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HIV-1 vaccines
Challenges and new perspectives

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The development of a safe and effective preventive HIV-1 vaccine remains a public health priority. Despite scientific difficulties and disappointing results, HIV-1 vaccine clinical development has, for the first time, established proof-of-concept efficacy against HIV-1 acquisition and identified vaccine-associated immune correlates of risk. The correlate of risk analysis showed that IgG antibodies against the gp120 V2 loop correlated with decreased risk of HIV infection, while Env-specific IgA directly correlated with increased risk. The development of vaccine strategies such as improved envelope proteins formulated with potent adjuvants and DNA and vectors expressing mosaics, or conserved sequences, capable of eliciting greater breadth and depth of potentially relevant immune responses including neutralizing and non-neutralizing antibodies, CD4+ and CD8+ cell-mediated immune responses, mucosal immune responses, and immunological memory, is now proceeding quickly. Additional human efficacy trials combined with other prevention modalities along with sustained funding and international collaboration remain key to bring an HIV-1 vaccine to licensure.

Introduction

According to UNAIDS, 35.3 million people were living with HIV-1 at the end of 2012, the vast majority being in sub-Saharan Africa. Worldwide the number of people including children with new HIV-1 infection fell by 33% since 2001.[1] This fragile although uneven success in prevention programs can be ascribed to the strengthening and scaling-up of antiretroviral treatment along with existing and new prevention methods such as behavioral interventions,[2] treatment of sexually transmitted diseases, harm reduction,[3] male circumcision,[4] and prevention of mother-to-child transmission.[5] New prevention strategies including pre-exposure prophylaxis (PrEP),[6] antiretroviral treatment (ART) for prevention,[7] topical microbicides,[8] and HIV-1 preventive vaccines must be further explored and their access ensured. A mathematical modeling analysis showed that the implementation of combined strategies such as medical male circumcision, earlier ART and PrEP could lead to dramatic declines in HIV-1 incidence, but will not stop transmission completely.[9] A preventive HIV-1 vaccine as part of a comprehensive prevention package[10] remains therefore among the best hopes for controlling the HIV/AIDS pandemic.[11]

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Goals of an HIV-1 Vaccine

One would expect that an HIV-1 vaccine would bring both individual and public health benefits. The first goal of an HIV-1 vaccine would be to prevent HIV-1 infection and provide sterilizing immunity. A Phase III community-based efficacy trial conducted in Thailand (RV144) in mostly heterosexual populations showed that the first goal was indeed achievable. The vaccine regimen conferred an estimated efficacy of 31% against HIV-1 acquisition after 42 mo of follow-up, with a vaccine efficacy of 60% at month 12 and declining thereafter.[12,13] It provided the first opportunity to study immune correlations with vaccine efficacy against HIV-1,[14] which may permit rational vaccine design and iterative improvement.

A second goal would be to reduce peak and set point viral load by controlling viral replication and to stop progression to clinical disease in vaccine recipients who became infected. These 2 goals are complementary. However, the acceptance of a preventive vaccine that would only reduce viral load seems unlikely, as the validation of immune markers that counter viral replication[15] would need to be supported by the demonstration of clinical benefit against progression to disease. In an era where the benefits of early highly active antiretroviral treatment are well established, this might be difficult ethically.

Scientific Challenges

The development of HIV-1 vaccines faces multiple scientific challenges inherent to the biological properties of HIV-1. HIV-1 integrates as a provirus into the chromosomes of long-lived reservoir memory T-cells where it can persist in a latent state.[16] HIV-1 globally presents extraordinary sequence diversity within and between subtypes and multiple circulating recombinant forms have been generated.[17,18] Natural infection does not in general induce protective immunity that eradicates (sterilizing) the virus or prevents progression to disease. The trimeric HIV-1 envelope glycoprotein is composed of variable regions

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Table 1. Phase IIb and III efficacy trials conducted in humans

Study	Year of publication	Vaccines	Phase	Volunteers' risk	Location	Result
Vax004	2005	AIDSVAX B/B gp120 in alum	III	MSM and women at high risk	USA Europe	No efficacy
Vax003	2006	AIDSVAX B/E gp120 in alum	III	Injecting drug users	Thailand	No efficacy
HVTN 502 Step trial	2008	MRKAd5 HIV-1 gag/pol/nef B	II b	MSM and heterosexual women and men	USA	No efficacy; transient increased infection rate in vaccinees
RV144	2009	ALVAC-HIV vCP1521 and AIDSVAX B/E rgp120 in alum	III	Community-risk	Thailand	31.2% efficacy at 42 mo, 60% at 12 mo against HIV acquisition. No effect on plasma viral load and CD4 count
HVTN 503 Phambili trial	2011	MRKAd5 HIV-1 gag/pol/nef B	II b	Heterosexual men and women	Republic of South Africa	No efficacy; increased HIV infection rate in vaccinees
HVTN 505	2013	DNA and rAd5 (A, B, and C)	II b	MSM with Ad5-specific antibody titers < 1:18 (negative)	USA	Stopped for futility; no efficacy on HIV acquisition, plasma viral load and CD4 count

that are immunodominant and induce type-specific neutralizing antibodies of limited breadth, while the conserved regions such as the CD4 binding site are cryptic and poorly accessible to the immune system.[19] Broadly neutralizing antibodies (bNAb) develop in roughly 20% of HIV-infected after 2–3 y, but these bNAb do not appear to limit disease progression.[20] HIV-1 Env is covered with glycans that shield conserved epitopes from antibody recognition and evade the neutralizing antibody response.[21] An effective HIV-1 vaccine should therefore induce responses that differ qualitatively and quantitatively from that induced by natural infection, and able to cross-protect against various HIV-1 clades.[22]

The limited although increasing knowledge of immune correlates of protection in humans and the poor positive predictive value of animal models mean that further empirical proof-of-concept trials are justified.

