



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

AVAC report on the 15th Conference on Retroviruses and Opportunistic Infections 3-7 February 2008

This is an AVAC report on and discussion of select data from the 15th Conference on Retroviruses and Opportunistic Infections (CROI) held February 3-7 in Boston. CROI is one of the major US-based AIDS science conferences and is held annually. This year's gathering included results from several HIV prevention trials, and saw intense discussion and critical analysis of the AIDS vaccine field.

Disappointment from one of two HSV-2 trials

Connie Celum (University of Washington) presented the results of an efficacy trial testing the hypothesis that ongoing, suppressive treatment of herpes simplex virus type 2 (HSV-2) would reduce the risk of HIV infection. In this study, HIV-negative people infected with HSV-2 were asked to take the antiviral acyclovir twice a day to suppress outbreaks of herpes infection. The rationale behind this trial and an ongoing companion trial (see below), comes from a range of studies that have shown a link between HSV-2 and risk of transmitting or acquiring HIV.

The HSV-2 study enrolled high-risk, HIV-negative, HSV-2 seropositive women at study sites in Zambia, South Africa and Zimbabwe. HIV-negative, HSV-2 seropositive men who have sex with men (MSM) were enrolled at study sites in Peru and the US. More than 3000 participants enrolled in the study; Celum presented analysis of data from 3172 individuals. In what she called a "surprising, disappointing and important result for HIV prevention," there was no difference in rates of HIV infection between individuals who received acyclovir and those who received a placebo.

As Celum explained in her introduction, the rationale for the trial was more than twenty years of epidemiological data showing a linkage between HSV-2 infection and susceptibility to HIV infection. There is also a wealth of data exploring the linkages between HSV-2 infection and rates of "shedding" of HIV in the genital tract. However, in this trial—known as HPTN 039—there was no observed benefit in terms of reducing risk of HIV infection.

The study also looked at the amount of HSV-2 DNA present in genital ulcers which emerged in study participants. (People with HSV-2 can have outbreaks even in the presence of suppressive therapy.) Here, there were no significant differences between the experimental and placebo recipients in Africa or Peru. In both of these settings, participants had comparable levels of HSV-2 DNA in their lesions during outbreaks. This is a somewhat surprising finding, since it is plausible to assume that ongoing suppressive therapy might dampen or alter the level HSV-2

replication during an outbreak. A difference along these lines was observed among the MSM population in the US but not in other populations.

Celum discussed possible explanations for the study findings. It is possible that the HSV infections among people in the trial responded less well to acyclovir (as measured by rates of genital ulcer disease and quantity of HSV) than trial planners had anticipated at the outset. She also said that perhaps they had underestimated HSV-2 in terms of frequency of reactivation and genital immune response. These data may also point to gaps in our current understanding of genital tract immune activation. Ongoing suppressive therapy might not be sufficient to change the local immune environment in the genital tract—the site of sexual transmission. Perhaps adherence was not as high as the trial's measures estimated. (Participants were counseled on the importance of adhering to the study regimen, and Celum reported high rates of adherence (>94%) based on self-report and pill count, which were the two adherence measures used in the study.) Or perhaps combination strategies might be more effective.

Celum closed with an important reminder that additional ongoing trials are asking other questions about the link between HSV-2 and HIV—and that these studies could still yield positive results about using HSV-2 treatment as an HIV risk reduction tool. Specifically, she mentioned a study known as “Partners in Prevention,” which is looking at whether ongoing suppressive treatment in HSV-2, HIV co-infected individuals reduces their risk of transmitting HIV to sexual partners. There is also work going on to explore the impact of HSV-2 treatment on HIV disease progression, and on viral setpoint among the HPTN 039 participants. Data from the “Partners in Prevention” study are expected in 2009.

The web cast of the presentation of this study, and the other CROI presentations discussed in this report, here can be found at

http://www.retroconference.org/2008/data/files/retro2008_frameset.htm.

Questions and concerns from a male circumcision study

CROI featured two presentations of data from studies of male circumcision that were conducted in Rakai, Uganda. One of the presentations shared additional data from a trial that evaluated the safety and efficacy of male circumcision in HIV-positive men. This trial, which was conducted by the Rakai Health Sciences Program and funded by the Bill & Melinda Gates Foundation, asked whether circumcised, HIV-positive men were less likely to transmit HIV to their female sexual partners, as compared to uncircumcised, HIV-positive men. It also gathered information on the safety of the surgical procedure in HIV-positive men, and on the impact of male circumcision on rates of other sexually transmitted infections.

