

# Moving the HIV vaccine field forward: concepts of protective immunity



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Vaccine-induced prevention of HIV infection is widely viewed as requiring both humoral and cellular immunity. Although the evidence for such a multipronged approach is not strong, this strategy increases the possibility that at least one mechanism of immunity could work to diminish new infections. The concept of broad immunity to HIV is attractive to funding bodies that seek at least some success from expensive trials. However, trying simultaneously to achieve both robust cellular and humoral immunity against HIV might be difficult. Furthermore, a multipronged approach increases the difficulty of later dissecting the immune correlates of protection and thereby iteratively improving HIV vaccines. This Viewpoint briefly discusses different approaches to tackling the challenge of inducing protective immunity to HIV and speculates on how results will move the field forward. We posit that, given the uncertain nature of immunity to HIV at present, focusing on inducing, evaluating, and optimising discrete individual mechanisms of immunity to HIV could provide the most rapid pathway to an effective HIV vaccine.

## Learning from a partially successful trial

Only one partially successful HIV vaccine trial has been documented, the RV144 trial in Thailand (31% efficacy,  $p=0.04$ ).<sup>1</sup> This vaccine included the administration of a canarypox virus vector that expressed HIV Gag, Pol, and Env antigens, followed by the administration of an Envelope (Env) protein boost in an alum adjuvant. The priming canarypox vector was designed to induce CD8 T-cell immunity and included the more conserved Gag and Pol antigens (in addition to the highly variable Env antigen). Unfortunately, this vector induced minimal CD8 T-cell responses.<sup>1</sup> Moreover, two other efficacy studies, which induced increased anti-HIV CD8 T-cell responses, did not protect from HIV (STEP/Phambili and HVTN 505).<sup>2,3</sup> The aim of the RV144 booster vaccination with Env protein was to induce antibody responses. Trials with this Env protein as a stand-alone vaccine were unsuccessful.<sup>4</sup> Importantly, in this prime-boost strategy, the only priming by canarypox that could be boosted by the later administration of Env was to this antigen. CD4 T-cell responses to Env are primed by the canarypox vector,<sup>5</sup> and subsequently boosted by the protein antigen, supporting Env-specific antibody responses. Several lines of evidence suggest that non-neutralising antibodies to Env (with Fc-mediated functions) reduced the risk of HIV acquisition in this trial.<sup>6,7</sup>

## Antibody immunity

Non-human primate models have helped guide HIV vaccine efforts. Passive transfer of broadly neutralising antibodies active against chimeric simian immunodeficiency virus SIV-HIV (SHIV) challenges protects Rhesus macaques and Pigtail macaques from cell-free and cell-associated challenges that can be intravenous or mucosal.<sup>8,9</sup> Prolonging the antibody half-life produces more durable protection<sup>10</sup> and neutralising antibodies can also be used to treat early SHIV infection of macaques.<sup>11</sup> Initial evidence (obtained from using first-generation neutralising antibodies mutated in their Fc domains)

suggested that Fc-mediated antibody functions also assist in protection seen with neutralising antibodies.<sup>12</sup> Work over the past year with more potent neutralising antibodies suggests Fc-mediated antibody functions might not be essential for protection.<sup>13,14</sup> Inducing broadly-reactive neutralising antibodies by vaccination remains a major scientific challenge.<sup>15</sup>

Non-neutralising antibodies to Env with Fc-mediated functions can lead to killing of infected cells, phagocytosis of viruses in immune complexes, and several other functions. Non-neutralising antibodies are thought to best explain the modest amounts of protection observed in the RV144 trial.<sup>16</sup> However, only weak direct evidence from preclinical trials exists for this concept. Passive transfer studies in non-human primates of non-neutralising antibodies to Env with Fc-mediated functions have showed minimal protection; at best some selection for reduced numbers of transmitted variants.<sup>17</sup> A murine passive transfer study of non-neutralising antibodies showed evidence of selection of immune escape variants.<sup>18</sup> The strength and breadth needed for non-neutralising antibodies to Env with Fc-mediated functions to be protective is not as clear as with neutralising antibodies in preclinical models. Evidence has shown that the breadth of these antibodies induced in the RV144 trial was modest, perhaps reflecting the low efficacy observed in the trial.<sup>19</sup> Some non-human primate vaccination studies have suggested non-neutralising antibodies with Fc-mediated functions (such as antibody-dependent cellular cytotoxicity [ADCC] or antibody-dependent phagocytosis [ADP]) can correlate with protection,<sup>20,21</sup> although this suggestion was not supported by a further study.<sup>22</sup> Many antibodies require CD4 to be present on the surface of cells for high Fc-mediated function;<sup>23</sup> however, this requirement is problematic since HIV infection of cells rapidly downregulates CD4. Although ADP can be shown using in-vitro phagocytosis of protein coated beads, HIV virions can be relatively poor targets.<sup>24</sup>

