Preparing for the availability of a partially effective HIV vaccine

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Background

The 2009 RV144 trial in Thailand shows that a partially effective vaccine against human immunodeficiency virus (HIV) acquisition is possible.

What are some "downstream" considerations for implementation of a partially effective HIV vaccine with RV-144 parameters in developed and developing world currently?

This question was the focus of an AIDS Vaccine 2010 Conference satellite symposium. This poster summarizes the key presentations including:

- Results of mathematical models (some with health economic parameters) from different research groups applying a priori consensus RV144 trial results
- Relevant lessons from implementation of hepatitis B vaccine (HBV), human papillomavirus (HPV) vaccine, planning for pre-exposure prophylaxis (PrEP) with antiretroviral (ARV), annual influenza vaccine strain selection, potential annual HIV vaccine strain selection, and post-RV144 planning in Thailand.
- Ideas that might facilitate the introduction of a future licensed HIV vaccine.

Fig. 1: Cumulative and interval-specific vaccine efficacies from the clinical trial of RV144. The estimates in figure 1a are located at the ends of successive 6 month intervals, with those at 12, 24, 36, and 42 months having been reported, while those in figure 1b are located at their mid-points.

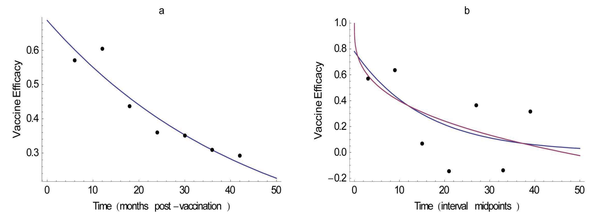

Table 1: Key issues raised during moderated audience discussion at AIDS Vaccine 2010 Satellite Symposium "Preapring for the Availability of a Partially Effective HIV Vaccine" Atlanta, GA — Sept. 28, 2010.

1. Considerations for low and middle income countries:
   - 1.1. Need help with algorithm for introduction of HIV biomedical interventions; need to start by identifying gaps in knowledge in each country/setting
   - 1.2. The lesson from hepatitis B vaccine that there was poor availability in countries at greatest need for decades; this was only solved by manufacturing in the region
   - 1.3. Access to licensed vaccines is still poor in many countries; what will be the impact of the current funding gap for Global Alliance on Vaccines and Immunizations (GAVI) and advanced market initiative on future HIV vaccines?
   - 1.4. Adult vaccination programs need improving globally in each country
   - 1.5. Countries differ in their risk groups for HIV and the relative maturity of their national immunization program; probably will not be single size fits all
   - 1.6. The health care workers are already overworked; therefore the logistics of a future HIV vaccine will be critical (e.g., multiple doses in high risk groups ≥ low coverage)
   - 1.7. Need to better translate meaning of "partial" efficacy for the general public
   - 1.8. Consult community more with messaging on the results before dissemination
2. Considerations for high income countries:
   - 2.1 Much practical/implementation resource already available in the routine immunization program
   - 2.2 Mostly an issue of competing priorities, especially if HIV prevalence/incidence is low
   - 2.3 Funding for childhood vaccines well established; adolescents/adults more challenging
   - 2.4 Need to think about incentives vs. removing barriers to immunizations

Mathematical Models:

In follow up to a recommendation from March, 2010 consultation on the future utility of RV144 trial results, modeling teams the cost and impact on the HIV epidemic of a RV 144-like vaccine regimen, with agreement to:

- Use the same function to model the decay in vaccine efficacy (figure 1)
- Evaluate a common scenario (mass vaccination of 30%, 60% of sexually active adults) with indicated variations (e.g., boosting).
- Report results in a common format (i.e., cases averted over 10 years)

Methods:

- Applied models to Thailand, South Africa, United States and Australia.
- Focused on heterosexuals and men who have sex with men (MSM).
- Included condoms, ARV therapy, all sexually active adults or only those at higher than average risk; explored risk compensation.
- Calculated cost-effectiveness and compared with other interventions.
- Used stochastic individual-based and deterministic compartmental models.

Results:

- Vaccination had modest initial impact (i.e., 5-15% of cases averted).
- Periodic boosting needed to sustain, shorter the interval, more the impact (+ cost).
- Established price ranges required for cost-effectiveness in different settings.

Limitations:

- Insufficient power to detect differences in efficacy among sub-populations that would indicate mode of vaccine action.
- No information about ability to boost efficacy, or impact on transmission in MSM.
- Assumed exponentially declining proportion of vaccinees were (waning efficacy as opposed to 'take'), and that revaccination restored efficacy.

Introduction of hepatitis B vaccine (HepB) (Dale Hu)

Hepatitis B virus (HBV) has similar transmission patterns as HIV. Unlike HIV, HepB development proceeded fairly quickly to licensure 13 years after antigen discovery.

Although adults at high risk [e.g., health providers, injection drug users (IDU), men who have sex with men (MSM)] were initially targeted to receive the newly licensed HepB coverage rates remain unacceptably low and impact on HBV incidence minimal.

Since 1991, many factors => expansion of HepB recommendations in many countries > high risk groups alone to include: (a) routine infant and childhood HepB, enforced via school entry immunization laws, and (b) prevention of perinatal transmission.

