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HIV vaccine efficacy trial

Glimmers of hope and the potential role of antibody-dependent cellular cytotoxicity

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The partial efficacy of the recent HIV-1 vaccine trial in Thailand has rejuvenated the HIV vaccine field. There are now clear opportunities to dissect the potential correlates of protection against HIV-1. Comparisons of three major HIV-1 vaccine strategies used in human efficacy trials to date highlight a possible role for antibody-dependent cellular cytotoxicty (ADCC), rather than cytotoxic T lymphocyte or neutralizing antibody responses, in protective immunity. This review explores the HIV vaccine efficacy trials performed to date and the potential role for ADCC antibodies in assisting protective immunity.

Key words: HIV-1, vaccines, ADCC, efficacy, antibodies, neutralization, cytotoxic T lymphocyte

Abbreviations: HIV, human immunodeficiency virus; ADCC, antibody-dependant cellular cytotoxicity; Ab, antibody; NAb, neutralizing antibody; CTL, cytotoxic T lymphocyte; LTNP, long-term non-progressors

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Need for a HIV Vaccine

Over 33 million people worldwide are infected with the human immunodeficiency virus (HIV) and over 4 million new infections are occurring every year. Although antiretroviral therapy is saving many lives, new infections are greatly exceeding the number of people able to be treated through current global financial efforts.[1] There is a critical need for a vaccine to prevent new infections.

The development of a safe and effective HIV vaccine poses one of the greatest medical and scientific challenges of the 21st century. There are nine genetically distinct subtypes of HIV-1 and the amino acid sequences of just the envelope glycoprotein's can vary from 25–30% between subtypes.[2-5] The genetic diversity of HIV-1 along with the high mutation rate, are among several major obstacles for HIV-1 vaccine development.[6-8]

Despite these tribulations, several non-human primate studies suggest a HIV-1 vaccine is possible. Protection has been afforded in primate models using a number of strategies including the passive transfer of broadly neutralizing antibodies (NAb),[9-13] vaccination with rhesus cytomegalovirus (RhCMV) vectors encoding SIV Gag, Env and a Rev-Tat-Nef fusion protein[14] and vaccination with live attenuated simian immunodeficiency virus (SIV) carrying deletions of the *nef*, *nef* and *vpr* genes or an antibody-sensitive strain with complete deletion of the V1 and V2 regions of the envelope protein to attenuate the virus.[15-20] However, although these vaccine concepts provide proof-of-principle that a HIV vaccine can be achieved, none of these successful approaches are readily applicable in human trials.[21]

Human Efficacy Trials to Date

The real test comes when HIV-1 vaccine candidates progress into human efficacy trials. Here the vaccines must protect against the genetically diverse primary isolates encountered at varying viral loads and overcome the immune escape mechanisms employed by the viruses. Three concepts have been tested in large-scale human efficacy trials to date (see **Table 1**).

Vaxgen gp120 trials. Two phase III efficacy trials were carried out with variations of Vaxgen's Env subunit rgp120 vaccine (AIDSVAX™), one predominantly in men who have sex with men (MSM) in North America and the other in injecting drug users in Thailand (see **Table 1**).[22,23] Both trials assessed the efficacy of recombinant HIV-1 envelope (Env) glycoprotein

Table 1. Efficacy of human HIV-1 vaccine trials

Trial	Type of vaccine	Total #	# vaccine	# placebo	# infections vaccine group	# infections placebo group	% efficacy	Ref.
Vaxgen B/E	Gp120 protein	2527	1267	1260	106	105	none	24
Vaxgen B/B	Gp120 protein	5403	3598	1805	241	127	none	22
STEP	Adenovirus vector	3000	1494	1506	19	11	none	29
RV144	Canarypox vector prime, gp120 protein boost	16395	8197	8198	51	74	31.2	39

(rgp) 120 antigens from two strains (either 2 subtype B strains or a subtype B and a subtype E strain).[4,23,24]

Both trials were double-blind, randomized, placebo-controlled, phase III efficacy trials among high risk participants and used 7 IM doses of 300 μg of each antigen in aluminum hydroxide (Alum) adjuvant.[22,24] Robust binding antibody (Ab) titers were induced after the 3rd (6 month) dose and high NAb titers (limited primarily to the vaccine strains and related viruses) were induced after the fourth (12 month) dose.[25,26] Both trials failed to protect subjects from HIV. Some reduction in HIV acquisition was observed among black and Asian volunteers although this was not statistically significant after adjusting for the subgroup analysis.[23,27] None-the-less, these racial groups (who were in a minority in the trial) appeared to produce higher Ab titers against HIV-1 during the trial of AIDSVAX™ B/B.[23]

