HIV Vaccines in Asia:-

Welcome Address given by WR Thailand.

Introduction of attendants, Designation of Chairman - Dr.

Designation of Rapporteur- Dr.

Overview of current HIV vaccines- Manufacturing, Research and Development of HIV Vaccines.

Presentation by M/s. Merck USA - Dr. E. Esber through Teleconference.

MRK Ad5 HIV-1 --- recombinant viral vector-- gag gene from HIV-1 subtype B expressed in an adenovirus-5 vector. A modified version of the Merck Ad5 vector. The Step Study is part of an international effort to test and find an HIV vaccine that will work safety in diverse population. Step Study vaccine is Ad5 HIV-1 gag/pol/nef. This is a Phase II study, designed to yield limited information on the efficacy of the vaccine. Investigational HIV Vaccine (V 520) Proof-of-Concept Study--This study is currently recruiting patients in USA. This study will test the safety and efficacy of an investigational HIV vaccine in 3000 participants. Efficacy will be measured by either prevention of HIV infection or control of HIV viral load in subjects who become HIV infected.

Vaxgen -- by Dr. M. Gurwith.

Vaxgen has two HIV vaccine namely Vaxgen Bivalent B/B vaccine containing MN-rgp120, GNE8-rpg120 subtype(clade) and Vaxgen B/E vaccine containing subtype(clade) MN-rgp120, A244-rpg120. It is region specific-AIDSVAX B/B for N. America, Europe and the Caribbean, where as AIDSVAX B/E for Southeast and East Asia. It is recombinant gp 120 produces in CHO cells formulated with alum adjuvant. Clinical trials Phase I,II,&III in North America and Thailand. It is randomized, double blind placebo-controlled trials. Vaccine administration -0, 1,6,12,18,24,30 month, and duration of follow-up--36 months. Primary end points-prevention of infection- HIV Seroconversion by ELISA and timing of infection confirmed by nucleic acid test. Secondary end point--slowing of progression of HIV(reduction of in viremia-PCR and time to ART), antibody
response, sequence analysis and safety. VAX 004- Antibody results--MN CD4 blocking, GNE8 CD4 blocking, GNE8 V2, GNE8 V3, MN Neutralizing responses correlates with infection risk. It seems that antibody responses are only *markers* of susceptibility to HIV infection, i.e. they did not cause increased or decreased susceptibility to infection. Relative risk of HIV infection lowest quartile=1.86 & Relative risk of HIV infection highest quartile=0.81. VAX 004- antibody results-subgroup analysis-- The combination of higher estimates of VEs and higher immune response in women and non-Whites raises the possibility that the responses conferred protection for some individuals in these subgroups. VAX 003 - Antibody results-- Robust immune response, peak pre-infection immune responses comparable among infected and uninfected vaccine recipients. In vaccine recipients, the level of peak pre-infection immune responses did not correlate with the rate of HIV 1 infection.

VAX 003 Safety Summary-- Vaccine well tolerated-local and systemic reactogenicity substantially less than in VAX003 (both Vaccine and placebo). No difference between treatment arms for reactogenicity. No significant differences in AEs/SAEs between treatment arms. No evidence of enhanced susceptibility to infection. No evidence for increased disease progression in HIV infected vaccines.

VAX 004 Safety Summary-- Vaccine well tolerated-most common AEs were mild to moderate reactogenicity symptoms w/i 3 days of vaccination. Higher local reactogenicity in vaccines. No significant differences in AEs/SAEs between treatment arms. No evidence of enhanced susceptibility to infection. No evidence for increased disease progression in HIV infected vaccines.

**Preliminary Conclusions-**

- Vaccination elicited a potent neutralizing antibody response against Tier 1 viruses (MN &SF 162).
- Vaccination elicited a weak neutralizing Ab response against some tier 2 viruses (no neutralization > 80%).
- Neutralizing antibody responses were weak whether measured with a standard panel of clade B reference strains or with a panel of viruses from clinical trial participants.
- Prior vaccination had no significant effect on the neutralizing Ab response post -infection i.e. no interference or augmentation.
- The average vaccine-elicited response resembled the response seen after 1-2 years of HIV-1 infection in placebo recipient.
**Role of Fc receptor Genotype in VAX004** –

- HH/VV genotype (approx 6% of population) is associated with decreased HIV risk in placebo group, but increased HIV risk in vaccine group.

- No effect on post-infection endpoints.

**Other VAX 003/004 Analysis**-

- Sequencing analysis- identify novel gp120 sequences, follow-up possible efficacy in non-whites.
- Molecular and functional characterization of unusual disulfide variants from VAX004.
- Functional assays of CMI, Antibody assays-- avidity restricted GNE8 CD4 Blocking, and GNE8 V2 or V3 ELISA.

**Future VaxGen AIDSVAX Activities**-

- Future AIDSVAX development will require outside funding/ partnership-
- NIH / CDC collaboration to complete analysis.
- NIH / WRAIR- Thailand prime-boost Phase III trial.
- Transfer the data and materials from VaxGen's VAX003 AND 004 studies to Global Solution for Infectious Diseases (GSID) for further statistical analysis etc.