Human Efficacy Trials—What Works and What Doesn't for Protection

Six HIV-1 vaccine efficacy trials had been conducted, which, put in perspective offer some insights into possible immune correlates for protection (**Table 1**).

Vax003 and Vax004

Monomeric gp120 HIV-1 envelope proteins failed to protect high-risk volunteers in 2 efficacy trials. Vax004 tested a bivalent recombinant HIV-1 subtype B (GN08 and MN) envelope glycoprotein subunit vaccine in US, Canada, and Netherlands men who have sex with men (MSM) and women at high risk for heterosexual transmission of HIV-1.[23] The vaccine did not prevent HIV-1 acquisition nor did it affect HIV-1 disease progression.[24] High neutralizing antibody levels against easy-to-neutralize MN strain were however significantly inversely correlated with HIV-1 incidence while low levels against more-difficult-to-neutralize viruses suggests that level and breadth were not sufficient for protection.[25] Whether the final level of efficacy reflects positive and negative effects on acquisition remains speculation.[26] The level of vaccine-induced antibody-dependent cellular virus inhibition activity (ADCVI) correlated inversely with the rate of acquiring HIV-1 infection following vaccination, However, ADCVI activity correlated poorly with neutralizing or CD4-gp120-blocking antibody activity measured against laboratory strains and was modulated by FcR polymorphisms.[27] Vax003 tested a bivalent recombinant HIV-1 subtype B/E (A244 CRF01_AE and MN subtype B) envelope glycoprotein subunit vaccine in injecting drug users (IDU) in Bangkok, Thailand.[28] The vaccine did not prevent HIV-1 acquisition nor did it affect HIV-1 disease progression. The failure of these 2 antibody-inducing vaccines led to developing and testing vaccines inducing cell-mediated immune responses.

Step and Phambili

The Step (HVTN 502/Merck 023) and Phambili (HVTN 503) vaccine trials explored whether cell-mediated immune response-inducing vaccines could prevent infection or reduce post-infection plasma viral load. The Merck vaccine (MRKAd5 HIV-1) was a mixture of replication-defective Ad5 vectors expressing HIV-1–1 *gag, pol*, and *nef* subtype B genes. The Step study enrolled predominantly high-risk populations including MSM as well as heterosexual women and men.[29,30] The Phambili study enrolled heterosexual men and women in South Africa.[31] The Step trial was halted after a pre-specified interim analysis (when 30 per-protocol events had arisen in the group with Ad5 antibody titer 200 or less) that showed no protection against HIV-1 acquisition. This finding prompted the Phambili trial Ethics Committee to halt the study. There were excess HIV infections in the vaccine group but statistical significance was not seen in the primary study; post-hoc follow-up of data from both Step and Phambili rAd5 trials has suggested increased risk of HIV infection in vaccine recipients, though methodologic problems are significant. There was no significant decrease in HIV-1 viral load in the vaccine group compared with the placebo recipients in Step or Phambili. However, Phambili was unblinded prior to complete enrollment and vaccination, and interpretation of

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results is subject to multiple biases.[32] Post-hoc multivariate analysis of the Step study suggested that risk was greatest in uncircumcised men with pre-existing Ad5-NAb were at greatest increased risk for HIV-1 acquisition,[33] waned with time from vaccination,[34] and was not explained by behavioral factors.[35] The presence of Ad5-NAb was not linked to the risk of HIV-1 acquisition among unvaccinated populations at elevated risk of HIV-1 infection.[36] In addition, subjects infected during the Step trial seemed to have qualitative immune differences that increased their risk of HIV-1 infection independent of vaccination.[37] A sieve analysis showed evidence of vaccine-elicited immune pressure on the founder virus though no specific CD8+ CTL recognizing that epitope could be identified.[38] Moreover vaccinees with HLA alleles associated with HIV-1 control had a significantly lower mean viral load over time.[39] Interestingly, the most highly conserved epitopes were detected at a lower frequency, suggesting that stronger responses to conserved sequences may be as important as breadth for protection.[40]

Similar Ad5 vector–based vaccines did not protect macaques from infection with SHIV89.6P but reduced viral load and preserved CD4+ T cell post-infection, findings that were not reproduced in the human trials.[41] The outcome of the Step trial was recapitulated in an Indian rhesus macaque study where animals vaccinated with a regimen similar to that employed in the Step trial were not protected against a SIVE660 challenge.[42] Rhesus macaques chronically infected with a host-range mutant Ad5 (Ad5hr) and immunized with a rAd5 SIVmac239 *gag/pol/nef* vaccine were challenged with a series of escalating dose penile exposures to SIVmac251. Despite inducing CD8+ T-cell responses in 70% of the monkeys the vaccine did not protect vaccinated animals from penile SIV challenge.[43]

HVTN 505

Aiming at inducing both functional antibodies and cell-mediated responses,[44] a regimen with DNA vaccine prime composed of DNA plasmids encoding Gag, Pol, and Nef from HIV-1 subtype B and Env from subtypes A, B, and C and replication-defective rAd5-HIV-1 vaccine boost containing a mixture of 4 rAd5 vectors encoding the HIV-1 subtype B Gag-Pol and Env matching the DNA Env components was tested in Phase I[45-47] and IIa[48] clinical trials. As opposed to the MRKAd5 HIV-1 vaccine that did not contain an envelope gene, the HVTN 505 vaccine contained 3 envelope genes. The vaccine regimen induced polyfunctional CD4+ and CD8+ T-cells, multi-clade anti-Env binding antibodies, and Nab against easy to neutralize Tier 1 viruses. The Phase IIB trial (HVTN 505) was recently stopped for futility, showing no efficacy and no statistically significant effect on viral load and a non-significant excess of HIV infection in the vaccinated group.[49] Further analysis is ongoing.