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## Problems dissecting the protective mechanisms of antibodies

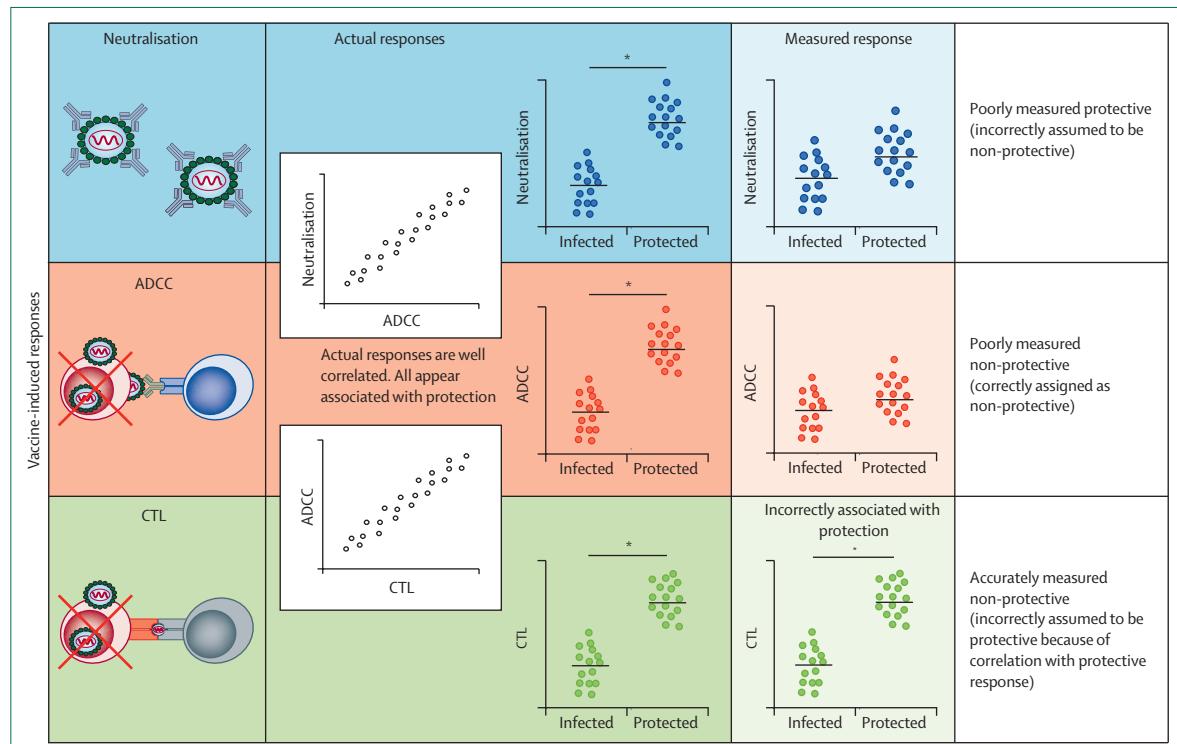
Although the partially effective RV144 trial identified non-neutralising antibody activity as the major correlate of infection, non-neutralising antibody activities have not commonly been shown to be crucially important in pre-clinical studies. A major issue is that the different antibody-mediated functions, such as neutralisation, or non-neutralising activities including ADCC or ADP, do not act in isolation. When a polyclonal antibody response is induced, it is directed to multiple epitopes, some of which might be neutralising, and others that act via mechanisms such as ADCC. Even for a given specificity of the antibody, the response of a single B cell will lead to a variety of antibodies of different isotypes, some of which might have stronger or weaker Fc-mediated functions.<sup>25</sup> Finally, the fact that an antibody molecule is neutralising does not mean that it might not also have non-neutralising functions.