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**USAMMDA** : Clinical Development of HIV Vaccines in Thailand:


- A Phase III trial is being conducted in some province of Thailand, as a collaboration between the Thai Ministry of Public Health, the US Military HIV Research Programme, and the US-NIH. This is community based trial involving 16000 volunteers. This trial is to assess the efficacy of a prime-boost combination using ALVAC vCP1521 from Aventis Pasteur, and rpg 120 BE (MN/A244) from VaxGen. This study is still on going in Thailand.

- **WHO Perspective** :

“Progress in the development and scientific consideration for regulation
A critical need for a safe, effective and affordable HIV vaccine drives a push for moving multiple vaccine candidates into clinical trials.
- If some of the trials are successful, there would be a need to secure license from local National Regulatory Authorities.
- To facilitate this decision making by NRAs there is a need to develop regulatory frameworks for HIV vaccines addressing multiple scientific, ethical and logistical challenges related to the preparation and conduct of HIV vaccine trial.
- The current Genetic classification of HIV--Types-: HIV-1, HIV-2, Groups: M,N,O Subtypes: A-D,F-H, J,and K. Intersubtype recombinants:- CRF01_AE, CRF02_AG etc.
- Role and Value of Animal models-- Currently available animal models do not provide for go/no-go check points in pre-clinical research. Different models produce controversial results.
- Laboratory assays being used in HIV vaccine development and trials—
  - Assays to detect and measures vaccine-induced response(s):- binding and neutralizing Ab, CTLs, ELISPOT, intracellular cytokine staining (ICS), etc.
  - Assays to identify / characterize HIV infection and disease progression: viral load, CD4 / CD8 counts etc.

**IN CONCLUSION :-**

- An HIV vaccine (complementing other interventions) remains the best long-term hope for the control of the AIDS pandemics, especially in developing countries.
- Present activities to develop an HIV vaccine are not sufficient to produce a vaccine with the required urgency.
- An enhanced and better coordinated efforts is needed to accelerate HIV vaccine development, and this effort should involve the full participation of developing countries.
- The role of the National Regulatory Authorities will be of key importance to expedite the conduct of scientifically and ethically sound trials, licensing of successful vaccines and laying grounds for future access and availability to all countries and population in need.

**FUTURE CHALLENGES ON SITE DEVELOPMENT- :**

- Need to increase clinical trial capacity worldwide.
- Multiple sites needed to test different candidate vaccines, against different HIV subtypes, in population with different transmission partners.
- Comprehensively developed sites could be used for vaccines other HIV preventive research (including microbicides).
- Consider impact of scaling-up ART on vaccine trials, HIV incidence, level of care etc.
- Need to ensure that the "most appropriate" candidate vaccines are tested in the "most appropriate" sites, regardless of who have developed the product or strengthened the sites.

**NIH Perspective: Dr. Rebecca Sheets NIH, Washington USA.**

- Mission Statements--
  - DAIDS - To help end the HIV / AIDS epidemic by:
  - Increasing basic knowledge of the pathogenesis and transmission of HIV, The development of therapies for HIV infection and its complications, and the development of vaccines and other prevention strategies.
  - VRC - The mission of the Vaccine Research Center (VRC) is to conduct research that facilitates the development of effective vaccines for human disease. The primary focus of research will be the development of vaccines for AIDS.
- Candidates in most advanced trial -- Phase 2 (expanded safety & immunogenecity) = VRC multi-gene multi-clade DNA plasmid prime-adenovirus type 5 vector boost(HVTN 204)
- Phase 2b (proof-of-concept efficacy trial)--- Merck clade B multi-gene adenovirus type 5 vector (HVTN052, Merck 023).
- Phase 3 (efficacy trial) --Thai trial multi-genic Clade B & E ALVAC vector prime-recombinant gp120 boost.
- Result will be available in 2008-9.

Discussion -- on subjects like use of animal model in pre-clinical studies. No consensus reached.

**Clinical Trials in Asia:-**
- Thailand - Dr. Supachai Rerks-Ngarm:
  
  **HIV Vaccine Trial in Thai Adults** -- A phase-III trial of Aventis Pasteur Live Recombinant ALVAC-HIV (vCP 1521) Priming with VaxGen gp 120 B/E (AIDSVAX B/E) Boosting in HIV-Uninfected Thai Adults.

In this phase –III efficacy trial, a prime-boost’ vaccine strategy is evaluated for prevention of infection and amelioration of disease course. ALVAC-HIV (vCP1521) from Sanofi-Pasteur is given as the ‘prime’ vaccine at months 0,1,3 and 6, AIDSVAX gp 120 B/E from VaxGen is given as the “boost” at months 3 and 6. This regimen will be given to 8000 adult Thai subjects, while another 8000 will be given placebos in a double-blinded, randomized manner. Following the completion of each subjects immunization phase, he/she will be followed for 3 years with clinic visits
every 6 months with HIV testing, pre-and post-test counseling. Subjects who become HIV infected guidelines, and offered enrollment in a protocol for extended follow-up.