This prime-boost vaccine regimen failed to protect NHP against SIVmac251 infection, but 50% of vaccinated monkeys were protected from infection with SIVsmE660 with about a one-log reduction in peak plasma virus RNA in Mamu-A*01-positive animals, suggested a role of cytotoxic T lymphocytes in the control of SIV replication. However, low levels of neutralizing antibodies and an envelope-specific CD4+ T-cell response were associated with vaccine protection in these monkeys.[50] SIV-specific CD8+ T cells of effector memory phenotype showed strong virus-inhibitory activity (VIA) and correlated with high levels of CD107a mobilization and perforin expression.[51]

RV144

A Phase III community-based trial conducted in Thailand (RV144) provided the first evidence that an HIV-1 vaccine could confer protective efficacy against HIV-1 acquisition. The prime-boost vaccine regimen consisted of a recombinant canarypox vector, ALVAC-HIV prime (vCP1521, expressing *gag, protease* subtype B [LAI] and *env* gp120 CRF01_AE with a gp41 subtype B [LAI] transmembrane anchor) and a bivalent AIDSVAX® gp120 B/E MN and CRF01_AE (A244) boost. The vaccine regimen was safe and well tolerated.[52] The modified intent-to-treat analysis showed an estimated 31.2% efficacy after 42 mo of follow-up post first vaccination.[12,53] Post hoc analysis of the interaction of risk status and acquisition efficacy was significant with greater benefit in low-risk individuals.[13] Vaccine efficacy appeared to be higher (60%) at 12 mo post first vaccination, suggesting an early, but nondurable, vaccine effect. There was no effect on early post-infection HIV-1 RNA VL or CD4+ T-cell count. Vaccination did not affect the clinical course of HIV-1 disease after infection, though there was evidence of reduction in seminal fluid viral load.[54]

IFN-γ ELISPOT positive responses were detected in 41% of the vaccinees and predominantly CD4+ T cell-mediated. Responses were targeted within the HIV-1 Env region, with up to 60% of vaccinees recognizing peptides derived from the Env V2 region, which includes the α4β7 integrin binding site. Intracellular cytokine staining confirmed that Env responses predominated and were mediated by polyfunctional effector memory CD4+ T cells displaying a cytolytic phenotype.[55]

Binding antibody against Env was nearly uniformly present to the MN and A244 vaccine antigens, but dropped 15-fold after 6 mo; p24 responses were less frequent. Antibody-dependent cell-mediated cytotoxicity (ADCC) in vaccine recipients and mediated by monoclonal (mAb) antibodies from vaccine recipients were described.[56,57] Neutralization of Tier 1 viruses was detected in both RV144 and Vax003. The RV144 regimen was superior to 2 gp120 protein administrations alone, confirming a priming effect for ALVAC-HIV, but was inferior to a 12-mo regimen of 4 AIDSVAX® B/E inoculations.[58] Further analysis suggested that the lack of response to a vaccine designed to induce clade-specific HIV-1 NAb is associated with the presence of certain HLA class II alleles in Southeast Asians.[59]

Correlates of protection—new perspectives

The RV144 trial provided a unique opportunity to perform a case control study of correlates of risk. Plasma IgG binding antibody to scaffolded gp70 V1V2 envelope proteins correlated inversely with risk of infection (higher antibody levels correlated with lower rates of infection.), while Env plasma IgA correlated directly with a higher rate of infection, raising the hypotheses that IgA responses against Env and IgG responses directed against V1V2 may be mechanistically associated with protection. Neither low levels of V1V2 antibodies nor high levels of Env-specific IgA antibodies were associated with higher rates of infection than in the placebo group. In vaccinees with low levels of Env-specific

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Table 2. Correlates of protection: lessons learned in human efficacy trials

