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# Response to Letter to the Editor

Evgeny Shmelkov* and Timothy Cardozo

Department of Biochemistry and Molecular Pharmacology; New York University School of Medicine; New York, NY USA

The Letter to the Editor commenting on our recent paper,[1] provides a concern regarding the statement "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. This result once again emphasized that HIV vaccines can potentially have adverse effects leading to enhancement of infection."

First of all, we would like to highlight that the statement regarding the RV144 trial is a minor speculation in the paper. We presented data that is statistically sound, and, for the purposes of discussion, also presented some speculative inferences from our data and data published by others, and we tried to make the latter quite easily distinguishable from the former for the average reader. Data in our paper pertains entirely to the AIDSVAX trial and not the RV144 trial.

Second, we would like to emphasize that nowhere in the paper did we conclude that the RV144 vaccine enhanced HIV infection in humans, only that this was a theoretical possibility for some subset of antibodies elicited by that vaccine. Specifically, the above-mentioned citation from our paper is a speculation that the simplest explanation for a direct correlation of any antibody level with infection generally is enhancement. As the IgA levels were a primary variable in the immune correlates analysis of the trial,[2] that result carries more weight than the subsequent follow-up studies as suggested by the Letter author. Nevertheless, our phrasing "can potentially" only means that occult enhancement by *specific* antibodies cannot be ruled out, not that it occurred to a physiologically significant degree. We fully agree that the RV144 trial clearly shows that antibodies can protect against HIV acquisition in humans, which is a major unprecedented positive result in the field.

Our paper suggests that, in the setting of improved prospects for a protective HIV vaccine, the field should be more cognizant of the possibility of enhancement by *specific* anti-HIV antibodies. The precise mechanisms leading to enhancement of HIV infection by vaccination remain poorly studied. This, in part, is due to the fact that vaccine-induced enhancement of HIV has been largely ignored by the HIV research community during the recent decades. In this light, our paper presenting statistical findings that may suggest potential enhancement of HIV infection in AIDSVAX VAX004 trial[3] can be helpful in distinguishing protective from enhancing antibodies in future research in this field.

## References

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*Correspondence to: Evgeny Shmelkov; Email: eshmelkov@gmail.com
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