OUR CURRENT MICROBICIDE TRIALS: LESSONS LEARNED AND TO BE LEARNED

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The era of large trials of second-generation microbicide products is upon us. Several late-stage trials testing the efficacy of microbicides to prevent HIV infection have begun within the past two years. With their implementation, complex design and operational issues have emerged that exceed the traditional clinical trial challenges of recruiting participants and maintaining protocol adherence. They also extend beyond vaginal microbicides to relevance for other HIV prevention technologies.

Recent meetings have convened investigators from various organizations to examine these issues and share ideas about strategies for overcoming them.1,2,3,4 This paper is a first attempt to lay out the most difficult of these challenges, together with solutions either implemented or suggested to confront them so that study power and validity are not compromised. Our intent is to spur a dialogue that will lead to better approaches to testing the next generations of this highly innovative technology for which there is so much promise but only limited instructional precedent.

Lower Than Estimated HIV Incidence

The Family Health International (FHI) Phase 3 trial of Savvy™ (C31G) in Ghana was recently halted by the study’s Data Safety Monitoring Board due to concerns that the unexpectedly low HIV incidence found in the enrolled population meant that the study would be unable to determine whether or not the product could prevent HIV infection. Lower-than-estimated HIV incidence has been an increasing problem, not just for microbicide trials but for evaluations of other approaches to HIV prevention such as HPTN 037, an evaluation of the efficacy of network-oriented peer education interventions among injection drug users. Discrepancies between actual and expected incidence are critical for prevention trials because it is expected

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incidence that is used to determine sample size and that constitutes the baseline against which the success of a given prevention strategy is projected.

Changing disease patterns and a greater-than-expected effect from ethically necessary trial risk reduction procedures, can both contribute to a lower-than-presumed incidence. For example, analysis of FHI results from West Africa showed that prevalence-to-incidence ratios depended on the phase of the HIV epidemic. And while the HIV screening prevalence in a recent Cameroon oral tenofovir (TDF) study (2004) was slightly higher than that seen in a previous Cameroon N-9 film study (1996), the actual incidence had dropped to almost half in the interval between the two studies.

To address this issue, recruitment strategies are being modified to increase the likelihood of targeting high-risk populations where incidence is likely to be higher than it is in the general population. Since younger women are often at the highest risk for new HIV infection, current efficacy trials are focusing on recruiting younger participants. Trial groups and sponsors are also working together to explore the use of new assays and surveillance techniques to better estimate HIV incidence during screening and/or through pilot studies, in order to arrive at estimates of HIV incidence that are as accurate as possible.

Measuring Product Use

Calculations performed by FHI statisticians demonstrate the importance of high product adherence relative to HIV incidence in a prevention study. Assuming a trial designed to have 85% power to detect 40% effectiveness, if the incidence rate observed in the study proves to be half of what was planned (e.g., 70 infections are observed rather than the 140 infections expected), the power of the study is still approximately 60%. In contrast, however, if the incidence rate is as expected (i.e., 140 events are observed), but product adherence is low (e.g., 50% instead of an expectation of 80% compliance), the study power drops from 85% to 45%.

In most of the current microbicide studies, a trial participant’s use of product can only be assessed by self-report, which is generally considered undependable. Behavioral data about product use and sexual activity that are generated in the context of face-to-face interviews, especially after extensive counseling on the importance of consistent product use, are also considered unreliable. However, self-administered questionnaires are inappropriate in communities with low literacy and therefore cannot take the place of such interviews. Pharmacokinetic assessment of product adherence in vaginal microbicide trials is difficult because, typically, products are not absorbed and therefore not readily susceptible to such assessment.

By way of remedy for this particular set of challenges, novel technologies have been developed to improve estimates of product use and protocol adherence. Sensitive behavior can, for instance, be assessed using Audio Computer-Assisted Self-Interviewing (ACASI) approaches that allow even illiterate study participants to answer questions simply and privately, which enhances the likelihood of data validity.

Another approach has been undertaken in the context of the Population Council (PC) Phase 3 trial of Carraguard®, which is using a biological adherence marker to assess product use. Trial participants are asked to return all used and unused applicators at each study visit. Each opened applicator is then tested with a sensitive and specific spray assay which, through characteristic patterns, can reveal which applicators have been inserted vaginally. The advantages of this procedure are

7 Taylor D. Personal communication, 2006.
two-fold: tracking returned applicators can help identify gel-sharing so that counseling can be tailored to emphasize the importance of using one’s own gel. The spray assay can also help identify women who are feigning use (those who return open applicators that have never been vaginally inserted), at the same time that it can identify women who are reliable users, thereby enabling a separate (per-protocol) analysis on a subset of adherent women. Further, the clinic flow has been modified at trial sites so that participants return their applicators to counselors rather than to intake staff, but this modification has not yet been assessed to determine whether it does, in fact, fulfill its objective, which is to enhance participant adherence to product use by increasing accountability.

High Pregnancy Rates Leading to Interruption of Product Use

The likelihood of pregnancy in reproductive-age women having multiple sexual encounters (e.g., 20 acts per month) is quite high even with relatively high condom use. Using Wilcox’s estimates of the probability of pregnancy resulting after one or more unprotected acts for each day of the menstrual cycle (and assuming 12 x 30 day cycles per year), we expect that if women have two days with unprotected acts on average during each cycle (e.g., 90% condom use, 20 acts per cycle, and no other contraceptive method use), the 12-month cumulative pregnancy probability would be 51%.\footnote{Dominik R. Personal communication, 2005.}

The non-clinical studies—specifically, Segment 3 toxicology—that are required to allow pregnant women to use an Investigational New Drug have typically not been completed before Phase 3 begins. Thus, all current microbicide efficacy protocols—as well as the trial of acyclovir to determine if HSV treatment reduces HIV transmission—require product interruption once pregnancy is detected, at least until evidence of non-pregnancy is produced (e.g., a negative pregnancy test). While all trials include in their eligibility criteria a requirement that participants pledge their intention to not become pregnant during study participation, our current trials have found pregnancy rates as high as 70%, despite all vows and best intentions.

