

September 2007 - Herpes Suppression: It All Seemed So Simple • Diaphragms: A Strangely Permeable Wall • Cellulose Sulfate: Two Times More HIV, or Not • Abstinence: Saying No Over and Over Again • Congress: Despite the Bad Reviews, Abstinence Continues its Run

Summertime, and the Research Isn't Easy

The path of true medicine never did run smooth. Biomedical HIV prevention found itself in a rocky patch this summer as researchers reported unexpected failures at two conferences (the [17th Meeting](#) of the International Society for STD Research [ISSTD]/10th International Union against STIs World Congress, and the 4th International AIDS Society [IAS] [Conference](#) on HIV Pathogenesis, Treatment and Prevention). Trials with such promising medical strategies as herpes suppression, the cellulose sulfate microbicide and the diaphragm as an HIV barrier all produced dismaying results. And then there were yet more reports that abstinence education has no meaningful effect. Still, the circumcision results and the availability of the vaccine against HPV, which conference presentations closely associated with HIV risk, illustrate the promise of adding medical interventions to behavioral ones in the struggle to contain the HIV epidemic. Circumcision and the HPV vaccine are one-time actions, though. The problematic results have involved new prevention strategies that require daily or pre-coital repetition.

King K. Holmes, the director of the University of Washington Center for AIDS and STDs, remained optimistic when he considered the widening possibilities for HIV prevention. He told *HHSWatch*, "It would be foolish to advocate solely abstinence and fidelity. We need to take our blinders off and offer combinations, like with HIV therapy. There is HAART [highly active antiretroviral therapy]; there should also be HARP – highly active retroviral prevention."

Herpes Suppression: It All Seemed So Simple

The connection between chronic genital herpes (HSV-2) and HIV risk has grown ever stronger.

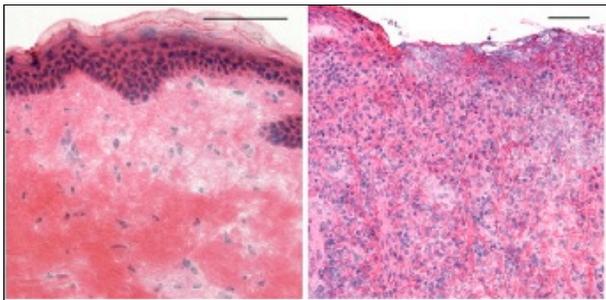
A 2006 meta-analysis of previous studies noted that preexisting HSV-2 infection tripled the risk of acquiring HIV in men and women generally ([Freeman et al. AIDS 2006](#)). (For gay men, the added risk seemed somewhat lower, while studies in female sex workers were ambiguous.) A new study ([Brown et al. AIDS 2007](#)) published at the time of the conferences calculated that 42% of the HIV contracted by Ugandan women and 65% of that contracted by Zimbabwean women could have been avoided in the absence of HSV-2.

There is a strong biological rationale that genital ulcers open a portal through the protective outer mucosal layers. These inflammatory zones, in addition, contain a concentration of the types of immune cells infected by HIV (see, for example, Donaghy et al. IAS 2007 abstract [MOPEA091](#)). The reverse is also quite likely true: genital herpes coinfection can increase infectiousness of persons who already have HIV. University of Washington researchers reported two years ago that genital tract HIV levels increased during periods of HSV-2 reactivation and were related to the quantity of herpes virus present ([Baeten et al. JID 2005](#)). At ISSTD, the same group reported on the effect of the anti-herpes drug valacyclovir on 20 otherwise untreated Peruvian HIV positive women. Both plasma and cervical HIV levels were moderately lower than in women taking placebo, by 45% and 56%, respectively (Baeten et al. ISSTD 2007 abstract [O-096](#)). A study of 136 HIV positive Burkina Faso women published similar results earlier this year ([Nagot et al. NEJM 2007](#)).

At ISSTD, the HIM (Health in Men) gay male cohort from Sydney led off the conference with unsettling findings (Fengyi et al. ISSTD 2007 abstract [O-001](#)). HIM observed a significant association between HSV-1 and HIV infection, but not between HSV-2 and HIV. HSV-1 generally

causes cold sores and can also infect the genital and anal regions. HSV-1 infection is often associated with oral sex. In contrast with HSV-2, anogenital HSV-1 is usually self-limiting. Nonetheless, its role in genital ulcer disease is thought to be growing, especially in such populations as MSM and college students ([Xu et al. JAMA 2006](#); [Lafferty et al. JID 2000](#); [Roberts et al. Sex Trans Dis 2003](#))

Stained Biopsies of Normal Skin (left) and Herpes Lesion (Right)



The herpes lesion biopsy shows a loss of the outer skin layer and invasion by immune cells.

