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Lessons Learned from HIV Vaccine Clinical Efficacy Trials

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Abstract

The past few years have witnessed many promising advances in HIV prevention strategies involving pre-exposure prophylaxis approaches. Some may now wonder whether an HIV vaccine is still needed, and whether developing one is even possible. The partial efficacy reported in the RV144 trial and the encouraging results of the accompanying immune correlates analysis suggest that an effective HIV vaccine is achievable. These successes have provided a large impetus and guidance for conducting more HIV vaccine trials. A key lesson learned from RV144 is that assessment of HIV acquisition is now a feasible and valuable primary objective for HIV preventive vaccine trials. In this article we review how RV144 and other HIV vaccine efficacy trials have instructed the field and highlight some of the HIV vaccine concepts in clinical development. After a long and significant investment, HIV vaccine clinical research is paying off in the form of valuable lessons that, if applied effectively, will accelerate the path toward a safe and effective vaccine. Together with other HIV prevention approaches, preventive and therapeutic HIV vaccines will be invaluable tools in bringing the epidemic to an end.

Introduction

To stop the AIDS epidemic, we must prevent new HIV infections from occurring, as well as optimally treat and attempt to ultimately cure the 33 million HIV infected people in the world. For prevention, condom use and sterile needles are highly effective, but insufficient access and adherence limit their impact. Several new prevention measures in development have demonstrated efficacy, including male circumcision, early antiretroviral therapy (ART) of infected individuals and pre-exposure prophylaxis (PrEP) [1-3]. These advances provide new tools to prevent HIV transmission, however; their ability to reduce HIV infection rates may also be blunted by access and adherence problems. Vaccination gets around many of these challenges and, because of its potential to eradicate the virus, has been a major goal of HIV prevention research for over 25 years. Despite these intense efforts, host immune mechanisms capable of preventing initial HIV infection or clearing an existing infection remain elusive. Nonetheless, the last few years have witnessed significant progress in HIV vaccine development. Here we describe how lessons learned from efficacy trials are being applied to current studies and thereby accelerating progress toward HIV vaccine discovery.

Is an HIV vaccine possible?

The ability of HIV to evade host immunity and constantly mutate makes development of a preventive vaccine enormously challenging. Indeed, the biological plausibility of developing an HIV vaccine has been called into question repeatedly over the past 20 years. However,

there is increasing evidence that the early stages of HIV transmission are vulnerable to immune intervention [4]. An optimized prime boost regimen was shown to protect non-human primates (NHP) from acquisition using a stringent heterologous virus challenge model [5], and a clinical trial -- RV144 -- achieved partial efficacy in preventing HIV acquisition in humans [6]. In both studies, HIV envelope glycoprotein (Env) specific antibodies correlated with reduced infection risk. Cytotoxic T-lymphocytes (CTLs) are known to play an important role in controlling levels of the virus during natural HIV infection, and therefore, targeting these responses has also been a priority for vaccine research and development. An effective HIV vaccine will likely need to induce a combination of broadly reactive humoral and cellular responses. A highly efficacious vaccine would naturally have the largest impact on curbing the epidemic, but a vaccine with partial efficacy could play a significant role in preventing infections, particularly as part of a broader HIV prevention strategy [7].

Despite the enormous challenge, multiple setbacks, and long wait, the recent successes provide evidence that an HIV vaccine is possible. Moreover, valuable information has emerged from RV144 and the other completed efficacy trials and is serving to guide vaccine discovery efforts.

Completed and ongoing efficacy trials

The clinical efficacy studies completed thus far have provided important clues as to which immune responses are applicable to a preventive HIV vaccine. To date, three concepts have been tested for efficacy in humans: a gp120 Env protein eliciting antibodies, an adenovirus vector eliciting high levels of CTLs, and a combined regimen of a canarypox viral vector and an Env (gp120) protein.