~ 20 years after HepB first licensed, factors allowing more countries with a high prevalence of chronic HBV infection to increase HepB coverage and decrease disease:

- increase in number of HepB manufacturers (e.g., from South Korea and India);
- Decrease in UNICEF HepB cost: $3-6/dose in 1990s to $0.18-0.40/dose in 2010;
- Combined HBV & pediatric diphtheria-tetanus-pertussis (DTP-HepB) vaccine;
- Global Alliance on Vaccines and Immunization (GAVI) to finance introduction.

Successful and sustainable future HIV immunization program will require:

- preparation of medical providers, the general community and high-risk populations to create a favorable environment,
- development of a medical infrastructure that can access and follow these varied high-risk populations,
- expansion of comprehensive, ongoing prevention programs, for which vaccination would be one component of the prevention effort, and
- establishing funding mechanisms for adult vaccinations

Introduction of HPV vaccine (Eileen Dunne & Lauri Markowitz)

Two HPV vaccines are licensed. In US, recommended for girls aged 11-12 years; or females 13-26 years who have not started or completed the vaccine. Lessons include:

Vaccine delivery:

- In the US, many adolescents do not routinely visit a provider for a prevention visit. The requirement for 3 doses, requiring multiple visits adds to this challenge.
- Some countries (Australia, UK, Canada) achieved high HPV vaccine coverage through school located immunization programs. But US has few schools with health clinics, limited vaccination staff, and complicated reimbursement.

Provider, parental and adolescent acceptability of the vaccine:

- Uptake in older adolescents > younger adolescents; may be because discussions about sexual behavior with parents/providers more likely at older adolescence.
- Some worry about sexual behavioral disinhibition. Adolescent sexual behavior shaped by complex interplay of individual, family, peer, school and community factors, unlikely HPV vaccine would have a direct influence on process.
- "New vaccine" issues (e.g., duration of protection and vaccine safety)

Vaccine costs:

- US private sector: ~US$130/dose (~US$500 total including administration). Vaccine For Children (VFC) provides vaccine without cost to eligible <19 y.o.)
- For less developed settings, both HPV manufacturers are making each dose of vaccine available at US$5, a price that is found to be cost effective.

Vaccine policies:

- US: only VA and DC have school requirements for HPV vaccine (broad opt out).
- Early push (by industry) for HPV vaccine school requirements controversial.

Influenza vaccine strain selection (Michael Shaw)

Influenza vaccines introduced in late 1930's; antigenic changes in circulating strains required frequent reformulation => closest match + optimize effectiveness.

WHO Influenza Surveillance Network (1952+): collect 150K samples from >100 nations + exchange info on nature and epidemiology of viruses (e.g. pandemic potential).

Factors considered when recommending new influenza vaccine strains:

- *Are there new antigenic variants?*
- *Are these new variants spreading in the human population?*
- *Do current vaccines induce antibodies effective against the new strains?*
- *Are there new variants suitable for vaccine production?*

Data needed with sufficient lead time for vaccine production, licensure, + distribution:

- In the Northern Hemisphere, issued by mid-Feb for Oct/Nov vaccination
- In the Southern Hemisphere, by mid-August to September

Risk of a new variant appearing after the selection => incentive for new vaccine technologies with shorter lead times so the strains chosen can be as current as possible.

Annual consensus strain antigens improve HIV vaccine formulations? (Jim Mullins)

The genetic variation that accrues within the days to weeks in which flu viruses replicate within one human before passing the virus along to another is small.

HIV infections are permanent, giving HIV an greatly extended period for intrahost evolution (~0.2-1%/year, depending on the gene). The evolution of HIV continues apace in all infected individuals throughout their lifetime (unless treated). ***Level of global diversification of influenza A haemagglutinin gene over 10 years ~ one person infected with HIV-1 x 1 year.***

Sequential infection with HIV strains (superinfection) not rare; can recombine to form novel genomes with superior growth properties and wider transmissibility in populations (similar reassortment in flu leads to strains with pandemic potential).

HIV evolves in a star-like phylogeny; within each host it explores new evolutionary space, finding new ways to evolve away from structures attacked by host immune responses => How produce temporally specific (e.g., annual consensus) HIV vaccine?

A likely component of HIV-1 evolution permitting exploration of so much evolutionary space is development of compensatory mutations. As mutations that result in escape from immunologic targeting, viral fitness can be impaired; hence, compensatory mutations are selected for that permit maintenance of escape while improving viral fitness.

>24 compensatory mutations have been identified using computational methods in influenza. Hundreds of interacting, potentially compensatory amino acid changes have been identified in individual HIV genes. Hence, fitness of HIV can apparently be maintained while continuing to adopt increasingly diverse primary structures.

Several current approaches to HIV vaccine design and implementation, including:

- Circulating strains
- Founder strains, those found to clonally dominate early in infection
- Computationally-derived central strains (e.g., consensus, ancestor, center of tree).
- Variation inclusive antigens.
- Conserved components of the HIV proteome.

There may be future utility in determining annual consensus HIV strains to:

- Identify new outbreaks with divergent viral strains
- Define host population immunologic imprinting on the virus
- Identify changes to conserved regions
- Identify limits to evolutionary expansion. Combining these surveys with co-variation analysis => deconvolute 1° and compensatory mutations => preserved viral function.

Post-RV144 planning in Thailand (Supachai Rerks-Ngarm)

http://www.vaccineenterprise.org/sites/default/files/RV144_March16-18_Meeting_Report_FINAL.pdf)

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