The Unexpected Impact of Mock Responses

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L Pattacini

The month of December starts with World AIDS day, dedicated to improve awareness of the HIV pandemic that continues to spread and affect millions of lives. While awareness and prevention are key in controlling the pandemic, there is a broad scientific consensus that an efficacious vaccine is a requirement to reach zero new infections.

So far, a limited number of clinical trials aimed at testing potential HIV vaccines have been run with alternate results. The recently terminated RV144 Thai trial showed a limited protection from infection, while the previous Step study had to be stopped prematurely because of lack of efficacy. But how can we better predict the outcome of a vaccine trial?

In a Fred Hutch study published last November in PLoS One, Dr. Yunda Huang and her colleagues from the Vaccine and Infectious Disease Division (VIDD) addressed this question by analyzing data obtained from the Step study and HVTN 504, which enrolled participants for an extended follow-up up to a 4-year period.

The Step study tested a vaccination regimen consisting of three administrations of the adenovirus serotype 5 (Ad5) vector carrying the HIV sequences of gag, pol and nef. One of the observations that emerged from the trial was an increased infection rate between vaccinated subjects with pre-existing immunity to Ad5, possibly due to the expansion and activation of Ad5-specific CD4+ T cells by the vaccine potentially increasing the number of cells supporting HIV replication. In fact, while HIV can infect all CD4+ T cells, it predominantly replicates in activated ones. However, no systematic quantitative analyses linking these immunological measurements and the risk of HIV infection in Step have been reported due to the limited number of relevant data. "As the first proof-of-concept efficacy trial of a cell-mediated immunity HIV-1 vaccine, the Step Study provides unique data to investigate the roles of cellular responses in predicting trial outcomes", wrote us an enthusiastic Dr. Huang.

Therefore, the investigators decided to evaluate the correlation between HIV-specific and non-specific cellular responses as well as the risk of HIV acquisition in vaccine and placebo recipients at week 8 (two weeks after the first boost). For all samples (112 cases and 962 uninfected), cellular responses were analyzed by ELISPOT, a method to detect IFN-γ secretion from peripheral blood
mononuclear cells, either following stimulation with HIV, Ad5 and CMV peptides or with no stimulation (mock responses). For a subset of the samples, intracellular staining was performed as well to identify the cell type responsible for IFN-γ production, which turned out to be CD4+ T cells. The analyses compared the immune responses in cases (infected subjects at week 12) and controls (uninfected) in both the placebo and vaccine groups. All analyses had been adjusted to take into account Ad5 and HSV-2 serostatus, and other potential confounding factors.

The researchers showed that non-HIV specific responses directly correlated with risk of HIV infection amongst vaccine recipients. In particular, a 62% risk increase was observed per log increase of mock responses, while no correlation was observed with HIV-specific responses. To further understand if this increased infection rate was due to the expansion of Ad5 specific responses, the authors looked at the correlation between mock and Ad5 response magnitude, but once again, no correlation was observed.

"This is one of the first studies that reports a possible link between a biomarker and the risk of HIV-1 infection. It generates an important hypothesis of the relationship between IFN-γ secreting CD4+ T cells and underlying causes of vaccine-associated enhanced infection risk in Step study participants" concludes Dr. Huang. Indeed, through her extensive analyses, she has been able to identify non vaccine-specific immunity as a potential marker for the risk of HIV infection in vaccine trials.

Image provided by Dr. Yunda Huang, Vaccine and Infectious Disease Division.

Distribution of immune responses in infected and uninfected vaccine and placebo recipients in the immune correlates analysis of the Step Study. Panel A shows IFN-γ-secreting cellular responses as the number of spot-forming cells (SFC) per million Peripheral Blood Mononuclear Cells, in the absence of any antigen stimulation (media only). Panel B shows the IFN-γ-secreting cellular responses under Gag, Pol or Nef HIV-1 antigen stimulation. Panel C shows CD4+ and CD8+ T-cell activation responses measured by flow cytometry. Box-plots show the 25th percentile (lower edge of the box), 50th percentile (horizontal line in the box), and 75th percentile (upper edge of the box) for the immune responses, with participants stratified according to HIV-1 infection status and treatment assignment. The tip of the vertical bars indicate the most extreme data points, which are no more than 1.5 times the interquartile range from the box.