Vax004: No prevention of HIV acquisition or disease progression
High neutralizing antibody levels against MN strain inversely correlated with HIV incidence
ADCVI correlated inversely with the rate of acquiring HIV infection
ADCVI correlated poorly with neutralizing or CD4-gp120-blocking antibody activity and was modulated by FcR polymorphisms
Vax003: No prevention of HIV acquisition or disease progression
No correlate whatsoever identified
Step (HVTN 502) and Phambili (HVTN 503): No prevention of HIV acquisition or disease progression
Sieve analysis showed evidence of vaccine-elicited immune pressure on the founder virus though no specific CD8+ CTL recognizing that epitope could be identified
Vaccinees with HLA alleles associated with HIV-1 control had a significantly lower mean viral load
HVTN 505: No prevention of HIV acquisition or disease progression
Analysis on going
RV144: 31.2% efficacy for HIV acquisition at 42 mo, 60% at 12 mo. No prevention of disease progression
Plasma IgG binding antibody to scaffolded gp70 V1V2 envelope proteins and V3 peptide correlated inversely with risk of infection (high antibody level correlated with lower rate of infection.) Env IgG3 antibodies correlate inversely with risk of infection.
Env plasma IgA correlated directly with higher rate of infection
Low levels of Env-specific IgA antibodies, IgG avidity, ADCC, neutralizing antibodies, and Env-specific CD4+ T cells, were inversely correlated with higher rate of infection. Plasma Env IgA can block ADCC.
Sieve analysis identified 2 vaccine-associated genetic signatures in V2 corresponding to sites 169 and 181, further supporting the hypothesis that vaccination-induced immune responses directed against the V2 loop were associated with protection. Sieve analysis identified a V3 signature suggesting a potential role of V3 antibodies in protection.
V2-specific antibodies can mediate ADCC, neutralization and low-level virus capture FcγRIIC polymorphism is associated with vaccine efficacy and correlates of HIV-1 infection risk
Exploration of mucosal immune responses on going in follow-up Phase II trials

IgA antibodies, IgG avidity, ADCC, neutralizing antibodies, and Env-specific CD4+ T cells, correlated inversely with risk of infection.[14,60-62] Two weeks post last vaccination 97% of RV144 studied plasma samples from vaccine recipients contained antibodies to V2 region synthetic peptides, falling to 19% at 48 wk, suggesting that waning vaccine efficacy may be correlated with waning V2 antibody response. Interestingly, gp70 V1V2 antibodies were lower in HVTN 505 compared with RV144.[63] The response to V3 CRF01_AE also correlated inversely with the risk of HIV infection in vaccine recipients with lower levels of Env-specific plasma IgA and neutralizing antibodies. In Vax003 and Vax004 (no protection), serum IgG responses targeted the same epitopes as in RV144 with the exception of an additional C1 reactivity in Vax003 and infrequent V2 reactivity in Vax004. These results along with a recent sieve analysis[64] generate the hypothesis that IgG to linear epitopes in the V2 and V3 regions of gp120 are part of a complex interplay of immune responses that contributed to protection in RV144.[65]

Approximately 90% of incident infections in RV144 were CRF01_AE, the predominant circulating strain in much of South East Asia. A sieve analysis identified 2 vaccine-associated genetic signatures in V2 corresponding to sites 169 and 181, further supporting the hypothesis that vaccination-induced immune responses directed against the V2 loop were associated with protection.[66] Monoclonal antibodies from RV144 vaccine recipients contact the V2 K169 residue, providing further evidence that vaccine-induced antibodies correspond to the observed sieve effect. These V2-specific antibodies can mediate ADCC, neutralization, and low-level virus capture.[67,68] These findings generate the hypothesis that V2 IgG may play a role in protection against HIV-1 acquisition but do not provide evidence of a mechanistic or non-mechanistic correlate of protection.[69]

Sequences in gp70 V1V2 antigens other than V2, such as C1 and V1, may significantly contribute to the binding responses. Some light has recently been shed on the role of plasma IgA in RV144. In the presence of low anti-Env IgA, both ADCC and NAb responses correlated with decreased risk of infection. ADCC responses were predominantly directed to the C1 conformational region of gp120.[57,70,71] IgA antibodies elicited by RV144 block C1 region-specific IgG-mediated ADCC.[72] Whether V2 antibodies might block the gp120-α4β7 interaction[73,74] and contribute at least partially to the protective effect against HIV-1 sexual transmission remains to be demonstrated.[75] In future trials, assessing IgG and IgA to V1V2 binding antibody immune responses in the mucosal compartments will be key.

In previous clinical studies, monomeric gp120 induced high levels of Env-specific IgG4 antibodies[76] while ALVAC (vCP1452) prime and gp120 MN in alum boost elicited lower IgG4 relative to IgG1 and IgG3 antibodies.[77] Antigen-specific IgG3 antibodies are associated with long-term control of *Plasmodium falciparum*[78]

