ACCELERATING THE DEVELOPMENT OF AN AIDS VACCINE: THE AIDS VACCINE FOR ASIA NETWORK (AVAN)

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Abstract. HIV/AIDS is a major public health problem worldwide, especially in developing countries. The development of a safe and effective HIV vaccine is central to stopping the epidemic and would be a great public health tool. The AIDS Vaccine for Asia Network (AVAN) is a group of concerned investigators committed to assisting regional and global HIV vaccine efforts. AVAN's focus on improving the coordination and harmonization of research, ethical reviews, clinical trial capacity, regulatory frameworks, vaccine manufacturing, community participation, and government advocacy could help accelerate HIV vaccine efforts in the region. At a meeting in November 2010, researchers from various countries in Asia presented their progress in HIV vaccine research and development. Six working groups discussed the current status, gaps and methods to strengthen capacity and infrastructure in various areas related to AIDS vaccine research and development. These discussions led to the development of prioritized action plans for the next 5 years. This report describes the gaps and challenges HIV vaccine research faces in the region and recommends improvement and standardization of facilities, and coordination and harmonization of all activities related to AIDS vaccine research and development, including possible technology transfer when a vaccine becomes available.

Key words: AIDS, accelerating, vaccine, AIDS Vaccine for Asia Network (AVAN)

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INTRODUCTION

Evolution of the AIDS Vaccine for Asia Network (AVAN)

HIV/AIDS is associated with high morbidity and mortality and is recognized as a major public health problem worldwide, especially in developing countries, despite preventive and therapeutic efforts (UNAIDS, 2009). Development of a safe and effective HIV vaccine is desperately needed as a public health tool to stop the epidemic. Development of such a vaccine is extremely challenging due to the nature of the virus and the pathogenesis of the disease. Some scientific communities in Asia, such as China, India and Thailand, have been working in HIV vaccine development for the last 15 years (The Council of the Global HIV Vaccine Enterprise, 2010).

As part of the global effort to produce a vaccine, a group of concerned investigators from Asia committed to assisting regional HIV vaccine efforts, along with other international organizations, including the World Health Organization (WHO) and the Global HIV Vaccine Enterprise, launched the AIDS Vaccine for Asia Network (AVAN). The first Asian meeting focused on AIDS vaccine research was organized by the WHO-UNAIDS and the Japanese National Institute for Infectious Disease (NIID) and was held in 1998 and again in 2006 (Excler *et al*, 2008). AVAN was proposed and established to create a forum to coordinate regional activities and to implement the recommendations of the Sapporo meeting. A follow-up meeting was organized in Beijing, China, in 2009 and led to a clear vision and mission (Kent *et al*, 2010; Rerks-Ngarm *et al*, 2010). The AVAN taskforce was established to define its objectives and time frame. The meeting also discussed the opportunities and challenges of the member countries in the development of an HIV vaccine and the plan to cooperate with the strategic plan of the Global HIV Vaccine Enterprise (Enterprise) (The Council of the Global HIV Vaccine Enterprise, 2010).

Two important proof-of-concept HIV vaccine efficacy studies were published during the past two years. One was the STEP trial, which showed a disappointing lack of efficacy and a suggestion of increased risk of HIV infection in uncircumcised, Ad5 seropositive men who received the vaccine (Buchbinder *et al*, 2008). The other efficacy trial ended in 2009 in Thailand testing a prime boost regimen with ALVAC-HIV and bivalent AIDSVAX® showed modest but promising result (Rerks-Ngarm *et al*, 2009). This results of the RV 144 trial are now the subject of intensive scientific investigation to better understand its correlation with immunity.

AVAN emphasizes a regional approach to facilitate the development and evaluation of vaccine candidates against the prevalent strains circulating in the Asian region (UNAIDS, 2009). AVAN would contribute significantly to HIV vaccine research by enhancing the capacity of all aspects of research and development. AVAN should help support regional coordination, harmonization and networking to reduce duplication of efforts. AVAN aims to establish regional resource centers for sharing resources and knowledge, thus utilizing the strengths of several Asian countries to help move forward AIDS vaccine research in the region. The network could seek collaborative support from international organizations, developed nations, and funding agencies to assist with AIDS vaccine development activities in Asia.

