Two Months of AIDS Reports: Critical Lessons for HIV Biology and Medicine

January 01, 2008
By AIDS Reader [1]

Reviewing just a 2-month interval of HIV/AIDS-related publications and announcements, from mid-September to mid-November of 2007, produced discouraging news in 3 key areas: vaccine development, female-initiated barrier protection, and HIV treatment in the resource-poor world.

Reviewing just a 2-month interval of HIV/AIDS-related publications and announcements, from mid-September to mid-November of 2007, produced discouraging news in 3 key areas: vaccine development, female-initiated barrier protection, and HIV treatment in the resource-poor world.

VACCINES
“Translating uncertain data into policy is always a difficult issue” is how Gary Nabel, director of the Vaccine Research Center at the NIH, succinctly characterized the new issues complicating the design of AIDS vaccine candidates. Concerns arose following not only failure of the latest product but also its association with an increased risk of HIV acquisition.

The STEP study (also known as the HVTN 502 or Merck V520-023 study) was a multicenter, randomized, double-blind, placebo-controlled phase 2b AIDS vaccine trial, which began in December 2004. The study enrolled 3000 HIV-negative volunteers aged 18 to 45 years at high risk for HIV infection and was conducted in 15 US and 3 Canadian cities as well as study sites in Peru, Brazil, Haiti, the Dominican Republic, Jamaica, and Australia. Participants were given 3 doses of vaccine over 6 months and followed up for a mean of 13 months.

Most of the men in this study were men who have sex with men. They were evenly divided between the experimental and control groups based on circumcision status (about 65%) and prevalence of unprotected receptive or insertive anal intercourse. A few months later in South Africa, another trial—Phambili—enrolled 801 men and women, aged 18 to 35 years, most of whom were heterosexual.

The vaccine used in both trials was a replication-defective adenovirus type 5 (Ad5) vector including, in a 1:1:1 admixture, 3 Ad5 viruses, each containing codon-optimized, near consensus transgenes for 1 of 3 HIV-1 clade B gene products, Gag, Pol, or Nef. The placebo was the vaccine dilution buffer. The STEP Study Oversight Committee halted all trials of the vaccine on September 21, 2007, after it became clear that it failed to protect against infection and may have even promoted it. Among the 741 volunteers in the V520 trial who received at least 1 dose of the 3-dose vaccine series, 24 cases of HIV infection were observed versus 21 cases in the 762 volunteers who received placebo. In the subgroup, those who had received at least 2 vaccinations and who were HIV-negative for at least the first 12 weeks of the trial, 19 infections were seen in the 672 who received vaccine versus 11 among 691 who received placebo.

In addition, the vaccine did not reduce the viral load in those who became infected. The mean plasma HIV RNA levels 8 to 12 weeks after infection were 40,000 copies/mL in the vaccine group and 37,000 copies/mL in the placebo group. Of additional interest, even though about 40% of the trial participants were female, only 1 woman developed HIV infection.

These data present some extraordinary challenges, none with particularly salutary consequences. First, there is the potential for heightened difficulty in recruitment of future volunteers, related not only to the unexpected outcome of this trial but also to the adverse outcomes associated with another biomedical means of HIV prevention, microbicides. Trials of 2 vaginal microbicide gels, nonoxynol-9 and cellulose sulphate, led to more infections among those using the products than among those receiving placebo. “This is my worst nightmare,” said Glenda Gray, the principal investigator for the Phambili trial. “I haven’t slept for days. I have a headache. I’m ready to resign from trials for the rest of my life.”

Second, there is the issue as to whether ongoing trials of other viral-based vectors used to augment immunity to HIV gene products might carry a similar risk. It is possible that vaccination in those with preexisting immunity may have triggered production of activated CD4+ T cells, the preferred host...
cell for HIV infection. Those with preexisting immunity to Ad5 were more likely to have become HIV-infected after receiving the V520 vaccine. Among 778 male volunteers who had a high level of preexisting adenovirus immunity, 21 of those receiving the vaccine developed HIV infection versus 9 in the placebo group. For those with Ad5 antibody titers greater than 1000, the relative incidence of HIV infection compared with those with lesser immunity in the vaccinated group was 3.5. Although the statistical analysis of these results is ambiguous because the study was not designed to evaluate the potential for an increase in infections among those vaccinated, the outcome is extremely disconcerting. Those with high Ad5 antibody titers also had higher levels of CCR5-expressing, activated CD4 T cells (CCR5 being the primary coreceptor for HIV).