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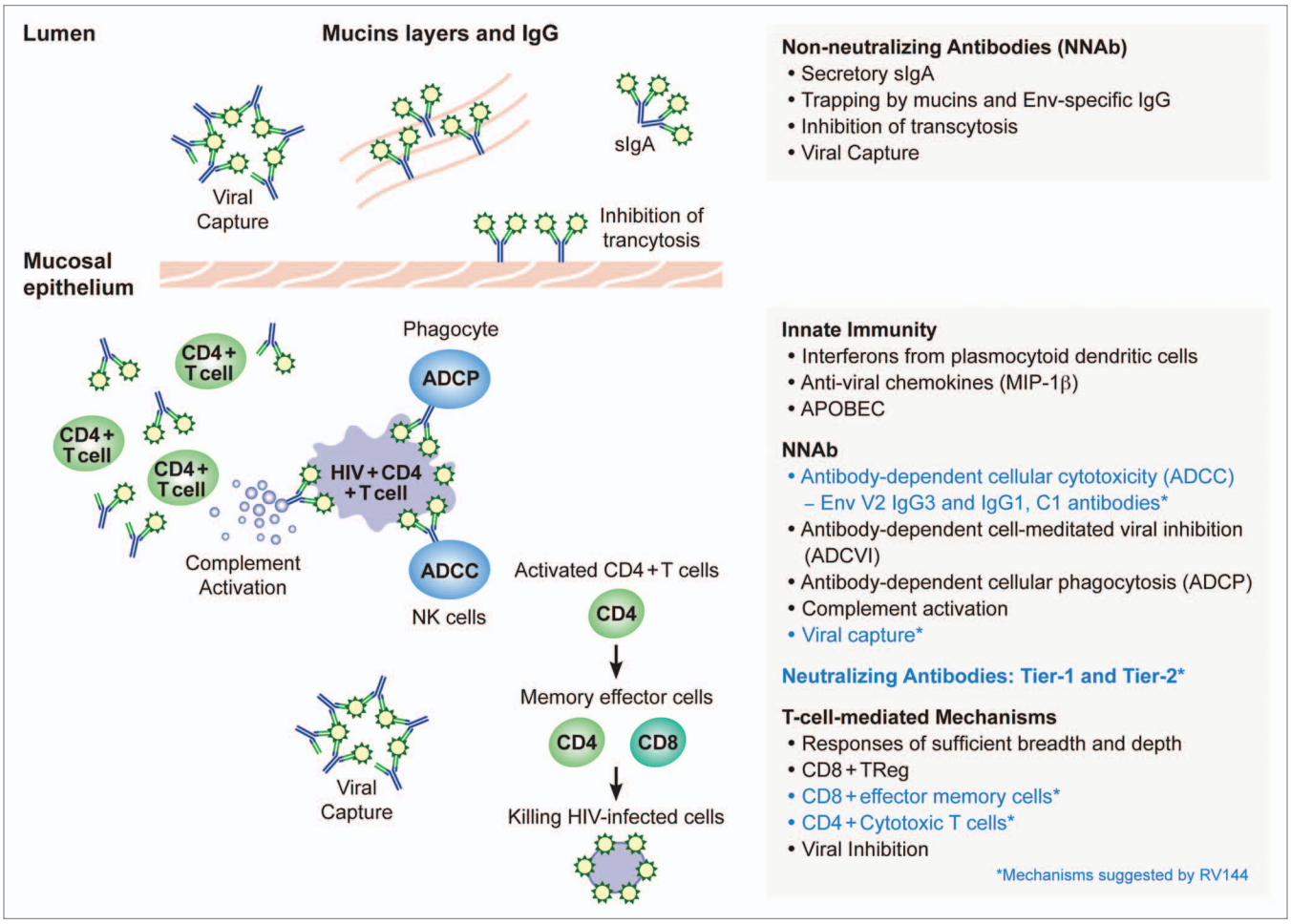

Figure 1. Possible vaccine-induced immune mechanisms of protection against HIV-1 acquisition in humans.

and monocyte-mediated cellular inhibition of parasite growth in vitro.[79] Similarly, early appearance of chikungunya virus-specific IgG3 neutralizing antibodies is associated with clearance of the virus and long-term clinical protection.[80] Conversely, IgG4 have been associated with progression to AIDS.[81] IgG3 can fix the complement and has high affinity for FcγR. A recent comparison of RV144 and Vax003 showed that Env-specific IgG3 and V1/V2 IgG3 response rates were higher in recipients of the RV144 vaccine compared with those of Vax003 vaccinees and conversely that IgG4 were considerably lower in RV144. V1/V2 IgG3 responses and IgG3 responses specific for V1/V2 169K correlated with decreased risk of HIV-1 infection after IgA adjustment.[82] It is speculated that ALVAC priming due to its unique proinflammatory cytokine and chemokine response following vaccination in rhesus monkeys and infection in human PBMC[83] may shape the IgG subclass response to IgG3 in response to envelope protein boost in humans compared with envelope vaccination alone. The contribution of Fc–FcγR interaction-mediated antibody function through mechanisms including ADCC, antibody-dependent cell mediated viral inhibition (ADCVI), and antibody-dependent cellular phagocytosis (ADCP) remains to be explored.[84,85] A recent post hoc analysis of RV144 showed an association between the FcγRIIC polymorphism and vaccine efficacy and correlates of risk, emphasizing the potential role of FcR genetics in predicting vaccine efficacy.[86]

Lessons learned from non-human primate challenge studies

Several NHP studies support the RV144 findings. ALVAC-SIV conferred protection from infection in neonates macaques exposed to repeated low-dose challenge.[87] An immunization regimen recapitulating the RV144 regimen protected against mucosal challenge of SIVmac251 acquisition in 30% of the vaccinated animals. Protected animals had a higher avidity antibodies to gp120, recognized the V2 variable envelope region, and reduced SIVmac251 infectivity in cells expressing high level of α4β7, suggesting a functional role of V2 antibodies.[88] Microarray analysis showed that NK cell-associated genes were upregulated after the first protein boost with increased frequency of NK22 cells expressing CCR6 (a gut homing marker) at mucosal sites and of NKG2A+ cells expressing either CD107a or IFN-γ.[89]

Similarly, an Ad26 prime and MVA boost regimen using vaccines expressing *gag-pol* and *env* from SIVsme543 conferred 80–83% reduction in the per-exposure probability of infection against repeated low dose intrarectal inoculations of the heterologous neutralization-resistant SIVmac251. Post-infection set point viremia was reduced of 2.3 log by vaccination and was correlated with magnitude and breadth of T-cell responses to

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Gag. Protection against SIV acquisition correlated with Env and V2-specific binding and Tier 1 strain-neutralizing antibodies. Responses to Env are critical to prevent acquisition, as monkeys vaccinated with an Ad35/Ad26 prime-boost regimen expressing either Gag-Pol and Env or only Gag-Pol showed significantly greater protection when Env was present. Both vaccine regimens resulted in significant reductions of set point viral loads compared with controls. Immunological correlates of protection were consistent with the first experiment.[90] A recent intrarectal SIVsmE660 NHP challenge study where animals were vaccinated with DNA/Ad5 expressing mosaic envelopes confirmed that Env-elicited immune responses are necessary and sufficient to provide protection from acquisition.[91] The availability of pathogenic SHIV constructs with HIV-1 E, C, or B envelopes remains critically needed for assessing the efficacy of the ALVAC-AIDSVAX combination, other new HIV vaccines, passive HIV-1-specific immunoglobulin studies (e.g., V2-specific mAb from RV144 vaccine recipients, bNAb).