Source: [Zhu, J. et al. J. Exp. Med. 2007;204:595-603](#)

The accumulation of STDs in high-risk populations may confuse the observed associations. Still, the HIM results imply that you have to test for and treat HSV-1 as well as HSV-2 (not to mention other STDs) to have an effect on HIV transmission. Fortunately, the same drugs attack both types of herpes. The big surprise this summer emerged from the initial large studies of herpes suppression, in both HIV positive and HIV negative women from northern Tanzania. Both studies involved acyclovir, an older, much cheaper version of valacyclovir. The HIV negative study is the first to test whether a continuous anti-herpes regimen would reduce the likelihood of contracting HIV in people already infected with genital herpes (Watson-Jones et al. ISSTD 2007 abstract [O-100](#)). The answer from this study was *no*: among the 821 women enrolled, the rate of contracting HIV was practically the same whether they received acyclovir (400 mg twice a day) or placebo (above 4 per 100 person-years).

Only about half the trial participants faithfully took their assigned medication, however. When considering just those who took more than 90% of their pills, the acyclovir recipients had a markedly lower HIV incidence rate compared to the women on placebo, 2.5 versus 4.3 per 100 person-years. But there weren't enough HIV cases within this subpopulation to make the results statistically significant.

Even more surprising were the findings from the accompanying cohort of 383 HIV+/HSV-2+ coinfecting women (Tanton et al. ISSTD 2007 abstract [O-99](#)). Here, daily acyclovir showed no significant benefit over placebo in reducing levels of either genital HIV or genital HSV-2. Again, only about half the cohort took more than 90% of their assigned pills. It would seem that a more potent herpes medication is called for. (The HSV-2 results were not reported for the HIV negative trial.) Certainly, better adherence to the medication schedule is necessary.

The need for successful, continual HSV-2 suppression to protect against HIV transmission was stressed by another report at ISSTD (Mark et al. ISSTD 2007 abstract [O-30](#)). Twenty-five HSV-2 + adults had their genital secretions checked four times a day for 60 days. HSV-2 was detectable on 20% of the days, representing 1.5 reactivations per month. More than half of these reactivations were asymptomatic and lasted less than 12 hours

The United States National Institutes of Health, meanwhile, is sponsoring a much larger multinational trial (in the U.S., Peru and southern Africa) comparing acyclovir with placebo in nearly 3,000 HIV-, HSV-2+ women and gay men. The trial's main goal is to see whether acyclovir reduces HIV acquisition, but it will also check on medication adherence and HSV-2 suppression. The chances of statistically significant results are enhanced by the larger trial population, which greatly helps to break down the results by adherence. There's a chance that the trial will confirm that acyclovir is not the right drug for this task. The results will not be available for another two to three years.

Summary of HIV Prevention Trial Results

Trial	New HIV infection ratio (95% confidence interval)*, intervention vs. placebo
HSV-2 suppression, daily acyclovir vs. placebo	1.12 (0.7-1.9)
HSV-2 suppression, participants with 90+% adherence	0.58 (0.3-1.4)
Diaphragm plus condoms vs. condoms alone	1.05 (0.84-1.32)
Diaphragm vs. condoms, no condom use 3 months prior to study entry	0.74 (0.46-1.19)
Microbicide, cellulose sulfate vs. placebo gel (CONRAD)	2.17 (1.06-4.45)
Microbicide, cellulose sulfate vs. placebo gel (FHI)	0.9 (0.3-2.5)

*The 95% confidence ratio (95% CI) is in parentheses. The infection ratio indicates the extent to which the trials' active agents block (rate ratio less than 1.0) or promote (rate ratio above 1.0) HIV transmission. The 95% CI is the range within which the ratios are likely to occur 95% of the time, due to the impact of chance fluctuations. If that range crosses 1.0, then the result is not considered statistically significant. The greater number of people in a trial, the narrower the 95% CI, and the more trustworthy the observed results.

Diaphragms: A Strangely Permeable Wall

One even larger trial yielded negative results that resonated through both conferences ([Padian et al., Lancet July 2007](#) and IAS 2007 abstracts [TUAC101 \[Govender et al.\]](#), [TUAC102 \[van der Straten et al.\]](#), [TUAC104 \[Wataadzaushe et al.\]](#), [TUAC105 \[Montgomery et al.\]](#), [WEPEC046 \[Milford et al.\]](#), [WESS304 \[Padian\]](#), and [WEPL103 \[Padian\]](#)). That trial enrolled 5,000 southern African HIV negative women to test the protective effect of a standard contraceptive barrier device, cervical diaphragms. The relatively thin cervical lining is considered a potentially sensitive area for HIV infection in women.

