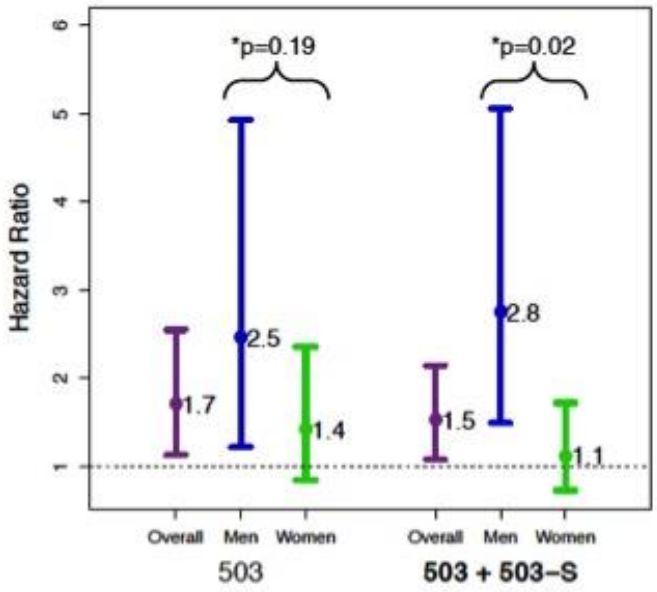
Time gives answers and raises questions

November 15, 2015

L Pattacini



Hazard ratios for HIV in vaccine versus placebo in men and women combined (purple), men (blue) and women (green) in Phambili (503) and Phambili (503) plus 503-S.

Image provided by Dr. Zoe Moodie

Time gives answers, but they are not always what we expect, and may raise more questions. This is the case for the HVTN 503-S study, designed to obtain further data on uninfected participants in the Phambili HIV vaccine trial. The Phambili trial, similarly to the Step trial, evaluated the safety and efficacy of an adenovirus 5 (Ad5) based vaccine, where the vector encoded for Gag, Pol and Nef proteins of HIV. Vaccinations in both studies were stopped after the Step study's interim analysis met its pre-specified futility criteria.

The Phambili trial, or HVTN 503, was run in a principally heterosexual population in South Africa, where clade C is the predominant HIV-1 circulating subtype, in a principally heterosexual population. At the time enrollment and vaccinations were stopped, Phambili had enrolled 800 HIV-1 uninfected participants who were subsequently unblinded to their treatment assignment and continued followed-up to 42 months. The first analysis conducted after twenty-five months of follow-up showed a statistically non-significant increased risk of HIV acquisition in the vaccine arm as compared to the placebo arm. A subsequent analysis at the end of follow-up showed a significant increase in HIV acquisition in the vaccine arm. HVTN 503-S was designed to recall all uninfected participants for an additional HIV test, circumcision status evaluation and to expand information on behavioral risk.

Dr. Zoe Moodie, a senior staff scientist in the Vaccine and Infectious Disease Division at Fred Hutch, reported the results obtained from the HVTN 503-S trial in a recent publication in the journal *PLOS One* produced in collaboration with HIV vaccine trial network (HVTN) investigators in South Africa and the United States. In the publication, she reported that in the combined Phambili and HVTN 503-S follow-up period (seventy-two months average after enrollment), significantly more infections were detected in the vaccine arm, with an incidence rate of 4.7%, as compared to the placebo arm, for which the incidence rate was 3.0%. The vaccine to placebo hazard ratio (HR), adjusted for herpes virus -2 status at enrollment, was 1.52 in the combined Phambili and HVTN 503-S and 1.70 in Phambili alone. Thus, the follow-up study confirmed the results seen in the Phambili trial. Strikingly, the effect of vaccination on HIV-1 infection was more pronounced in men (HR=2.75, 95% CI=(1.49, 5.06)) and less in women (HR=1.12, 95% CI=(0.73, 1.72)). There was no evidence that the effect of vaccination varied by baseline Ad5 status, age, study site or, in men, by circumcision status.

One of the hypotheses to explain the increased HIV acquisition rate in the vaccine arm is that the vaccine would expand Ad5-specific memory CD4+ T cells for Ad5, therefore increasing the pool of possible target cells. Interestingly, while the Step study showed an effect of Ad5 serostatus on increased HIV acquisition in men in the vaccine arm, the Phambili study did not confirm this finding. Another hypothesis, although not verified, is that the vaccine led to changes in inflammation in men, but not in women. "It is difficult to explain the observed gender difference. The vaccine may have induced subclinical inflammation in men that contributed to the increased rate of HIV-1 acquisition whereas in women the subclinical inflammation didn't exceed the high levels already present due to genital inflammation. However, this hasn't been demonstrated- it remains a hypothesis" said Dr. Moodie.

The study confirms some of the previous findings and raises more questions about which kind of immune response we want to induce and avoid in HIV-1 vaccine design. Hopefully the lessons learned will drive researchers to design a successful future trial.

The research was supported by grants from the National Institutes of Health.

Moodie Z, Metch B, Bekker L-G, Churchyard G, Nchabeleng M, Mlisana K, Laher F, Roux S, Mngadi K, Innes C, Mathebula M, Allen M, Bentley C, Gilbert PB, Robertson M, Kublin J, Corey L, Gray GE. 2015. Continued Follow-Up of Phambili Phase 2b Randomized HIV-1 Vaccine Trial Participants Supports Increased HIV-1 Acquisition among Vaccinated Men. *PLoS One*. 10(9):e0137666. doi: 10.1371/journal.pone.0137666.