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HIV Vaccine Efficacy Trials: A Brief History, and Options for Going Forward

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Abstract

HIV vaccine research has recently produced a number of efficacy results, in addition to some promising preclinical developments. Some of these have been surprising, leading to parallel calls for a better understanding of HIV pathogenesis and immunity, while accelerating the number of candidates that can be tested empirically in clinical trials. In this review, we describe the development of three HIV vaccine efficacy trials to date, and highlight some of the possible avenues available for the field of biomedical HIV prevention to proceed. **(AIDS Rev. 2010;12:209-17)**

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Introduction

In 1984, shortly after HIV was confirmed as the cause AIDS[1,2], then US Health and Human Services Secretary Margaret Heckler famously promised that a vaccine would be available within two years[3]. Although it is easy to be critical in hindsight, at the time the vaccine field was brimming with confidence. Smallpox had been eradicated less than five years prior, and polio eradication appeared to be on the horizon. However, in the case of HIV, despite many lessons in virology and immunology, the first hint of vaccine efficacy was observed more than 25 years later.

Many obstacles to the development an effective HIV vaccine have been tabled[4], but at the foremost of these are the many scientific challenges that HIV poses when compared to traditional vaccine development paradigms[5]. For instance, the most effective vaccines to date were developed empirically to prevent acute viral infections and elicit neutralizing antibodies. Several lines of evidence, from animal models and human studies, suggest that the avidity and/or titer of neutralizing antibodies are correlates of protection for these vaccines[6]. However, HIV rapidly escapes and avoids these responses in the majority of subjects, such that contemporary antibodies can rarely neutralize circulating strains of HIV[7]. Although broad neutralizing antibodies can protect monkeys from SIV challenge[8], this activity is rare in HIV-infected subjects and correlated positively with viral load[9].

The majority of traditional vaccine development has been empirical, in many cases before a very good understanding of host immunity was available[10]. These include whole killed and attenuated vaccines, both of which had limited success in HIV. While live attenuated vaccines are perhaps the most protective SIV vaccines in animal models[11], these vaccines are thought to be too dangerous for human use. This is based on the

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pathogenicity of live attenuated vaccines in neonatal monkeys[12], eventual progression in the Australian nef-deleted HIV-infected cohort[13], and recent studies showing that recombination between challenge and vaccine strain can cause monkeys to progress rapidly to AIDS[14].

To further complicate matters, several aspects of natural HIV infection stand in the way of an easy path to vaccine development. Once HIV reaches the lymphatic system, a latent viral reservoir is established for life[15], and even in the face of highly effective therapy, the estimated half-life of this reservoir is near the human lifespan[16]. Secondly, HIV targets the immune system itself, such that attempts to induce protective immunity against HIV often bring the virus into contact with the $CD4^+$ T-cells it prefers to infect[17]. The depletion of $CD4^+$ T-cells, rapidly in the mucosa and more slowly in the blood[18-22], leading to opportunistic infections, forms part of the evidence of the importance of these cells in host immunity. Also, the constant exposure of the immune system to HIV causes profound immune dysregulation as a consequence of chronic activation, further debilitating many subsets of immune cells[23,24]. Thirdly, HIV exhibits extreme genetic diversity, leading to rapid escape from many immune responses[25]. Therefore, even when protective responses are induced, whether these responses will provide coverage for all of the HIV strains a vaccinee may encounter remains an unanswered question.

HIV vaccine efficacy trials

There have been three HIV vaccine products tested in clinical efficacy trials to date. The first were two double-blinded, placebo-controlled phase III efficacy trials of HIV-1 envelope proteins completed by VaxGen in 2003, which showed no efficacy[26,27]. The second was the STEP (and the related Phambili) phase IIb proof-of-concept trials that used an adenovirus (Ad5) vector with the aim of inducing HIV-specific T-cell responses. The STEP trial was stopped prematurely by the Data Safety and Monitoring Board (DSMB) in late 2007, and subsequent analyses suggest this vaccine might have actually increased HIV susceptibility in uncircumcised, Ad5-seropositive men[28]. Finally, a recently completed phase III community-based trial called RV144 in Thailand garnered much press attention when in late 2009 – to the surprise of many – a 31.2% protective effect was observed in a modified intent-to-treat analysis[29]. This vaccine included a series of canarypox vector primes followed by VaxGen's Env protein boost. We discuss these trials in detail below, and consider the implications of this series of expectations and surprises for future HIV vaccine development.

