

Analysis of Step Study Confirms Early Vaccine-Enhanced Risk of HIV Acquisition

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The development of a prophylactic HIV vaccine remains one of the best long-term strategies to prevent HIV infection and AIDS. A phase 2B trial, the Step study, examined the efficacy of an HIV vaccine consisting of a replication-defective adenovirus serotype 5 (Ad5) vector with HIV clade B subtype gag/pol/nef inserts (HIV genes). This vaccine had previously been shown to elicit high T cell responses in humans, and the Step study tested whether an Ad 5-vectored vaccine could reduce viral load after infection and/or prevent HIV acquisition. Between December 2004 and March 2007, three thousand participants were enrolled in the study and stratified based on pre-existing neutralizing antibody titers to the Ad 5 vector. The participants received vaccine or placebo at baseline, four, and 26 weeks. At the first interim analysis in September 2007, no-efficacy criteria for the study were met, causing the study and vaccinations to be suspended. The researchers were then unblinded in regards to the participant treatment groups, and the initial analyses showed that more HIV infections occurred in vaccines vs. placebo (V:P) recipients in men who had Ad5 neutralizing antibodies and/or were uncircumcised. As part of the Step/HVTN 504 study team, Dr. Ann Duerr, Dr. Yunda Huang, Dr. Peter Gilbert, and Dr. Larry Corey (all of the Vaccine and Infectious Disease Division) conducted a follow-up analysis to assess the relative risk of HIV acquisition (V:P) over time.

Step study participants could enroll in HVTN 504 for follow-up until the end of 2009, or for up to four years from their original enrollment. The objectives of the study analysis included measuring the vaccine's effect on HIV infection, studying interaction effects of baseline Ad5 sero-status and circumcision status on vaccine-induced HIV infection risk, and evaluating possible changes of relative risk (V:P) with time since vaccination. Duerr and colleagues found, over the entire follow-up period, that there was a higher risk of HIV infection among the vaccine recipients versus placebo recipients (Hazard Ratio (HR) 1.44, 95% confidence interval (CI): [1.05-1.97]). In the first 18 months, there was a significant three-way interaction between circumcision status, Ad5 serostatus, and treatment ($p=0.04$), which suggests a joint effect of the two baseline factors on the relative risk of HIV infection. Uncircumcised, Ad5 seropositive men had an HR that was 4 times greater in the vaccine recipients, compared to the placebo recipients. Concerning the vaccine's effect on HIV

infection over time, the elevated risk of infection in the vaccine group (uncircumcised and/or Ad5 seropositive men) during the first 18 months appeared to wane over time.

The conclusions of Duerr and colleagues extend the findings of the initial analyses in the Step study, confirming the increased vaccine-associated risk of infection during the first 18 months, which decreased over time. The authors' results also show limitations associated with the use of Ad5 vectored vaccines in populations of uncircumcised and/or Ad5 seropositive men. A biologic effect of prior Ad5 immunity on susceptibility to HIV infection may be suggested, but further study is necessary to prove and define these mechanisms.

[Duerr A, Huang Y, Buchbinder S, Coombs RW, Sanchez J, Del Rio C, Casapia M, Santiago S, Gilbert P, Corey L, Robertson MN; for the Step/ HVTN 504 study team.](#) 2012. 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 Diseases*. May 4; doi: 10.1093/infdis/jis342

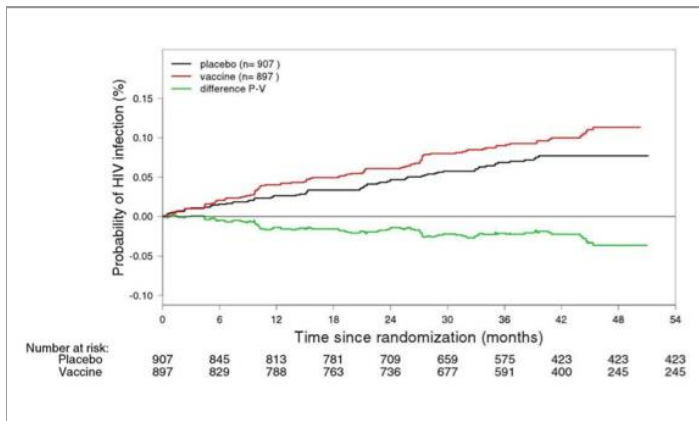


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Overall incidence of HIV infections over 48 months of follow-up