The implications of high pregnancy rates are major. Excessive product interruption can compromise study power, complicate risk assessment and, possibly, bias analysis. The ethical, statistical, and behavioral issues around pregnancy in microbicide studies have been discussed in depth but there is, so far, no obvious consensus around how this dilemma is to be confronted in any systematic way. Some ongoing trials have begun offering contraceptives on site to reduce pregnancy rates, while others refer for these services because of operational limitations, concerns about coercion, and lack of sustainability in countries where contraception is not otherwise readily available. The issue of product interruption due to pregnancy could be moot if the necessary and sufficient preclinical studies were to be completed prior to the launch of late-stage trials, so that women who become pregnant might continue product use until scheduled study completion. This possibility remains to be further explored and may not be applicable to all product classes.

Evolution in Prevention Standard of Care (SOC)

… for study participants

As part of any HIV prevention trial, all study participants are provided with the current standard of prevention care. Most prevention trials include safer sex counseling, provision of male condoms, and treatment for sexually transmitted infections (STIs) (although the frequency of STI testing may vary between studies), and female condoms have recently been added to the prevention SOC in some studies. However, the field is dynamic and other approaches such as male circumcision may soon become accepted as possible prevention practices. Researchers need to continue to stay abreast of the current literature to address both evolving scientific practices and ethical imperatives.

… for screen failures and trial seroconverters

During recruitment for a microbicide or other HIV prevention trial, hundreds of women may test HIV-positive at screening, be ineligible for the trial, and are consequently referred into the local system.
The issue of what level of care to provide these women, as well as those who become infected during a prevention study, has been at the forefront of global discussions of research ethics and multiple local, regional, and global meetings over the past year. Since the launch of the current microbicide efficacy studies, resources for HIV care and treatment in countries with generalized HIV epidemics have increased greatly. In some places, the available SOC in the community may have even surpassed the IRB-determined ethical SOC described in a particular protocol. At the same time, it is still the case that many trial communities lack adequate services. Despite funding limitations, current studies have managed to implement a range of strategies for helping women who test HIV-positive, at both the trial and community levels. For women who test HIV-positive at screening and those who seroconvert within the trial, services may include partner counseling and/or testing, referrals to private physicians for WHO staging, accompaniment of participants to the referral clinic for the first visit, and immediate referral into seroconverter studies, which often enable access to state-of-the-art care while advancing scientific knowledge. Referral clinics are often offered support in the form of financial and/or human resources, which may include full- and part-time positions; some HPTN 035 sites even provide staff on rotation from the trial clinic itself. The Carraguard® trial is conducting formal evaluations to assess barriers to referral use and identify specific areas of need in referral clinics. Researchers across all the organizations presently sponsoring trials recommend that established arrangements with local clinics be supported by written documents.

More challenging is the matter of pledging funding for provision of anti-retrovirals (ARVs) for any set amount of time. This has a great deal to do with the feasibility and accountability difficulties associated with establishing an insurance fund for individuals who have recently seroconverted and may well not need ARVs for an unknown number of years. This does not mean that nothing can be done: women who seroconvert during a trial often need psychosocial support before they need medical care. At one Population Council site, a support group for HIV-positive women was established, with the goal of being sustainable beyond the conclusion of the trial. For the time being, until guidance is clearer and there is some kind of consensus around the range of what is feasible and ethical, researchers must persist in advocating for the availability of care and monitoring the quality of care that HIV-positive study participants receive.

Costs/Complexity of Focusing on “Multiple Communities”

The microbicide field has made substantial efforts to involve local communities in its work. As a rule, most trial sites have a community advisory group or other mechanism designed to facilitate communication between researchers and those living in the site catchment areas. For a variety of reasons, including the instantaneous and global reach of the Internet, the gravity of HIV, and the history of research abuses in developing countries, communication with civil society through the media has become an essential dimension of prevention science. The negative media attention surrounding the trials of pre-exposure prophylaxis (PREP) of oral tenofovir[12,13,14] highlighted the urgency of soliciting input to trial design and implementation from a broader, more heterogeneous range of “communities” and stakeholders than previously contemplated. Such engagement must go beyond potential participants and the immediate trial site communities to academics, activists, advocates, policy-makers, politicians, providers, and the local, national, and global media that act so critically at the interface of science, practice, and ethics.[15]

Following on the tenofovir experience, current trials have deepened and enlarged their focus on media training and

preparedness, ensuring that both central and local teams are equipped with standard and accurate messages, and a communication/crisis plan. Although the costs and time entailed in these efforts are not trivial, the investment appears to be well worthwhile, particularly given the costs of aborting or not implementing a trial of a promising technology. The examples of recent, successful communications in connection with closure of the Savvy™ trial in Ghana and the responses to a misleading newspaper article about the Carraguard® trial in South Africa, demonstrate what trained, diligent staff can achieve when communicating globally with multiple stakeholders. The Microbicide Media Initiative (MMI), spearheaded by the Global Campaign for Microbicides, is a group of microbicide stakeholders that includes researchers and communication specialists in active ongoing communication with one another, across the microbicide field, and between stakeholders and the media. The central notions are that researchers must continuously build their own “community literacy”—just as communities need greater “research literacy”—in order to improve support for trials, at their inception and once under way.

Variability in Political Support for Prevention Trials

Research within any country depends on the support of political leadership. In past years, research teams have been forced to abandon well-developed research infrastructures because of political violence (i.e., Congo, Côte d’Ivoire, Dominican Republic, Haiti, Rwanda). Even democratic changes of government (i.e., Cambodia, Cameroon, Malawi) and shifts in national research priorities can result in study disruptions and even closure. Such challenges cannot always be anticipated and there are no categorical solutions for addressing them once they arise, so that researchers are left with the imperative for obtaining clear national and local governmental support for projects at the outset and a state of constant alert to changing political situations that could undermine their efforts.

Effort/Costs of Registration-level Compliance in Resource-poor Settings

Since the eventual goal of efficacy trials is regulatory approval, protocols must be implemented according to registration standards. Achieving this goal even at experienced sites requires extensive training, supervision, monitoring, and support to ensure that the key elements of voluntary informed consent, participant safety, and data integrity are intact. In developing countries, getting to this level of study quality with limited infrastructure can be extremely taxing.