The predictive value of NHP studies is challenged by the results of the Step study[41] and more recently of HVTN 505. Several rhesus macaque studies support the role of CD8+ T cells in preventing HIV-1 infection and disease[92-94] but results widely differ depending on the modes of administration, virus challenge, and immunological endpoints used.[95-98] Rhesus macaques were generally immunologically more responsive to vaccination than humans while the hierarchy in potency of single-modality (same vaccine product) prime–boost regimens using several vector approaches seem well predicted. In contrast, prime–boost vaccine regimens and vaccines using adjuvant formulations did not correlate between rhesus macaques and humans.[99]

An emerging understanding of the early events in mucosal SIV, SHIV, and HIV-1 infections has been recently reviewed[100,101] justifying the need to develop vaccines inducing both humoral (either local produced or resulting from transudation of plasma antibodies) and cell-mediated mucosal immune responses. A relatively small number of immune effectors at the mucosal site of entry might be at the right place at the right time to be "enough and soon enough" to clear infection. T cell-inducing HIV-1 and SIV vaccines using non-replicating vectors classically induce CD8+ central memory T-cell (TCM) responses whose protective ability depends on an anamnestic expansion to combat infection. In contrast, a replication-competent Rhesus cytomegalovirus (RhCMV)-based vaccine expressing SIV proteins was able to induce and maintain high frequency of SIV-specific CD4+ and CD8+ T-cell effector memory (TEM) responses at extra-lymphoid sites without measurable antibody responses to SIV. Fifty percent of vaccinated monkeys showed a stringent control of intra-rectally administered highly pathogenic SIVmac239 for more than a year. The outcome of challenge in RhCMV vector-vaccinated monkeys was predicted by peak SIV-specific CD8+ TEM frequencies in peripheral blood pre-challenge.[102,103] RhCMV vectors are unaffected by pre-existing CMV-specific immunity and can repeatedly super-infect RhCMV-positive monkeys and elicit high frequency SIV-specific CD4+ and CD8+ TEM responses.[104]

Prior infection of rhesus macaques with an attenuated SHIV conferred protection against vaginal challenge associated with SIV-specific CTL in cervical vaginal tissues,[105] suggesting that a modest vaccine-induced CD8+ T-cell response in the context of immunoregulatory suppression of T-cell activation may protect against vaginal HIV-1 transmission.[106] Supporting this hypothesis, macaques immunized with an oral vaccine comprised of *Lactobacillus plantarum*, a commensal bacterium that favors immune tolerance, and inactivated SIVmac239 induced CD8+ regulatory T cells (Tregs) completely protected 15 of 16 animals without inducing SIV-specific antibodies or CTL. Infection was seen after re-challenge but viral load was undetectable. Infusion of CD8 antibodies confirmed the role of CD8+ Tregs in preventing/suppressing SIV in vivo in the absence of vaccine-induced antibodies in mucosal secretions. These findings suggest a new avenue of research toward developing an HIV-1 vaccine.[107]

Interestingly, human dimeric IgA1 mAb-treated rhesus macaques remained free of virus after intrarectal SHIV challenge while treatment with dimeric IgA2 was much less effective. Protection was correlated with virus capture and inhibition of transcytosis of cell-free virus.[108]

New vaccine concepts

The various vaccine concepts tested in humans and lessons learned have recently been reviewed.[109] Countering HIV-1 variability remains one of the main hurdles for HIV-1 vaccines. Although considerable efforts are deployed to better understand the mechanisms of neutralization and develop a vaccine capable of inducing broadly neutralizing antibodies,[110,111] these concepts have not yet been evaluated in human clinical trial. Other Env subunit protein approaches aim at improving the results observed in RV144. The analysis of A244 gp120 used in RV144 demonstrated that the deletion of 11 N terminus aminoacids of gp120 (Δ11) enhanced the antigenicity to gp120 C1 region and to V2 conformational epitopes. Conformational V1/V2 mAbs gave significantly higher levels of blocking of plasma IgG from A244 Δ11 gp120 immunized animals than IgG from animals immunized with unmodified A244 gp120.[112] Another approach using gp41 protein and derived peptide administered by mixed intramuscular and intranasal modalities was capable of protecting immunized monkeys against SHIV challenge[113] and of eliciting systemic and mucosal antibodies inhibiting HIV transcytosis in the absence of neutralizing antibodies in humans.[114]

Bypassing the immune system by intramuscular delivery of an adeno-associated virus type 1 gene transfer vector expressing HIV-1-specific broadly neutralizing antibodies is an attractive strategy and is now in clinical trial with vector-expressed bNAb PG9. HIV-1-specific antibodies are endogenously synthesized in myofibers and passively distributed to the peripheral blood. Long-lasting neutralizing activity in serum of macaques administered with a vector expressing SIV-specific antibodies conferred complete protection against SIV intravenous challenge.[115] The same strategy was immunogenic in humanized mice[116] and able to protect against SHIV challenge.[117]