STEP trial. The STEP Adenovirus vector trial was a multicentre, double-blind, randomized, placebo-controlled, phase IIb, test-of-concept and efficacy study.[28,29] Volunteers, primarily MSM, were enrolled in sites within the Americas, Caribbean and Australia, where the predominant HIV-1 subtype is clade B (see **Table 1**).[28] The vaccine used was a 1:1:1 mixture of three recombinant replication defective Adenovirus subtype 5 (Ad5) vectors each containing a HIV-1 subtype B gene (*gag*, *pol* or *nef*) inserted into the deleted E1 region of the vector.[29-31] The vaccine was given on day 0, week 4 and week 26 as a 1 ml intramuscular injection containing 1.5 x 10^{10} adenovirus genomes.[30] This dosage was equivalent to the 3 x 10^{10} viral particle dose used in previous vaccine trials.[32,33]

The STEP trial aimed to prevent HIV-1 acquisition or to decrease plasma HIV-1 viral-load in infected vaccinees, a clinical correlate of disease progression and transmission. The vaccine induced a reasonably robust T lymphocyte-mediated immune response but the trial was stopped at the first interim analysis due to lack of efficacy and even some suggestion of an increased rate of HIV-1 acquisition in the vaccinated cohort (see **Table 1**).[28,29] Initially this result was thought to be due to detrimental anamnestic Ad5-specific responses,[34-36] although subsequent analyses showed lack of circumcision was found to be a bigger risk factor for HIV acquisition.[37,38]

RV144 trial. Although the gp120 protein vaccines did not reduce HIV-1 acquisition or plasma viral loads post-infection during the stand-alone phase III efficacy trial, it's ability to induce robust Ab responses in vaccinees made it a candidate as a boost for another HIV-1 vaccine. AIDSVAX™ B/E was therefore used in combination with a recombinant canarypox vector vaccine ALVAC-HIV in a prime-boost vaccine trial (RV144) in Thailand, the 3rd vaccine strategy to enter phase III efficacy trials. The study was a community-based, randomized, multicentre, double-blind, placebo-controlled assessment of efficacy in HIV-negative men and women between the ages of 18 and 30 with no regard for their risk of HIV-1 infection, i.e., at community risk of infection primarily through heterosexual transmission (see **Table 1**).[39]

The ALVAC-HIV vaccine used was a recombinant canarypox vector expressing HIV-1 gp120 from HIV-1 subtype E (CRF01_AE) strain 92TH023. This was linked to the transmembrane-anchoring portion of gp41 from HIV-1 subtype B, strain LAI, which carried a deletion in the immunodominant region. The vector also expressed HIV-1_{LAI} Gag and Protease.[39,40] Four priming injections of ALVAC-HIV at a dose of $10^{6.5}$ 50% tissue culture infectious dose ($TCID_{50}$) per injection, was given at day 0, week 4, 12 and 24.[39] The AIDSVAX B/E boost, vaccine described above, was given at weeks 12 and 24 at the same 600 μg (300 μg each) dose as was used previously in the phase III trial of this vaccine.[24,39,40]

Inhibition of HIV-1 acquisition or a reduction in plasma viral load post-infection was set as co-primary endpoints for the RV144 trial. The study showed a moderate 31.2% reduction in the risk of HIV-1 acquisition among vaccinees compared to those who received placebo in the primary endpoint analysis, the modified intention to treat analysis (see **Table 1**).[39] Plasma viral loads and $CD4^+$ T lymphocyte counts were not altered in those who became infected in the vaccine group compared to the placebo group.[39] The highest Ab titers were present during the first year following vaccination and may have been in part responsible for the protection afforded given that as Ab titers dropped off so to did the efficacy of the vaccine.[39]