HIV envelope protein vaccines

Like many trials since, the VaxGen trials were conducted amid much skepticism and controversy[30,31]. These protein vaccines were used in two parallel trials: AIDSVAX B/B (VAX004), which was conducted in Europe and North America and enrolled 5,403 volunteers (men who have sex with men, n = 5,095; high-risk women, n = 308) and AIDSVAX B/E (VAX003), which was conducted in Thailand in 2,546 intravenous drug users.

Vaccines and schedule

AIDSVAX B/B was comprised of two recombinant gp120 (rgp120) antigens derived from the CXCR4-dependent HIV_{MN} and CCR5-dependent HIV_{GNE8} clade B strains of HIV-1, which were delivered as seven injections over 30 months of vaccine or placebo (randomized 2:1), with HIV-1 acquisition at 36 months as the primary endpoint. AIDSVAX B/E contained two recombinant gp120 antigens derived from one clade B strain (CXCR4-dependent HIV_{MN}) and one clade E strain (CCR5-dependent primary isolate CRF01_AE) of HIV-1[27]. Similarly, these were given as seven injections over 30 months of vaccine or placebo (randomized 1:1) with HIV-1 acquisition at 36 months as the primary endpoint.

Immunogenicity

Phase I/II trials of AIDSVAX B/B and AIDSVAX B/E both demonstrated induction of significant antibody titers against HIV envelope strains included in the vaccine[32,33]. These antibodies were capable of binding gp120 V2 and V3 loop peptides and blocking binding of soluble CD4 to rgp120 strains included in the vaccine. Although it was thought that vaccination with HIV_{MN} (clade B) rgp120 alone could elicit clade E immunity, sera from monovalent AIDSVAX MN vaccinees demonstrated a lack of antibody cross-reactivity to HIV_{A244} (clade E) peptides and failed to block sCD4 binding to HIV_{A244} rgp120, supporting the use of AIDSVAX B/E in Thailand where both clades circulate. These data suggest antibodies generated by the vaccine may be limited in their ability to protect against strains with gp120 sequences that vary compared to vaccine strains. In support of this, while neutralizing activity of

antisera against laboratory strains was seen in both AIDSVAX B/E and AIDSVAX B/B recipients, antisera from these individuals failed to neutralize primary HIV-1 isolates in phase I trials[34]. However, antibodies generated by AIDSVAX B/E vaccination were capable of binding oligomeric gp120 on cells infected with primary isolates, suggesting at least some level of cross-recognition[33] (though oligomeric gp120 binding to vaccine strains was not available for comparison purposes).

Efficacy

The VaxGen trial results were disappointing. For AIDSVAX B/B, there was no difference in HIV-1 incidence between vaccine and placebo recipients (6.7 vs. 7%, respectively)[26]. Similarly, AIDSVAX B/E showed no difference in HIV-1 incidence between vaccinees and controls (8.4% in vaccine and 8.3% in placebo)[27]. This is despite induction of antibody responses in most vaccinees. Exploratory subgroup analyses revealed that peak antibody levels correlated inversely with HIV incidence. However, further analysis suggested that this correlation was a marker of susceptibility and did not represent a direct effect of antibody responses on HIV-1 acquistion[35]. Indeed, the quality of the antibodies elicited by vaccination was suspect, which fueled skepticism about how effective the trial would be even prior to its completion[30,31].

Adenovirus-based HIV vaccines

The STEP trial was conducted by the Vaccine Research Centre (VRC) at NIH and Merck, and was based on several continents including North America, the Caribbean, South America, and Australia. The trial enrolled 3,000 participants aged 18-45, most of whom were either men who have sex with men or high-risk women.