With many anti-HIV immune responses being highly correlated, identifying the mechanism of protective immunity becomes difficult. In some cases, the choice of best correlate could be more associated with the accuracy of measuring the response, rather than its efficacy in controlling HIV replication (figure 1). Vaccination might

often induce multiple responses in parallel, only a subset of which are protective. If all responses are well correlated with each other, then all will be associated with protection. However, the assays used to measure the different immune responses will vary in accuracy. In this scenario, the response that is best associated with protection would simply be the response measured most accurately, rather than the truly protective response. Subsequently, a non-protective response might then be selected as the best correlate of immunity, despite its lack of mechanistic involvement in protection. This could be a substantial issue for typical assays measuring ADCC and ADP responses, for which data suggest some common assays do not model the most relevant responses against virions or HIV-infected cells.

## CD8 T-cell immunity

T-cell immunity is a logical mechanism to control viral infection. A large body of evidence emphasises the crucial role of T cells in controlling existing HIV infection in humans and SIV infection in non-human primates.<sup>26</sup> Two human efficacy trials did not support a role for pre-existing CD8 cell responses in protecting humans from HIV.<sup>2,3</sup> However, these two studies induced relatively



**Figure 1:** How measurement can confound association with immune protection

Hypothetical scenario in which vaccination induces at least some neutralising antibodies (top row), ADCC (middle row), and CTL (bottom row), but that only neutralising antibodies are truly protective. If the major source of variation between individuals is simply in the overall level of the immune response, then all three responses would be correlated (middle column). Because of this correlation, all three responses would be associated with protection if measured accurately (even though in this scenario only neutralisation is mechanistically protective). However, if assays are poor at measuring the real levels of neutralisation and ADCC (right hand column), then these would not be observed to be associated with protection. If assays accurately measure CTL response, and this is well correlated with real levels of protective neutralisation, then an incorrect association between CTL and protection is concluded. ADCC=antibody-dependent cellular cytotoxicity. CTL=cytotoxic T cells. Asterisk indicates significant difference.

low-level and variant-specific CD8 T-cell responses to HIV. The lack of efficacy of Env-specific CD8 cells in HVTN505 is supported by evidence from non-human primate studies,<sup>27</sup> and most studies now focus on the induction of CD8 cells to conserved elements of Gag and Pol.<sup>28</sup> The selection of virus variants with relevant CD8 cell immune escape mutations in the STEP efficacy trial was not sufficient to lower set point viral loads.<sup>29</sup> Induction of CD8 cell immunity might occur too late to prevent establishment of HIV infection.<sup>30</sup> For example, vaccine-induced CD8 cell responses to SIV are not induced until viral loads reach around 500 000 copies per mL.<sup>30</sup> Even in animals with very high concentrations of SIV-specific CD8 cells, vaccination does not measurably alter the trajectory of viral growth before day 10.<sup>31</sup> In non-human primate models, persistent viral vector vaccine regimens that induce well directed CD8 cell immunity have provided considerable protection from infection.<sup>32</sup> Studies investigating HLA-E restricted SIV-specific T-cell responses induced by cytomegalovirus (CMV) vectored vaccines show promise in their capacity to protect around 50% of macaques from ongoing SIV infection.<sup>33</sup> The protection induced by this type of T-cell immunity is not sterilising but results in the gradual clearance of the virus.<sup>34</sup> Studies investigating why only around 50% of macaques are protected by this vaccine, despite all generating robust T-cell immunity, remain a priority.

### Complementarity of antibodies and CD8 cells

One rationale for combining antibody and CD8 cell responses might be that they could synergise to protect from infection. However, these responses act at different stages during the establishment of infection. Neutralising antibodies are thought to act by blocking initial establishment of infection. By contrast, CD8 cells typically control infections once they have been established. However, the timing of CD8 cell immunity (acting after infection ensues) is problematic for HIV infection in humans in which infection is rarely, if ever, cured naturally once established.<sup>26</sup> Since antibodies and CD8 cells act at different stages of infection, they might not synergise (figure 2). Most infections of humans are established by single viral variants;<sup>35</sup> if these variants elude antibody control, T-cell immunity has the same challenge (controlling an early focus of infection) it had without an antibody response. Non-human primate studies suggest that very early infections can in some instances be cleared by passively infused neutralising antibodies<sup>36</sup> and by the broad T-cell immunity induced by CMV vaccine vectors;<sup>34</sup> however, these approaches have not been assessed for synergistic effects.