VAX003/VAX004

The first efficacy trials evaluated the bivalent Env (gp120) protein, predominantly in men who have sex with men (MSM) [8] and injection drug users [9]. Although no vaccine efficacy (VE) was observed in these two Phase 3 trials, which were designed to detect efficacy > 30%, subgroup analyses suggested that HIV incidence was lower among those individuals with high antibody responses [10;11]. Subsequent analyses of antibody responses were not encouraging for broadly neutralizing activity that, based on NHP studies, was a presumed requirement for preventing infection [12-16]. Thus, the field was redirected toward vaccines eliciting CTL responses that could potentially reduce viral load setpoints or delay disease progression.

Step Study

In general, DNA plasmid and viral vector strategies have been the most effective at eliciting T-cell responses. Having met the safety and immunogenicity thresholds, an adenovirus type 5 (Ad5) vaccine inducing strong CTL responses (MrkAd5, Merck) proceeded to phase 2b evaluations in an attempt to screen for vaccine efficacy > 0. Two trials were conducted by Merck and the HIV Vaccine Trials Network (HVTN) in the Americas and South Africa (Step study/HVTN 502/Merck 023 and Phambili/HVTN 503) [17;18]. Both trials were

stopped early, in September 2007, when the first interim analysis of the Step study met futility thresholds. Analyses of available data subsequently revealed a transient increase in HIV incidence among vaccine recipients who were uncircumcised and had prior immunity to the Ad5 vector [17;19].

With this failure and the alarming evidence that the vaccine may have enhanced acquisition among some participants, improvement of NHP models and basic vaccine discovery research became a priority [20]. A large number of studies have sought to identify the mechanism behind the increased acquisition rate [21-27]; however, this remains to be conclusively determined. Studies of this phenomenon have continued in NHP and have recently achieved significant advances. In one study, investigators describe a new NHP model involving low dose penile virus challenges that has showed increased infection rates under circumstances similar to those in the Step study [28]. In another study, Perreau et al. observed that immune complexes comprised of adenovirus vector and specific neutralizing antibodies potently induce dendritic cell (DC) maturation and proposed that this could lead to more favorable conditions for HIV spread at the port of entry [29]. In this way, pre-existing Ad5 immunity, in the form of neutralizing antibodies, could have contributed to increased acquisition among vaccine recipients. In a subsequent study it was shown that vectors derived from rare adenovirus serotypes (i.e. Ad6, Ad26, Ad35, Ad36, and Ad41 vectors) were less potent at inducing DC maturation and that this correlated with the number of TLR9 agonist motifs present in the vector genomes [30]. If confirmed, these results support current efforts to develop rare adenovirus serotype vectors [31].

Meanwhile, efforts to improve NHP models for use in predicting vaccine efficacy have led to low dose mucosal challenge models that measure reduction in acquisition rather than disease progression [4;32]. These models seem to more closely resemble HIV-1 pathogenesis in humans, including the mucosal bottleneck whereby only a few virus strains are ultimately transmitted, and have become standards for evaluating candidate vaccine for protection from infection. In contrast to the NHP models used to develop the MrkAd5 vaccine used in the Step study, a recent study using one of the newer models produced comparable results to those in the Step trial [33].

The Step study was one of the first to assess the effects of a vaccine inducing robust cellular immune responses on protection from HIV. Although the vaccine induced HIV-specific T cell responses in over 75% of the vaccinated subjects, it did not reduce HIV acquisition or post-infection viral loads. Nonetheless, an ancillary study found that the vaccine did impact the infecting virus strains. Utilizing Step study samples, Rolland et al. performed a sieve analysis study that compared the viral genome sequences in breakthrough infections that occurred in vaccine versus placebo recipients [34]. This study found that viruses infecting vaccine recipients were more likely to encode epitopes that differed from those encoded in the vaccine. This suggests that the vaccine induced T cell responses had the effect of “sifting out” certain virus strains. The data represents the first evidence that a vaccine designed to induce T cell responses put immune pressure on the virus.