AVAN's efforts on improving co-

ordination and harmonization of research include: ethical reviews, clinical trial capacity, regulatory frameworks, vaccine manufacturing, community participation, and government advocacy, which could help speed up HIV vaccine efforts across the region (Kent *et al*, 2010). AVAN's vision is to develop a safe and effective HIV vaccine and ensure its access as a part of a comprehensive public health strategy for the control of new HIV infections across the region. This requires collaboration and global support of all stakeholders, including WHO-UNAIDS, the Global HIV Vaccine Enterprise, the US National Institutes of Health (NIH), the International AIDS Vaccine Initiative (IAVI), the Collaboration for AIDS Vaccine Discovery (CAVD), the Euro Vacc consortium for HIV vaccine researchers in Europe, and the US Military HIV Research Program (MHRP).

2010 AVAN MEETING

The 3rd annual AVAN meeting held in 2010 in Pattaya, Thailand was jointly organized by the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the Global HIV Vaccine Enterprise, the International AIDS Vaccine Initiative (IAVI), the US National Institute of Health (NIH) and the US Military HIV Research Program (MHRP) and was hosted by Faculty of Tropical Medicine, Mahidol University. Participants attended the 2010 AVAN Meeting are listed in Table 3.

The meeting was designed to provide a platform for the members to review the current HIV vaccine pipeline and each country's progress in AIDS vaccine research and development in Asia. The meeting, through six working groups, discussed the current status, gaps, and methods to strengthen the capacity and infrastructure in the various areas related to AIDS vaccine research and development. These include: public-private partnerships, clinical trial capacity, basic research, laboratory, non-human primates and animal models and young and early career investigators. These discussions led to the development of prioritized action plans for the next 5 years. As a result, the organizational structure of the permanent secretariat of the AVAN was established.

SELECTED ACTIVITIES FOR HIV VACCINE RESEARCH AND DEVELOPMENT IN ASIA

The prevalence of reported HIV/AIDS cases in China in 2009 was 326,163, but the actual number is estimated to be 740,000. Of the reported HIV/AIDS cases, 44.3% were heterosexual, 32.2% were injecting drug users (IDUs), 14% were men who have sex with men (MSM), 7.8% were former plasma donors, and 1% were pregnant women (UNAIDS, 2010). Regarding the HIV subtypes, 07_BC comprised 30.75% of cases tested; 01_AE and 08_BC comprised 323,163 cases (Tee *et al*, 2008). As part of the Chinese government's response to epidemics, the Chinese AIDS Vaccine Initiative (CAVI) has recently established a research model for the National Key Infectious Disease (NKID) Projects. This is comprised of replicating vector HIV vaccines, broader neutralizing antibodies, therapeutic vaccines, technical platforms for Non-Human Primates (NHP) and immune assays and mucosal vaccine projects (Shao, 2010). Table 2 lists the current HIV vaccine clinical trials in the pipeline in China. These trials include testing: DNA/EP and Modified Vaccinia Tiantan with or without gp140, non replicative Tiantan MVA and Adeno Associated Virus (AAV) and Sendai as a therapeutic vaccine candidate, Modified

Tiantan Vaccinia for mucosal use given with Adeno Virus type 5 (Ad5) HIV vaccine boost and others (Kent *et al*, 2010).

Japan

The number of HIV infections and AIDS cases has risen steadily from 1985 to 2008 with a slight decline in 2009 totaling 11,560 of HIV and 5,319 cases of AIDS reported (UNAIDS, 2010). Of these, 51.2% were MSM, and 31.5% were heterosexual transmissions. In 2009, 68% were MSM, 20.6% were heterosexual transmissions and 11.5% contacted HIV by other modes (UNAIDS, 2009). This suggests an increasing trend of HIV among MSM in Japan. Seventy-eight point two percent of HIV cases tested among MSM were subtype B, and 73.7% of HIV subtypes among heterosexual transmission cases tested CRF01_E (UNAIDS/WHO, 2009).