That said, operational difficulties in such sites as Nigeria (oral tenofovir) and Malawi (HIVNET 024) have demonstrated that constant vigilance is needed to assure compliance with Good Clinical Practice (GCP) standards. This requires sizeable investment in research infrastructure but, fortunately, scaling up infrastructure and training staff to adhere to GCP standards help build a foundation of technical capacity at trial sites.

Assurance of Laboratory Quality

Accurate laboratory data are the _sine qua non_ for microbicide studies since they do (or do not) determine both safety and efficacy endpoints. Difficulty in establishing laboratory quality has been among the most important factors contributing to delays in site initiation and difficulties during implementation. Even when independent or reference laboratories in university settings have supported trials, problems have been identified during monitoring or auditing visits—problems that have resulted in trial shutdown (Nigeria, oral tenofovir) or censorship of data (South Africa, HPTN 023). To prevent delays and interruptions of future trials, the solution is the establishment of guidelines for selecting and training the best laboratories and identifying measurement problems as they occur, buttressed with visits to labs by optimally qualified laboratory scientists to verify the raw data and assay results, monitor procedures, and inspect equipment to ensure continued proficiency.

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OUR CURRENT MICROBICIDE TRIALS (Continued from p.05)

Mediocre Retention and Poor Adherence to Follow-up Schedules

As a rule, the level of loss-to-follow-up in a trial should be lower than the rate of study endpoints. Unfortunately, loss-to-follow-up in many prevention studies has been 3- to 10-fold higher than the occurrence of study endpoints, thereby threatening study validity. Retention is especially challenging in developing country settings, where participants often lack phones, formal addresses, and reliable transport, and have considerable family obligations as well. Even when participants are retained throughout a trial, they often miss one or more scheduled visits. Missed visits complicate product adherence, since most protocols provide only enough supplies for the interval between visits, and as the interval between observation periods increases, the precision of per-protocol assessment, which is dependent on time of infection, decreases.

The programmatic implication here is that a balance has to be found between providing adequate amounts of product to cover intervals between missed visits and not providing excessive amounts of product so that storage becomes problematic. This is already an area of considerable innovation. Creative approaches have been developed to optimize retention and maximize adherence to visit schedules, and Global Positioning Systems (GPS), enhanced outreach, and satellite clinics are being utilized with encouraging results. As the current trials conclude, an evaluation of visit schedules will be conducted to determine their impact on retention. Researchers need to build on what seem to be rewarding approaches and continue to engage trial participants and communities to determine the optimal protocols for various future study populations.

In Conclusion

As in all HIV prevention trials, microbicide trials and the issues they generate are constantly evolving under influences from the ever-changing worlds of science, ethics, and politics. Unlike the products now in efficacy trials, the next generations of candidate microbicides are likely to include products containing anti-retroviral components that bring new concerns about their potential for development of drug resistance, about which there will be many lessons to be learned.

The present environment of open communication across different studies among trials, trialists and, it is hoped, trial populations, can only enhance, perhaps even accelerate further progress. Initiatives such as the MMI and Quick/Clinical Trials Working Group can do much to extract such learning and share it to a variety of constructive, collaborative ends. The variability among the products now in efficacy testing, the growth in the number of trial sites, and the diversity of the study designs have already enabled identification of challenges and possible solutions addressed, if only preliminarily, in this paper. A range of innovative research tools and guidelines will increase our ability to identify an efficacious microbicide, just as a range of different prevention options will increase a woman’s power to protect herself from HIV infection.

TABLE 1. CURRENT MICROBICIDE TRIALS: CHALLENGES ENCOUNTERED AND ISSUES FOR CONSIDERATION

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Consideration</th>
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<tbody>
<tr>
<td>Lower than estimated HIV incidence</td>
<td>Variability in political support for prevention trials</td>
</tr>
<tr>
<td>Measurement of product use</td>
<td>Effort/costs of registration-level compliance in resource-poor settings</td>
</tr>
<tr>
<td>High pregnancy rates leading to interruption of product use</td>
<td>Assurance of laboratory quality</td>
</tr>
<tr>
<td>Evolution in prevention standard of care</td>
<td>Retention and adherence to follow-up schedules</td>
</tr>
<tr>
<td>Costs/complexity of focusing on multiple communities</td>
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</tr>
</tbody>
</table>

CLINICAL TRIALS EXAMINING CERVICAL BARRIERS AS POTENTIAL METHODS FOR PREVENTION OF HIV AND OTHER SEXUALLY TRANSMITTED INFECTIONS

Julia Matthews, Ibis Reproductive Health

The scale of the AIDS pandemic demands more tools to stop the spread of new HIV infections. In urgent need are women and girls, who are most vulnerable to sexually transmitted infections (STIs), including HIV, for biological, economic, and sociocultural reasons. For example, the female reproductive tract is more vulnerable to infection than the male reproductive system, violence against women and girls is widespread, and the imbalance of power in relationships means that women and girls are often unable to negotiate safer sex practices.

Current cervical barrier methods, as well as new designs under development, are being looked at with renewed interest to determine whether they may offer a female-controlled method for preventing STIs and HIV. Depending on research results, microbicides and cervical barriers may be combined to increase the effectiveness of both methods for STI/HIV prevention. This paper provides background information on cervical barriers, evidence for the value of conducting clinical research, an up-to-date summary of current clinical trials, and ideas for future research.

Cervical Barriers of Yesterday and Today

Cervical barriers for contraception have existed for thousands of years in a variety of forms. Barrier methods that may seem crude today—the insertion of lemon halves, crocodile dung, and beeswax plugs, for example—were widely used by women in ancient times as family planning devices.

The designation “modern” cervical barrier typically refers to diaphragms and cervical caps. The diaphragm is a latex or silicone cup with a firm, flexible rim and shallow dome that can be coated with gel and inserted into the vagina. The cervical cap is smaller than the diaphragm and is designed to adhere to the cervix by suction and hold spermicidal gel close to the cervix. When used with a spermicide, the diaphragm is up to 94% effective in preventing pregnancy, while the cap can be up to 91% effective when used correctly and consistently.1

Other cervical barrier devices used for contraception include the sponge, marketed in the United States under the Today® brand, and Lea’s Shield®. The sponge is a one-size, over-the-counter, foam barrier impregnated with spermicide that fits against the cervix. Lea’s Shield® is a reusable silicone barrier with a valve that allows the passage of cervical secretions and air, and a loop that assists in removal; it does not require clinician fitting, but in the United States is available by prescription only.