HVTN 505

The enhanced acquisition reported for the Ad5-based vaccine in the Step study resulted in the cancellation of a large scale efficacy trial (PAVE 100) planned for a different recombinant Ad5-containing prime boost regimen. The vaccine regimen was developed by the Vaccine Research Center (VRC) and the National Institutes of Allergy and Infectious Diseases (NIAID), and consists of a DNA prime containing clade B *gag*, *pol*, *nef*, and multiclade *env* genes followed by a recombinant Ad5 boost with matching *gag*, *pol*, and *env* inserts. The VRC recombinant Ad5 vector differs substantially from the MrKAd5 vector used in the Step study. For example, due to full E1 and E4 and partial E3 gene deletions it does not produce several Ad5 structural proteins that are targets of pre-existing Ad5 immunity. Nevertheless, PAVE 100 was cancelled prior to enrollment. Numerous stakeholders, including the NIAID Division of Acquired Immunodeficiency Syndrome (DAIDS) and trial site community members, were then involved in discussing the next steps for Ad5-based HIV vaccines. It was decided that a study of the VRC DNA/rAd5 regimen should commence because of its potential to yield valuable information, as the regimen demonstrated safety and promising immunogenicity results in early phase clinical trials [35]. The contingency was made, however, that individuals who were uncircumcised or had pre-existing neutralizing antibodies to Ad5—those who demonstrated enhanced HIV acquisition in the Step study— would be excluded. In addition, the Step study results and possible risks from Ad5 vector vaccines would be clearly communicated to participants as part of the informed consent process. In June 2009, HVTN 505 was opened as a test of concept study to evaluate the VRC regimen in men and transgender women who have sex with men. The trial was conducted by the HVTN, a NIAID supported international collaboration of scientists and educators with a large number of clinical trial sites in the U.S. and throughout the world [36]. 2,504 participants were enrolled in HVTN 505 from 21 sites in 19 U.S. cities. In April 2013, HVTN 505 vaccinations were discontinued based on a scheduled interim analysis indicating that this regimen was not efficacious in either preventing HIV infection or in reducing setpoint viral load after infection. [http://www.niaid.nih.gov/news/newsreleases/2013/Pages/HVTN505April2013.aspx].

RV144

Encouraging results were reported in September 2009 for a vaccine with an estimated efficacy of 31.2% [6]. This study, known as RV144, was conducted by the U.S. Military Research Program in collaboration with several Thai institutions in over 16,000 Thai participants with no predefined HIV risk. The regimen consisted of a recombinant canarypox vector vaccine prime (ALVAC-HIV, Sanofi Pasteur) and a gp120 protein boost (AIDSVAX B/E, Global Solutions for Infectious Diseases). This regimen was initially criticized based on its failure to induce either strong CTL or broadly neutralizing antibody (bNAb) responses [37]. Rather the regimen elicited primarily CD4+ T cell responses and Env-specific binding antibodies. Post-hoc analyses indicated that higher vaccine efficacies occurred in the first year following vaccination (VE ~60%), and that reductions in efficacy over time correlated with waning antibody responses [6;38;39]. Although more durable antibody responses would have been preferred, this observation provides further support to the reliability of the observed efficacy.

The evidence for low-level efficacy from the RV144 trial provided a unique opportunity to look for immune correlates of risk: vaccine induced immune responses that correlated with HIV-1 infection risk. An enormous collaborative effort, led by Bart Haynes, undertook this goal, and succeeded in identifying two correlates of risk for this study: Env variable region 1 and 2 (V1/V2) binding IgG antibodies, and Env-specific plasma IgA antibodies [39]. These results suggest that V1/V2 antibodies may have contributed to protection against HIV and that high levels of Env-specific IgA antibodies may have interfered with the vaccine induced protective responses. More specifically, the presence of high levels of Env-specific IgA antibodies correlated with reduced vaccine efficacy but did not result in increased infection rates for vaccine recipients [39].

Further research is needed to determine whether these Env-specific immune responses measure the degree of vaccine induced protection (i.e., correlates of protection) or whether they are merely markers correlating with risk, such as susceptibility to infection [40-43]. One way to assess the credibility of immune correlates is to analyze HIV sequences from infected trial participants using sieve analysis methods [44;45]. Because this approach evaluates a vaccine's effect from the perspective of the breakthrough infecting viruses, it represents the other side of the coin from immune response correlates. A targeted sieve analysis has been performed on breakthrough viruses from RV144 and found that the vaccine induced differential acquisition of HIV-1 based on the viral sequence in the V2 region [46]. This data supports the hypothesis that V1/V2 responses are associated with vaccine induced protection. If confirmed, these and other immune correlates discovered in the future could be used to rationally guide an iterative process to improve vaccine efficacy.

