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Letter to the Editor on: The RV144 vaccine regimen was not associated with enhancement of infection

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In the October 1, 2014 issue of this journal, Shmelkov et al. stated that "the immune-correlate analysis of the RV144 clinical trial revealed that human plasma IgA immune responses elicited by the RV144 vaccine correlated positively with a risk for HIV acquisition," and inferred that this analysis supported vaccine-induced enhancement of HIV acquisition risk.[1] This inference of vaccine-induced enhancement of HIV acquisition risk is incorrect, since the immune correlate analysis directly demonstrated that there was no vaccine-associated enhancement of infection risk in the trial.[2]

RV144 was a randomized, placebo-controlled Phase 3 clinical trial in Thailand testing the ability of the ALVAC-HIV (vCP1521) recombinant canarypox vector vaccine[3] and AIDSVAX-B/E, a recombinant gp120 protein formulated in alum,[4] to protect healthy heterosexual volunteers from HIV acquisition in comparison to placebo recipients. This was the only HIV vaccine efficacy trial to date to demonstrate any level of protection from HIV acquisition, as vaccine efficacy was estimated at 31.2% (95% CI 1.1 – 52.1; $P = 0.04$) at 3.5 y after enrollment in the modified intent-to-treat (mITT) analysis,[5] and 60% (95% CI 22–80%) at one year after enrollment in a subsequent *post hoc* analysis.[6] Haynes et al. published an analysis of immunologic correlates of risk of infection in vaccine recipients which demonstrated an inverse correlation between V1V2 antibody levels and the risk of infection (estimated odds ratio of infection per SD increase, 0.57; $P = 0.02$; estimated odds ratio for the highest versus lowest third of responders, 0.29; $P = 0.02$) and a direct correlation between plasma IgA antibody levels and the risk of infection (estimated odds ratio per SD increase, 1.54; $P = 0.03$; estimated odds ratio for the highest vs. lowest third of responders, 1.89; $P = 0.17$).[2] However, because these analyses included the vaccine group only, they, by themselves, do not provide evidence for or against a vaccine-induced increase in the rate of HIV infection. Rather, to address that objective the HIV infection rate in the placebo group must be integrated into the analysis, as done by Haynes et al. and reported in Figure S3. That analysis demonstrated that neither low levels of V1V2 antibodies nor high levels of Env-specific IgA antibodies in vaccines were associated with higher rates of infection than were found among placebo recipients (estimated VE = 3.4%, 95% confidence interval −77% to 47% for lowest third V1V2 responders versus placebo; estimated VE = −5.4%, 95% confidence interval −87% to 40% for highest third IgA responders vs. placebo). Thus, this analysis failed to detect evidence for enhancement of infection, and do not support the claim by Shmelkov et al., "this result once again emphasized that HIV vaccines can potentially have adverse effects leading to enhancement of infection." Rather, the most appropriate interpretation of the association of Env-specific IgA antibodies with HIV risk is that vaccine recipients with high IgA received no protection, due to IgA blocking and interference with effector functions of IgG that was indicated by the correlates of risk interaction analyses in Haynes et al.[2] In particular, the interaction analyses supported that IgA inhibited antibody dependent cellular cytotoxicity (ADCC) protection, and follow-up research on the antibody repertoire of RV144 vaccines that isolated both natural IgG1 and IgA antibodies from vaccines directly demonstrated that IgA antibodies reacting with the same target epitopes on HIV envelope can indeed block IgG ADCC activity. Thus, there is now direct evidence that RV144 vaccine-induced IgA envelope antibodies have the capacity to block effector functions of IgG.[7]

RV144 remains the only trial of a candidate HIV vaccine regimen to demonstrate prevention of HIV acquisition. While protection from HIV infection in RV144 vaccines was correlated, both directly and inversely, with vaccine-induced antibody responses, there is no evidence that the vaccine regimen was associated with enhancement of infection.

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