In December 2006 this study stopped circumcisions in HIV-positive men based on a Data and Safety Monitoring Board finding of futility for the trial—meaning that if it continued to its scheduled end date, it would not have the statistical power to answer the study question. The same DSMB also noted a trend towards increased rates of HIV transmission from these men to their female partners. This trend appeared most pronounced in women whose male partners resumed sex before wound healing was completed.

Because the numbers of infections in women were so small, it was difficult to tell whether this trend was “real” and in fact related to the intervention, or whether it was due to chance. Maria Wawer, one of the principal investigators of the trial, presented additional data, which she characterized as “preliminary.” These data came from longer-term follow up of men who had been circumcised before the 2006 DSMB recommendation. The trial team has also revised the protocol to include more intensive counseling and post-surgery follow-up of the HIV-positive men to emphasize the importance of abstinence until wound healing. More data will come from this population.

Looking at rates of male-to-female transmission, Wawer presented data from a subset of 161 HIV-positive men (93 circumcised, 68 uncircumcised) who were enrolled at the same time as their HIV-negative female partners. In this small group, the incidence of HIV infection in female partners was 14.4% in circumcised men and 9.1% in uncircumcised men. Wawer described this difference as not significant but suggesting increased risk among female partners of circumcised, HIV-positive men. Additional analysis showed that this trend was strongest among men who resumed sex prior to wound healing. (Wawer noted that HIV-positive men were more likely to be married. This suggests that the possible relationship between marital status and likelihood of resuming sex prior to wound healing should be explored in scale-up programs.)

The same study also found a significant reduction in frequency of genital ulcer disease in HIV-positive circumcised men versus uncircumcised men. The Rakai team looked at percentage of circumcised volunteers who were healed by 30 days post surgery. Here, they compared data from the HIV-positive men’s study and a separate study, funded by the US National Institutes of Health, which looked at male circumcision in HIV-negative men. A significantly lower proportion of HIV-positive men were healed by 30 days, as compared to HIV-negative men, suggesting a slower rate of wound healing in HIV-positive men.

These findings raise some critical concerns about strategies for rolling out male circumcision for HIV prevention. At present, the World Health Organization’s analysis of programme implications related to male circumcision state that every effort should be made to link voluntary counseling and testing (VCT) to male circumcision programs, but that it should not be a requirement. Likewise, the WHO analysis says that HIV-positive status or unknown HIV status should not be a barrier to men looking to obtain male circumcision from medical points of service.

Restricting male circumcision to HIV-negative men could stigmatize uncircumcised men as HIV-positive, and lead HIV-positive men to seek surgeries from providers who lack training and materials for safe, sterile surgery. Wawer concluded her presentation with a strong recommendation that all men who are circumcised, regardless of HIV status, be counseled about the importance of delaying sex until wound-healing, and of continuing to use condoms throughout.

The webcast for this presentation and for others dealing with the impact of male circumcision on HSV-2 acquisition in HIV-negative men; and on the global scale-up effort can be found at http://www.retroconference.org/2008/data/files/retro2008_frameset.htm.

For AVAC, these results underscore the necessity that all male circumcision programs directly address the issue of women's increased vulnerability to infection by recently-circumcised, HIV-positive men. Specific programs which emphasize couples counseling and VCT should be piloted, along with clear and consistent messages that state the risks and benefits of male circumcision for HIV-positive men and their partners. AVAC will continue to follow this issue carefully with analysis and recommendations. [Click here](#) for AVAC's recent publication on male circumcision for HIV prevention.

AIDS vaccines, the STEP study and possible ways forward

STEP study update

AIDS vaccines are just a part of the overall CROI agenda but this year, as the vaccine field continued to take stock in the wake of the failure of the Merck candidate, they earned considerably more attention in plenary sessions—and heated conversation in hallways and satellite meetings.

On the STEP front, principal investigators Mike Robertson (Merck and Co.) and Susan Buchbinder (San Francisco Department of Public Health) gave updates which expanded slightly on the data presented at a December 12 public meeting held in Bethesda, Maryland (see http://avac.org/ANRS_mtnng_summary.htm for AVAC's report of the meeting). Specifically, Merck's Mike Robertson presented preliminary data on the immune responses in STEP study participants. As had been presented before, one of the unexpected findings from the STEP study was that vaccine recipients were more likely to become infected than placebo recipients, and that this increased risk, or "enhancement" effect, was associated with pre-existing immunity to adenovirus type 5 (Ad5). Ad5 is cold-causing virus which is used, in a disabled form, as a vector in the Merck vaccine candidate.