### Ongoing HIV vaccine studies aiming to induce both T-cell and B-cell mediated immunity

A follow-up efficacy trial attempting to repeat and improve upon the results of the partially effective RV144 trial is now underway in South Africa using clade C

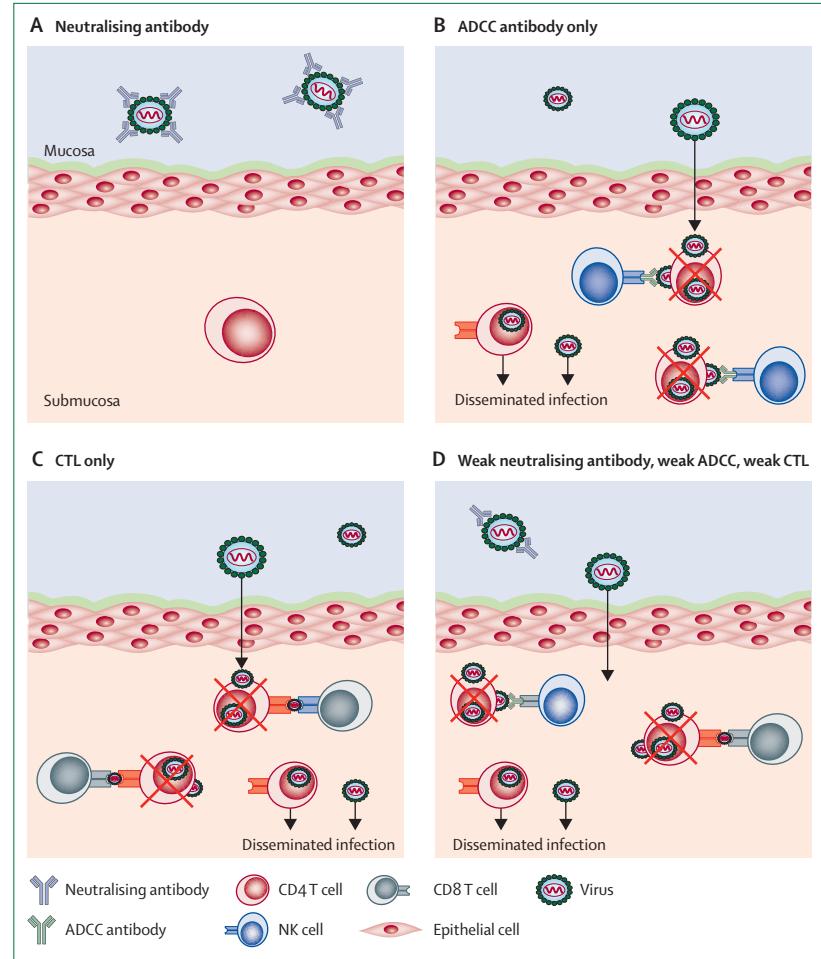


Figure 2: Combinations of immune responses against HIV

Diagrammatic representation of limiting infection at the portal of entry. (A) If a robust neutralising antibody response binds the virus it is likely to block infection early. ADCC antibodies (B) and CTL (C) act on infected cells and depending on the frequency and potency might not block dissemination of infection. (D) In a vaccine scenario in which multiple responses are induced, if a weaker neutralising antibody response does not block infection, ADCC antibodies and CTL might still not act early enough to block dissemination of infection. ADCC=antibody-dependent cellular cytotoxicity. CTL=cytotoxic T cells. NK=natural killer.

antigens (HVTN702). Gag and Pol antigens are still included in the revised canarypox vector despite their apparent lack of utility in the previous trial, even though the vectors had to be remade for the new subtype.<sup>37</sup> The inclusion of these antigens presumably reflects a desire to make as few changes as possible to the RV144 regimen. Nonetheless, the inclusion of Gag and Pol antigens suggests some hope among the trial investigators that CD8 cell immunity might still be useful, even though this vaccine regimen rarely induces this type of cell immunity. The effect of the CD8 cell response could be observed on viral sequences in patients for whom the vaccine was ineffective in the STEP trial,<sup>29</sup> but not in the RV144 trial,<sup>38</sup> further suggesting that CD8 cell responses are not helpful in regimens similar to RV144. We are not suggesting that vaccine-induced CD8 cell immunity might not ultimately prove to be a protective

immune response, only that the vaccines tested to induce such responses, to date, provide a benchmark of what not to pursue further.

