Study confirms early elevated HIV infection risk in some Step Study participants

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A long-term follow-up analysis of participants in the Step Study, an international HIV-vaccine trial, has confirmed that certain subgroups of male study participants were at higher risk of becoming infected after receiving the experimental vaccine compared to those who received a placebo. The vaccine used in the study did not contain the HIV virus, but it did contain HIV genes which were delivered to cells using a vector that employed a type of cold virus known as adenovirus serotype 5 (Ad5).

Of the 1,836 men examined in this study, 172 became infected with HIV. Within 18 months of enrollment or one year after the last vaccination, men who had neutralizing antibodies to Ad5 or who were uncircumcised, or both, had a two- to four-fold increased risk of acquiring an HIV infection, according to findings published in the May 4 online edition issue of the Journal of Infectious Disease.

However, the study also found that the risk level waned after about 18 months to be equal to that of volunteers who received a placebo.

Why this association occurred, what the biological mechanisms were and why the risk of infection lessened with time are unknown and require more study, according to Ann Duerr, M.D., a member of the Vaccine and Infectious Disease Division of Fred Hutchinson Cancer Research Center, who led the data analysis.

"There seems to be some kind of biologic phenomena that affects infection risk," she said.

The current study indicated that self-reported risk behaviors, such as unprotected sex, did not differ significantly between the vaccine and placebo arms of the Step trial.

The research also confirmed there was no elevated risk of infection in vaccinated men who were circumcised and who were Ad 5 seronegative (men who had no neutralizing antibodies to the adenovirus vector used in the vaccine). An earlier interim analysis of the Step Study data, done after immunizations in the vaccine trial were halted in 2007, also detected this relationship between Ad5 sero-status and vaccine-associated HIV risk. Today, only men who are circumcised and Ad5 seronegative are eligible to receive experimental HIV vaccines that use the adenovirus serotype 5 as a biological delivery mechanism.

Duerr said scientists need a better understanding of what happened biologically to men who became infected, before those who are uncircumcised or seropositive for Ad 5 are enrolled in future vaccine trials in which the adenovirus serotype 5 vector is used.

Ad 5 is used as a vector because it elicits a strong immune response by CD8 T cells. These cytotoxic T lymphocytes are thought to be responsible for controlling HIV infection.

In the current study, researchers analyzed data from male Step Study participants who enrolled in a trial that provided follow-up for up to four years after they enrolled in the Step study, or until Dec. 31, 2009, whichever came first.

The Step Study enrolled 3,000 male and female volunteers in North and South America, the Caribbean and Australia between 2004 and 2007. Injections in the study were halted in September 2007 after researchers detected a lack of effectiveness by the vaccine to prevent HIV acquisition or reduce HIV viral load in infected participants, and a

higher-than-expected number of HIV infections in certain subgroups of vaccinees.

More information: "Extended follow-up confirms early vaccine-enhanced risk of HIV acquisition and demonstrates waning effect over time among participants in a randomized trial of recombinant adenovirus HIV vaccine (Step study)." *Journal of Infectious Disease*.

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