Two new cervical barriers under development are the SILCS diaphragm and the BufferGel Duet®. The SILCS diaphragm is a one-size-fits-most silicone device that has a pre-shaped rim to cling high in the vaginal vault and a finger cup on one edge for easy removal. The BufferGel Duet® is a disposable, pre-coated, one-size-fits-all diaphragm-like device made of polyurethane that delivers and distributes BufferGel™, a candidate microbicide and contraceptive, to the opening and interior of the vagina and cervix. These new devices attempt to address concerns about the diaphragm such as insertion, removal, and cleaning, by improving upon design elements (see Figures 1 and 2).

Evidence for the Value of Conducting Clinical Trials

Why is there new emphasis on cervical barrier methods? Researchers have revived their interest in cervical barriers partly due to observational research that demonstrates an association between diaphragm use and reduced risk of STIs (see Table 1), including cervical neoplasia, chlamydia, gonorrhea, pelvic inflammatory disease, and trichomoniasis.

There is also accumulating evidence that certain characteristics of the cervix, which is protected by these various barrier technologies, may make it more vulnerable to STIs, perhaps particularly HIV infection, than is the case for other areas of the female reproductive tract. For example, the cervix:

- has a high concentration of HIV-susceptible cells, resulting in a heightened vulnerability to HIV infection;
- is more fragile than the thicker cell lining of the vagina because it is covered by a single layer of cells, making it more vulnerable to trauma and consequent infection than other areas of the reproductive system;
- is the preferential site for many STIs, including chlamydia, gonorrhea, and the human papilloma virus (HPV); and
- is the entryway to the upper genital tract (fallopian tubes, ovaries, and uterus), which may also be an important site for HIV infection.

It is nevertheless important to bear in mind that the results listed in Table 1 below must be seen as suggestive rather than definitive, since the studies from which they were derived were not designed to test whether the diaphragm could prevent STIs. Future research will be needed to clearly determine whether cervical barriers could significantly reduce a woman's risk of STI/HIV infection.

Cervical Barrier Research for STI/HIV Prevention and Acceptability

There is a growing body of research whose objective is to evaluate the acceptability, feasibility, performance, safety, and effectiveness of cervical barriers for STI/HIV prevention. Five studies are using the diaphragm in combination with the candidate microbicides ACIDFORM™/Amphora™, BufferGel™, and/or cellulose sulfate/CS (Ushercell). Study sites are located in Madagascar, South Africa, the United States, and Zimbabwe. Also under way are a randomized controlled trial of the diaphragm in combination with a lubricant gel in South Africa and Zimbabwe, and a trial in the United States and the Dominican Republic of the BufferGel Duet®.

Two studies in Kenya are looking at user acceptability and/or safety of the diaphragm while another in Zimbabwe is assessing compliance and acceptability for contraception and HIV prevention. The diaphragm is also being compared to the SILCS diaphragm for fit, safety, and

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acceptability in the Dominican Republic. Another study is looking at these same endpoints for the SILCS diaphragm with K-Y Jelly® in South Africa and Thailand. In the United States, the SILCS diaphragm with K-Y Jelly® is being evaluated against the SILCS with N-9 for effectiveness, fit, safety, and user acceptability.

Cervical barriers are also being tested among diverse populations. For example, in the Dominican Republic, researchers recently tested the acceptability of the diaphragm as a potential STI prevention method among sex workers. This research will inform a future study to introduce and measure the acceptability of the diaphragm as well as the female condom in this high-risk population. Although not a clinical trial, another study being undertaken in South Africa, the United States, and Zimbabwe seeks to gain a better understanding of providers’ perceptions of the diaphragm and their willingness to recommend use to their clients (see Table 2).

Future Research

The range of studies described above reflects the current interest in determining whether the promise of cervical barriers as female-controlled STI/HIV prevention methods can be realized and whether women will find these methods practical and acceptable as ongoing protection from STIs and HIV.

Although these studies will provide answers to important questions, there are related

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### TABLE 1. OBSERVATIONAL STUDIES REPORTING ASSOCIATION BETWEEN DIAPHRAGM USE AND STIs*

<table>
<thead>
<tr>
<th>DESIGN</th>
<th>SAMPLE</th>
<th>STI</th>
<th>ODDS RATIO</th>
<th>95% CONFIDENCE INTERVAL</th>
<th>AUTHOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>STI clinic</td>
<td>cervical neoplasia (CIN I, II)</td>
<td>.3+</td>
<td>.1–.8</td>
<td>Becker, et al.³</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>STI clinic</td>
<td>gonorrhea</td>
<td>.8</td>
<td></td>
<td>Magder, et al.⁴</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>STI clinic</td>
<td>gonorrhea/chlamydia trichomonias</td>
<td>.32+</td>
<td>.16–.45</td>
<td>Rosenberg, et al.⁵</td>
</tr>
<tr>
<td>Case-control</td>
<td>STI clinic</td>
<td>pelvic inflammatory disease (PID)</td>
<td>.3</td>
<td>.09–.75</td>
<td>Wolter-Hanssen, et al.⁶</td>
</tr>
<tr>
<td>Case-control</td>
<td>hospital</td>
<td>pelvic inflammatory disease (PID)</td>
<td>.4</td>
<td>.2–.7</td>
<td>Kelaghan, et al.⁷</td>
</tr>
</tbody>
</table>

* Listed alphabetically by STI.
+ Also significantly protective when compared specifically to condom users.