Half the trial participants received the diaphragms plus a neutral lubricating gel to ease insertion. Everyone received randomized repeated safe sex counseling with free condoms. They also were treated at study entry for curable (i.e. bacterial) STDs. Notably, 59% of enrollees tested positive for HSV-2 at enrollment.

After 24 months, the rate of HIV acquisition was virtually the same, about 4%, in the diaphragm and control groups. The incidence rates were also the same in each arm for women with

baseline positive tests for bacterial STDs or herpes. (But the HSV-2-positive women as a whole acquired HIV at a rate of almost 5%, compared with 3% for the HSV-2-negative women.) Reproductive tract infections were also equal in the diaphragm and non-diaphragm arms, as was the pregnancy rate.

Diaphragm use left something to be desired: Over the course of the study, women in the diaphragm arm reported using diaphragms at 73% of their most recent sexual activity. In any case, the high-adherence population did not show a reduced risk for HIV. One important difference between the diaphragm and control groups was condom use: After entry into the trial, women in both groups greatly increased their use of condoms during sex, but the non-diaphragm arm increased its rate still more. Yet, the groups' HIV rates were equal. There might be some protective effect after all.

But one suspects that participants' reports of their condom use were inaccurate: in the regular clinical surveys, 85% of the control group members reported that they had used condoms during their most recent sexual act, yet 6% of them acquired HIV. It doesn't add up. And here's another aspect that doesn't make sense:

The yearly pregnancy rate in both arms was 13%. You might well conclude from this trial that diaphragms are not protective against pregnancy as well as HIV.

This trial wasn't designed to compare diaphragms to no condoms, and didn't have the size and statistical power to look only at high condom adherers, either. A trial that focuses on the sizable number of women who are unable to use condoms due to lack of partner cooperation might provide some valuable insights.

When diaphragms are used for contraception, a spermicidal cream or gel is added. The cream was not used in this study for fear that it would prove irritating and, hence, promote HIV transmission. For HIV protection, it might be necessary to add an antiretroviral microbicide. An initial safety and acceptability trial of that combination recently took place in Madagascar with 192 women (Behets et al. ISSTD 2007 abstract [O-021](#) and Norris Turner et al. abstract [P-493](#)). That trial used the AcidForm microbicide, which keeps the cervicovaginal environment mildly acidic and hostile to HIV. An agent that directly kills HIV might be used instead. One example is tenofovir gel, now the subject of a 1,000-woman South African trial testing its value as a standalone microbicide.

Cellulose Sulfate: Two Times More HIV, or Not

The reason for searching out more focused anti-HIV microbicides is the failure of the cellulose sulfate (CS) microbicide testing effort (see [HHSWatch March 2007](#)). CS is a broadly active charged molecule that interferes with viral coatings and cellular membranes. Two major cellulose sulfate efficacy trials, taking place mainly in Africa, were closed down prematurely last January. One was sponsored by Family Health International (FHI) in North Carolina, the other by Virginia-based CONRAD. Preliminary results from the CONRAD trial appeared to show that cellulose sulfate was paradoxically linked to a higher rate of new HIV than placebo. Researchers presented both trials' complete results at the IAS conference, but they still do not have an explanation for what went wrong.

In the CONRAD trial, the HIV rate was 60% to 120% higher in the cellulose sulfate arm than in the placebo arm, depending on how you count the results. In contrast, the FHI cellulose sulfate trial observed no effect on HIV transmission from cellulose sulfate. HIV rates among the cellulose sulfate recipients were actually less than among those who used the placebo gel, although the trial stopped too early to tell whether this difference was statistically significant.

The contrasting results might be related to differences in the two trial populations: the CONRAD enrollees were somewhat older (30 years versus 23 years for the FHI group) and had sex more often (11 times per week compared with 6 times per week in the FHI trial). If cellulose sulfate causes minor vaginal disruption, it might have been aggravated by very frequent sex plus older age. This in turn would have led to more susceptibility to HIV.

Such possibilities are under investigation. Meanwhile, major trials of two similar-acting microbicides continue without reported difficulty.

