COMMUNITY HIV/AIDS CHAMP MOBILIZATION PROJECT
HHS WATCH

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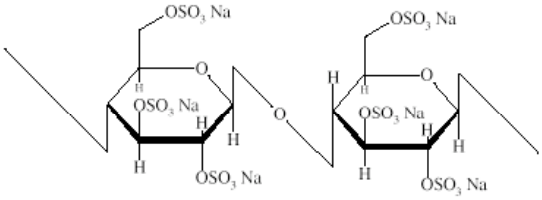
A Microbicide Conundrum

By David Gilden

The January 31 announcement came like a bolt out of the blue: Researchers had prematurely terminated the two large efficacy trials for the microbicide cellulose sulfate. The trials were expected to show that vaginal applications of the microbicide, commercially known as Ushercell, would reduce HIV transmission during sex. But in one trial, women using cellulose sulfate paradoxically had higher rates of HIV acquisition than those using an inactive placebo gel. The Gates Foundation and USAID had poured $24 million into the trial program. Jeff Spieler, Chief of USAID's Research, Technology and Utilization Division, Office of Population and Reproductive Health, reacted to the closure by saying, "I am surprised and disappointed by these findings given the pre-clinical effectiveness and safety profile of CS [cellulose sulfate] and its safety profile demonstrated in Phase I trials."

Cellulose sulfate, a derivative of cotton, is a member of the group of promising microbicides technically known as "anionic polymers." These compounds attach themselves to viral surfaces and disrupt virus-cell binding. They are active against HIV and other STDs, including such bacterial infections as gonorrhea and Chlamydia as well as herpes simplex virus. Some of the candidate microbicides, including cellulose sulfate, have contraceptive potential. They disrupt sperm membrane function, causing reduced mobility and egg penetration. Two other anionic polymers, Carraguard and PRO 2000, are also the subjects of advanced microbicide trials.

The closed trials tested cellulose sulfate under particularly rigorous conditions. One trial, sponsored by CONRAD (associated with the Eastern Virginia Medical School) was recruiting 2,574 HIV-negative women in India, Benin, Uganda and South Africa. The women had to have had at least three male sex partners in the three months before enrollment and to have averaged at least three sex acts a week. Most, but not all, were commercial sex workers. Half of the trial participants applied a cellulose sulfate gel prior to having sex. The remaining participants used a placebo gel without the cellulose sulfate. Neither group knew which gel they had been given. All participants also received regular safe-sex counseling and supplies of condoms. The other trial was sponsored by Family Health International (FHI) and took place in Nigeria. This 2,160-person trial followed a similar design except that enrollees needed to have had two or more male sex partners in the previous three months.



Cellulose Sulfate Building Block

The CONRAD trial was the one that observed a higher rate of new HIV infections among the cellulose sulfate recipients. It is important to note that CONRAD recorded only 35 HIV transmissions in all. Both trials together were only half-enrolled when they closed. Data collection is not complete and CONRAD foresees no further release of information on its trial until next fall at the earliest. The two trials suffered from serious statistical weaknesses: HIV rates during the trials were lower than anticipated and pregnancy rates higher. The low rates of HIV transmission made it difficult to detect any effect of the microbicide unless the trials enrolled more women or followed them longer. Since pregnancy led to temporary exclusion from the trials, the resulting reductions in gel use further undercut the trials' statistical power.

In light of the small number of HIV cases to work with, Luc Van Damme, the lead researcher for the CONRAD trial commented, "The recommendation to close was a big shock. We chose to err on the side of women. When we have the final data, it may show that cellulose sulfate was not unsafe. But even it kept going, the trial may not have been large enough to show efficacy."

HIV, Pregnancy and Trial Design

The cellulose sulfate trials were designed with the expectation that HIV transmission rates among placebo recipients would be at least four percent per year of observation. The rate instead was around 2%. At that low incidence, the trials would have had to expand enrollment several fold to demonstrate that cellulose sulfate was effective. Already, FHI had stopped enrollment at its Nigerian sites and was preparing new sites in South Africa. CONRAD had contingency plans to shift enrollment to southern Africa and increase total trial size.

It has proven very difficult to anticipate the background HIV incidence rate in the populations enrolling in prevention trials. Ten years ago, large trials for nonoxynol-9 vaginal microbicides were conducted in similar populations as the present cellulose sulfate trials. The trial designs were also comparable: participants received similar safe-sex counseling, condom provision and STD treatment. Yet, the observed HIV transmission rates in the nonoxynol-9 trials were much higher: 7% to 10% – and up to 14% among one trial's nonoxynol-9 recipients. (Nonoxynol-9 was the original big microbicide failure – see below.)