Robertson's presentation reviewed data on immune responses in vaccine and placebo recipients with high and low levels of pre-existing immunity to Ad5, as measured by antibody titers. There is no clear explanation for the apparent enhancement—and there may never be. Immune responses to the vaccine were similar in infected and uninfected individuals. As described at the December 12 meeting, people with high Ad5 titers had higher levels of activated T cells, compared to individuals with low Ad5 titers. Activated T cells are targets for HIV so, in theory, a higher level of immune activation could increase susceptibility to HIV infection. However this was true for both vaccine and placebo recipients and so is not, in itself, an explanation for the apparent enhancement effect in vaccine recipients.

STEP co-principal investigator Susan Buchbinder presented additional data from the trial, including the first results of multivariate analyses. A multivariate analysis is a statistical analysis in which multiple variables are analyzed simultaneously, with correction for confounding associations. It is a strategy used to attempt to calculate the potential contribution made by each variable to an observed outcome.

One of the findings that she discussed—which also received considerable attention in the media—was that the increased risk of HIV infection was most pronounced in uncircumcised men with pre-existing immunity to Ad5. Circumcision status alone also had an impact on susceptibility: the estimated relative risk of HIV infection was higher in uncircumcised versus

circumcised men regardless of pre-existing Ad titer. Circumcised men with no pre-existing immunity had equivalent risk whether they were in the placebo or the vaccine group.

What's the bottom line from this? Lack of circumcision and higher Ad5 titer levels both seem to increase participants' risk of acquiring HIV and the contributions of each have not been teased apart, and may not be even in further analysis. Buchbinder said that because so many of the men with high Ad5 titers were also uncircumcised, it is difficult to tell whether there is increased risk among men with one but not both risk factors ("either/or Ad5 seropositive or uncircumcised"). There are other factors which were not explored in the multivariate analyses to date, but which will be examined in coming months. These include the potential role of infection with HSV-2, background genetic make-up (HLA genotype), immune responses in semen and other issues.

At this point, with many questions outstanding, there is still a trend towards increased infections in vaccine versus placebo recipients which has not been explained by any other variable. More information will become available as time goes on. All available information must be carefully considered in developing the redesigned protocol for PAVE 100 a planned efficacy trial of a combination vaccine strategy which contains a DNA vaccine with a different Ad5-based vaccine. (See below for more information.)

Two views on next steps

Ever since the September announcement that the Merck candidate had failed in the STEP study, the question hanging over the AIDS vaccine field has been: Where to from here? Two back-to-back presentations, made by Ron Desrosiers (Harvard University) and Neal Nathanson (University of Pennsylvania), tackled this critical question.

For both Desrosiers and Nathanson, the answer to the question "where to from here?" boiled down to: back to basic science. Desrosiers enumerated the major outstanding challenges facing AIDS vaccine development—from viral diversity, to the elusive nature of broadly-neutralizing antibodies, to the lack of candidates providing significant protection in many non-human primate models. As he acknowledged, many of his main points harkened back to a presentation he made four years ago, at the same conference.

Nathanson's presentation likewise emphasized the challenges and the long time horizon for identifying an effective vaccine. He used his talk to acknowledge the strides made in addressing the epidemic through existing interventions, including antiretroviral treatment and comprehensive HIV care and prevention. Slides such as Nathanson's enumerating the benefits of ARV rollout in Botswana have been a rarity in AIDS vaccine presentations. Whatever direction the field takes, it is critical that AIDS vaccine stakeholders heed this broader perspective and explicitly acknowledge the need to scale up existing prevention and treatment strategies.

The Nathanson-Desrosiers presentations generated a flurry of media coverage; articles in [Science magazine](#) and the [San Francisco Chronicle](#) gave further context for the opinions shared at CROI. In January, Desrosiers, along with 13 other scientists, wrote a letter to NIAID head Tony Fauci calling for a major re-examination of priorities and scientific agendas within the AIDS vaccine field. As part of the response to this call, NIAID will be hosting a vaccine "summit" currently planned for March 25.

From an AVAC perspective, both Nathanson and Desrosiers identified many of the scientific challenges that are the major obstacles to developing an effective AIDS vaccine. In this respect, they covered challenges which are widely recognized in the field. The key question is whether and how these challenges can be surmounted.

Both Nathanson and Desrosiers called for a step back from clinical trials, and a major investment in basic scientific research. Here, there is need for caution. Human clinical trials have and will continue to play a role in shedding light on the path to an effective vaccine. These can include exploratory Phase I studies, studies tackling specific questions about immunology and vaccine design, as well as larger test of concept and efficacy trials.

It is also important to place the calls for basic science in the context of ongoing work in this arena. The emergence of major, discovery-oriented scientific consortia such as the Gates-funded Collaboration for AIDS Vaccine Discovery (CAVD) and the NIH-funded Center for HIV/AIDS Vaccine Initiative (CHAVI) are evidence of an emphasis on preclinical and basic scientific research as a priority alongside clinical trials which had begun in the field even before the disappointing STEP study result.