The correlates analysis has provided an invaluable contribution to the field: plausible and testable hypotheses for the clinical efficacy observed in RV144. It also raised many questions relevant to HIV vaccine development. Would this approach be effective in high risk populations? Or against another virus subtype with clade matched antigens? And can the protective responses be extended beyond the first year by additional protein boosts? Addressing these questions and other issues pertinent to confirming and extending the RV144 study findings is directive major aim of the Pox Protein Public Private Partnership (P5). The P5 is a novel collaboration between pharmaceutical companies and non-profit organizations consisting of the Bill & Melinda Gates Foundation, the HVTN, the National Institute for Allergy and Infectious Diseases (NIAID), Novartis Vaccines, Sanofi Pasteur, and the U.S. Military HIV Research Program (MHRP). Clinical trials being planned by the group aim to improve on the RV144 results and to prepare a path for vaccine licensure in South Africa and Thailand. These efforts are discussed in more detail below.

Insights from efficacy trials

The few efficacy studies conducted thus far have yielded valuable lessons for the design and implementation of future vaccine trials. Completed trials and the RV144 correlates analysis have provided scientific clues about which immune responses may be relevant. They have also taught us a great deal about how to optimize trial designs to yield more reliable data. Lessons have also been learned regarding trial implementation and operational considerations that affect recruitment and outcome interpretation.

Scientific lessons

Most importantly, we have learned that protection from HIV-1 acquisition is possible through vaccination. The partial efficacy in preventing infection observed in RV144 was unexpected but this achievement has transformed the field. The challenge of inducing bNAbs via vaccination and the prevailing belief that such responses are required for preventing HIV infection, as has been shown in some NHP studies, had previously impeded interest in efficacy trials [13-15;47-49]. Few doubt that vaccines eliciting bNAbs would be successful, however, that certain types of Env-specific binding antibodies may be sufficient to prevent HIV acquisition, as is hinted by the RV144 immune correlates analysis, could mean that meeting the high bar of bNAbs induction may not be required. As a result, there has been a renewed interest in Env protein-based immunogens. Some early responses to the RV144 results were to add a protein component to ongoing vaccine trials (HVTN 073E) and those in active development (HVTN 086, HVTN 088). Moreover, in part due to the RV144 trial results, HTVN 505 was modified to elevate protection against HIV acquisition from a secondary to a primary objective and its sample size was increased accordingly from 1350 to 2500 participants. Although the HVTN 505 regimen differed from RV144, both elicit Env-specific antibody responses, which may have played a role in protection in the RV144 trial [35]. Furthermore, a reduction in HIV acquisition was demonstrated among NHP that received SIV versions of the HVTN 505 vaccine [50]. Taken together, these results supported the elevation of HIV acquisition to a primary endpoint for HVTN 505. Although the regimen was ultimately found to not be efficacious for reducing acquisition in a prespecified interim efficacy analysis, the study succeeded in reaching this conclusion swiftly and it is expected that follow up analyses will provide useful information for the field.

Given the success of the RV144 vaccine regimen, there is currently great interest in further evaluating the poxvirus/gp120 protein combination. As previously mentioned, the P5 collaboration is coordinating several such initiatives to address specific questions relevant to validating and improving on the RV144 regimen. One of two RV144 late boost studies, RV305 (MHRP), is currently underway in Thailand. This study will evaluate immune responses induced by further boosting some RV144 trial participants with the same regimen products used in RV144; the canarypox vaccine (ALVAC-HIV), the gp120 vaccine (AIDSVAX B/E), or both. The study will provide more samples for immunogenicity studies including mucosal samples that will enable investigators to characterize mucosal antibody responses generated by these regimens that could have been involved in the protection. Other studies, such as the HVTN 097 ongoing study, will assess immunogenicity of the RV144 regimen products in different populations (ie. South Africa). A licensure track series is also being planned and will evaluate Sanofi Pasteur's ALVAC-HIV product together with next generation Env protein products in Novartis's MF59 adjuvant in southern Africa. Another series of trials will evaluate regimens containing a promising next generation vaccinia virus vector, known as NYVAC-C (EuroVacc), in combination with DNA and Env protein vaccines [51]. Regimens using these different combinations may elicit vaccine induced responses of distinct immunologic profiles that may strengthen correlates of protection analyses [52].

