of drugs. FDA is charged first with addressing the safety profile of new drugs for approval. Safety concerns in this large-scale, high-quality trial (Caprisa 004), were virtually non-existent. The preset effectiveness standards of the trial were met. The arguments for continued testing of tenofovir gel in the context of clinical trials thus lose their ground, since Phase 3 testing is not the forum for investigating future potential risks in a larger, more general population - the appropriate remedy for the further investigations of different dosing schedules, or extremely rare effects in younger (than 18 years of age) women, is in Phase 4, or drug surveillance phase, post-release. Stein and Susser make careful suggestions regarding important paths to pursue to increase the rigor of Phase 4 activities, citing education and intervention approaches. But certainly, the drug should not be subjected to an even higher standard than any other drug (ie. repeat Phase 3 testing) in what amounts to a very long debate over magic numbers. The lives of too many women are at stake.

Experience with the female condom points to the multiple levels of paternalism in the drug/device regulatory system, and community at large. Regulatory authorities were not sure women could use the device correctly. This device, the first woman-initiated means of protection, suffered absent support from federal agencies and constant lampooning from the media, resulting in widespread negative views among providers and even potential users. These are some of the multiple challenges ahead for tenofovir gel. Pro-active support and vigorous promotion will be necessary from the AIDS prevention community to support women's adoption, use and the flow of consistent supplies.

There will never be a consensus on "how much protection is enough", because the answer is not - in the main - a scientific one. While we continue to debate these issues, women continue to be infected and die. If lessons from the past decades have any value, we will always have 'potential future harm' with newly-released products to contend with, but the present harm for millions of women, should be where we keep our focus.

HIV prevention for women... when?

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New data were presented this summer demonstrating the efficacy of an antiretroviral drug-containing gel that can be used intra-vaginally to reduce the risk of sexual transmission of HIV to women.[1] Rightly, the findings were accorded a high prominence at the International AIDS meeting in Vienna and were published simultaneously in the journal Science.[1]

Front page articles in the New York Times, amongst others, lauded the study as a breakthrough for HIV prevention.

Yet what action has followed from these scientific data? Are there plans afoot to make the gel available to all sexually-active women? Or even to sexually-active women in high prevalence settings where one in three likely partners

will be HIV-infected? Not to my knowledge. The most proactive developments in this field appear to be decisions to continue with already planned, *placebo-controlled*, clinical trials of similar antiretroviral drug products, albeit used in slightly different ways.

Sixteen years ago, the first proof concept that antiretroviral drugs can be used around the time of HIV exposure to prevent transmission was published.[2] These results pertained to perinatal transmission of HIV from mother-to-child and involved a combination of maternal and infant prophylaxis.[2] These results set in motion a scientific agenda that simplified and refined the use of antiretroviral agents to prevent mother-to-child transmission so successful that some are talking about the "eradication" of pediatric HIV infection.[3] Hundreds of thousands, perhaps millions, of infants born to HIV-infected mothers have now been exposed to antiretroviral drugs and tens of thousands who otherwise would have acquired infection have been spared this challenging disease.

Initially, a few trials designed immediately after the first proof-of-concept trial were placebo-controlled. This sparked a divisive controversy about ethics.[4] Whatever the merits of the arguments at that time, it would be unthinkable today to propose a placebo-controlled trial of any intervention to prevent perinatal transmission. Today many studies have been completed examining the safety of antiretroviral drugs for prophylaxis, as well as a many studies demonstrating efficacy to prevent perinatal, and now too breastfeeding-associated, HIV transmission.[3] And this among yet-to-be-born and newborn infants – the quintessential vulnerable population. If there are voices raised against the ethics of placebo-controlled trials in women of an already proven intervention, an intervention further bolstered by a substantial body of related research in younger members of the same species, then I haven't heard them.

Placebo-controlled trials are not necessary for development of appropriate public health policies, as the example of post-exposure prophylaxis for health care workers with occupational exposure to HIV shows.

Antiretroviral drugs are routinely given to doctors and nurses with needle stick injuries and other invasive exposures to HIV. A case-control study based on passive surveillance was the basis for these recommendations.[5] For obvious reasons, a placebo- controlled trial has never met with much enthusiasm from eligible participants. Rape survivors in who access better-organized programs are also routinely offered antiretroviral post-exposure prophylaxis. I doubt whether even the most brazen "evidence-based medicine" fan would argue for the withdrawal of these interventions.