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### TABLE 2. TRIALS EVALUATING CERVICAL BARRIERS FOR STI/HIV PREVENTION*+

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>PRODUCT</th>
<th>PURPOSE/ENDPOINT</th>
<th>RESEARCHERS/SPONSOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominican Republic</td>
<td>diaphragm and female condom</td>
<td>user acceptability for STI prevention among sex workers</td>
<td>• Bill and Melinda Gates Foundation</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>• Population Council</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>SILCS diaphragm compared to diaphragm with K-Y Jelly®</td>
<td>fit, safety, user acceptability</td>
<td>• PATH</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Profamilia</td>
</tr>
<tr>
<td>Kenya</td>
<td>diaphragm</td>
<td>safety and user acceptability</td>
<td>• International Centre for Reproductive Health</td>
</tr>
<tr>
<td>Kenya</td>
<td>diaphragm and K-Y Jelly®</td>
<td>user acceptability</td>
<td>• Centers for Disease Control and Prevention (CDC)</td>
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<td></td>
<td></td>
<td></td>
<td>• CONRAD</td>
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<td></td>
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<td></td>
<td>• University of Nairobi</td>
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<td></td>
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<td></td>
<td>• University of Washington</td>
</tr>
<tr>
<td>Madagascar</td>
<td>diaphragm and ACIDFORM™/Amphora™ gel or placebo gel</td>
<td>effectiveness</td>
<td>• CDC</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• CONRAD</td>
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<td></td>
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<td></td>
<td>• University of North Carolina</td>
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<td></td>
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<td></td>
<td>• USAID</td>
</tr>
<tr>
<td>South Africa</td>
<td>diaphragm and ACIDFORM™/Amphora™ gel or K-Y Jelly®</td>
<td>safety and feasibility</td>
<td>• CONRAD</td>
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<td>• USAID</td>
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<tr>
<td>South Africa, Thailand</td>
<td>SILCS diaphragm with K-Y Jelly®</td>
<td>fit, safety, user acceptability</td>
<td>• Khon Kaen University</td>
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<td></td>
<td>• PATH</td>
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<td></td>
<td></td>
<td></td>
<td>• Reproductive Health Research Unit</td>
</tr>
<tr>
<td>South Africa, Zimbabwe</td>
<td>diaphragm and Replens® gel</td>
<td>effectiveness</td>
<td>• Ibis Reproductive Health</td>
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<td></td>
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<td>• Medical Research Council</td>
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<td></td>
<td>• Perinatal HIV Research Unit</td>
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<td></td>
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<td></td>
<td>• University of California at San Francisco (UCSF)</td>
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<td></td>
<td></td>
<td></td>
<td>• University of Zimbabwe (UZ)-UCSF</td>
</tr>
<tr>
<td>United States</td>
<td>diaphragm and ACIDFORM™/Amphora™ gel or BufferGel™ or K-Y Jelly®</td>
<td>safety</td>
<td>• Eastern Virginia Medical School</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Magee Women’s Hospital</td>
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<td>• University of Pennsylvania</td>
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<tr>
<td>United States</td>
<td>diaphragm and BufferGel™ or Gynol II</td>
<td>efficacy, feasibility, user acceptability</td>
<td>• California Family Health Council</td>
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<td>• Columbia University</td>
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<td>• Eastern Virginia Medical School</td>
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<td>• RWJ School of Medicine</td>
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<td>• University of Colorado</td>
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+ Includes recently completed, ongoing, or planned trials.
* Listed alphabetically by country.
issues that might justify further inquiry and, therefore, new studies. For example, it is widely assumed that the clinician fitting and prescribing required by current diaphragm labeling is essential for safe, effective, and acceptable use, even though there is evidence suggesting that this clinical dependence might not really be necessary.

It might also be counterproductive from a user perspective, since providing the same size diaphragm to all women would simplify supply and access to the device for a potentially much larger population of users. For this reason, the new methods being tested are either one-size-fits-most or one-size-fits-all devices.

Another question of interest is whether diaphragm users should be encouraged to use the diaphragm continuously and only remove it for cleaning every 24 hours. The premise here is that such a use pattern might increase user adherence and decrease the need for coital dependence; in other words, women would not have to decide to insert the device immediately before sex but would instead have the diaphragm already in place.

Finally, although without exhausting the universe of other unknowns, further research is needed to determine whether cervical barrier methods used without N-9 are effective contraceptives. Some studies have attempted to answer this question, but a definitive conclusion has not been reached. Of course, all these questions become far more urgent if cervical barriers are, in fact, shown to be effective in reducing STI and HIV transmission. However, at this time, we do not know the answer to this critical question so will have to watch and wait for the results of the ongoing Phase 3 clinical trials.

For more information about cervical barrier research, visit the website of the Cervical Barrier Advancement Society (CBAS) at www.cervicalbarriers.org. You can also subscribe to the CBAS newsletter, which includes regular research updates, by emailing info@cervicalbarriers.org.

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**TABLE 2. TRIALS EVALUATING CERVICAL BARRIERS FOR STI/HIV PREVENTION**

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>PRODUCT</th>
<th>PURPOSE/ENDPOINT</th>
<th>RESEARCHERS/SPONSOR</th>
</tr>
</thead>
</table>
| United States | SILCS diaphragm with K-Y Jelly® compared to SILCS with N-9 | barrier effectiveness, fit, safety, and user acceptability | • CONRAD  
• Eastern Virginia Medical School  
• University of Pittsburgh Medical Center |
| United States and Dominican Republic | BufferGel Duet® | performance, safety, user acceptability | • CONRAD |
| United States, South Africa, Zimbabwe | diaphragm | provider perceptions of diaphragm and willingness to recommend use | • Ibis Reproductive Health  
• UCSF  
• NICHD |
| Zimbabwe | diaphragm and cellulose sulfate/CS (Ushercell) gel | safety | • CONRAD  
• UCSF  
• UZ-UCSF |
| Zimbabwe | diaphragm and K-Y Jelly® | compliance, user acceptability for contraception and STI/HIV prevention | • UCSF  
• UZ-UCSF |

+ Includes recently completed, ongoing, or planned trials.  
* Listed alphabetically by country.

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NOTES FROM THE FIELD

14th International Conference for AIDS and STIs in Africa (ICASA 2005)

Paul Galatowitsch, Consultant, Global Health Strategies

The 14th International Conference for AIDS and STIs in Africa (ICASA 2005) was held 4-9 December 2005 in Abuja, Nigeria. This note reviews and elaborates on the panel discussion, “Vaccine and Drug Trials in HIV/AIDS in Africa,” which explored the operational and ethical issues associated with providing ARV therapy and related care to the participants of clinical trials who seroconvert during the course of HIV prevention trials.