Potential Immune Correlates

Neutralizing antibodies. Initial HIV-1 vaccine research was directed towards inducing NAb responses against HIV-1 antigens.[41] NAbs aggregate virions by binding to specific epitopes on their surface. This prevents virion entry into host cells and targets the virions for degradation via complement or phagocytosis (see **Fig. 1A and Table 2**).[42,43] So far attempts at eliciting protective HIV-1-specific NAb responses by vaccination have returned conflicting results.[41] Some promising non-human primate studies show protection but the dose and strain of the challenge virus may have played a large role in these trials.[44-46] The Vaxgen gp120 trials aimed to induce Env-specific humoral immune responses and indeed showed the induction of both binding and neutralizing Abs

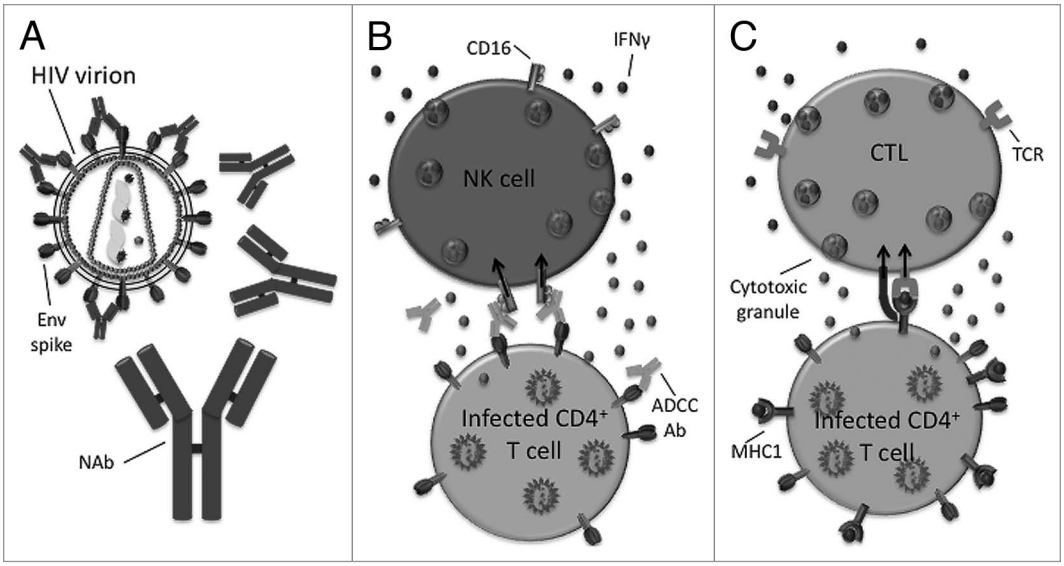

Figure 1. HIV-specific immune mechanisms. (A) NAbs attached to the Env proteins of a HIV-1 virion, (B) ADCC Abs mediating the killing of a virus infected CD4+ T lymphocyte, (C) CTL killing a virus infected CD4+ T lymphocyte.

in vaccine recipients.[25] However during the AIDSVAX™ B/E trial, blocking of HIV-1_{A244} binding to CD4 and HIV-1_{MN} neutralization were not significantly different between the 106 HIV-1 infected and 115 randomly selected uninfected vaccine recipients.[23] The lack of efficacy of the AIDSVAX™ vaccines suggests that the breadth of the NAb responses elicited by this strategy was insufficient to protect against HIV-1 infection. The inability of current vaccine strategies to induce broadly reactive NAbs against HIV-1 is probably multifactorial and a major obstacle for the design of HIV vaccines (see **Table 3**).

The Env spike found on the surface of HIV-1 consists of a trimer of non-covalently bound Env gp120 and gp41 heterodimers.[47] Conserved regions of the Env spike are shielded by extensive N-linked glycosylation and immunogenic variable loops may function to redirect Ab responses away from functionally important conserved regions.[48-52] In addition, acquired mutations in N-linked glycans have been shown to lead to the rapid escape of HIV-1 from host NAb responses.[48,53] HIV-1 can also evade antibody-mediated neutralization through conformational masking of crucial receptor-binding sites.[54,55]

The antigenic structures that induce broadly NAbs are very difficult to mimic. Currently known broadly NAbs target conserved sites such as the CD4 binding site (b12) and the membrane-proximal external region (MPER) of gp41 (2F5 and 4E10).[47,56,57] However the CD4 binding site is recessed within the Env spike and only partially accessible for Ab binding and MPER is sequestered in the lipid membrane and is only transiently exposed during viral entry, making these difficult targets to elicit NAb responses against by vaccination.[47,56,57] Further, many of the best NAbs isolated from HIV+ subjects require extensive maturation to acquire a broadly reactive phenotype—how to mimic this by vaccination is not clear. Although developing successful NAb-based HIV vaccines remains a major research priority, there are many obstacles at present.

