A prime/boosting strategy for a successful HIV vaccine?

To find the best strategy for designing a successful HIV vaccine, researchers have varied vaccine immunogens, dose, vaccination schedule and route of administration. Most critical has been the choice of immunogen. For other viruses, live attenuated vaccines and inactivated virus induce extremely effective protective immune responses; however, due to safety concerns about HIV regaining replication capabilities or integrating into the host genome, these strategies cannot be used for HIV[5]. Therefore, scientists have focused on newer approaches involving different strategies of introducing antigen with synthetic envelopes, naked DNA or viral vectors from different origins. Since the first successful HIV-1 vaccine trial to date, RV144, employed a prime and boost-based vaccination design with multiple immunizations, the attention and hopes of the field have been focusing on this vaccination strategy. RV144 used a canarypox vector as prime and a heterologous protein boost, administering two rounds of primes followed by two rounds of prime and boost jointly[6].

Vaccine priming is meant to establish a basic level of immunogenicity, whereas the boost should result in expansion of effector cells, a stronger immune response, and more durable protection[7]. Priming and boosting typically includes either a vector containing variable HIV constructs, naked DNA or envelope protein. Moreover, prime boosting strategies can be homologous or heterologous: in a homologous approach, prime and boost deliver the same immunogen whereas a heterologous strategy includes different antigens. Both offer different outcomes; a homologous strategy primarily boosts the humoral immunity whereas heterologous approaches result in synergistic enhancement of immune responses[8].

Pox- or adenovirus derived vectors are most commonly used. Pox vectors are able to induce cytotoxic T lymphocyte responses in humans but do not elicit high titers or neutralizing antibodies[9]. Vectors from the pox family tested in clinical trials include the modified vaccinia ankara (MVA) or the nonreplicating attenuated poxvirus vector (NYVAC); in RV144 the pox vector ALVAC was used. The other group of vectors used for HIV-vaccine candidates are in the adenovirus family: Ad5 and Ad35 are most commonly chosen/applied. These vectors have been shown to have a comparable safety profile and induce innate and adaptive immunity alike. However, Ad5 has a higher risk of re-activating pre-existing immunity since it's a very common serotype[10], which was an issue in the STEP trial that had to be terminated due to higher rates of HIV infection upon vaccination[11].

Another way to deliver immunogens is via administration of naked DNA. DNA regimens are able to elicit T cell responses but induce low immunogenicity overall. Therefore, DNA is more often used for priming and has been proven successful in human DNA prime/ protein boost approaches[12]. Protein regimen such as the AIDSVAX used in RV144, consistent of two gp120 proteins at the same concentration, have especially been studied in combination with a DNA or vector prime, but rarely alone because envelope glycoproteins fail to elicit T cell responses[13]. However, envelope proteins are able to induce specific non- neutralizing and neutralizing antibodies and a strong overall humoral response. The RV144 used two heterologous boosts injections with gp120 protein from two different clades indicated that repeated boosting can increase the antibody response, whereas Vax003 suggested that excessive boosting can be disadvantageous due to class switching away from functional subclasses[14].

Since recent studies indicate that T cell responses as well as neutralizing and non-neutralizing antibodies are important for a protective vaccine against HIV, researchers have focused on designing vaccines that combine the strengths of different regimens to find the ideal combination. Aside from composition of the regimen, vaccine candidate population, order of the prime/boost administration, vaccine dosage, interval between various antigen exposures, route of vaccine administration and pre-existing immunity heavily influence the efficacy of vaccines. This resulting complexity as well as analytical and organizational challenges with different administration schedules makes it difficult to investigate and compare the characteristics of different prime boost vaccination trials[7].

In order to dissect the optimal vaccination strategy, the HIV vaccine trial network collaboration conducted a number of HIV-1 trials in humans with different prime and boost regimens and schedules including DNA-, vector- and protein-based regimens which now allows for a unique opportunity to compare the induced immune response between the different prime/boost compositions. We will apply a comprehensive systems serology approach to five different vaccine trials HVTN 71, 78, 105, 204 and 205 to define the unique antibody profile elicited by different vaccination strategies. The measurements include antigen-specific antibody Fc isotyping and Fc-receptor binding as well as an array of functional assays quantifying phagocytosis by monocytes (ADCP) and neutrophils (ADNP), the assessment of complement deposition (ADCD), and NK cell activation and degranulation. With this approach, we expect to observe quantitative and qualitative differences between the elicited immune responses by the different vaccine strategies. Our plasma sample set is placebo controlled, with a pre-immunization time point, a peak immunogenicity and memory time point. Figure 1 shows the different HVTN trials and trial arms that we will compare using a consensus gp140 antigen.

Study	Prime	Boost	Env Prime	Env Boost
077	Ad35 (gag/pol/nef/Env)	Ad5 (gag/pol/nef/Env)	92RW020 (clade A)	92RW020 (clade A)
	DNA (gag/pol/nef/Env)	Ad35 (gag/pol/nef/Env)	92RW020 (clade A)	92RW020 (clade A)
	DNA (gag/pol/nef/Env)	Ad5 (gag/pol/nef/Env)	92RW020 (clade A)	92RW020 (clade A)
078	NYVAC (gag/pol/nef/Env)	Ad5 (gag/pol/nef/Env)	BX08 (clade B)	92RW020 (clade A) HXB2 (clade B) 97ZA012 (clade C)
	Ad5 (gag/pol/nef/Env)	NYVAC (gag/pol/nef/Env)	92RW020 (clade A) HXB2 (clade B) 97ZA012 (clade C)	BX08 (clade B)
105	Protein (Env)	DNA (gag/pol/nef/Env)	AIDSVAX B/E (MN/A244)	ZM96 (clade C)
204	DNA (gag/pol/nef/Env)	Ad5 (gag/pol/nef/Env)	92RW020 (clade A) HXB2 (clade B) 97ZA012 (clade C)	92RW020 (clade A) HXB2 (clade B) 97ZA012 (clade C)
205	DNA (gag/pol/nef/tat/rev/vpu/Env)	MVA (gag/pol/Env)	HXB-2/ADA recombinant (clade B)	HXB-2/ADA recombinant (clade B)
	MVA (gag/pol/Env)	MVA (gag/pol/Env)		

Figure 1: Figure 2: Vaccination strategies for HVTN 077, 078, 105, 204 and 205 trials. Image courtesy of HVTN

Preliminary results have shown that a DNA prime with either rAd5 or DNA/Aidsvax boost was superior to other vaccines including NYVAC, Ad35 and MVA vectors in terms of antibody titer. Trials 78 and 105, which used DNA prime and rAd5 or DNA/Aidsvax boost, elicited the highest levels of IgG1, whereas only the Ad5 boost resulted in high levels of IgG3. Additionally, DNA prime and Ad5 or DNA and Aidsvax boosts induced the strongest antibody-dependent cellular phagocytosis (ADCP) by monocytes and the most NK degranulation. This suggests that a DNA prime combined with different boost strategies induced an IgG1 and IgG3 driven polyfunctional antibody profile. More in depth analysis is needed to reveal the contribution of the different regimens to the unique antibody profiles.

These preliminary results showing drastic differences between prime/boosting strategies highlight the importance of the prime/boost composition and suggests that a DNA prime is the key to induce qualitatively and quantitatively superior antibodies, which could be employed for future HIV vaccine design studies.

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