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Author for correspondence:

Anthony L. DeVico
e-mail: adevico@ihv.umaryland.edu

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Modulating the durability of anti-HIV gp120 antibody responses after vaccination: a comment on Wilson & Karp (2015)

Anthony L. DeVico, George K. Lewis and Robert C. Gallo

Divisions of Basic Science and Vaccine Research, Institute of Human Virology, University of Maryland School of Medicine, University of Maryland, 725 West Lombard Street, Baltimore, MD 21201, USA

In their opinion piece [1], Wilson and Karp discuss the poor durability of the anti-gp120 humoral response, an important feature that poses a significant difficulty for HIV vaccine development [2]. The authors make the case that short-lived anti-gp120 responses are not seen in all studies of HIV-envelope-based vaccines, suggesting that the problem might be solved via vaccine formulation strategies and existing adjuvants. They argue that two clinical trials by Goepfert *et al.* [3] and Leroux-Roels *et al.* [4] already show that vaccines containing gp120 formulated in monophosphoryl lipid A-containing adjuvants raise humoral responses that are considerably more durable than what was observed by Yates *et al.* [5] in the RV144 trial, which tested a different vaccination regimen. We agree with the use of RV144 as a benchmark for comparing HIV-envelope-based vaccine trials as this was a case where humoral anti-gp120 responses were correlates of risk [6]. Vaccine efficacy was roughly 60% early in the trial but declined to about 30% overall as humoral responses waned over time [7].

However, we disagree with the view that the Goepfert *et al.* and Leroux-Roels *et al.* examples cited in the opinion piece demonstrate unusually durable anti-gp120 responses or point towards any particular vaccine formulation that solves the durability problem. Questions emerge when one considers the differences in data collection and reporting between studies. One disparity is that timescales vary among the studies. Goepfert *et al.* report responses in days; Yates *et al.*, in weeks; Leroux-Roels *et al.*, in months. Another variance is that humoral responses are not quantified or reported in the same way. Goepfert *et al.* report humoral responses as 50% maximal gp120 ELISA binding titres; Leroux-Roels *et al.*, as gp120 ELISA units ml⁻¹. The Yates *et al.* RV144 study reports anti-gp120 humoral responses as percentages of vaccinees with antibody titres above baseline (per cent 'responders'). One approach to compensate for such differences is to track all humoral responses as a fraction of the apparent peak response (i.e. what is evident from the reported data) versus a normalized timescale. Figure 1 depicts the application of this approach to data from the three studies cited here. It is visually apparent that the persistence of the peak anti-gp120 response is quite similar for all regimens in the Goepfert *et al.* and Leroux-Roels *et al.* studies (red and green lines, respectively) after the respective final boosts. Responses decline rapidly to approximately 10% of peak in every case, regardless of gp120 dose or formulation (note in the Leroux-Roels *et al.* study the assay cut-off for seropositivity equated with 3–5% of peak measures). Calculations of decay rates from the curves in figure 1 indicate similar response half-lives of 25–31 days for Goepfert *et al.*; 50–56 days for Leroux-Roels *et al.* These kinetics resemble what has been seen in other vaccine trials with gp120 [2,8]. In the Yates *et al.* study, the apparent peak response is reported as 97–100% responders. The subsequent rate of decline in per cent responders reflects the decay of immune responses to background among vaccinees. Time-normalized tracking of the per cent responders against V1V2 epitopes, a specificity that correlated with risk in RV144, produces a curve (figure 1, blue line) that closely resembles those derived from the Goepfert *et al.* and Leroux-Roels *et al.* studies. The half-life of the anti-V1V2 response calculated from this plot is 54 days, in line with the apparent half-life of 11.7 weeks (82 days) determined by Yates *et al.* and equating with the values determined for the Goepfert *et al.* and Leroux-Roels *et al.* data curves in figure 1. In comparison, the same plotting of