Vaccine and schedule

The MRKAd5 vaccine used in the STEP trial was a trivalent vaccine consisting of a 1:1:1 mixture of three replication-defective adenovirus serotype 5 (Ad5) viral vectors expressing *gag* (HIV_{CAM-1}), *pol* ($HIV\text{-}1_{IIIB}$), or *nef* ($HIV\text{-}1_{JR-FL}$). The vaccine was given as three doses (baseline, week 4, week 26) with primary endpoints of HIV acquisition and viral load set point in those who became infected[28]. The trial analysis was stratified by baseline Ad5 titers, based on the prediction that preexisting neutralizing antibodies to the vaccine vector (Ad5) might limit effectiveness of the vaccine.

Immunogenicity

Vaccination with MRKAd5 in phase I trials elicited positive interferon (IFN)-γ ELISPOT responses to two or more peptide pools in the majority (72%) of volunteers[36]. All three HIV proteins were targeted by 44% of vaccinees. $CD8^+$ T-cells dominated, based on intracellular cytokine staining, but $CD4^+$ T-cell responses were also detected. Cross-clade reactivity was observed in 61-67% of clade-B responders to clades A and C, respectively. Interestingly, individuals with higher baseline anti-Ad5 antibody titers had reduced ELISPOT responses, suggesting the possibility of lower vaccine immunogenicity in individuals with high preexisting vector immunity.

Efficacy

The STEP trial had a predetermined interim analysis scheduled when 30 per-protocol events were observed in those with Ad5 titers < 200. In the modified intent-to-treat analysis at this time point, 24 infections (3%) were observed in the vaccine versus 21 (3%) in the placebo arm, and there was also no difference in set point viral loads between groups (4.61 vs. 4.41 $\log_{10}$ copies/ml in the vaccine and placebo arms, respectively). Similarly, the per-protocol analysis also showed no significant differences in either primary endpoint: 19 infections (4%) in vaccine vs. 10 (2.12%) in the placebo arm, and again there were no differences in viral loads between the vaccine and placebo arms (4.6 vs. 4.57 $\log_{10}$ copies/ml). Based on these data, the STEP trial was stopped in September 2007 due to futility (i.e. it was unlikely that if the trial was extended, it would produce a positive result). A very similar trial called Phambili, based in South Africa, had enrolled 801 volunteers, but was stopped at the same time as STEP. The failure of this trial occurred despite the regular detection of T-cell responses (by IFN-γ ELISPOT) in 75% of vaccinees tested[37], although whether the breadth of these responses was sufficient has been debated and is discussed as follows.

Since 2007, there have been several subgroup analyses of the STEP trial[38]. Of most concern was the trend towards an increased risk for HIV infection in vaccinated men who were Ad5-seropositive and uncircumcised. The mechanism(s) responsible for this remain unknown. The possibility of increased immune activation, such as increases in $CD4^+CCR5^+$ T-cells in the high Ad5 titer subgroup, has been raised. Although

two recent studies have presented negative data in response to this question[39,40], since no mucosal samples were collected, this possibility is difficult to rule out. Why the vaccine did not provide protection is also unknown, but possibilities include that dual CD4/CD8 responses were only seen in 31% of vaccinated participants[37], which is of lower magnitude and quality than in HIV-positive long-term non-progressors. Furthermore, these T-cell responses may not have been cross-reactive enough, given the genetic difference between vaccine and infecting strain observed in breakthrough infections[38]. Other potential shortcomings of the quality of cytotoxic T-lymphocyte (CTL) elicited by MRKAd5 include inadequate recognition of infected cells and inappropriate CTL trafficking in vaccinees[41], underscoring the importance of considering all aspects of CTL function during vaccine design.

The STEP trial, although a negative result, raised many questions[42,43]. Because many considered this the best "T-cell vaccine" in the pipeline, some wondered if this meant a failure of the T-cell-based HIV vaccine concept. Others questioned whether it could mean the end of adenovirus vectors, or even merely of Ad5 vectors[44]. Interestingly, although the predicted difficulty with Ad5 as a vector was that preexisting Ad5 immunity would limit protectiveness, the trial suggested a worse scenario – that preexisting Ad5 immunity may result in enhanced HIV-1 susceptibility. This remains an important question to sort out as future vaccines are being considered.

