

Multivariate Analysis of the Step Study

(Merck V520 Protocol 023/HVTN 502)

Summary points

Framework

- In the univariate analysis, several variables were associated with increased risk of HIV infection.
- The multivariate analysis addressed the questions:
 1. Which variables are associated with increased risk of HIV infection regardless of vaccine status?
 2. After you control for these covariates, do you still see an independent risk of vaccination?
 3. Do you see a risk from vaccination in the entire population, or just in subpopulations?
- Summary of answers to questions 1-3 above:
 1. Age <30, non-white race, living in North America, and having unprotected receptive anal sex were all associated with HIV infection regardless of vaccine status.
 2. The multivariate analyses reaffirm the trend toward an overall increase in HIV infection risk in vaccine vs. placebo recipients. [estimated hazard ratio 1.6 to 2.0]
 3. After controlling for covariates, an independent risk of vaccination is observed in some subpopulations and not others; in some subpopulations it is unclear because of the small numbers of infections in the study.

Ad5 serostatus and relative risk of HIV acquisition among vaccinees compared with placebo recipients

- Those who were Ad5 seronegative had no excess risk from the vaccine compared to the placebo.
- We continue to see elevated risk from the vaccine compared to the placebo in the Ad5 seropositive group.
- These observations held steady through an increasing set of more complex multivariate models.
- Independent of vaccination, no association of Ad5 serostatus with risk of infection was observed after adjusting for other factors in the multivariate model.

Circumcision status and relative risk of HIV acquisition among vaccinees compared with placebo recipients

- Those who were circumcised had no excess risk from the vaccine compared to the placebo.
- We continue to see elevated risk from the vaccine compared to the placebo in the uncircumcised group.
- These observations held steady through an increasing set of more complex multivariate models.
- Independent of vaccination, no association of circumcision status with risk of infection was observed after adjusting for other factors in the multivariate model. A prospective randomized study would be better suited to address whether circumcision affects HIV acquisition risk among MSM.

Ad5 serostatus and circumcision status in combination

- Because we know that a substantial proportion of men who were uncircumcised also had high Ad5 titers, we divided the population into 4 subgroups: people with both risk factors (Ad5 seropositive and uncircumcised), people with neither risk factor, and people with only one risk factor or the other to see if they also had increased risk associated with vaccination.
- Increased risk of HIV infection among vaccinees is **most evident in uncircumcised men with pre-existing Ad5 immunity** [estimated vaccine HRs 4.2 to 4.8].
- In contrast, **no evidence of an increased risk among vaccinees in circumcised men without pre-existing Ad5 immunity** [estimated vaccine HRs 0.6 to 0.8].
- Uncertainty about whether there is increased risk among vaccinees if either Ad5 seropositive or uncircumcised (one but not both risk factors).

Durability of elevated risk among vaccinees compared with placebo recipients

- Was this a transient effect around vaccination time, or was it a durable effect?
- Through 52 weeks of follow-up, we observe an excess number of infections in the vaccine group compared with the placebo group when we look at those two groups as a whole.
- Those infection rates look as if they are fairly stable over time.
- We are following the STEP study volunteers forward in time to see if this effect lasts over a prolonged period of time, although the volunteers are now unblinded, and data may be confounded post-unblinding.

Future directions and hypotheses

- Awaiting data on HSV-2 status, HLA typing, sexual network clustering, longitudinal risk
 - Additional multivariate analyses will be performed
- Possible mechanisms for potential increased HIV acquisition among vaccinees are being explored in laboratory studies
 - Studies in STEP participants and non-human primates
- Data being considered in developing protocols with other Ad5 vectored approaches

FAQ

Q: Looking at the placebo recipients only, do these data shed any light on relative risk of infection among uncircumcised MSM compared with circumcised MSM?

A: The study was not designed to answer this question, e.g. participants were not randomized based on their circumcision status. The numbers of infections are too small and there are too many confounders to draw any conclusions. [Also, post-hoc analyses carry the usual caveats.]

FAQ

Q: In the data presented, it appears that the risk of HIV acquisition in the placebo group decreases as the Ad5 titers increase. Does this mean that Ad5 antibody titers are a marker that correlates with decreased susceptibility to infection?

A: Although the study was stratified on Ad5 titers, the Ad5 seropositive population differed substantially from the Ad5 seronegative population. When we looked in the multivariate analyses for association of Ad5 serostatus with infection risk independent of vaccination, Ad5 serostatus was not independently associated with HIV infection. We did find, though, that being North American was associated with an increased risk of acquisition. It may be that the reason for the higher rates of infection in the placebo arm among those who were Ad5 seronegative was because that subgroup was primarily in the North American cohorts, which reported riskier sexual practices and substance use. We are exploring this in other observational cohort studies.

FAQ

Q: Why were there so few infections among the women in the study?

A: Women were clearly having unprotected sex based on their high pregnancy rates. The challenge in clade B countries is that although there is substantial risk behavior, the question of whether or not they are exposed to HIV depends on the HIV prevalence among their male partners and other factors such as partner viral load, STIs, etc. If partners weren't HIV positive, the women would not have been exposed.

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Slides prepared by Dr. Katharine Kripke, NIAID

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