Panelists began by outlining the findings of a 2005 paper by Nandi Siegfried, et al. This innovative paper mapped the geographic distribution of HIV/AIDS clinical trials for treatment and prevention in Africa from 1987 to 2003 from the perspective of whether or not the Principal Investigator (PI) was based in Africa. During the period of their investigation, the authors documented that of 77 HIV/AIDS prevention and treatment clinical trials in Africa, the PI was based in Africa in only 19. Further, of the 58 clinical trials headed by a PI located in Western industrialized nations, nearly all supervised the trials from their home countries. Finally, their mapping exercise revealed that there are many countries in Africa where HIV/AIDS prevention and treatment research has yet to even occur (see Figures 1 and 2).

Panelists pointed out that under-representation of African PIs was not surprising as most African countries lack the research infrastructure necessary for funding and reviewing complex clinical trials. Consequently, most African researchers serve as co-PIs, who typically do most of the actual research since they are located on site and are therefore familiar with the local cultural and institutional terrains.

Nevertheless, while “not surprising,” the combination of a continent burdened by the highest number of HIV/AIDS cases worldwide and a disproportionately small number of clinical trials headed by African-based investigators, has contributed to political tensions among HIV/AIDS activists, advocacy organizations, and institutional research sponsors. With these structural and political issues as backdrop, panel members went on to discuss the policy and operational issues facing researchers currently engaged in or seeking to conduct clinical HIV prevention trials in Africa.

Four programmatic and conceptual areas were highlighted as requiring careful consideration:

1. What are the boundaries of care and treatment for study participants who seroconvert?

Panelists argued that study sponsors have a moral obligation to provide lifelong care, including antiretroviral treatment, to study participants who seroconvert during a clinical trial. While they recognized that making treatment available would present challenges in regions of Africa with weak health care infrastructures, they felt that practical challenges to providing care could be substantially addressed. One panelist pointed to a UNAIDS study (citation not provided), which predicted that the total number of participants in clinical trials in Africa who seroconvert would be low, if only because the number of trials was also low. This assessment was seen as reasonable in light of the Siegfried research, which documented only 43 clinical trials examining HIV prevention and the prevention of opportunistic infections in Africa from 1987 to 2003.

2. What are the costs of providing care and treatment to participants who seroconvert?

Panelists noted that the annual cost of providing ARV therapy in Africa is currently about US$300.00. They suggested that investigators conducting clinical trials could reasonably estimate the costs of providing ARV therapy and related care to seroconverters so as to build those costs into the budget and structure of research proposals.

3. What is the feasibility of proving lifelong ARV treatment?

Panelists pointed out that procedural and ethical concerns surrounding future care

of seroconverters are more easily resolved in African countries that provide free ARV therapy. In countries that do not do so, study sponsors would have to arrange and manage systems to provide the necessary follow-up care to seroconverters. Panelists recognized the obvious: that building these systems would be easier in regions with modest or developed health care and transportation infrastructures than in areas without them. An additional challenge that confronts any system in any country setting is that seroconverters would require annual CD4 counts and viral loads to determine when to initiate ARV treatment and monitor adherence and ARV resistance. And, since ARV treatment is not typically recommended until CD4 counts drop below 300—an 8-10 year time frame on average—there would be the additional challenge of ensuring that seroconverters are not lost to follow-up.

4. How should study investigators treat a seroconverter, who is very likely to be in primary HIV infection (PHI), at the time of their diagnosis?

In studies where seroconversion is possible, even in circumstances where investigators do not plan to offer ARV treatment, investigators must educate participants to recognize the signs and symptoms of PHI. This includes educating clients about PHI symptoms, safer sex, viral load testing, and indeterminate tests; helping patients understand the time period from infection to onset of potential PHI symptoms; and counseling clients about the period between HIV infection and detection using standard HIV antibody tests. In studies where investigators can offer ARV therapy and where acute or primary HIV infection is diagnosed, investigators must

Continued on p.14
HIV Prevention Trials Network (HPTN) Microbicide Safety Consensus Meeting

Carolyn J. Plescia, Alliance for Microbicide Development

The expansion of microbicide clinical research has highlighted a variety of issues pertaining to safety assessment in preclinical and clinical microbicide development, including the potential for resistance associated with ARV microbicides; validation of new diagnostic techniques; development of microbicides for rectal use; assessment of safety in late-stage clinical trials and management of safety data generated by these trials; and requirements for regulatory approval in Europe, the United States, and the developing world.

To expand discussion of these emerging safety issues, the HPTN convened the “Microbicide Safety Consensus Meeting” in Bethesda, Maryland, 1-3 March 2006. The meeting, led by Sharon Hillier, PhD, and Ian McGowan, MD, PhD, aimed to produce a summary document addressing the optimal approach to safety monitoring in clinical trials. The specific objectives of the meeting were to (1) review current approaches to safety monitoring in microbicide clinical trials, (2) identify safety issues that require management guidelines, and (3) analyze the current status of safety monitoring and develop recommendations for modifications as necessary.

The meeting was attended by a variety of stakeholders, including representatives from the Alliance for Microbicide Development, Bill and Melinda Gates Foundation, CONRAD, Centers for Disease Prevention and Control, European Medicines Evaluation Agency, Family Health International, International Partnership for Microbicides, National Institutes of Health, Population Council, United Kingdom Medical Research Council, and US Food and Drug Administration, as well as developing-world investigators, microbicide advocates, academic scientists, and representatives from the pharmaceutical industry.

Presentations focused on safety monitoring in clinical trials from the perspective of the pharmaceutical industry, investigators, and communities; regulatory perspectives on safety reporting; optimizing safety and efficacy endpoints; and rectal safety. Each group of presentations was followed by a round-table discussion and breakout sessions on preclinical evaluation, phase-specific needs, and community issues around safety.

Participants recognized that, while a single meeting might be insufficient to finalize guidelines, the Microbicide Safety Consensus Meeting was a solid first step.
toward a framework for achieving consensus and developing guidelines. The list of presentations that follows provides a clear view of the breadth of material covered and the complexity of the issues requiring attention.