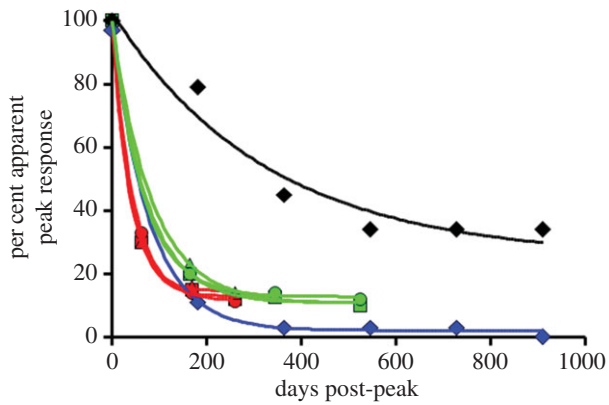


Figure 1. Temporal persistence of anti-gp120 antibody responses in the Goepfert *et al.*, Leroux-Roels *et al.* and Yates *et al.* reports. The apparent peak responses are set at 100% and later measures normalized accordingly. Values from various time points in the studies are spaced and plotted accordingly on a timescale normalized to days. The Goepfert *et al.* study tested three vaccines containing 5, 20 or 100 μg gp120 (red lines). The final boost was on day 84, and the apparent peak responses reported were on day 98, plotted here as day 0. Immune response data are extracted from fig. 2a in the paper. The Leroux-Roels *et al.* study tested three vaccine formulations each containing 20 μg gp120 (green lines). The final boost was at six months, and the apparent peak response reported was two weeks later, plotted as day 0. Immune response data are extracted from fig. 6 in the paper. The Yates *et al.* study tracked humoral immunity in RV144 as per cent responders. The apparent peak response was on week 26 (plotted as day 0), two weeks after the final immunization. Immune response data are from table 4 in the paper. Responses against the gp70B.Case A2 V1–V2 antigens are shown with a blue line; against A244 gp120 with a black line. Curve fitting was performed with GraphPad PRISM using an exponential decay model after Yates *et al.* (Online version in colour.)

responses against A244 gp120 suggests a more, not less, persistent humoral anti-gp120 immunity in RV144 (figure 1, black line) compared with regimens in Goepfert *et al.* and Leroux-Roels *et al.* This difference, however, may be more apparent than real. It might be speculated that the persistence of anti-gp120 responses in RV144 would appear inferior to the trends in the other studies (figure 1) had Yates *et al.* quantified actual antibody titres rather than per cent responders. However, there are no such published data available to resolve this question.

Taking cues from Yates *et al.*, comparisons based on per cent anti-gp120 responders might also be considered. As noted above, these are subjects with titres above the baseline cut-off for

seropositivity (not necessarily above the threshold of a putative protective response). Goepfert *et al.* do not formally report per cent anti-gp120 responders, but it may be inferred from the data that there were approximately 100% responders 39 weeks after the last vaccination. In a similar time frame, Yates *et al.* report 79% and 45% anti-gp120 responders at 28 and 48 weeks post-final vaccination, respectively. Leroux-Roels *et al.* report per cent responders for a single time point (72 weeks post-final vaccination). Measures were reported as 70.4–96.6% responders for the three vaccine antigens (gp120, Nef or Tat) across the three adjuvant formulation groups tested. Yates *et al.* report 45–34% anti-gp120 responders at 54–80 weeks post-final vaccination, respectively. Although it might be tempting to draw conclusions from such comparisons, caution is warranted given the data limitations, and the fact that the three publications reported different assay methods and/or target antigens to determine antibody titres. Further, sparse time point measures cannot be used to accurately determine antibody decay rates.

We recognize that data from the three reports may be subjected to alternative types of analyses. Regardless, the aggregate message from multiple approaches is likely to be equivocal, as indicated above. It should also be noted that the three reports do not include data representing the extended time frames needed to formally demonstrate a persistent humoral response, as the phenomenon is currently appreciated [2,9]. Extrapolation of existing information to long-term trends will be subjective.

Our alternative interpretation of the above studies (as with other published HIV vaccine trials) is that there is little if any available evidence to conclude that existing adjuvants and formulation methods mitigate the poor durability of anti-gp120 humoral responses to the degree necessary for an effective HIV-envelope-based vaccine. The above examples do, however, illustrate how attempts to understand the durability problem will require standardized methods to compare vaccine regimens over time and the development of models to accurately predict response durability with shorter-term studies. Moreover, these and related trials emphasize that an immunization strategy to overcome the durability problem while avoiding immune activation profiles that might increase infection risk [2] is not immediately apparent. Thus, a comprehensive, basic understanding of the immune parameters that produce and sustain the anti-gp120 humoral response will be needed to develop a safe and effective HIV vaccine.

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