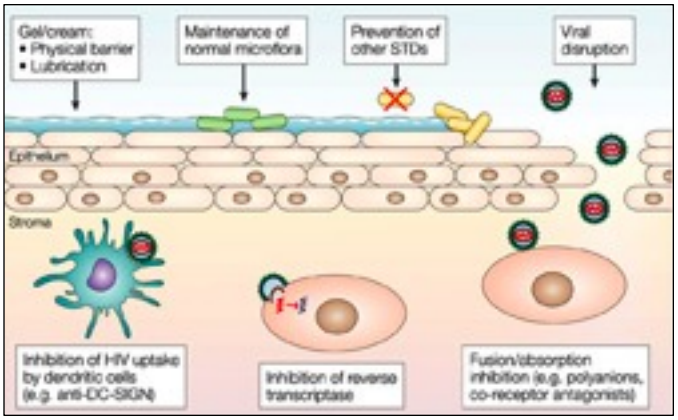
High community HIV levels do not mean that there are high current rates of transmission. An HIV epidemic reaches a mature stage when most people with behavioral and biologic risks for HIV are already infected.

It has proved very challenging to identify the best populations for testing microbicides. In the words of Lori Heise, director of the Global Campaign for Microbicides, "High HIV incidence occurs in newly exposed populations, where the epidemic is on the cusp. Vaccines and PrEP [pre-exposure prophylaxis] trials can recruit across settings. They can recruit men, including those who have sex with other men, and IV drug users. The current microbicide trials recruit only among women who are at risk for HIV through vaginal sex. They need women who are at high risk but consistently unable to use condoms. This is a very narrow group – even sex workers can use condoms well."

Pregnancy has proved another stumbling block. The FHI trial noted a pregnancy rate of 30% per year of observation. It also found that the women in its trial said they used their gel, whether placebo or active, for 80% of all sex acts. Reported condom use increased from 60% to 90% during the trial. A previous trial with monogamous couples in California found that cellulose sulfate compared favorably as a contraceptive with nonoxynol-9, the only vaginal agent marketed in the US. With very frequent sex, though, high pregnancy rates over fairly short periods could occur even with an average 80% usage, especially if there was a tendency to dispense with both condoms and gel on the same occasion.

Pregnant women were excluded from receiving their assigned trial product because reproductive toxicity studies have yet to be conducted on cellulose sulfate. This lapse meant that women did not have the microbicide when they appear to be particularly vulnerable to HIV. Despite their suspension, the trial counted them as if they were still part of their assigned trial cohort because of the researchers' planned "intent-to-treat" trial evaluation. "Intent-to-treat" is usually a valuable way to analyze medical products. It takes into account the fact that, in the real world, many people stop using products due to side effects or inconvenience. This trial, though, involved involuntary discontinuations that would not have occurred in the real world. Including the pregnant women in the trial results further weakened the trials' ability to show a benefit from cellulose sulfate.

Microbicides' Different Points of Attack



Source: Shattock RJ and Moore JP. Inhibiting sexual transmission of HIV-1 infection. Nature Reviews Microbiology. October 2003.

The Necessary Preliminaries to Advanced Human Trials

The large nonoxynol-9 trials suffered from neither of these issues. There, the problem was that heavy use of nonoxynol-9 increased the risk of acquiring HIV because it irritated the vaginal lining when applied. That increased risk was only apparent in trial participants who on average used nonoxynol-9 more than 3.5 times per day.

The nonoxynol-9 results led to a shake-up in the way microbicides are developed. Laboratory reports indicating nonoxynol-9's irritating effects became available only after the human trials had commenced. Since then, candidate microbicides have been carefully tested in the lab and in small human studies for signs that they disrupt vaginal surfaces.

Nonoxynol-9 is a surfactant that dissolves viral and cell membranes. Although cellulose sulfate has no such effect, it is a potent inhibitor of blood clotting. Previous cellulose sulfate trials did not notice any signs of vaginal irritation or non-menstrual bleeding. All but two of these trials were small and short, lasting at most four weeks. The major exception is the six-month, 200-person contraception trial conducted in monogamous California couples.

The latest trials took place in a considerably different environment. They involved high microbicide use and longer periods of time. Trial enrollees also were much more likely to have untreated STDs. Under such conditions, vaginal irritation and lesions would be greatly elevated. Bleeding during sex then would be more frequent. The presence of cellulose sulfate could increase the risk of HIV if it prolonged such bleeding. But this scenario is completely speculative due to the lack of intermediate trials in similar populations. Such "phase II" trials are common in drug development. They confirm the agent's safety within a larger population and provide initial measures of effectiveness.

Van Damme commented, "We moved forward because the previous trials did not indicate safety issues. Only the larger trials can measure HIV transmission endpoint."