These poxvirus/protein trials will provide valuable information, however, until the immune responses capable of preventing HIV infection are more clearly defined, a variety of vaccine candidates producing a wide range of immune responses should be tested. Some novel strategies include approaches eliciting more balanced CD4+/CD8+ T cell responses, those that may broaden the epitope coverage of cellular responses, and the production of envelope proteins to induce more potent and cross-reactive antibody responses. Comprehensive lists of ongoing HIV vaccine trials may be obtained from several sites (clinicaltrials.gov, iavireport.org, and avac.org). Below we highlight a few HIV vaccine concepts in current development.

Concepts in development

Despite the suggestion from the RV144 correlates analysis that bNAbs may not be required to protect from HIV acquisition [53], it is generally accepted that vaccines capable of eliciting bNAbs would likely be highly effective. In addition, RV144 was conducted among primarily low-risk populations and it remains to be seen whether Env-specific binding antibody will protect individuals at higher risk. This issue is being addressed in RV144 follow-up studies mentioned previously. Meanwhile, investigators have remained focused on understanding bNAb function and how these antibodies develop during natural HIV-1 infection. A result of these efforts has been that numerous bNAbs have now been isolated from chronically infected HIV patients and investigated in detail [54-57]. Although immunogens capable of eliciting bNAbs have not yet been identified, progress has been made in identifying antibody properties that result in broadly neutralizing activity. Another focus of current research is to trace the development of bNAbs in hopes that one day they can be generated via vaccination. Meanwhile, clinical trials are planned or in discussion to evaluate several potent bNAbs manufactured as monoclonal antibodies. VRC01 (Vaccine Research Center, NIAID) is an example of one such antibody that is planned to enter clinical testing in 2013 [58]. After safety and pharmacokinetic evaluations are made, the ultimate objective of trials utilizing passive immunotherapy approaches will be to test the concept that the presence of bNAbs in humans can prevent HIV infection. Further development of this type of product would likely require increases in antibody half-life or alternative formulations to reduce injection frequency. Despite the need for frequent injections, this approach may be useful for some uninfected high-risk populations or as a salvage therapy for patients with drug resistant infections. This approach has been shown to be effective in a phase 2 trial of the humanized anti-CD4 monoclonal antibody, ibalizumab (TaiMed Biologics Inc), in combination with optimized background therapy in HIV infected patients (Norris D., et al. 2006. TNX-355, in combination with optimized background regimen (OBR), achieves statistically significant viral load reduction and CD4 cell count increases when compared with OBR alone in phase 2 study at 48 weeks. (presented in abstract THLB0128. XVI Int. AIDS Conf., 13-18 August 2006, Toronto, Canada) [59;60]. Ibalizumab is also currently undergoing safety evaluation in healthy HIV-1 uninfected adults in a phase 1 trial conducted by TaiMed, the Aaron Diamond AIDS Research Center, and the Bill and Melinda Gates Foundation.

Improving on the immunogenicity of DNA plasmid products has been a major focus in the field, as these products have the advantage of being safe and relatively easy to manufacture.

A major advance in this effort has come from co-administration of DNA vaccines with cytokines and electroporation (HVTN 080, Inovio, Profectus). In a recently completed study, this regimen resulted in more robust CD4+ and CD8+ T-cell responses (89% positive response rate) at half the vaccine dose, and with fewer vaccinations, compared to the same vaccine delivered intramuscularly without electroporation [61]. A new strategy aims to direct vaccine induced immune responses toward mucosal compartments by supplementing DNA vaccines with mucosal chemokines, such as CCR10 ligands. In NHP studies, use of the CCR10 ligands, CCL27 and CCL28, as adjuvants promoted mucosal antibody responses and improved protection in vaginal SIV challenges, as compared to DNA alone [David Weiner personal communication].