Statistical Implications of Withholding Study Medication on the Outcome of Microbicide Trials
Doug Taylor, PhD

Plenary Talk: Urgency of Microbicide Development
Sharon Hillier, PhD

Pharmaceutical Industry/Investigator/Community Perspectives on Safety Monitoring in Trials

Monitoring Clinical Trials—the Large Pharma Perspective
Garrett Nichols, MD

Small Pharma Perspective on Microbicide Safety
Al Profy, PhD

Subject Safety—an Investigator’s Perspective
Mike Chirenje, MD

Subject Safety—a Community Perspective
Rhonda White, MBA

Regulatory Perspectives

Microbicide Safety Reporting—the FDA Perspective
Deborah Birnkrant, MD

Microbicide Safety Reporting—a European Perspective
Ian Weller, MD, FRCP

Post-trial, Post-licensure Safety Reporting
Timothy Farley, MD

Ethics and Microbicide Safety
Keymanthri Moodley, MBBS

Optimizing Safety and Efficacy Endpoints in Microbicide Trials

Retention and Product Adherence in Microbicide Trials
Benoit Masse, PhD

Gynecological Issues in Microbicide Studies
Bryna Harwood, MD

Pregnancy Issues in Microbicide Studies
Courtney Schreiber, MD

Rectal Safety Assessment

Epidemiology of Anal Intercourse
Pamina Gorbach, PhD

US Microbicide Policy Initiatives: An Update
Ellen Marshall

US Appropriations in Support of Microbicide Development

The FY06 spending bills—for the year ending 30 September 2006—were finalized in December 2005. Overall, Federal funding for microbicide research increased by nearly 8% from FY05, for a combined total at all agencies of US$107,606,000. The greatest increase was for USAID’s microbicide efforts, where the level of funding went from US$30 million to US$40 million. Most of this increase will be used to support the Phase 3 clinical trials now in progress in a number of developing countries, as well as some important next-generation microbicide development and access research. Our community extends its sincere appreciation to all of our supporters on Capitol Hill who understand the importance of microbicide development in preventing HIV and who continue to support it.

The appropriations process is now under way for FY07. Given current scientific momentum and the advancement of several candidate microbicides, efforts continue to ensure an increased commitment from the United States to help develop a safe and effective microbicide within five to seven years.

Microbicide Development Act (H.R.3854 and S.550)
A strategy for moving legislation forward is to have a large number of House and Senate members officially endorse it by becoming “co-sponsors.” Supporters of the Microbicide Development Act (MDA) have renewed efforts to gain additional support for the bill from their colleagues. Senator Jon Corzine (D-NJ) originally

Continued on p.16
introduced the bill and was a tireless supporter, but now that he has been elected to serve as governor of New Jersey, Senator Barack Obama (D-IL) has taken the lead on this bill in the Senate. Representatives Chris Shays (R-CT) and Jan Schakowsky (D-IL) are the bill’s House leaders. To date, there are 19 Senate cosponsors and 39 House co-sponsors of the bill. The legislation seeks to establish at the National Institutes of Health a “clearly defined and adequately staffed organizational unit charged with carrying out microbicide research and development” and provides for adequate support for the integration of basic science and clinical research on microbicides with particular emphasis on implementation of trials leading to product licensure. It also supports strengthening of efforts at USAID and CDC.

Congressional Human Rights Caucus Briefing Includes Microbicides

On 30 March 2006, the Congressional Human Rights Caucus hosted a briefing entitled “The Global Challenge of HIV/AIDS: The Impact of Gender Disparities on the Growth and Spread of AIDS.” Several members of Congress who are strong supporters of microbicides spoke at the event, including Representative Chris Shays (R-CT). In addition, the film produced by the Global Campaign for Microbicides, “In Women’s Hands,” was shown and Zeda Rosenberg, CEO of the International Partnership for Microbicides, presented an update on the state of microbicide research and clinical trials. The audience invited to participate comprised members of Congress, Congressional staff, and advocates.

PEPFAR Report Supports Microbicide Research

The Office of the Global AIDS Coordinator recently released its report on efforts undertaken during the second year of implementing the President’s Emergency Plan for AIDS Relief (PEPFAR), which includes several references to the potential power of microbicides as a prevention tool. The report states: “The United States has also maintained its position as the global leader in HIV/AIDS research and innovations, with an emphasis on developing safe and effective vaccines and microbicides.” The report also recognizes that to meet the PEPFAR prevention goals, new technologies and research findings must be incorporated, and notes the approximately US$97 million from PEPFAR dedicated to microbicide research efforts in FY05. The report discusses the partnership with NIH on microbicide research and the support from USAID on targeted research, development and dissemination of new technologies (including microbicides), and packaging and distribution mechanisms for antiretroviral drugs. Full report at http://www.state.gov/s/gac/rl/c16742.htm.

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“One in order for the emergency plan to be successful in meeting its prevention goals, validated new technologies and research findings must be rapidly incorporated. PEPFAR works with U.S. implementing agencies, including HHS/CDC, HHS/NIH and research divisions of USAID, to monitor such emerging prevention areas as male circumcision, female-controlled prevention technologies and microbicide development. The emergency plan contributed approximately $97 million for microbicide research efforts in fiscal year 2005.”1

January 2006

New Format for the Alliance News Digest
Following evaluation of reader preferences, the Alliance has just launched a new, web-based format for the News Digest that allows readers to easily browse and search articles included in each issue. Current and past issues can be accessed from the Alliance website at http://www.microbicide.org/publications/. From this webpage, readers can view, print, or email individual articles or full issues of the Digest; each issue can also be saved or printed in PDF format. Readers may also search issues of the Digest created on or after 27 January 2006. Note: Issues created prior to 27 January 2006 have been archived and are not searchable; these issues are available as PDFs through the “Archived Issues of the News Digest” link on the Digest webpage.

Members of the Alliance’s listserv now receive a weekly email containing the first 50 words of each article included in that week’s Digest followed by links to the full text of each article. To be added to the distribution list for the Digest, email Cecilia Fox at cfox@microbicide.org.

