Small Steps Forward in HIV Prevention

October 29, 2007 By David Evans

Slow but steady progress is being made on several HIV prevention fronts, say researchers in a special symposium on HIV prevention at the 11th European AIDS Conference. While the recent failure of the Merck HIV vaccine continues to cast a dark shadow on the world's immediate and long-term prevention needs, other vaccines in development may still hold promise. And there's much discussion surrounding other biomedical prevention approaches as well, said several speakers, notably pre- and post-exposure prophylaxis (PEP and PrEP) and male circumcision.

The first to address the symposium, Giuseppe Pantaleo, MD, of the department of medicine at the Centre Hosptialier Universitaire Vaudois (CHUV) University of Lausanne , Switzerland, put into perspective the recent failure of the Merck HIV vaccine. The compound, known as MRK Ad5, was found to offer no protection against HIV infection or disease progression in the large STEP trial. In fact, recent reports indicate that HIV-negative participants who received the vaccine may be more susceptible to HIV infection than those who received the study's placebo.

MRK Ad5 does not stimulate the production of antibodies against HIV—unlike most traditional vaccines—but instead triggers another part of the immune system, CD4 cells, to respond to the virus (for more information see, "Lessons From a Vaccine Failure").

Dr. Pantaleo explained that the Merck vaccine's vector—a virus or bacteria used to deliver the active part of a vaccine, in this case an adenovirus (responsible for the common cold)—may have caused the immune system to overreact, hence the increased risk of HIV infection among those who received the active agent. There are a couple of potential explanations for this. First, it may have created a large pool of activated CD4 cells that were especially vulnerable to HIV infection. Alternatively, it may have caused the immune system's regulatory arm, whose purpose is to rein in an overactive immune response, to shut down production of CD4 cells targeting the particular fragments of HIV delivered by the vaccine.

Dr. Pantaleo recommends that similar vaccines waiting in the wings should still be tested, as they differ from the Merck vaccine. The two most promising candidates yet to be tested use a pox virus as the vector, which may cause the immune system to react differently than it did to the adenovirus vector.

Dr. Pantaleo also explained that the vaccines waiting to be tested employ a different immunization strategy, known as DNA priming, which involves exposing the immune system to pieces of HIV's DNA before administering the actual vaccine candidate. In an experiment where researchers exposed macaque monkeys to an especially virulent form of the monkey version of HIV (called

SIV), the vaccine candidate protected the animals against infection only if a DNA prime had been used first.

In addition, Dr. Pantaleo commented that some scientists feel that we may need to go back to research on antibody-based vaccines and learn how to use them in combination with the CD4-based vaccines if we are ever to come up with an immunization strategy that will be sufficiently protective against HIV infection.

A presentation by Joep Lange, MD, PhD, of the University of Amsterdam in the Netherlands, focused on two other biomedical prevention strategies: post-exposure prophylaxis (PEP), where a person is given antiretroviral drugs after being exposed to HIV, and pre-exposure prophylaxis (PrEP), where a person is given drugs before and immediately after exposure to HIV.

Dr. Lange first reviewed data from cohorts involving medical workers who received PEP after occupational exposures. In these studies, where it would have been unethical to give some people a placebo as a control, there has been evidence that PEP offers some degree of protection. He also summarized studies in which Retrovir (zidovudine) was given to infants after being born to HIV-positive women who, against treatment guidelines, did not themselves take the drug either before or during labor. In these trials, transmission was reduced by about a third.

With PrEP, only one study has been completed thus far. It was conducted in Ghana and pitted PrEP with Viread (tenofovir) against a placebo. Unfortunately, this trial—which was originally designed to be much larger, with people from two other African nations, Nigeria and Cameroon—was reduced in size primarily because of politics. While there was some evidence that PrEP reduced the number of infections, with two HIV infections in the Viread group compared with five infections in the placebo group, the trial ended up being too small to generate definitive conclusions.

Several large PrEP studies are moving, involving high-risk sex workers, men who have sex with men (MSM) and in injection-drug users. Some are using Viread monotherapy, whereas others are using Truvada (tenofovir plus emtricitabine). Results from these trials are expected next year and in 2009.

Dr. Lange concluded that the support for PrEP trials has been appallingly limited, compared with the financial resources that have been allocated for the study of vaginal microbicides and vaccines. Although vaginal microbicides potentially offer women an empowering method of HIV prevention, he contends, so does PrEP. And since microbicides won't be of any use to injection-drug users—Dr. Lange adroitly commented, "You can't put a microbicide or a condom on a syringe"—PrEP may be one of the most promising prevention tools in development.

One of the final presentations, by Bertran Auvert, PhD, from the Institute National de le Santé et de la Recherche Médicale (INSERM), highlighted the connection between male circumcision and decreased rates of HIV transmission. He began his talk by showing how the prevalence of HIV cases in Africa almost perfectly correlates to the rates of circumcision in each country, with HIV rates highest in those countries where circumcision is most rare.

Auvert went on to describe African studies in which half of the men were circumcised and the other half were not. These studies were stopped early because it became clear, soon after they were started, that circumcision was reducing new infections by nearly 60 percent. No other

prevention method has produced such impressive results.

In an effort to counter the argument that circumcision will not be an effective prevention strategy in countries where the procedure is not culturally acceptable, Dr. Auvert reported results from surveys conducted in many such countries, finding that men considered the procedure acceptable if it was known to cut HIV risk. He also gave examples of countries, such as South Korea, where circumcision became the norm within a relatively short period of time. He concluded, with a wry comment, that men would gain a strong incentive to become circumcised if women would have sex only with circumcised men.