A variety of new recombinant viral vectors are being investigated in combination with DNA and protein products. These vectors include those based on alternative adenovirus serotypes, for which pre-existing immunity in the global population is significantly less than that for Ad5 [62]. Given the results from the 505 and Step studies, the future for Ad5 or alternative serotype vectored vaccines is currently uncertain and a current topic of discussion in the field. Other vector products under study include a DNA/modified vaccinia Ankara (MVA) prime/boost regimen (GeoVax) that is currently being assessed in a phase 2 trial (HVTN 205) [63]. This is one of the few clade B products undergoing advanced testing. A promising next generation product that includes co-expression of the cytokine GM-CSF has also begun clinical evaluations (HVTN 094, GeoVax) [64]. Another new viral vector in development is a vesicular stomatitis viral vector. This vector is currently being tested for safety in a first in humans study (HVTN 090, Profectus) [65-67]. Viral vector products containing novel computationally designed mosaic and consensus antigens will also enter human testing this year [68;69]. HVTN 099 is one such study being collaboratively developed by the HVTN, NIAID, the Center for HIV/AIDS Vaccine Immunology, Los Alamos National Laboratory, the IPPOX Foundation in Switzerland, and the Bill and Melinda Gates Foundation [70]. This study will determine whether mosaic or consensus inserts are superior to a natural founder/transmitted viral insert for eliciting the broadest immune responses within the context of a DNA prime and NYVAC boost regimen.

The HVTN is conducting a series of small phase Ib studies. These studies aim to address basic science questions and generate new hypotheses regarding vaccination strategies and their associated immune responses. In one such study, the influence of antigenic competition on the breadth and magnitude of vaccine-induced T-cell responses is being examined. In another, mucosal immune responses are being evaluated in response to a prime/boost vaccine regimen. It is expected that these early phase clinical trials will provide a wealth of information for vaccine platforms, which may be applied to other infectious diseases and immunotherapeutic strategies.

A few HIV vaccine candidates that have been previously evaluated as therapeutic vaccines in HIV-infected patients are now entering the preventive vaccine pipeline. An example is a vaccine utilizing the HIV-1 regulatory protein, Tat. The Tat protein is expressed early during viral rebound and is essential for viral spread [71-74]. A Tat-based vaccine (T1-alpha) is being developed by the National AIDS Centre (CNAIDS) of the Italian Istituto Superiore di Sanità (ISS). Two phase 2 therapeutic vaccine trials are currently underway. In an *ad hoc*

interim analysis of one trial, the vaccine improved immune function in ART treated HIV-infected patients [75]. This suggests that this vaccine could be used together with ART to restore immune systems in infected people. A phase 1 trial of HIV-1 Tat in combination with a Novartis Env protein is ongoing in healthy HIV-1 uninfected participants.

Attenuated HIV has been shown to be one of the most potent methods for inducing protection in NHP [76], but safety concerns rule out this approach for human studies [77;78]. Whole virus that has been inactivated by multiple methods has been regarded safe for use in humans in a couple of instances. The first was the vaccine Remune (The Immune Response Corp), which was composed of purified inactivated virions that had been stripped of surface gp120 and emulsified in incomplete Freund's adjuvant. A phase 3 trial was stopped early due to failure to improve clinical outcome and time to disease progression [79]. A new whole inactivated HIV vaccine candidate, SAV001, developed by Dr. Chil-Yong Kang and colleagues (University of Western Ontario and Sumagen Co. Ltd) recently received FDA approval for phase I clinical trials [http://communications.uwo.ca/media/hivvaccine] (NCT01546818 at http://www.clinicaltrials.gov). To increase the safety profile, the SAV001 virus is an attenuated strain that is also inactivated by both chemical treatment and radiation. The vaccine has appeared safe in rats and nonhuman primates, and should the initial evaluations in HIV-infected individuals appear sufficiently safe, the developers have proposed the candidate be evaluated as a preventive vaccine.

