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Invited reply

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A reply to DeVico, Lewis & Gallo (2015)

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We appreciate the thoughtful comments provided by DeVico *et al.* [1] regarding the section of our opinion piece (Wilson & Karp [2]) that discussed the problem of limited durability of HIV-vaccine-induced antibody responses in humans. They have done important work, and written thoughtfully and provocatively about this topic [3]. We share their view that durability of the vaccine-induced antibody response is a key issue and must be addressed as part of the community-wide effort to discover and develop an HIV vaccine that induces protective antibodies and which is practical and affordable for use globally. In our opinion piece, we stated that three studies cited as examples suggest that 'the duration of anti-HIV envelope antibody responses has not been unusually brief in all studies', a statement with which they do not agree.

The principal basis for their disagreement is presented in fig. 1 and the associated text of their commentary. We are puzzled by this analysis. Fig. 1 plots per cent responders (i.e. percentage of subjects with IgG antibody titres to gp120 above the baseline cut-off for seropositivity) versus time after last immunization for data from Yates *et al.* [4] and the percentage of the peak geometric mean concentration for the populations of vaccinated individuals from Goepfert *et al.* [5] and Leroux-Roels *et al.* [6]. Responder status and antibody concentration are fundamentally different in nature (binary versus continuous variables, respectively) and thus not directly comparable.

By contrast, per cent responders were presented in each of these reports at overlapping time points after immunization and can be directly compared. Yates *et al.* [4] presented per cent responders from the Rv144 trial over time in tabular form, whereas Goepfert *et al.* [5] and Leroux-Roels *et al.* [6] presented information in the text at the last time point assessed following immunization; additional information regarding responses at the final 18 month time point in the PRO HIV-002 study of Leroux-Roels *et al.* [6] is provided in Koutsoukos [7]. In each of these studies, all immunized individuals were responders immediately after immunization, but at later time points, per cent responders were considerably lower in the Rv144 trial than the other two reports (table 1*a*), consistent with the statement made in our opinion piece. We agree that comparisons such as these have limitations, and it is possible that if the studies had been conducted in a standardized and parallel manner the findings might have been different.

Nonetheless, when the IgG anti-V1, V2 antibody responses in the PRO HIV-002 study were analysed by the same laboratory reporting antibody responses for the Rv144 trial, the per cent responders declined rapidly in the Rv144 study [4,7] but persisted in the PRO HIV-002 study [7]. Consistent with this difference, the calculated half-life of IgG anti-V1, V2 antibodies was noted to be approximately three times longer in the PRO HIV-002 trial than in the Rv144 trial, although IgG3 anti-V1,V2 antibody responses and half-lives were similar in these two studies [7].

The difference in conclusions notwithstanding, the main focus of our opinion piece resonates very closely with the views expressed in the closing paragraph of the commentary by DeVico *et al*. We share the view that HIV-vaccine-induced antibody durability is a key issue that needs to be addressed in future studies using standardized and directly comparable approaches—ideally with head-to-head comparison of different vaccine compositions—and with sufficiently long follow-up that terminal elimination rates can be determined and the basis for any differences illuminated. The ultimate goal of HIV vaccine R&D will be more quickly reached if teams of investigators work across traditional disciplinary boundaries to apply basic immunological principles and contemporary virology,

Table 1. Per cent responders.

antibodies assessed	adjuvant	26–28 weeks[a]	39 weeks	48 weeks	54 weeks	78–80 weeks
(*a*) IgG anti-gp120						
Rv144 trial Yates *et al.* [4]	alum	79		45	34	34
Goepfert *et al.* [5]	AS02A		∼100			
PRO HIV-002 Leroux Roels *et al.* [6] & Koutsoukos [7]	AS01B					94[b]
(*b*) IgG anti-gp70 V1, V2 CaseA2, clade B						
Rv144 trial Yates *et al.* [4]	alum	11			3	3
PRO HIV-002 Koutsoukos [7]	AS01B	100			100	87

[a]Weeks following the final immunization—times reported in days by Goepfert *et al.* [5] and in months reported by Leroux-Roels *et al.* [6] and Koutsoukos [7] were converted to weeks.
[b]Data from Leroux-Roels *et al.* [6] as clarified in Koutsoukos [7].

systems immunology, structural and computational biology to learn the rules by which to produce vaccine compositions that are safe and induce protective and durable antibody responses to HIV.

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