**- AIDS Vaccine Development Programme in India:-** By Dr. Jean-Louis Excler, Sr, Medical Director IAVI India.

In India, there are two HIV vaccines are currently under Phase I Trial :-

i) tg AAC 09 vaccine (AAV2)- single stranded DNA (3471 nucleotides), encoding HIV-1 subtype C strain DU 422, developed by Targeted Genetic Inc, Seattle USA.

ii) TBC-M4 vaccine (MVA Therion)—Multigenic subtype C (Indian Strain isolated by the National AIDS Research Institute, Pune, India), this vaccine is developed by Therion Biologics, Cambridge MA, USA.

Both the above vaccines are under Phase-1 trial, double blind, placebo-controlled, dose –escalation, randomized on vaccine V/s Placebo in healthy HIV uninfected adult volunteers. Part of the multi-country trial in Belgium and Germany also.

Dr. Jean-Louis Excler, also explained the approval Process of said trial in India, which involves approval from DCG (I) (NRA), Min. of Health, and GEAC etc.

**Regulatory Challenges for Evaluating HIV Vaccines:** Thailand Perspective: -- By Dr. Yupin Lawanprasert.

The Strategy of Thailand’s National Plan for HIV/AIDS Vaccine Development is to promote the development, facilitate the evaluation and address the future availability and accessible HIV Vaccine while building up the national research & regulatory authority capacity.

In Thailand, the manufacture, importation HIV vaccines are regulated under Drug Act B.E. 2510(1967). Currently 3 trials under Phase -I, 6 trials under Phase I /II, and 2 trials under Phase –III.

**Current regulatory frame-work of HIV vaccines in Thailand--**
- Development Stage (not systematically regulated), Authorization of Clinical trial (decentralized).
- Approval of C/T Protocol and monitoring the trial, adverse effects by Vaccine trial Control Sub-committee (DDC). Approval of IND Vaccine by Thai FDA.
- Safety Evaluation- Animal safety tests (Pre-clinical data), Human safety data (clinical trial data).
- Efficacy Evaluation – For Preventive Vaccine – Clinical outcome i.e.
prevention of HIV infection. Surrogate outcome: Induction of Immunity. For Therapeutic Vaccine:- criteria for efficacy evaluation has not been established.

**Thailand Experience:** - Non conclusive issues:-
- Is Phase II or extended Phase II Sufficient?
- Are surrogate outcomes sufficient?
- What are “clinical benefits”? survival, prevention of opportunistic infections, quality of life, slow progression of disease, prolongation of the time to ARV therapy OR others?

The above questions were discussed thoroughly; it was recommended that NRA of specific country might take view based on National emergency without compromising the quality, safety and efficacy data of HIV vaccine.

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The following two presentations from FDA USA:-

1) **HIV Vaccines: Challenging Product Issues under IND – By Dr. Carol D. Weiss US FDA (CBER)**

2) **HIV Vaccines: Considerations for Future Trials—By Dr. Ann T. Schwartz, Div. Of Vaccines & Related Products Application FDA.**

Both the presentation describes Stages of Review and Regulation clinical investigational plan at US FDA, which includes IND applications (Phase I, II and III studies.), BLA ( Biological License Application), Phase IV and inspection, lot release etc.

*Vaccine Efficacy Trial Protocol:*- Randomized, well controlled trial in study population/ control group. Clinical & Lab: safety, immunogenicity, case surveillance (e.g. seroconversion, clinical). Save extra sera for future use.

*Efficacy Study End Points:*- Prospective Primary & Secondary end points, Specificity of case definition emphasized.


**Regulatory Forum:**

**Regulatory Challenges for Evaluating HIV Vaccines:**

DCVRN member country viz. Brazil, Indonesia, Thailand, Korea and India briefly present the current status of HIV Vaccine trial in their respective
country.

Closed Session for Regulators-

Discussion: Strategies for strengthening regulatory pathways: Next Step: ----

The Discussion focused on the issues as relevant to HIV Vaccine clinical trial and candidate product development (registration or licensing mechanisms). In addition, efforts were made to identify the existing systems and infrastructure.

The most rational way to accelerate HIV Vaccine development is to proceed with multiple clinical trials simultaneously, thereby permitting assessment of the protective efficacy of different candidate vaccines against different HIV subtype in different network countries and population.

The HIV vaccine with moderate efficacy (50%) could still play a significant role in preventing new infections, especially in population with higher incidence of HIV infection and where other preventive interventions are not readily available.

RECOMMENDATION:

The need for DCVRN member National Regulatory Agencies (NRAs) to exchange and share information on HIV vaccine candidate data in order to accelerate their review of dossier as per guidance given in present two days meeting and enhance their knowledge of product and trial reports. Creative approaches must be further explored to harmonized regulatory requirements for approval of HIV Vaccine in their country.

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