Therapeutic vaccines

There have been fewer efforts in testing therapeutic HIV vaccines, in part because attempts to eliminate latent viral reservoirs through immune stimulation have failed thus far [80]. Indeed, prior to this year there had been only one cure of an HIV infected person, the recipient of a CCR5Δ32 stem cell transplant procedure [81]. As presented at the 2013 International AIDS Society Meeting in Kuala Lumpur, 2 additional HIV-infected individuals who received bone marrow transplants for cancer treatment may have also been cured of their HIV infection. Thus far neither has any trace of HIV in their blood since stopping ART for 7 and 15 weeks. Although bone marrow transplant seems to be a potentially effective way to achieve an HIV cure, due to the risks, this approach is not feasible for widespread application. Alternatively, administration of ART early after infection has been proposed as a means to achieve a “functional cure” by limiting acute viral expansion and preserving immune responses [82]. Such a cure may have been achieved in a case involving a 2.5 year old child that was reported at the 2013 Conference on Retroviruses and Opportunistic Infections. The child's mother had an undiagnosed HIV infection and therefore ART was not administered during labor to prevent mother to child transmission of the virus. The child was administered a 3 drug ART regimen shortly after birth and has remained healthy despite stopping ART after 18 months. The success of this case may have hinged on the exceptionally early administration of ART, which is likely not achievable for the majority of transmissions. Indeed in many adult studies viral rebound has occurred during ART breaks. Achievement of a functional cure via ART alone, therefore, seems unlikely, and points to a need for enhanced immune responses through vaccination. Even a partially effective therapeutic vaccine that allowed for interruptions in ART would be helpful. Furthermore, until host mechanisms responsible for preventing vs. controlling infection are identified,

preventive vaccine candidates should also be evaluated in a therapeutic setting and vice versa. For more information on therapeutic HIV vaccines in development, the reader is directed to a recent review by Vanham et al and a recently published list of ongoing therapeutic vaccine trials at http://i-base.info/htb/16945 [83].

Lessons on trial design

Completed HIV vaccine trials have also provided insights into improvements that can be made in trial design. Among these, one of the most important comes from the RV144 correlates analysis, which represented the first study of its kind and taught us that the identification of correlates requires a concerted effort early on. Standard efficacy trials are not typically powered to identify correlates. The RV144 trial, for example, was underpowered to assess surrogate endpoints, which are more reliable than correlates as a basis for vaccine development [84]. To promote correlates discovery, trial designs should consider whether enough breakthrough infections will occur in the vaccine arm to provide adequate power for correlates assessment in the event of partial vaccine efficacy. In addition, trial designs that promote discovery of correlates of protection (i.e. collecting baseline risk and immune response estimates and vaccinating placebo recipients at the end of the trial) should be considered [40-42;84;85]. Mucosal responses should also be evaluated when possible, as mechanistically causative correlates may not be found in blood [84].

New so-called adaptive trial designs have been proposed as a means to maximize the value gained from efficacy trials [86;87]. Such designs aim to provide the earliest possible efficacy evaluation and permit the evaluation of multiple regimens in parallel with the idea that only those meeting predetermined criteria will be continued for the full length of the study. In this current climate of limited resources and expanding pipelines, trial designs that increase efficiency may help sustain progress in HIV vaccine development.

Lessons on trial implementation

The HIV vaccine efficacy trials conducted to date have also provided valuable lessons for improving trial implementation. The two phase 3 trials performed in Thailand, for example, have provided several lessons for future trials.

The Thai VAX004 trial was the first HIV vaccine phase 3 trial in a developing country, and was conducted in injection drug users, a high-risk group posing numerous recruitment and retention challenges. The RV144 trial was a very large phase 3 trial conducted in the Eastern-seaboard province communities of Thailand. 26,658 participants were screened to enroll the 16,403 participants [88]. Several factors have been noted as playing a critical role to the successful implementation of these trials [89]. Namely, actively including the community in the trial and conducting trial activities within the existing country healthcare system while also strengthening the health infrastructure and capacity.

In both RV144 and HVTN 505, providing active and open communication to trial site communities was especially critical after the reporting of the Step study results. Maintaining study participant enrollment required a concerted effort to educate communities about these results. Similarly, with the halting of the 505 study, the HVTN's swift response, discontinuing vaccinations within 24 hours and notifying study volunteers immediately, was

considered the best way to initiate communication about the futility results. Continued communication with study volunteers and communities will likewise be a crucial component of the Network's follow up efforts.