Which comes on to the question of pragmatism - how do we, as a public health community trying to be scientifically-informed, but operating with inevitably incomplete and perhaps even flawed data, take forward new findings that seem

to present such promise to do good? Is it by repeating placebo-controlled trials using the exact protocols and reporting requirements of regulatory agencies? Will dogged persistence and attention to bureaucratic minutia win the day? I hope so, because from the data presented from the study in South Africa[1] combined with the existing clinical, epidemiologic and basic science data on the use of antiretroviral drugs to prevent mother-to-child HIV transmission this looks like a winner.

We now know how to prevent HIV in women and the next generation of studies can figure out how to get women to use it. But right now we need to find a way to get it to women.

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A careful weighing of priorities...

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The results of the CAPRISA 004 trial of 1% tenofovir gel were greeted with cheers, applause and a standing ovation when announced at the Vienna AIDS conference in July 2010 (see webcast at http://globalhealth.kff.org/AIDS2010/July-20/Safety-and-Effectiveness.aspx). After nearly 20 years of research, CAPRISA 004 provided the first evidence that the use of a vaginal gel containing an antiretroviral drug (tenofovir) can prevent HIV infection in women. The trial demonstrated that 1% tenofovir gel reduced women's risk of acquiring HIV by 39% compared with the placebo, with the reduction in risk reaching 54% among women who reported using it most consistently.

The results were robust and consistent across a range of different analyses, with no apparent safety concerns.[1] The trial marked the first time that a vaginal microbicide has shown effectiveness against HIV in a clinical trial. As such this represents a major breakthrough in identifying a new method of HIV prevention and a potential new option for women to protect themselves.

There was vigorous debate in Vienna that has continued in other fora on whether and how the product can be made available to women most in need, what additional research is required to ensure licensure and effective roll out, and how the product could best be promoted and distributed. Stein and Susser argue strongly on ethical and moral grounds in favour of rapid roll out of 1% tenofovir gel with careful follow up to monitor for any side effects or other problems. Others have argued just as forcefully that the result must first be confirmed in a further placebo-controlled trial. How can these differing views be reconciled?

There is no single, correct answer to these difficult questions, but a careful weighing of priorities is necessary. We offer below some additional issues that need to be considered.

Generalizability

The CAPRISA 004 trial was conducted in two communities in KwaZulu Natal, one urban and the other rural. In the absence of confirmatory data, we cannot be sure that a similar protective effect will be seen elsewhere. Information on the safety, effectiveness and acceptability of the product in other settings with different epidemiologic and social profiles will be critically important before 1% tenofovir gel is used widely for HIV prevention.

Precision of the estimated effect

The CAPRISA 004 trial showed a 39% redution in HIV incidence, with a confidence interval ranging from 6% to 60% reduction. While the true effectiveness is most likely near the point estimate, we cannot exclude effectiveness near the lower end of the confidence interval. We need a better estimate of the true effectiveness so that women, providers, and national and international policymakers have a clear idea of the level of protection. This can better inform decisions on how the gel fits into individual and community HIV prevention programmes and strategies.

Risk compensation

The potential for risk compensation is a major concern with all new approaches to HIV prevention, particularly those that are partially effective. In the case of male circumcision to prevent HIV infection in men, the evidence comes from three independent randomized trials,[2-4] with a pooled effect of 50% reduction in HIV incidence (95% confidence interval 28% to 66%).[5] The lower confidence limit is sufficiently far from zero that modelling suggests that even with very large reductions in condom use there is an estimated net beneficial impact for individuals and communities.[6] During the international policy discussions and efforts to implement male circumcision and have an impact on the HIV epidemic, it was clear that there would have been very little interest to implement programmes if the degree of protection had been substantially lower. More and better data than are currently available from the CAPRISA study are required to ensure that the effectiveness of 1% tenofovir gel is sufficiently large that its overall benefits will not be offset by any potential behaviour changes.