This trial also raised questions regarding the limitations of monkey models. An Ad5/SIVgag vaccine protected rhesus macaques against $SHIV_{89.6}$ but not SIV_{mac239}[45,46], the latter of which is thought to be a more stringent challenge virus (i.e. is more difficult to protect against)[47]. One difficulty lies in the fact that it is difficult to know which models are predictive of clinical efficacy in the absence of an effective product; predicting a negative result is obviously not the same as predicting a positive result. Another problem with monkey models when it comes to T-cell vaccines is differences in human leukocyte antigen/major histocompatibility complex that may influence immunity. For example, Ad5 vaccines generate much broader $CD8^+$ T-cell responses in monkeys than were observed in the STEP trial[48], and broader responses, particularly to Gag, are thought to mediate protection in HIV infection[49]. Resolution of these issues will not be easy, but is critical to moving forward with future vaccine platforms.

An ongoing trial: HVTN 505

A vaccine trial related to the STEP trial is currently underway, and is expecting results by the end of 2011[50]. This phase II trial will enroll 1,350 men who have sex with men (who have been circumcised and lack Ad5 antibodies). This trial utilizes a prime-boost strategy: three immunizations with DNA vaccine followed by boost at week 24 with recombinant Ad5. The insert for this vaccine contains clades A, B, C Env, plus Gag/Pol/Nef (Nef has been included in DNA vaccine but not rAd5). The endpoint of this trial is reduction in HIV viral load in those who become infected. The Ad5 in this vaccine has been modified from the Merck vector, and unlike the STEP trial, this vaccine contains Env and a DNA prime, which it is thought will increase the breadth of vaccine-induced T-cell responses.

The canarypox/envelope prime-boost vaccine approach

Also referred to as the "Thai trial", RV144 was a phase III efficacy trial, the results of which were released in September 2009. This trial enrolled > 16,000 people in two provinces in Thailand, and was community representative, i.e. not merely high risk subjects. The primary endpoints for this trial were HIV-1 acquisition, and postinfection viral load and CD4 counts in those who became infected.

Vaccines and schedule

The vaccine consisted of Aventis Pasteur's ALVAC-HIV (vCP1521), a canarypox vector expressing HIV-1 subtype B Gag and protease (HIV_{LAI}) and gp120 (CRF01_AE) linked to transmembrane anchoring portion of gp41 (HIV_{LAI}). The ALVAC-HIV vaccine was given as a prime at four visits (baseline, 4, 12, 24 weeks). Following priming, VaxGen's AIDSVAX B/E, a bivalent envelope glycoprotein vaccine containing rgp120 from clade B (HIV_{MN}) and E (HIV_{A244}) viruses, was given as a boost at weeks 12 and 24. Notably, the AIDSVAX boost was the same vaccine as was used in one of the initial VaxGen trials described previously.

Immunogenicity

Preliminary immunogenicity phase I/II trials of RV144 suggested that the immune responses induced were modest. For example, administration of ALVAC alone did not result in production of neutralizing antibodies.

In those who also received AIDSVAX B/E, binding antibodies were detected in most vaccinated individuals and a high percentage of these neutralized one or more lab-adapted HIV-1 strains[51]. Despite these encouraging results, the failure of the earlier AIDSVAX B/E trial demonstrated that these antibody responses are not sufficient to protect against infection.

The use of a live vCP1251 vector as a delivery system for the vaccine was aimed at inducing potent HIV-specific T-cell responses. However, immunogenicity trials demonstrated CD8 CTL responses in only 24% of vaccinated individuals, and only 41% of responders showed repeat positive responses[51]. These results varied in comparison to similar trials of vCP205 (expressing the same gag, pol and gp41 genes as vCP1251), which ranged in HIV-specific CTL responses from 20 to 76% of vaccinated individuals[52-55]. Several of these studies demonstrated high background responses in placebo recipients, calling the immunogenicity of the vaccines into question. Lymphoproliferative responses were observed in 63 and 61% of vaccinees to clades E and B envelope proteins, respectively. However, lymphoproliferative responses as high as 24% in placebo recipients complicated the interpretation of these results[51].