Source: Alliance for Microbicide Development

The Alliance is pleased to announce the publication of an article authored by Alliance Writer/Research Associates Betsy Finley and Carolyn Plescia. The article, “The Future of HIV Prevention: New Tools, New Hope,” was published in the Winter 2005/06 ACRIA Update, which can be viewed online at http://www.acria.org/treatment/treatment edu_winterupdate2005_2006.html. The article summarizes for a lay audience a range of innovative tools for HIV prevention—currently-available tools as well as potential new methods—including prevention of STIs and bacterial vaginosis, male circumcision, microbicides, preventive HIV vaccines, barrier methods, and pre-exposure prophylaxis.

Source: Alliance for Microbicide Development

February 2006

California State Senator Introduces Joint Resolution in Support of the Microbicide Development Act
On 6 February 2006, California State Senator Jackie Speier introduced Senate Joint Resolution 22, relating to the Microbicide Development Act. SJR22 is the first-ever state-level resolution on microbicides. As stated in the introduction, “This measure would memorialize the United States Congress and the President to enact the Microbicide Development Act (H.R.3854 and S.550) to facilitate the development of microbicides to prevent the transmission of HIV and other diseases.” The full text of the bill is available at: http://www.leginfo.ca.gov/pub/bill/sen/sb_0001_0050/sjr_22_bill_20060206_introduced.html. Further information at www.global-campaign.org/legislativeadvocacy.htm or http://www.microbicide.org/microbicideinfo/legislation.shtml

Source: Global Campaign for Microbicides

CONRAD and Cellegy Pharmaceuticals Formalize Collaboration
In February 2006, longtime collaborators CONRAD and the Biosyn Division of Cellegy Pharmaceuticals, Inc., announced a non-exclusive licensing agreement to research and develop three Biosyn-patented microbicides for the prevention of HIV and other sexually transmitted diseases. The microbicides covered under the agreement are in various stages of development and have different mechanisms of action. They are Savvy™, a surfactant currently in Phase 3 clinical trials in Africa and the United States; UC781, an HIV-1 reverse transcriptase inhibitor, in expanded Phase 2 trials in Thailand and the United States; and cyanovirin-N (CV-N), a fusion inhibitor that is in preclinical testing.

Source: CONRAD

CONRAD Announces Results of Phase 2 Clinical Trial
CONRAD announced promising results of a Phase 2 study carried out to evaluate the contraceptive effectiveness of 6% cellulose sulfate/CS (Ushercell), a vaginal gel being developed to prevent pregnancy and sexually transmitted infections, including HIV. The study found a 13.4% chance of pregnancy in 6 menstrual cycles of typical use of the gel and a 3.9% chance of pregnancy in perfect use over the same time period. These figures compare very well with pregnancy probabilities for nonoxynol-9 (N-9), the only vaginal contraceptive drug now marketed in the United States. In a recent study, N-9 gels had 6-month typical use pregnancy probabilities ranging from 14.0 to 22.2%,

Continued on p.18
depending on the dose, and 6-cycle perfect-use probabilities ranged from 8.5 to 15.7%. The product is also in clinical trials to assess its efficacy in preventing HIV infection, chlamydia, and gonorrhea, and previous trials have documented its safety for use by women and their male sexual partners.

Source: CONRAD

Helene Gayle to Serve as President and CEO of CARE USA
In early 2006, Dr. Helene Gayle will become the first woman and the first person of color to serve as President and CEO of CARE USA. Dr. Gayle was previously the director of the Bill and Melinda Gates Foundation’s HIV, TB, and Reproductive Health Program. During her time with the Gates Foundation, she contributed to the development of numerous HIV prevention initiatives and provided leadership in the expansion of the Gates Foundation’s work in TB prevention, treatment, and research. Beginning in March 2006, Dr. Nicholas Hellmann will serve as interim director of HIV, TB, and Reproductive Health for the Gates Foundation.

Source: Bill and Melinda Gates Foundation, CARE

Newsmaker Event
On 8 February 2006, the Alliance for Microbicide Development, CONRAD, and the Global Campaign for Microbicides hosted a Newsmaker event on microbicides and HIV prevention at the National Press Club. Guest speakers included Dr. Helene Gayle, Bill and Melinda Gates Foundation, and Congressman Danny Davis (D-IL), a co-sponsor of H.R.3854, the Microbicide Development Act. Attending journalists included: Jack Zahora, WAMU; Mary Agnes Carey, Congressional Quarterly; Maggie Fox, Reuters; Laura Gilchrist, UPI; Charles Smith, South African outlet Media 24; Jacqueline Ruttman and Charlotte Schubert, Nature; Geraldine Ryerson Cruz, Bloomberg; and Sam Hussein, Accuracy in Reporting.

Traditionally, Newsmaker events are intended primarily for journalists to get information on breaking news or in-depth information on a topical issue from expert sources; however, this particular event drew a large number of non-media groups, including representatives from the Center for American Progress, Citibridge Foundation, Women’s Policy Inc., and the offices of Senator Barack Obama (D-IL), Senator Edward Kennedy (D-MA), and Representative Debbie Wasserman-Schultz (D-FL).

The goal of this Newsmaker was to draw attention to the high rates of HIV/AIDS in African Americans and the developing world and raise awareness about the potential of microbicides to curb the epidemic. The event was successful in reaching new groups and getting additional coverage on microbicides, including a UPI story on 8 February and a WAMU Morning Edition segment. The National Press Club will be providing an audio file on CD that can be downloaded from each participating group’s website.

Source: CONRAD

Microbicide-Specific Research
Published December 2005-February 2006


Continued on p.20


### MICROBICIDE CLINICAL TRIALS (March 2006)*

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<tr>
<th>PHASE</th>
<th>TRIALS</th>
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<tr>
<td>1</td>
<td>ACIDFORM™/Amphora™ gel</td>
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<td></td>
<td>Carraguard®</td>
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<td></td>
<td>Cellulose acetate 1, 2-benzenedicarboxylate (cellacefate/CAP)</td>
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<td>Savvy™ (C31G)</td>
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* This table is an attempt to give a picture that is as accurate as possible of the microbicide candidates that have reached the clinical stages of testing. Some of these products are being tested in more than one clinical phase. The trials that appear in this table may be (1) in the active planning stage, (2) ongoing, or (3) recently completed but with published analysis pending. For any modifications, please contact Carolyn Plescia, email cplescia@microbicide.org, tel. 301-587-3302.