The largest current viral vector-based trial is a phase 3 study in Thailand of vCP1521, sponsored jointly by Merck and Sanofi-Aventis. It involves a recombinant canarypox carrying gag and pol sequences along with gp120 from HIV-1 clade E. Carryover of the unanticipated vaccine-related enhancement seen with V520 to other types of viral vector-based HIV immunizations would be catastrophic.

Recent data also highlighted other vaccine issues. A study by the CDC of 13 diseases that children are routinely vaccinated against found that death rates in the United States for 9 of these have fallen by more than 90% since the vaccines were approved, and in the cases of smallpox, diphtheria, and polio, by 100%. Only invasive pneumococcal infection remained a problem, with an estimated 6500 deaths before vaccine approval, and 4850 deaths after its introduction. This is great news. But immunization against another potentially vaccine-preventable disease, cervical cancer, is facing resistance. Cervical cancer accounts for more sexually transmitted virus-based deaths among US women than does HIV infection; there were 4921 annual deaths from cervical cancer versus 4234 from HIV infection in one survey. Of US women aged 14 to 59, 26.8% are infected with the human papillomavirus (HPV), some strains of which are linked to cervical cancer and genital warts. Yet opposition to widespread use of the first FDA-approved HPV vaccine is growing, based not only on cost and reimbursement issues but also on misinformation concerning the role of sexual promiscuity in HPV acquisition. Much of the public fails to realize that a single unprotected sexual encounter can lead to high rates of infection.

**FEMALE CONDOMS**

When first introduced, the female condom, which has different names in different countries, such as Reality and Femidom, was hailed as one means to bring an HIV prevention strategy under the control of the susceptible partner. Originally introduced in 1992, it consisted of a loose-fitting polyurethane sheath and 2 flexible polyurethane rings. One ring lies inside the vagina at the closed end of the sheath and serves as an insertion aid and internal anchor. The outer ring forms the external edge to cover part of the labia, with the sheath hanging out about 1 inch. But acceptance wasn’t great. “‘Fun with a windsock’ is how 30-year-old marketing executive Louise Sandler recalls her first and only Femidom experience, in 1993, at university. ‘My boyfriend was up for it because it meant he wouldn’t have to wear a condom. But once was enough; first off, I couldn't get it in.’”

Given these problems and its relatively high price, only about 12 million female condoms were made available annually by the global health sector worldwide, equal to only 0.2% of the number of male condoms made available in this manner. Cost is a major issue. Although targeting of female commercial sex workers led to significant, if small, increases in consistent female condom use in several African countries, there was a high degree of its substitution for male condoms. This was associated with a cost per “additional consistent condom user” at a program level of $2160. It was therefore recommended that governments should limit promotion of the female condom in populations already successfully using the male condom. Cost was addressed some 13 years after the introduction of the first female condom (FC1) when a second-generation female condom (FC2) was developed for resource-poor countries. It is made of a different material, nitrile, with a concomitant reduction in average bulk quantity unit price from $0.72 to $0.22.

Another key issue is design. To increase acceptability of the female condom for use during vaginal intercourse or anal intercourse for men and women, problems related to difficulties with insertion as well as slippage and noise during intercourse must be solved. So it was quite disconcerting to learn that a major redesign may go nowhere. The next generation—the FC3 model—is made of a softer, thin-film polyurethane to better transmit warmth. It is easier to insert and “moves more like a vagina,” with adhesive foam dots along the inner sheath permitting expansion along with the vagina. But the FDA places female condoms in a Class 3 category, along with heart valves and pacemakers; the male condom bears only a Class 2 designation. Class 3
mandates expensive clinical testing, which no major AIDS funder seems willing to cover.\textsuperscript{17}

**Antiretroviral Therapy in the Developing World**

Most clinical trials in the resource-poor world demonstrate efficacy of antiretroviral therapy comparable to that in the resource-rich world. This is partly due to excellent medication adherence, rivaling, at least in the short term, that seen in the developed world. But a recent analysis of 32 studies involving over 74,000 patients in 13 African countries from 2000 to 2007 found that compared with the 80% patient treatment retention rate in the West after 2 years, Africa had only a 60% retention.\textsuperscript{18} Of those ostensibly dropping out of therapy, 40% had died and 56% were lost to follow-up. Conceivably, some of the latter could have resumed treatment elsewhere, although other studies in Africa and Asia indicate that 40% of patients stopping an antiretroviral regimen—usually because of drug adverse effects, not clinical failure—do not start another one.\textsuperscript{19}

**References:**