Efficacy

The RV144 results indicated a very modest protective effect (depending on the analysis), but regardless this was lower than the 50% protection level set by the Thai government at which licensure might be considered[29]. Overall, 132 HIV infections occurred during the study: 56 in vaccine and 76 in the placebo arm. The degree of vaccine efficacy was on the borderline of statistical significance, ranging from 26.2% ($p = 0.16$) in the per-protocol, 26.4% ($p = 0.08$) in the intent-to-treat, and 31.2% ($p = 0.04$) in the modified intent-to-treat. The latter analysis excluded seven randomized individuals who were later found to have seronegative HIV infection prior to the first vaccine dose. No significant difference was observed in postinfection viral load or CD4 counts between the vaccine and placebo arms. Therefore, although modestly protective, the confidence intervals were very wide (in the modified intent-to-treat, 95% CI ranged from 1.1 to 51.2%).

Further observations from RV144, although lacking in statistical power, are hypothesis generating in terms of how this vaccine may have worked in humans. Firstly, it seems that the majority of protection was observed in the first year after vaccination. After one year, there were 20 more infections in the placebo than vaccine arm, but the gap between these groups was more or less maintained for the duration of the study. Secondly, high-risk people did not seem to be protected. Since the trial was community-based, stratification of subjects by risk group was possible in sub-analyses. Although not statistically significant, estimated vaccine efficacy in lowest-risk subjects was 40% (17 vaccine vs. 29 placebo infections), 47.6% in medium risk (12 vaccine vs. 22 placebo infections), and 3.7% in highest risk (22 vaccine vs. 23 placebo infections). One interpretation of these data is that protection was transient and moderate, failing to protect for a long duration and in people at most risk for infection, which concurs with the modest efficacy observed overall. While one must be cautious with these interpretations, the implications for future trials can be considered (discussed in HIV vaccine research: where to go from here).

HIV vaccine research: where to go from here

Based on this history, it is clear that the road to an HIV vaccine has been anything but smooth or predictable. Yet the need for an HIV vaccine remains as pressing as ever, with more than two million new cases annually[56], and swelling numbers needing antiretroviral therapy in a world with finite resources[57]. While it would be ideal to evaluate as many candidates as possible, especially given the unexpected nature of results to date, financial issues complicate this strategy. Many doubts were raised as to whether the now-completed efficacy trials were justified, largely due to questionable potency and the associated financial costs (RV144 cost an estimated US$ 119 million). In addition to the huge amounts of time involved for each trial (more than five years), there have also been concerns that the public and volunteer recruitment may suffer in the face of repeated failures, even if these are necessary to get a positive outcome.

The question has been raised regarding how much preliminary data and rationale are necessary before a large trial proceeds. Many have argued that phase II immunogenicity data predicted the failure of VaxGen; namely, the antibodies induced could neutralize lab strains of HIV but not primary isolates (to which a vaccinee is exposed)[34]. Similarly, several leading HIV scientists called for an end to the Thai trial in 2004, arguing that the phase II ALVAC trials did not induce sufficient CTL, and AIDSVAX had already failed to induce protective antibodies in its own efficacy trial[58].

The counter rationale for going ahead was that this was the first test of a regimen aimed at inducing T-cells and antibody in combination, and the results turned out better than many expected. Finally, in the wake of the unexpected STEP failure, NIH canceled a trial called PAVE in 2008 (which was to be similar to STEP) and called for an emphasis on fundamental research[59].

Indeed, these three completed efficacy trials have led to extensive questioning of how to best direct HIV vaccine development efforts. Is a return to basic science ideal, aimed at better rationale vaccine design, or should we proceed with more smaller scale empirical trials, where we could determine protective correlates once we have a promising product? Between these extremes is the concept of translational research programs that link vaccine development with basic science, such that hypothesis-driven phase IIb proof-of-concept trials could be completed in conjunction with comprehensive basic science evaluations that would inform subsequent generations of a given product. Questions surrounding the design of novel immunogens to elicit better antibody and T-cell responses are prominent. Responses believed to be protective have been difficult to elicit in vaccination of humans. Better vector, adjuvant, and/or delivery systems could also be tested towards this goal. Should HIV vaccines prevent transmission, delay disease progression, or both? Some of the products developed to date have been tested to do both (as primary endpoints), but based on what we know of protective immunity against acquisition versus progression, is it realistic to think that a single vaccine could do both[60]? Finally, the usefulness of nonhuman primates for informing HIV vaccine development remains an open question. Better strains such as SIV_{mac239} or SIV_{E660} (a swarm of viruses, similar to the HIV at exposure in humans) and low-dose repeated mucosal challenges may improve on the usefulness of the model.