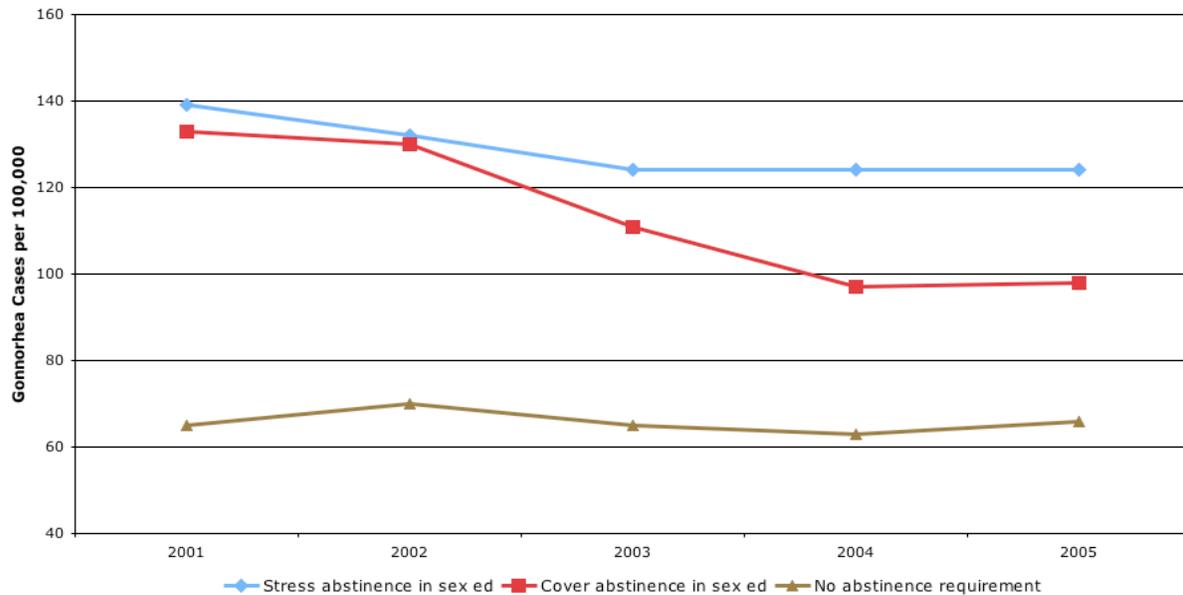
Abstinence: Saying No Over and Over Again

Abstinence is a prevention strategy that requires not only repeated attention, but also regular self-denial. Understandably, the poor results for abstinence education continue to pile up. In August, a review of U.S. abstinence education studies found that they made no difference in the HIV risk of U.S. youth ([Underhill et al. BMJ 2007](#)). The authors, from the University of Oxford's Centre for Evidence-Based Intervention, located 13 randomized controlled trials of abstinence interventions that explicitly focused on HIV prevention. The trials, appearing in eight papers, enrolled a total of 16,000 U.S. teens and young adults. Tellingly, the trials all evaluated vaginal intercourse; none looked at oral or anal sex or different sexual orientations. None of the trials detected any difference in vaginal sex rates or condom use when comparing the abstinence education students with those who received the comparison education (which might be the local schools' standard program, abstinence-plus, safe sex or no education at all).

HIV rates were not recorded and probably would be too small to analyze if they had been. Trials of seven abstinence programs did mention self-reported STD diagnoses. None could document any benefit from abstinence education over the comparison programs, and

one trial noted significantly higher rates of STDs among the abstinence education recipients. Pregnancy rates also were no different between the abstinence education recipients and the control groups in the eight trials reporting this measure.

Gonorrhea Rates according to State Sex Education Policy



Two CDC studies at ISSTD also described a lack of effect from abstinence education. The first noted that gonorrhea rates fell nationally from 2001 to 2005 (Hogben et al. ISSTD 2007 abstract [O-079](#)) and tried to relate that decline to differences in state education policy. It turned out that states with no policy regarding abstinence as part of sex education had by far the lowest gonorrhea rates and states that required a stress on abstinence the highest. In the middle were the states that required only that the curriculum “cover” abstinence. The decline in gonorrhea occurred almost entirely in this last group of states. Furthermore, the same trends were observed in older adults as in teenagers, indicating that sex education has little to do with the decline. It turns out that the proportion of African Americans in a state most determined where gonorrhea rates fell. Probably, other, unidentified factors are involved as well. Abstinence education really had

nothing to do with the drop. After adjusting for confounding factors, there was no difference between the three categories in the percentage answering yes to the survey question about ever having vaginal intercourse or an STD. The respondents with past comprehensive education did have a sharply lower risk of pregnancy compared to either of the other groups, 60% lower than the no sex education respondents and half that of the abstinence-only ones. Of course, the survey data depend on the reliability of the respondents. That’s a big weakness. Those who had abstinence-only education might be less inclined to reveal their sexual activity because they have been taught that it is undesirable. More fundamentally, it not clear that the survey respondents have a good grasp on what type of sex education they underwent in school. Still, this new study is the first nationwide summary of the fruits of abstinence-only education.