Table 2. Beneficial NAb and CTL responses and corresponding ADCC functions

Immune mechanism	Benefit	Corresponding ADCC function
NAbs	Prevents virion entry into host cell	Binding of some ADCC Abs to free virions inhibits entry
		Production of CCL3, CCL4 and CCL5, which compete for CCR5 binding
CTLs	Kill virus infected cells	Can quickly induce killing of virus infected cells

Cell mediated immunity. The difficulties in generating broadly NAbs combined with a plethora of data highlighting the importance of cell-mediated immune responses during HIV-1 infection led research efforts to explore the protection afforded by vaccines eliciting cell-mediated immunity (see **Fig. 1C and Table 2**). The emergence of virus-specific CD8+ cytotoxic T lymphocytes (CTLs) coincides with the initial control of primary viremia during natural infection and potent polyfunctional cell-mediated immune responses are elicited in cohorts of long-term non-progressors (LTNPs).[58-63] In addition, HIV-1 infected individuals with broad Gag CTL responses and the expression of specific HLA alleles more efficiently control viral replication.[64-71]

In support of these observations, depletion of CTLs in rhesus macaques greatly abrogates control of SIV replication and primary viremia.[72,73] However other groups have shown that depletion of CTLs prior to pathogenic SIV challenge does not abrogate the protection provided by vaccination with live attenuated SIV.[74] The STEP trial failed to elicit adequate protection from HIV-1 infection despite eliciting among the most robust CTL mediated immune responses yet induced.[29,30]

The tendency for CTL responses to be focused on a limited number of epitopes

Table 3. Challenges for eliciting effective HIV-1-specific immunity and potential solutions

Immune mechanism	Challenge	Improvement provided by ADCC responses
NAbs	Narrow NAb responses elicited	Abs against multiple epitopes can be elicited
	NAbs against recessed, transiently exposed or conformational epitopes hard to induce	Abs against multiple conserved epitopes can be elicited
	Infection via cell-associated virus	Able to kill virus infected cells
CTLs	Viral escape mutants	Responses elicited against more conserved epitopes
	Time required to elicit effective response	Abs present in all secretions and large number of potential effector cells in peripheral circulation
	Mucosal homing ability of CTLs	Abs present in all secretions

and the ability of HIV to efficiently introduce mutations into these epitopes enables the evolution of viral escape mutants with the ability to successfully evade cellular immune responses.[75-78] To this end, the breadth of CTL responses would have to be large enough to restrict viral escape as well as deal with the enormous genetic diversity of primary HIV-1 isolates. Generally the STEP trial HIV-1 vaccine elicited narrow CTL responses.[30] As a result, it has been reported that subjects infected despite vaccination, although maintaining a reduced viral load, have demonstrated some viral escape from CTL responses.[79]

It is possible that targeting the "right" epitope/s will also be essential for an effective vaccine-induced CTL response. For example, multiple epitopes within conserved regions of the Gag protein may need to be targeted. A novel treatment involving the pulsing of autologous cells with overlapping peptides (OPAL) has been shown to increase the breadth of vaccine-induced immunity in macaque studies.[80] This treatment may prove useful in combination with future vaccine candidates.

Other challenges faced by these vaccine strategies include the time required for vaccine-induced CTLs to expand and the mucosal homing ability of the differentiated cells. Within the first few days of acute HIV-1 infection the virus establishes latent reservoirs.[81-84] Therefore even if a cell-mediated immune response with sufficient breadth was elicited by vaccination, the response may not be recalled rapidly enough to protect against the acquisition and establishment of enduring HIV-1 infection (see **Table 3**). Continually replicating vectors, such as recombinant CMV, may maintain effector CTLs that can more rapidly control the initial viremia.[14] Such persistent vectors face significant regulatory hurdles to enter human trials however.