Researchers have generally felt that microbicide toxicity issues can be resolved with small, quick trials. In contrast, effectiveness is very difficult to measure. There is no preliminary indication of protection equivalent to the viral load declines seen with new anti-HIV drugs. Efficacy for microbicides is only observable by comparing how condoms plus microbicides decrease HIV rates compared to condoms plus placebo. Considering the effectiveness of condoms alone, that takes a very large trial indeed, even when a suitable high-risk population is selected. Still, cellulose sulfate results show the chances taken when so quickly ramping up.

Some version of phase II trials may be in the offing. According to Heise, "To manage the uncertainty, the field is moving toward a phase II run-in and then rollover to phase III." Such a strategy would imply looking at intermediate results in a moderate-size population before involving thousands of trial enrollees in a full-scale efficacy evaluation.

A report on the CONRAD trial was presented Tuesday, February 27, 2007 at the 14th Conference on Retroviruses and Opportunistic Infections (CROI): Oral Abstract 106LB**:** *Update on the CONRAD Cellulose Sulfate Trial,* Gustavo Doncel and Lut van Damme, CONRAD, Arlington, VA, US. For a video of this presentation, go to the following web page

and select the Tuesday session on Late Breaking Trials of New ARVs and Microbicides http://www.retroconference.org/2007/data/files/webpage_for_CROI.htm.

See also the World Health Organization's January 31, 2007 statement about the cellulose sulfate trial closure: http://www.who.int/mediacentre/news/statements/2007/s01/en/index.html.

Other Microbicides Quietly Pine Away

More trials mean greater development costs for successful microbicides, and financing is already tenuous for the loose network of nonprofit organizations, small businesses and academic investigators who conduct microbicide research. Just how tenuous was illustrated last fall, when development of a new promising microbicide, cellulose acetate phthalate, or CAP, ground to a halt. CAP has a structure related to the sulfated anionic polymers but offers several potential advantages. It is particularly effective at deactivating HIV and does not retard blood-clotting. CAP is widely used to coat pills and considered innocuous.

Scientists at the New York Blood Center spent nearly 10 years and $10 million doing lab studies. A consortium of research centers led by the Blood Center recently received $6 million from the NIH to conduct early human trials. But the chief researcher, Robert Neurath, has retired after a dispute with the Blood Center management over research funding. Neurath's retirement left the new human trial consortium in limbo. He now says, "As far as I know, not much is happening now regarding a commercially and medically viable CAP formulation since my efforts have been blocked."

Suspension of Minority AIDS Initiative Funding A Major Blow to AIDS Care in Communities of Color

By Julie Davids

On March 1 – just days before the release of the long-awaited CDC prevention plan for African-Americans that (surprise, surprise) relies upon getting more folks tested who would then have to enter a severely overburdened care system – funding for care programs through the federal Minority AIDS Initiative (MAI) was suspended.

The funds are expected to flow again in the fall, once they have been incorporated into the Ryan White CARE Act process – but they will then be disbursed to regions through a competitive bidding process that may marginalize some current recipients.

So, the bottom line – programs serving communities of color just took a substantial funding hit, the infrastructure of AIDS care has been significantly undercut across the country, and there's no guarantee that those programs that can hang in until the fall (and many can't) will be refunded.

In some cases, people will be able to fight back. Project TEACH, for example, is a treatment education training program that I helped start in Philadelphia in 1996. It has graduated over 2,000 people, most of whom are low income African-Americans living with HIV. The program helps them learn and then share information about staying healthy with HIV. Two weeks ago, the service category that funds Project TEACH was eliminated wholesale in order to deal with the impact of funding cuts – including the MAI mess. The AIDS community has had to drop everything to mobilize to get the cuts reinstated, with TEACH graduates leading the effort.
In parts of the country with less resources to begin with and less of an organizing infrastructure, MAI-related cuts are, and will be, just as shocking, severe, and even harder to overturn, with few spare bucks available to keep essential programs afloat.

Over 70 groups across the country signed a letter urging the Tri-Caucus to deal with this situation. (The Tri-Caucus includes the Congressional Black Caucus, the Congressional Hispanic Caucus, and the Congressional Asian Pacific American Caucus. The Congressional Black Caucus started the MAI.) Unfortunately, there's a lot of buck-passing going on. Some say that the Administration could interpret the law in such a way as to allow funding to continue as-is until the fall. Others say that Congress passed a law that ties HRSA's hands and needs to deal with it. Can the authorizers of Ryan White light a fire that will get more people who are tasked to HRSA speed up the process so that the MAI gets up and running faster? Can the Administration reach out to Congress to address the quagmire of the new CARE Act and intervene on behalf of the MAI?