Vectors encoding conserved HIV-1 sequences[118] are now tested in humans.[119] Vaccine-elicited responses toward conserved regions could afford partial protection against a high-dose intrarectal SIVmac251 challenge.[120] However, NHP immunized

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with full-length HIV-1 immunogens elicited increased magnitude and breadth of cellular immune responses compared with conserved-region-only HIV-1 immunogens, including against conserved sequences.[121] Mosaic HIV-1 antigens expressed by Ad26 vectors markedly augmented both the breadth and depth of antigen-specific CMI responses as compared with consensus or natural sequence HIV-1 antigens in rhesus monkeys.[122] Recently, Ad26/MVA and Ad26/Ad35 vector-based vaccines expressing HIV-1 mosaic Env, Gag, and Pol afforded a significant reduction in the per-exposure acquisition risk following repetitive, intrarectal SHIV-SF162P3 challenges. Protection against acquisition of infection correlated with vaccine-elicited binding (although not with V2 responses), neutralizing, and functional non-neutralizing antibodies, suggesting that the coordinated activity of multiple antibody functions may contribute to protection against difficult-to-neutralize viruses.[123] In-depth analysis of the HVTN 505 results and underlying immune responses and sieve analysis might inform the development of other non-Ad5 rare serotype adenoviruses vectors such as Ad26, Ad35,[124] or ChAdV63[125] and more generally of T-cell-inducing vaccine strategies. DNA administered intramuscularly by electroporation augmented elicited T-cell immune responses compared with needle injection.[126] While successful in macaques,[95] the adjuvant effect of added genes expressing IL-12 or IL-15 cytokines did not dramatically improve T-cell immune responses in humans.[127]

The degree of live-attenuated SIV vaccine-mediated protection against SIVmac239 challenge strongly correlated with the magnitude and function of SIV-specific, effector-differentiated T cells in the lymph node but not with the responses of such T cells in the blood or with other cellular, humoral, and innate immune parameters. The maintenance of protective T-cell responses was associated with persistent live-attenuated vaccine replication in the lymph node, which occurred almost exclusively in Tfh cells. The maintenance of lymphoid tissue-based, effector-differentiated, SIV-specific T cells that intercept and suppress early wild-type SIV amplification and can control and perhaps clear infection, provides a rationale for the development of persistent vectors that can elicit and maintain such response.[128] Several replication-competent vectors are in preclinical development or early clinical development.[129]

Research Priorities

New efficacy trials of pox-protein vaccines

The pox-protein or DNA-pox-protein vaccine strategies remain the most likely to proceed to new efficacy trials. Although RV144 protective efficacy was 31.2% 42 mo after first vaccination, the highest efficacy (60%) was observed at 6–12 mo. The Pox Protein Public Private Partnership or P5 (Sanofi Pasteur, Novartis, Bill and Melinda Gates Foundation, US National Institutes of Health, HIV Vaccine Trial Network, and US Military HIV Research Program) is dedicated to building on the RV144 result and developing pox-protein HIV-1 vaccines with the potential for broad public health impact. A vaccination regimen with ALVAC-HIV prime and gp120 Env subunit protein boost will be tested in efficacy studies in Thailand and South Africa in high risk populations (MSM and heterosexual, respectively) with different HIV-1 subtypes (CRF01_AE and subtype C, respectively).

Independently, a Phase IIB trial with subtype C DNA prime followed by another recombinant pox vector (replication-defective vaccinia, NYVAC) boost with or without additional envelope protein subunit boost is planned in high-risk heterosexual populations Southern Africa. A similar strategy using DNA prime and replicating vaccinia Tiantan boost[130] is under consideration for efficacy testing in a Phase IIB in MSM in China.

However, less advanced in development, it is anticipated that a next wave of efficacy trials might test vaccines expressing bNAb, mosaic antigens or conserved sequences or other less advanced vaccine strategies such as gp41 virosomes (described above) as well as full-length single chain gp120-CD4 complex (FLSC)[131] in prime-boost with a pox vector.

Correlates of risk

Table 2 summarizes the main findings on correlates of risk identified in the different human efficacy trials while **Figure 1** displays possible immune mechanisms involved in protection. The identification of potential immune correlates of risk in RV144 has raised numerous scientific questions. Follow-up clinical trials are planned to assess the respective roles of the RV144 vaccination regimen components (ALVAC-HIV and AIDSVAX B/E) in eliciting immune responses in the peripheral blood and in mucosal compartments, the patterns of gene activation immune signature and their prediction of immune responses, the levels of innate apolipoprotein B expression, whether HIV-specific antibody titers, in particular V2 antibodies can be increased and sustained with additional envelope boosts, and the immune memory with late (>7 y) booster injections to RV144 vaccine recipients. The role of humoral and cell-mediated immune responses in the mucosal compartments deserves further exploration including the fine specificity of HIV-1-specific antibody response in mucosal secretions (IgG subclasses, IgA, and IgG V2 antibodies) and their possible hindrance of HIV mobility[132,133] and virus replication ex vivo.[134] While V2 antibodies generated by the RV144 vaccine regimen are cross-reactive with other HIV-1 subtypes, it remains equally critical to assess whether Env subunit proteins derived from different HIV-1 subtypes can elicit cross-reactive V2 antibodies.