The HVTN705 (Imbokodo) efficacy study (NCT03060629) has been initiated with an Adenovirus type 26 priming vector and recombinant protein Env gp140 protein boosting. The priming vector includes Gag and Pol (as well as Env) with the initial goal of inducing CD8 cell immunity. The mosaic design of the antigens aims to induce improved CD8 cell responses.<sup>39</sup> The Env gp140 proteins in the boost do not have a mosaic design and are included to induce antibody responses. Non-human primate studies suggested that antibodies to Env primarily mediated some protection.<sup>20,21,40</sup> A further non-human primate study used a correlation matrix of ELISA antibody responses and ELISPOT T-cell responses to suggest that a combination of non-neutralising antibody responses and T-cell responses are protective.<sup>41</sup> This technique to study immune correlates was unusual and other combinations of immune responses could possibly have yielded similar correlations in this trial or other non-human primate trials. Such a correlation using multiple immune parameters might reflect the enhanced immunogenicity within a given host (ie, a better vaccine take in that host) rather than an inherent benefit of both responses together. Similar to the RV144 trial, whether the HVTN705 efficacy trial is well suited to teasing out the efficacy of the various individual or combined immune responses induced (if at least modest efficacy is observed) remains unclear. If detectable but modest non-licensable efficacy is observed, and this efficacy correlates with multiple immune parameters (as in the non-human primate trial),<sup>41</sup> a pathway to enhance multiple immune parameters to improve efficacy in the future is uncertain.

### Neutralising antibody efficacy trial

An alternative to a multipronged approach is to test an individual mechanism. A human efficacy trial (HVTN 703, AMP study, NCT02568215 and NCT02716675) is underway that uses passive transfer of the HIV neutralising antibody VRC01 as a proof of principle test that neutralising antibodies alone can protect from HIV.<sup>42</sup> The antibody will have both neutralising and non-neutralising activity, so might not be entirely specific as to mechanism of action; however, if successful, it will show that a specific agent or response is effective. This is a logical and insightful path to move the field forward. The challenge in inducing neutralising antibodies that recognise a broad array of HIV strains by vaccination is substantial, but considerable efforts are underway.<sup>43</sup> Combinations of neutralising antibodies will probably be required to cover large proportions of HIV-1 strains.<sup>44,45</sup> Translating success of a passive antibody trial towards an active vaccination approach to induce neutralising antibodies is difficult. Use of stabilised native Env trimers is an approach that induces some useful neutralising antibodies but requires optimisation for improved efficacy.<sup>22</sup>

### Conclusion

Following the absence of vaccine efficacy shown in the STEP trial in 2007, the field promoted a so-called back-to basics approach to HIV vaccine development.<sup>46</sup> However, over a decade later, studies are repeating RV144 in clade C, and using an Ad26 instead of the Ad5, now with an Env protein boost. In both approaches, multiple immune mechanisms could be induced, but the post-hoc correlates of immunity might not be substantially clearer than they were in RV144. The desire to pursue multifaceted approaches among researchers designing and testing HIV vaccines is understandable.<sup>47–49</sup> When a specific approach is seen as potent and protective in non-human primates, specific testing of this mechanism alone is justified. This is the case for testing passive transfer of neutralising antibodies in human trials. The result should move the field forward substantially. Evidence of whether more robust T-cell immunity or non-neutralising antibody approaches alone can also protect humans from HIV is urgently needed. When vaccine approaches induce multilayered immune responses, we speculate that resolving the immune parameters of protection to enable future improvements will remain difficult.

#### Contributors

SJK and MPD contributed equally.

#### Declaration of interests

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