15-19 Year Olds' Reports of Sex Education compared with their Sexual Experiences, National Survey of Family Growth

Adjusted Rate Ratios with 95% Confidence Intervals

	Abstinence ed vs. no sex ed	Comprehensive sex ed vs. no sex ed
Ever had vaginal sex	0.82 (0.51-1.31)	0.70 (0.49-1.02)
Ever pregnant	0.74 (0.38-1.45)	0.39 (0.22-0.69)
Ever diagnosed with an STD	1.65 (0.57-4.76)	1.82 (0.67-5.00)

See remarks about 95% confidence intervals above. The only significant finding here is the reduction in pregnancies among respondents reporting comprehensive sex education.

In a provocative ISSTD talk (no abstract, see [Monday 2:30 symposium](#)), Dennis Fortenberry of the University of Indiana School of Medicine looked at first sex as a developmental milestone, giving a theoretical basis to the observations that programs urging teenagers to defer sex seem to have little ultimate impact. Fortenberry and his colleagues follow about 400 Indianapolis women, who are mostly African American, into their twenties. Every other three-month period, study participants keep sexual diaries that investigators review. Again the data is from self-reports, but the follow-up is rigorous and doesn't depend on distant memories.

Fortenberry's team has noticed that the women who have their first sexual intercourse in early adolescence, before age 14, have very intermittent sexual activity, with a high proportion of condom use. They have few sex partners until age 18, when there is a sudden burst that subsides by age 20. Women who start sex later have a still larger burst in sex partners centered at age 20. At this point, they catch up with their more advanced counterparts. When they reach their early 20s, the women have the same number of lifetime sex partners regardless of the timing of their sexual debut. By late adolescence, the period of highest sexual activity, condom use is likewise low for everyone. STD history turns out not to be much higher in the women with earlier first sex.

Fortenberry recalled that, in the past, he had been a prime proponent of programs to delay teens' sexual initiation. Now, he says, "The

enhanced STD risk of earlier first coitus may be overstated... There are different periods of risk but similar developmental trajectories."

Congress: Despite the Bad Reviews, Abstinence Continues its Run

Even with the Democrats in control, the House of Representatives has voted major extensions of the administration's abstinence education programs. In July, the full House passed the FY 2008 Health and Human Services (HHS) budget, including a \$28 million (25%) increase in community-based abstinence-only education grants. The Senate Appropriations Committee version of the budget specifies a \$28 million cut instead. The two versions will have to be reconciled in the fall. Also, rather than terminate the Title V grants to states for abstinence-only education, as widely expected (see [HHSWatch, April 2007](#)), the House voted to extend them for another two years. The Title V grants total \$50 million per year from the federal government plus \$37.5 million contributed by the states that distribute them.

As a "compromise," the House loosened the restrictions on the Title V grants so that they can now go to a program "which promotes abstinence and educates those who are currently sexually active or at risk of sexual activity about additional methods to prevent unintended pregnancy or reduce other health risks." Abstinence-plus, in a word. In contrast, the appropriation bill language defining the

community-based grants continues to specifically exclude grantees from providing "any other education regarding sexual conduct."

The new Title V language also demands that the programs provide only information not "unsupported or contradicted by the preponderance of the peer-reviewed scientific literature." Then it goes on to restrict the grants to programs "based on a model that has been demonstrated to be effective in preventing unintended pregnancy, or in reducing the transmission of a sexually transmitted disease, including the human immunodeficiency virus." There are no programs that currently meet this standard. At most, abstinence programs have been found to reduce teens' sexual activity for a year or two, without an effect on STD rates

(Brückner and Bearman, *J Adolesc Health* 2005). If the law were strictly enforced, nobody would qualify for the grants.

Of course, the Bush administration would be the final arbiters of the grant process. Then there are the 39 states that now accept Title V grants under HHS's strict abstinence-only guidelines. In the past, these bodies haven't been troubled much by scientific accuracy or evidence of effectiveness (see *HHSWatch*, November 2006). The new law may provide a new venue for debating abstinence education's merits, but it is difficult to see any change over the next two years in the way the Title V grants are administered, not to mention the larger community-based program.

This HHSWatch was written by David Gilden

HHSWatch, 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.



COMMUNITY HIV/AIDS MOBILIZATION PROJECT (CHAMP)
32 Broadway, Suite 1801 New York, NY 10004
tel. (212) 937-7955 x 10 Website: <http://www.champnetwork.org/>