Broadly neutralizing antibodies

The study of bNAb and their induction by immunogens remains a focus of research activity and were recently reviewed.[19,110,135] Broadly cross-reactive HIV-1 NAb selected from the bone marrow (BM) of HIV-1-infected long-term non-progressors contains numerous somatic mutations. The recent finding that a transmitted/founder Env can be the stimulator of a potent bNAb and bind optimally to that bNAb unmutated ancestor may be key for vaccine design and could allow the induction of bNAb by targeting unmutated ancestors and intermediate ancestors of bNAb clonal lineage trees.[136] The overall architecture of a soluble trimeric envelope, as well as the secondary, tertiary, and quaternary interactions between gp120 and gp41 involved in its assembly were recently described. In particular, the gp120 subunits are held together by

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association of the V1/V2/V3 regions at the apex of the trimer.[137] The complete definition of how neutralization epitopes are presented in the context of a trimeric envelope should help the design of new immunogens as candidate vaccines. The study of B cells in the peripheral blood, BM and gut of vaccine recipients may help elucidate the rapidly waning antibody response observed in RV144.[138] It remains however critical to demonstrate that bNAb may confer protection against HIV infection in humans.

T-helper cells

Immunization with soluble Env was reported to induce short-lived antibody responses with robust peak followed by rapid contraction of circulating antibody and memory B cells.[139] Optimizing CD4+ T-cell responses in HIV-1 vaccine development has gained renewed attention,[140] in particular T follicular helper cells (Tfh). Tfh play an essential role for B-cell selection and proliferation in germinal centers, for somatic hypermutations and the development of high-affinity and broadly neutralizing antibodies. The frequency of a subpopulation of circulating memory PD-1+ CXCR5+ CD4+ T cells that are resting memory cells most related to bona fide germinal center Tfh cells by gene expression profile, cytokine profile, and functional properties was correlated with the development of HIV-specific bNAbs in HIV-infected individuals.[141] A better understanding of CD4+ T-cell fine specificity and functions in particular the coordinating mechanisms that lead to persistent protective CD8+ T-cell and B-cell responses, is critically needed to improve the efficacy of HIV-1 vaccine candidates. Experiments of nanoparticle malaria vaccines suggest that an increased antigen deposition/retention locally in the tissue drives B-cell responses, enhancing dendritic cell antigen presentation, compared with soluble protein immunizations.[142] Prolonged antigen presentation mediated by nanoparticle vaccines may have also contributed to the stimulation the formation of germinal centers[143] with enhanced development of CD4+ Tfh cells,[144] which provide critical cytokines and signals required to initiate somatic hypermutation and affinity maturation for effective B cell memory.[145]

Non-human primates studies

It has been argued that NHP challenge studies were not predictive of the outcome of HIV-1 vaccine efficacy trials and therefore should not be gatekeepers of efficacy trials in humans. However, it must be acknowledged that the methodology used varied greatly and might not have been representative of human transmission risk. Although imperfect, the recently improved repeat, low-dose mucosal NHP challenge model[146] with better standardized SIV and, to a lesser extent, SHIV challenge viruses, is likely closer to recapitulating HIV-1 transmission in humans.[147] The availability of new SHIV constructs derived from different HIV-1 clades (C, A, and E) would allow assessing the homologous or heterologous protective efficacy of V2-specific monoclonal antibodies derived from B cells of RV144 vaccine recipients (CH58 and CH59), of new HIV-1 subtype C or A-specific vaccine regimens, in particular Env subunit proteins. Humanized mice models have been recently improved and may offer an interesting alternative to non-human primates in testing HIV vaccines.[148]

Although non-human primate studies may help defining immunogenicity selection criteria for advancing candidate vaccines into human testing as well as correlates of protection jointly with human efficacy trials, they remain of poor positive predictive value and are in no case substitutes of human clinical trials, in particular efficacy trials.[149]

Deployment, impact, and cost-benefits

Several models have emphasized the public health and cost-benefit advantages of HIV-1 vaccines.[150] According to the World Health Organization, cost-effective vaccines provide an additional year of life at a cost less than a country's per capita Gross National Income. Vaccines that provide cost-savings are those in which the cost of vaccination multiplied by the number of infections averted by vaccination is less than the lifetime cost of treatment averted.[151] Immunization strategies of a safe and efficacious HIV-1 vaccine will largely depend on its acceptability by target populations, the type, level and duration of vaccine efficacy for a given mode of HIV-1 transmission within the community, stability and thermostability, and the possible need to couple vaccination with other prevention technologies. It is important to recognize that the cost of a vaccine is more than the price. It includes the logistics around vaccine deployment (transportation, storage, delivery mechanisms, and mode of administration). Local production of vaccines may alleviate the costs and contribute to better access at the regional level. Deployment strategies will require ample consultations with regulatory, scientific and health authorities, and civil society stakeholders on a country-by-country basis.

Conclusion

Knowledge of the immune correlates of protection against HIV-1 is key to accelerating HIV-1 vaccine development. RV144 and further studies of correlates of risk have opened large and unforeseen avenues of exploration and hope for the most exciting time of HIV-1 vaccine development. The still uncertain predictive value of animal models and biomarkers of immune protection against HIV-1 necessitate however that vaccines be tested in clinical efficacy trials. A long-term strategy to ultimately end the AIDS pandemic must include both scale-up of existing HIV-1 combination prevention, treatment, and care programming, and sustained investment in research and development for a preventive HIV-1 vaccine.[152]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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