Comment on Clinical Development of Candidate HIV Vaccines: Different Problems for Different Vaccines

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EDITOR: Stuart Shapiro makes some very important points about the development of HIV vaccines and conduct of HIV vaccine efficacy trials in his article¹ that ought to be widely discussed.

He points out that many vaccines being considered may not achieve the immediate sterilizing immunity that broadly neutralizing antibodies could provide. Vaccines that stimulate antibodies mediating antibody-dependent cell-mediated cytotoxicity (ADCC) or CD8⁺ T cells might be able to reduce virus load at set point several weeks after infection. Until recently it was thought that this was the best that a vaccine stimulating CD8⁺ T cells could do, but Hansen *et al.*^{2,3} have shown that CD8⁺ T cells, stimulated by a cytomegalovirus (CMV) vectored SIV vaccine, are capable of completely clearing SIVmac239 infection over several weeks.

In the efficacy trials that have been conducted in humans, STEP, Phambili, RV144, and HVTN505, set point virus load was a primary or secondary end point but none of these trials showed a reduction compared to placebo controls.^{4–6} That does not mean that a future more potent vaccine might not achieve this, but as Shapiro points out there are problems with this end point. He focuses on the increasing trend for physicians in the United States to offer immediate antiretroviral therapy (ART) after early diagnosis, arguing that vaccine trials will need to adopt this same ethical standard.

The WHO has moved closer to this point with its recently revised recommendation to start ART at CD4 T cell counts of 500 rather than 350 (www.who.int/hiv/pub/guidelines/arv2013). It should be borne in mind that while this is underpinned by high-quality evidence in the context of prevention of heterosexual transmission, evidence for long-term benefit to the individual is weaker. Furthermore, this high ethical standard is difficult to attain even in a well-resourced country such as the United States, where the majority of people initiate ART with a CD4 <500. Cost, capacity to retain patients in long-term care, and individual risk/benefit depending on available drug regimens will be the key determinants of successful implementation of the new WHO guidelines.

One incentive in the United States for patients and physicians to start treatment early is the expectation that it will be

possible to cure patients in the near future, but only those who initiated therapy early. Such cures are probably much further off in developing countries because they are likely to be very costly and to require specialist treatment centers. However, for trial participants, investigators, and stakeholders planning vaccine trials in Africa and Asia, provision of ART to trial participants who acquire HIV for prevention of onward transmission may be a greater priority and may justify rejection of early viral load as an end point. Immediate ART should be feasible since it is anticipated that the number of participants seroconverting during a given trial would be small; nevertheless, it would depend on local healthcare infrastructure, availability of other prevention strategies, and the commitment of funders and governments to support it.

There are other problems with set point virus load as an end point for vaccine trials. It is well known that HLA type has a strong influence with up to 20% of Africans carrying a protective HLA allele (such as B*5703, B*5801, or B*8101). Even more important may be the virulence of the transmitted founder virus. Alizon *et al.*⁷ have argued that properties of the virus itself can contribute to around 50% of set point. Given that 70% of new infections are caused by a single founder virus⁸ and that it is impossible at present to predict fitness from a virus sequence, this will probably always be a confounder in studies that try to explain or depend on virus set point.

Together, all of these issues make virus load set point an unsatisfactory end point for vaccine efficacy trials. Single point nonquantitative assays for plasma RNA and cell-associated DNA should be enough to demonstrate whether an infection has been prevented or cleared early, provided enough time is allowed to cover delayed clearance by T cells or ADCC. In the SIV experiments described by Hansen *et al.*,^{2,3} virus load was undetectable by 21 days after infection, although transient blips occurred in some animals during the following 6 months. Measurement of plasma virus loads, quantitative assessment of the latent reservoir, CD4⁺ T cell decline rates, and sequence searches for sieving effects would be good secondary end points however.

What is really needed is a good predictor of efficacy, that could be used to select which of the available vaccine regimens should proceed to efficacy trials. This is relatively easy

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for antibodies, where breadth of neutralization of tier-two viruses would be a good measure; any vaccine that can stimulate these at high titer in 60–70% of people would be well worth testing for efficacy. Induction of nonneutralizing IgG antibodies to the V2 region⁹ that mediate ADCC might also be useful, but this needs further critical analysis as attempts to repeat the RV144 trial results come through.

For T cells we have argued that assays of virus suppression *in vitro* are likely to be the most predictive.¹⁰ Some vaccines tested in Phase I trials have generated T cells that can suppress virus¹¹ but not yet as well as CD8 T cells from infected patients who control HIV-1 well. Yang *et al.*¹⁰ have shown that this immune parameter, when measured in early infection, is inversely correlated with viral load set point and can predict the rate of CD4 T cell decline; if that result can be confirmed on a larger scale it would be a very useful measure to test potential vaccine effectiveness. In addition, any T cell-inducing vaccine would have to induce very broad T cell responses to multiple conserved epitopes. Judging candidate vaccines by these criteria might lead to a better trial success rate.

None of these issues should impede the development of novel vaccine strategies, but as Shapiro argues, each should have a clear pathway to a test of efficacy. We would insert a filtering step that measures potential efficacy in well-defined assays, as above, even if the T cell assay needs some further development. This ought to lead to just a few being assessed as suitable for efficacy clinical trials.

Author Disclosure Statement

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