The RV144 trial generated even more questions than STEP, given that the latter was expected to work and the former was expected to fail. The consensus emerging from a recent NIH HIV Vaccine meeting was that RV144 appears to be "a signal", but what next[61]? Some follow-up trials are already in progress[62]. Immediate plans include a boost of HIV-negative vaccinees, to determine whether their immunity can be augmented by another vaccine dose. This trial, called RV305, is in the planning phase, and is obviously time-dependent; the longer the vaccinees are from receiving the initial vaccine, the less likely this approach will provide answers. A second idea is a more detailed immunogenicity study (called RV306). Since the immunogenicity of RV144's components was evaluated 5-10 years ago, advances in immunology, particularly in systems biology[63] and flow cytometry[64], could provide a more detailed picture of how this vaccine elicits immune responses. A third idea is a new phase IIb trial in South Africa, where HIV incidence in some places remains quite high. The aims of this trial would be to test vaccine modifications, dissect which vector did what, and to get a more rapid evaluation of efficacy (possibly in 24 months) in a population where HIV risk could again be stratified amongst vaccinees.

Several new ideas have been reported at recent HIV vaccine conferences. Multiple groups are considering passive neutralizing antibody infusion as a proof-of-concept trial to indicate that these are the types of antibodies we should be aiming to generate[65]. Similar studies have given encouraging results in nonhuman primates[8,66]. Another possible way to deliver effective antibodies is through AAV-vectored gene therapy, and this concept is also under evaluation[67]. The impetus for reevaluating antibody-based vaccine efforts stem in part from the recent identification of additional antibodies that can broadly neutralize HIV[68-70], but also because of the RV144 trial, where non-neutralizing antibodies and $CD4^+$ T-cell proliferation were the most common responses. Although no data has emerged, some have considered the possibility that other antibody effector mechanisms, such as complement activation or antibody-dependent cellular cytotoxicity (ADCC)[71], could be protective against HIV.

Other ideas for eliciting cell-mediated immunity include the use of other vectors such as DNA/NYVAC, which is under evaluation[72]. Cytomegalovirus looks promising in preclinical studies, generating very durable mucosal effector memory T-cell responses and protecting 50% of monkeys from a low-dose challenge[73]. As to the problem of HIV diversity, the testing of mosaic vaccine antigens might be a strategy to increase the breadth of T-cell responses generated by vaccination[74,75]. In general, given the unexpected history of HIV vaccine efficacy trials, a further diversification of approaches, rather than the parallel testing of similar, competing approaches, should be seen in coming years.

There are also emerging ethical and logistical issues that face the HIV vaccine field. One is whether there is enough production capacity to generate enough RV144 components to do follow-up studies. Since this vaccine was made long ago and expected to fail, these capacities need to be regenerated. A second issue is

whether future trials need to provide the RV144 vaccine as a placebo. Given its modest efficacy, one could argue that RV144 should become a standard-of-care in the setting of further vaccine evaluations. Conversely, in light of the STEP results, should trials in men only be conducted on those who are circumcised? Although we now know that circumcision is protective on its own, another trial that increased risk for uncircumcised men would certainly be unwelcome. Finally, given the high expectations of ongoing pre-exposure prophylaxis trials to show efficacy, will all future vaccinees be on antiretroviral therapy as the new standard-of-care for individuals at high risk for HIV? This would surely impact on the logistics of carrying out evaluations of HIV vaccines, if the new goal of the vaccine was to improve upon something that is already effective.