Scale up

The challenges in scaling up male circumcision programmes since the evidence of effectiveness was published in 2007 highlight another compelling reason why stronger data are needed. Despite convincing evidence from three independent trials, a wealth of supporting epidemiological and demographic data and good biological support, progress in male circumcision scale up is lamentably slow.[7] For a new pharmaceutical product the views of national drug regulatory authorities are absolutely critical as they determine whether or not a product is licensed. But other actors are also critical: programme managers must be convinced that a new intervention is feasible, that investing HIV prevention resources in the new intervention will be cost effective compared with other interventions, ministries of health and finance must be prepared to allocate or reallocate resources, bilateral and multi-lateral donors must feel confident in the product and that the investment is worthwhile, and individual users must make the effort and commitment to access and use the new product. Unless all these actors are convinced and aligned, the product will fail to achieve the widespread availability and use we all hope for.

So in the context of these uncertainties is it ethical to implement a randomized controlled trial in which some women are allocated the active product and others the inert placebo? Stein and Susser correctly point out that the information provided to participants in future trials must include the new data generated by the CAPRISA study. Previously there were only data from animal models and laboratory studies that the product most likely reduces their risk of HIV infection; now there are also data from women. All research involves a careful balancing of risks and benefits. Frequently the risks are borne by the individual while the benefits accrue to society. However in placebo-controlled microbicide trials there are also well-documented benefits for the individual participant, including improved care, and intensive counselling and help with reducing the risk of HIV infection. In addition there is an expectation that the product, once shown safe and effective, will be made available preferentially to former trial participants and their communities. It is the job of independent ethics review committees to ensure that the balance of risks and benefits is reasonable, and the information provided to potential participants is accurate and understandable so that they can make an informed decision whether or not to participate in the study. If a potential participant is not comfortable with the balance of risks and benefits, she is not obliged to enrol. If during follow up an actual participant no longer feels the balance of risk and benefits to her is appropriate she can tell the study team she wants to discontinue.

We are of the view that confirmation of the CAPRISA result in further placebo-controlled studies is essential if the product is to be supported, marketed and used by the large number of women at risk who have few alternative ways of reducing their vulnerability to HIV infection. Exactly what form any confirmatory studies should take is, at the time of writing, being vigorously debated.

Key design issues include assessing different dosing regimens, determining safety and effectiveness among women 16-17 years old, and expanding the evidence of safety and effectiveness to women living in different epidemiological and social contexts. There will be challenges in planning and implementing such trials, which we must face together if the ultimate aim of the research is to be realized – an urgently needed new tool for women to reduce their risk of HIV infection.

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Yes to placebo-controlled trial with updated informed consent!

Mitchell Warren, Emily Bass and Manju Chatani

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Can a placebo-controlled trial be conducted in the wake of the CAPRISA 004 findings that the gel reduced HIV-negative women's risk by an estimated 39 percent overall? AVAC believes the answer is "yes", provided that the informed consent processes for all ongoing and planned trials of 1% tenofovir gel include explicit explanation of the existing data on 1% tenofovir gel. This intensive effort to ensure comprehension on the part of trial participants must be backed up by additional consultations with a range of community groups both in South Africa and in other countries where 1% tenofovir gel has the potential to be a powerful HIV prevention tool. The substance of these consultations will vary by setting, but should focus on the existing data regarding 1% tenofovir gel, emerging findings on oral ARV-based prevention, and in gauging and soliciting community understandings and definitions of "equipoise" around 1% tenofovir gel and other forms of ARV-based prevention, and of concerns regarding follow-up studies.

Like many other groups and individuals, including Zena Stein and Ida Susser, authors of the main article in this newsletter, AVAC celebrates the news from CAPRISA 004 as a landmark event in the search for new biomedical HIV prevention strategies. The trial provided compelling evidence that the gel reduces women's risk of HIV infection and that this benefit is related to levels of adherence: women with more consistent use of the gel, as measured by self report and returned applicators, had lower rates of HIV infection than women with moderate or low adherence who also received 1% tenofovir gel.

Given this evidence that "the gel works," why is it ethical to conduct additional trials with a placebo? Guidance on this subject comes from many sources, including the WHO/UNAIDS Ethical Guidance for Biomedical Prevention Trials which states, *"Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial. New HIV-risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities."*

In this instance, the question is whether 1% tenofovir gel is "scientifically validated" on the basis of data from CAPRISA 004.