Antibody-dependant cellular cytotoxicity. The recent RV144 trial attempted to induce both humoral and cell-mediated immunity to HIV-1. In light of the modest protection afforded by the vaccine regime (see **Table 1**),[39] immune responses elicited by the vaccine components are of enormous interest. The vectors used in the RV144 trial induced very limited CTL responses and the NAb responses were generally very narrow. Immunogenicity studies carried out on samples from vaccinees involved in the phase I/II trials of the RV144 prime boost strategy have highlighted a potential role for antibody-dependant cellular cytotoxicity (ADCC) in protection against HIV-1 infection.[40]

ADCC is a process which co-ordinates parts of both the adaptive and innate arms of the immune system and is a very important early immune mechanism against viral infection and tumor development.[85,86] An efficient ADCC response requires the presence of three components (see **Fig. 1B**): infected target cells that express foreign antigen on their surface, antigen specific Abs of the IgG isotype and effector cells that express Fcgamma receptors (FcγR).[85,87,88] ADCC effector cells bind via FcγRs to the cross-linked Fc portion of ADCC-mediating Abs coating the surface of a target cell. Once bound, the effector cells releases pro-inflammatory cytokines such as Interferon-gamma (IFNγ) and Tumor necrosis factor-alpha (TNFα) and initiate killing of the target cell via the release of cytotoxic granules containing perforin and granzymes.[85,89,90]

A major population of ADCC mediating effector cells are the FcγRIII (CD16) bearing natural killer (NK) cells.[88] NK cells comprise 15% of the circulating lymphocyte pool and also kill tumor and virus-infected cells via a number of antigen-non-specific mechanisms (NK activity).[85,91] Other cells including macrophages, neutrophils and eosinophils can also mediate ADCC, although these cells typically require larger Ab titers and higher antigen expression by target cells.[92,93]

The strength of an ADCC response is highly dependent on the affinity of the interaction between effector cell receptor and Ab.[94] NK cell mediated ADCC can be amplified by increasing the affinity of the Fc portion of an ADCC Ab (2G12) for CD16 (FcγRIII).[94]

The Way Forward

Could ADCC correlate with efficacy? ADCC responses during HIV infection have received some attention in the past; with researchers trying to elucidate the exact role this immune mechanism plays in natural immunity to HIV-1. ADCC responses are first detected early during primary infection.[95] Titers of ADCC Abs are the highest and the magnitudes of ADCC responses are often the greatest during early infection.[96] CD16, a key receptor for the induction of ADCC, binds with the highest affinity to the Fc portion of IgG1 and IgG3 and these are the isotypes more frequently induced during HIV-1 infection.[97,98] HIV-1 infection can lead to the reduced expression of CD16 by NK cells and the overall dysfunction of NK cell-mediated immune functions over time, which is associated with the progression of clinical disease.[99-101]

Higher titers of ADCC Abs are found in individuals infected with the less pathogenic HIV-2 than in those infected with HIV-1.[83] In light of these findings, and

spurred on by the encouraging results of the RV144 trial, attention has turned to exploring the features of an optimal ADCC Ab and key ADCC epitopes. Many of the results point to a role for ADCC in overcoming the challenges associated with inducing NAb or CTL immunity able to prevent HIV-1 acquisition and hint at a correlation between ADCC induction and a successful paradigm for protection from HIV-1 (see **Fig. 1 and Table 3**).

Firstly, in a pre-primed situation, ADCC has been shown to induce killing responses at mucosal sites of infection faster than CTLs. This is in part due to the presence of antigen-specific Abs in mucosal secretions and also to the large number of potential ADCC effector cells in the peripheral circulation (see **Table 3**).[102,103] CTLs need to traffic to the site of infection, encounter cognate antigen and also require time to expand before an effective response is elicited.[30] The temporal appearance of ADCC responses in a pre-primed milieu may have huge implications for the mounting of an effective anti-HIV immune response before the infecting virus can establish a latent infection.

ADCC Abs may also act as neutralizing Abs enabling both the killing of virus-infected cells via ADCC and the aggregation and prevention of cell entry by virions (see **Table 2**).[104] Hessel et al. have explored this dual role for NAbs with ADCC functions and shown a reduction in efficacy when mutated NAbs with an inability to engage FcRs are passively transferred into macaques prior to SHIV challenge.[105] CD16 cross-linked NK cells also produce the β-chemokines CCL3, CCL4 and CCL5, which are the natural ligands for the HIV entry co-receptor CCR5. These chemokines can compete for binding and in doing so inhibit the entry of HIV-1 into cells.[106] Therefore in addition to mediating killing of infected cells, CD16 activated NK cells can suppress viral replication by β-chemokine-mediated mechanisms (see **Table 2**).