The expansion of HVTN 505 to include acquisition as a primary endpoint imposed several additional challenges for enrollment: notably the exclusion criteria mentioned above. Embracing modern modes of communication improved recruitment and retention efforts, for example, reminding participants of appointments via text message. Similarly, social media networks can provide an efficient means to reach target groups of potential participants. However, the speed and relative lack of control of this method require frequent monitoring for misinformation and can make proactive communication with communities challenging.

HVTN 505 also modified its exploratory objectives in response to the recent progress in other HIV prevention approaches, namely, the efficacy observed in several trials evaluating the ability of various PrEP regimens to prevent HIV infection [1;2]. It is likely that PrEP usage will increase as result of these findings. Evaluating its use among volunteers who chose to use it in HVTN 505 was considered a means to provide important insights into the interaction between PrEP and preventive HIV vaccines and improve the ability to accommodate for these effects. Future studies should directly investigate vaccination in combination with other HIV prevention modalities. Approaches for conducting vaccine trials in the context of background PrEP usage or where PrEP usage is included in the study have been proposed [90].

Another lesson learned from various trials conducted thus far, is the importance of conducting social and behavioral science research in conjunction with HIV vaccine trials [91-93]. These studies provide valuable information relevant to numerous aspects of vaccine development and implementation such as community engagement, trial recruitment and retention, risk of HIV exposure, and vaccine efficacy among different participant subgroups.

Assessment of participant risk of HIV exposure, for example, is essential to determine whether virus exposure is equivalent across study arms. For example, a possible explanation of the increased acquisition observed in the Step study that participants in the vaccine arm had engaged in higher risk behaviors. A recent study by Koblin et al, did not find evidence supporting differential risk behavior and points to a biological mechanism as being more likely [94].

Another example of the value of social science comes from research at the HVTN that has provided insights into recruitment of MSM and transgender women into HVTN 505. Lack of knowledge and awareness about HIV vaccines was found to be a major barrier for participation [95]. Concerns about testing positive in standard HIV tests (vaccine induced seropositivity, VISP) and the perception that the Network had no mechanisms in place to address this were also significant deterrents. In addition, recruitment efforts aimed at MSM were found to unintentionally exclude male to female transgender persons who did not consider themselves as MSM. As this group is at particularly high risk for HIV infection, recruitment efforts have been modified to attempt to reach such individuals [95].

Conclusion

Efficacy trials have the greatest potential to advance the field, but they are costly, lengthy, and not without limitations. By applying the lessons learned from completed efficacy trials to evaluating the vaccine candidates in development, we will maximize the information and progress made from these endeavors. Looking to the future, vaccines will likely be one of several tools used in the battle to end the AIDS epidemic. We should, therefore begin to consider how best to integrate HIV vaccines within the broader HIV prevention package.

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Box 1

Lessons from preventive HIV vaccine efficacy trials

- Scientific lessons
  - Protection from HIV-1 acquisition is possible through vaccination.
  - Too few clinical efficacy studies have been conducted.
  - Pre-clinical models are informative but do not yet reliably predict human efficacy studies.
  - The pox virus/protein combination warrants further efficacy testing.
  - Vaccine candidates evaluating untested and varied immunological concepts should also be evaluated.
- Lessons on trial design
  - Identifying immune correlates is a high priority and requires an early concerted effort.
  - Standard efficacy trials are underpowered to identify correlates and surrogates of protection.
  - Trial designs should promote correlates discovery.
  - Adaptive designs providing earlier efficacy evaluations simultaneously for several regimens should be used.
- Lessons on trial implementation
  - Community engagement is a critical component of HIV vaccine development.
  - Embracing modern communication modes improves recruitment and retention.
  - Conducting social and behavioral science in conjunction with HIV vaccine trials provides valuable information for trial implementation and outcome interpretation.
- HIV vaccines are urgently needed in the HIV prevention toolbox.
  - The potential benefits of an HIV vaccine can have great impact on the AIDS epidemic.
  - Even if highly efficacious vaccines are developed, we must consider how they will be integrated into the broader prevention package.