Discussion of these initiatives was missing from both talks—and would have helped add depth to the suggestions that basic scientific research be a priority. Are CAVD, CHAVI and other consortia such as those convened by the International AIDS Vaccine Initiative (IAVI) set up in a way to address some of the fundamental challenges facing AIDS vaccine research? Are the agendas—which existed before the STEP result—still on track? These questions, which were not raised in the plenaries described above, are perhaps more critical than the query of whether a vaccine is possible at all.

It is critical to view initiatives like CAVD and CHAVI not only in light of the questions they seek to answer, but also in terms of how they do, or do not, provide opportunities for new researchers to make a career in the field of AIDS vaccine research. Given the long timeframes and the outstanding scientific challenges, it is essential that new, young researchers in an array of fields have access to funding and clear career paths in AIDS vaccine research which will make it both possible and attractive to start and remain active in research that contributes to the search.

Another question—glancingly addressed in Nathanson's presentation—was whether the planned PAVE 100 efficacy trial should go forward. Is the VRC strategy candidate that the PAVE 100 trial looks to test, sufficiently different from the Merck candidate? And, as Desrosiers asked, can the field sustain additional failures in efficacy trials and still maintain support from donors, volunteers and the scientific community?

With regard to the former question: AVAC's view at this time is that scientific arguments for evaluating the VRC strategy which have been presented so far are compelling enough not to be easily dismissed. However decisions about where the trial takes place and in what populations are complex and must be made in light of an evaluation of feasibility, community acceptability, a clear product development pathway and a realistic assessment of the human and financial resources needed to conduct a trial in a reasonable timeframe.

As to the latter question, AVAC argues that the answer is yes, the field can sustain additional negative results in efficacy trials – and the history of vaccine and drug development tells us that there may well be more trials with negative results. There is almost no doubt that the field can and must prepare for additional efficacy trials with negative results on the road to a successful vaccine. Does this mean that PAVE 100 should go forward? Not necessarily. But there is no guarantee that any amount of renewed basic scientific inquiry will yield a sure-shot vaccine. These kinds of scientific setbacks are, quite simply, part of the equation.

How the field grapples with failure was one of the subjects addressed at a dinner and discussion hosted by AVAC at CROI. We brought together a broad range of stakeholders in what must be one of many opportunities to reflect on the implications of the STEP trial and think creatively and constructively about the future directions of the field and specifically about whether PAVE 100 should go forward at all, and, if so, how should it be best designed to move the field forward.

What Next? No simple answers, no simple solutions

As AIDS vaccine and prevention research advocates, we are of course disappointed by the results presented at CROI. The dedication, time and hope invested by scientists, clinicians, participants and their communities are immeasurable and invaluable; and all involved had wished fervently for positive results in the search for new biomedical prevention options to add to the existing, proven strategies available worldwide.

Having made the case that the field must brace for failure, it is also important for us to acknowledge just how disappointing and challenging recent events have been in the HIV prevention research arena. The failure of the HSV-2 susceptibility trial, of the [diaphragm study](#), of [cellulose sulfate](#) and SAVVY microbicides and of the Merck candidate underscore the difficulties inherent in identifying new biomedical strategies.

Looking ahead, there are a range of pre-exposure prophylaxis trials that will provide additional information about PrEP as a risk-reduction tool. The trial of HSV-2 treatment to reduce infectiousness is also ongoing, as are new studies of ARV-containing microbicides and the Thai prime-boost HIV vaccine trial.

There are no simple solutions or slogans that can be applied to the current situation. Yes, we must continue searching for new biomedical prevention options. Yes, we must be honest about when it is time to reevaluate the strategy behind our search. And yes, we must be prepared for a long road ahead.

But we must recognize that a meeting like CROI fails to feature the voices of people hardest hit by the epidemic. We must keep in mind that abandoning the search for strategies to supplement condoms, clean needles and other strategies would be abandoning individuals who cannot access or negotiate these and other proven interventions. More strategies are needed and we believe more will be found.

The next weeks and months will bring critical announcements and decisions on vaccines, microbicides and important lessons about the implementation of male circumcision alongside other prevention strategies. As the robust debate and, frankly, emotional discussion at CROI underscored, all of these developments will require open minds, clear communication and broad consultation to ensure that the views of the range of communities invested in HIV prevention are heard.

Here at AVAC, we'll continue to keep you informed of emerging news, our evolving analysis and critical questions facing the field. Please contact us with questions or comments (advocates_network@avac.org). We look forward to hearing from you!