None of this is likely unless all parties hear a lot more from advocates. People at the grassroots are so busy gasping for air, fighting such a large epidemic with so few resources, that it's hard to look upstream to go after the guys cutting off the oxygen. And how can you scream when you have no air? If you can, let your voice be heard now. Or hold your breath until September…

Prevention Takes to the Red Carpet at CROI - Community Lacks Tickets, But Everyone Can Watch at Home

By Julie Davids

The last week of February in Los Angeles was notable not just for the Academy Awards, but also for the annual Conference on Retroviruses and Opportunistic Infections (CROI). Those selected by the Academy (aka the Scientific Program Committee) for the best performances in HIV/AIDS bench and clinical research were called to the LA Convention Center for four days of frenetic activity, presentations, and discussions.

For nearly a decade, the dialogue at CROI has been enriched by the presence of AIDS treatment advocates, educators, and community press thanks to the vociferous insistence of activists such as the late Kiyoshi Kuromiya and ACT UP members, who demanded community inclusion and won a scholarship program for treatment community educators.

Now that key *prevention* data is being presented at CROI and the boundaries between treatment and prevention start to melt, CHAMP is calling for expansion of the scholarship program to include prevention-focused community members. In the course of the conference, 30 organizations and eight current and former members of the conference's tiny Community Liaison Subcommittee endorsed a letter asking for the addition of five full and 15 partial scholarships for prevention community educators.

As in all places where people with ideas and resources gather, the chatter in the hallways between sessions provide some of the most productive parts of CROI – and make it imperative that more prevention people are included. Thankfully, everyone can now view the conference sessions via webcast at http://www.retroconference.org/2007/data/files/webpage_for_CROI.htm

Here are some prevention-related sessions you might want to check out:

Sunday, February 25:
Kevin De Cock of WHO: **"Changing Patterns of US and Global Epidemiology"**
(look for the **Program Committee Workshop for New Investigators and Trainees - Part 2**)
The pit-bull of "routinized" HIV testing steps away from that platform to walk us through a cogent, useful, and compelling understanding of HIV incidence and prevalence, shining a spotlight on key factors in the epidemic such as the reality that infections among men who have sex with men is an "international phenomenon that deserves much, much more attention."

Monday, February 26:
Plenary: **Prevention of HIV Transmission from Breastfeeding**
Oral Abstracts: **Issues in Prevention of HIV Transmission and ART**
The first four sessions deal with a range of biomedical research from animal data linking

microbicides and pre-exposure prophylaxis, to presumptive treatment of STDs at time of HIV diagnosis in San Francisco.

Symposium: **Drivers of the HIV Epidemic and Potential Interventions**
Presentations include "What's Driving the Global MSM Epidemic," "The STD - HIV Connection from Research to Action: Are We Lost in Translation?" and the question that's on everyone's mind lately: "New HIV Prevention Technologies: What if They Work?"

Tuesday, February 27:
Plenary: **Status of the US HIV/AIDS Epidemic: Is It Changing and If Not, Why Not?**
Harold Jaffe, 27-year-CDC-veteran-now-at-Oxford, notes that "funding risk reduction programs makes a lot more sense than wishing risks away," and that Bush's proposed budget for 2007 calls for $204 million to support abstinence-only education at the same time that federal funding for needle exchange is zero. No administration, Democratic or Republican, he added, has put "any money whatsoever" into needle exchange programs. Otherwise, his analysis hews close to the CDC cloth.

Oral Abstracts: **Advances in HIV Vaccine Development**

Oral Abstracts: **Late Breaking Trials of New ARVs and Microbicides**
The final two presenters are from CONRAD, and speak about the cellulose sulfate trials that are the subject of this month's HHS Watch *feature.*

Wednesday, February 28:
Oral Abstracts: **Epidemiology: Transmission Dynamics and Risk**
Includes two analyses of the circumcision data delivered by trial leader Ron Gray, data showing the usefulness of NYC bathhouses in assessing and sharing HIV knowledge, and other juicy topics.

Symposium: **Management of HIV and Sexual Risk in Adolescents**
The broad-based title aside, this session may seem arcane to many but looks at youthful immunology, vaccine trials, and the potential impact of the HPV vaccine.

***HSWatch**, a watchdog newsletter from CHAMP, monitors and reports on activities related to HIV prevention at Health and Human Services agencies, including CDC, NIH, HRSA and SAMHSA.*

HHSWatch is a resource for community members, policy advocates, researchers and anyone interested in more fully understanding and tracking the committees, panels and administrators whose recommendations and decisions affect our work.

HHSWatch is committed to providing an outlet for those concerned about infringements upon science-based HIV prevention and treatment, and will respect your wishes for confidentiality. If you are interested in contributing information or suggesting a story, please contact champ@champnetwork.org.

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