Another key advantage of ADCC Abs is that they can target more conserved regions of HIV proteins, which may be less susceptible to viral escape.[107] The mode of spread could also have implications for the success of a HIV-1 vaccine, infection via cell-associated virus through the single cell epithelia of the colorectum or cervical canal could not be contained by NAbs.[108,109] NAbs can only sequester free virions, in this situation ADCC Abs could rapidly and efficiently mediated the killing of the transmitted infected cells (see **Table 3**).

Designing better ADCC vaccines. Further research needs to be undertaken in a few key areas in order to better direct the design of vaccines that elicit potent ADCC Abs. It is well established that broadly reactive immune responses will be required to achieve immunity to HIV-1 and there is no reason to assume that the same will not be the case for an ADCC-inducing vaccine. In order to achieve an effective, broad immune response against HIV-1, epitope-specific ADCC responses elicited naturally during infection that contribute to reducing viral replication need to be determined and subdominant and specific epitopes identified. ADCC Abs, in addition to targeting more conserved regions of HIV, are also able to recognize short linear epitopes.[107] In order to map these responses, precise and sensitive techniques are required.

In the past, the primary ADCC measuring assay used involved the labeling of antigen-coated or virus infected target cells with Chromium (^{51}Cr). The target cells were then incubated with patient serum and either patient or donor peripheral blood mononuclear cells (PBMCs), and the killing of target cells determined by the release of ^{51}Cr (^{51}Cr-release assay).[110] More modern versions of this assay employ CSFE and a fluorescent cell marker to label target cells and flow cytometric analysis of the loss of CSFE fluorescence to determine killing.[111] The nature of the target cells, the level and nature of the expression of antigen on target cells, as well as the effector-to-target cell ratio used may all contribute to variability in these assays. In addition, these assays require whole protein to coat immortalized target cells making the fine mapping of epitopes difficult.

To overcome a number of these issues, Stratov et al. developed an alternative ADCC measuring assay. This assay involves incubating patient whole blood or donor whole blood plus patient plasma with antigen and then staining with fluorescently labeled monoclonal Abs. Flow cytometric analysis of the NK cell population is performed and the ADCC response recorded as the percentage of activated NK cells based on intracellular IFNγ and degranulation marker CD107α expression.[107] As well as overcoming some of the variability issues raised by the other assays discussed, the major advantage of this assay is the ability to use small peptides or overlapping peptide pools as the antigen. Enabling the short linear epitopes of ADCC Abs as well as conformational epitopes to be determined.[107]

ADCC Abs targeting epitopes on a number of HIV proteins may also enhance the efficacy of a vaccine candidate. Once HIV begins replication, the first proteins synthesized are those involved in regulatory functions namely Rev, Tat, Vpr, Vif, Vpu and Nef.[112] ADCC Ab recognition of these initially synthesized antigens may facilitate the elimination of infected cells prior to the assembly and release of infectious virions. The additional targeting of replication and structural proteins, Pol, Env and Gag, synthesized later would provide a second line of defense and protect against infection with cell-associated virus.[112] Utilizing the ADCC measuring assay developed by Stratov et al. it may be possible to determine epitopes within these proteins able to induce potent ADCC responses.[107] Combined, this work would lead the way for the engineering of mosaic immunogens containing a greater number and more specific immunogenic epitopes within a vaccine candidate. This could potentially provide a broader array of potent ADCC Abs at mucosal sites.

Conclusions

The observation that ADCC responses are induced by the partially successful RV144 trial vaccine strategy underscores the need for further exploration and improvement of ADCC inducing vaccines. A vaccine that stimulates both cell-mediated and humoral responses may be required to achieve sterilizing immunity against HIV-1. However, we speculate that induction of ADCC Abs could play a role in the success of vaccine candidates to come. The development of new flow-cytometric

assays for measuring the ADCC mediating capabilities and epitope specificities of Abs opens the door for determining the targets and Ab isotypes that will best correlate with protection. Lessons learned from the human efficacy trials, coalesced with the results of future studies using newer technologies, should inform the design of innovative HIV-1 vaccine candidates. In turn this should bring the elusive goal of achieving high levels of immunity to HIV-1 within reach.

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