At this moment, AVAC believes that there are still important questions to be answered about the level of protection provided by 1% tenofovir gel over time and in different populations, and that these data are missing pieces in the process of full, scientific validation of the product and in the regulatory approval process. These are not academic questions but are, instead, essential to the process of building a solid, package of information that can be used in regulatory submissions and as the basis of clear, specific communication with potential users. Given the challenges of introducing and marketing a partially effective product to donors, policy makers, users, their partners, medical providers and all the other stakeholders whose support will be required to realize the benefit of this or any other new intervention, such validation is essential.

If regulatory bodies indicated that they would accept data from a non-traditional follow-up trial, i.e. one that did not include a placebo arm, that would open a new route for proceeding. In the absence of such an indication, though, there is a risk of conducting research that is perceived as leaving doubts or imprecision around the true effectiveness of the product in the eyes of regulatory authorities. (The US Food and Drug Administration has recently stated that it would fast track 1% tenofovir gel on the basis of data from the ongoing VOICE trial in addition to CAPRISA 004. It is not yet clear what studies will be required by the South African Medicines Control Council to register the product in South Africa.)

Next steps should be taken with the twin priorities of ensuring safety and learning more about effectiveness in the shortest possible timeframe, and with the greatest degree of certainty possible. Assuming that safety and effectiveness are validated, this is the best course for ultimately making this new prevention tool available to all who need it and to translating clinical trial results into public health impact.

The CAPRISA 004 Trial: Ensuring women's empowerment remains central

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Full policy brief: www.heard.org.za/downloads/microbicide-issue-brief-14-July-2010.pdf

The impressive results of the CAPRISA 004 trial, demonstrating a 39 percent reduction in HIV-incidence amongst women involved in the tenofvir gel arm[1] compared to the placebo arm were greeted warmly at the Vienna International AIDS Conference. Such results should indeed be celebrated, but as such products move to the fore of HIV-prevention globally, we need to ensure that women's rights and empowerment remains a central focus of microbicides, alongside HIV-prevention. As a female controlled technology, a microbicide has the ability to link women's empowerment and HIV prevention. However, in the rush to ensure a microbicide is widely available, without asking the right questions, there is a risk microbicides do little to empower women.

There are three key questions that need to be raised to enable a microbicide, when eventually released onto the market, supports women's empowerment as well as HIV-prevention:

Will microbicides, once available, be free at the point of access for women?

User fees at the point of access for healthcare and medicines limit women's access. However, given the current financial constraints around HIV/AIDS arguments may be made that women should pay to access microbicides to increase funding availability. As activists, it is important we ensure that microbicides are free at the point of access, and financing is sustainable enough to ensure all women who wish to use microbicides can do so.

How do we bring men into the conversation around microbicide use, while still empowering women?

Men need to be part of the conversation around microbicide introduction and use. We know that often women discuss microbicide use with their partners, particularly in long-term relationships. How can we ensure that when these discussions emerge, men have the necessary knowledge, framed in appropriate ways that allows them to support microbicide use, particularly given the social interpretations of sexual faithfulness that HIV prevention tools often suggest? More widely, how do we make sure the focus always remains on women, and male perceptions do not become the main concern?

How can microbicides be marketed in ways that do not stigmatise them or women who use them?

Microbicides, once ready for national markets, will be marketed as an HIV prevention tool. Therefore, any woman who decides to use a microbicide is clearly sexually active. As sexuality remains relatively un-discussed and stigmatised, the challenge is how to develop a social marketing strategy that avoids stigmatising women and the product, and actively promotes women's sexuality and reproductive health.

As microbicides move towards becoming a reality for women in sub-Saharan Africa there is a need to ensure that women's empowerment is integral in the promotion and distribution of microbicides – at all levels. We can only ensure that this happens if we start to discuss and mobilise around some of the key issues around access to microbicides that relate to women's rights.

References

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ATHENA: Advancing gender equity and human rights in the global response to HIV and AIDS. For more information, please visit http://www.athenanetwork.org.