On the other hand, the concept of combining successful prevention approaches may be an effective way to slow the pandemic. There are several other biomedical interventions, in addition to vaccines, that could prevent HIV transmission[76]. Some promising preclinical results are from a compound called glycerol monolaurate, which suppresses the recruitment of target cells, limiting expansion of HIV-infected founder T-cell populations. This microbicide was effective in preventing SIV acquisition during repeated vaginal challenges[77]. Until recently, clinical trials of microbicides in humans have ranged from ineffective to harmful[78]. There was optimism when Pro2000 showed 30% efficacy in phase IIb, but this product showed no protection in its phase III trial. However, the new generation of topical microbicides is focusing on compounds with a specific mode of action[79], such as those containing antiretrovirals, including CCR5 inhibitors: CCR5-tropic strains of HIV almost universally are those that establish infection. CAPRISA 004 was the first trial to test the efficacy of this approach. The microbicide candidate in this trial was a vaginal gel formulation of tenofovir, a nucleotide reverse transcriptase inhibitor. The gel reduced HIV acquisition by 39% overall, and by 54% in women with high (> 80%) gel adherence[80]. In addition, this gel also prevented acquisition of HSV2. Although this efficacy may be too low for licensure, these results are very encouraging for the HIV prevention field.

Recent debate has focused on the extent to which ART can prevent HIV transmission at a population level. Some have questioned, on the basis of modeling data, whether wide-scale testing and treatment programs could eventually eradicate HIV; if the reproductive rate is reduced below 1, epidemics eventually extinguish[81]. Although the ability of ART to reduce to HIV transmission could be substantial, on the basis of reducing plasma viral load, a major predictor of transmission[82], there are possible drawbacks to this concept. These include financial and practical feasibility, considering that even covering those with CD4 < 200 has been a major challenge. Further worries include the possibility that more widespread use of ART might cause an increase in drug resistance, and that taking ART for a much longer time period might lead to increased exposure to side effects and possibly poor adherence. Finally, the reduced autonomy of individuals in choices of care may represent a human rights hurdle to this approach. However, data in favor of this approach have recently been presented, including evidence of modest decreases in HIV incidence that correspond temporally with increased ART use[83]. More direct evidence comes from a study of discordant couples that showed a 92% decrease in transmission in ART-naive compared to subjects on ART[84]. Therefore, the implications of ART on transmission cannot be ignored.

Conclusions

The need to develop an HIV vaccine remains a major global public health priority. Prevention remains the cornerstone of public health, and vaccination is one of the most important public health advances of the 20th century. Yet the advocacy for prevention is never as high as it is compared to when someone is affected by a disease; the benefits of prevention lie in the future, its beneficiaries are unknown, and when something is prevented, it is often invisible (i.e. it's difficult to prove that something didn't happen)[85]. However, while in the early days HIV was kept as a low priority by many governments of the world, delaying the effectiveness of the response, there has since then been a remarkable investment in fighting this disease. Prior to the current global financial crisis, there was a 20-fold increase in HIV/AIDS funding from 1998 to 2008, an increase from US$ 485 million to US$ 10 billion[86], including approximately US$ 868 million on HIV vaccine development in 2008[87].

The clues gathered from the failed STEP and partially successful RV144 trials, as well as promising ongoing preclinical vaccine data, offer unprecedented opportunities to build on these efforts towards an effective HIV vaccine. Altering RV144, and/or uncovering its mode of action, could be most critical in this regard. Furthermore, the immunological knowledge and available

research tools are increasing exponentially, resulting in increased capacity to discern correlates of protection. This has to a large extent been driven by HIV, prompting some to say that immunology has been "taught by viruses"[88]. However, in line with the claim that a vaccine has never been made by an immunologist[89], STEP and RV144 have also implied that we need to evaluate as many candidates as is feasible, while nesting detailed immunological and epidemiological evaluations for future iterations of any product that shows promise. In the meantime, there is hope that investment in research, treatment, and prevention of HIV now will help to reduce healthcare costs later, given the costs associated with lifetime treatment for growing numbers of HIV-infected individuals[57]. In the continued search for new prevention technologies, access to prevention tools that are known to be effective, such as male circumcision and prevention of mother-to-child transmission, needs to be increased[90]. In light of the recent CAPRISA results, ART-based microbicides may also become available in the near future and could be combined with a successful vaccine. The realization of an effective vaccine for other infectious agents has taken decades[91], and now is the time to further concentrate HIV vaccine efforts. Since this will require continued investment from multiple sectors, it is hoped that the promise of a breakthrough that leads to an effective HIV vaccine will be an acceptable pay-off.

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