The HIV vaccine currently being studied in Japan includes a low dose codon-optimized rBCG/SIV gag-prime and a rVV-Dis/SIV gag-boost regimen that induced protective immunity in macaques showing a decrease in viral load (Yamamoto *et al*, 2003). Other HIV vaccine candidates undergoing research are a Vaccinia m8 strain and a rBCG/VVm8Δ, a replication competent vaccine (Shida, 2010).

India

India's Integrated HIV Vaccine Program states the prevalence and people living with HIV/AIDS in India have been declining since 2002. The HIV prevalence reported among in 2008-2009 was 0.49% in antenatal clinics (ANC) attendees, 2.5% among Sexually Transmitted Disease (STD) clinic attendees, 4.9% among Female Sex Workers (FSWs), 9.2 among IDU, and 7.4% among MSM (UNAIDS, 2009). There are a series of phase I vaccine trials in India. The first phase I trial was an Adeno-associated virus vaccine, followed by a phase I trial of a TBC-M4 (modified vaccine Ankara) HIV-1 multigenic subtype C vaccine, a phase I trial with a prime-boost regimen with ADVAX and TBC-M4, and a DNA vaccine with priming and MVA boosting *versus* a MVA vaccine alone (UNAIDS, 2009). All were shown to be safe and immunogenic (Ramanathan *et al*, 2009, 2010). There is also expanding applied research, including an Indo-South African collaboration aimed at defining HIV antigens for further development of HIV vaccines, identifying neutralizing antibody epitopes on Indian and South African HIV-1 subtype C viruses for HIV vaccine designs (UNAIDS, 2009).

Philippines

The preference of reported HIV/AIDS cases in the Philippines through April 2010 was 4,971. There was a dramatic 38% increase in cases during the past 2.5 years (UNAIDS, 2009). There has also been an increase in the proportion of reported cases that are related to homosexual transmission, approximately 50% of those reported in 2010 (UNAIDS, 2010). There has been a marked decline in the proportion of heterosexual transmission cases, accounting for 20% in 2010 (UNAIDS, 2010). There has been a marked increase in the reported numbers of seropositive IDUs. There were 44 IDUs reported as having HIV between 1984 and 2009 (UNAIDS, 2010). However, this increased to 297 cases by April 2010 (UNAIDS, 2010). The majority of subtypes tested were B (35), CRF01_AE (30), C (4), D (1), and CRF02_AG (1) (UNAIDS, 2009).

Thailand

There has been a decline in the national prevalence of HIV positive cases among ANC attendees, from a high of 2.5% to < 1% by the end of 2009 (UNAIDS, 2010). The prevalence among military

recruits has been constant at about 0.5% since 2001 (UNAIDS, 2009). There has been a decrease in HIV prevalence rates among at risk groups (direct and indirect FSWs, male sex workers, and STI patients) (UNAIDS, 2009). In various surveys, IDUs had the highest prevalence rates since 2004, ranging from 28.8% to 46.8%; the prevalence among MSM has ranged from 13.5% to 24.6%, and for FSWs from 2.79% to 6.7% (UNAIDS, 2009). It is anticipated, based on modeling, in 2010 the majority of cases will be MSM, with females being infected by their husbands as the 2nd leading mode of transmission (UNGASS, 2010).

A series of preventive HIV vaccine trials have been conducted, including 2 phase III trials (UNAIDS, 2009). The first efficacy trial testing was the AIDSVAX B/E among IDU failed to prevent HIV infection (Pitisuttithum *et al*, 2006). However, the modest efficacy of the ALVAC-HIV prime and AIDSVAX boost was a medical breakthrough in HIV vaccine research, which showed a HIV vaccine is possible (Rerks-Ngarm *et al*, 2009). A tremendous amount of work has gone into discovering immune correlates and follow-up RV144 studies are also planned. The current activities include improving vaccine constructs, including rBCG and vaccinia, a DNA mosaic vaccine, and continuing cohorts among special groups, especially MSM, and sex workers, with high HIV infection rates. Continuing studies of molecular epidemiology of the circulating HIV strains is also an ongoing priority (Pitisuttithum *et al*, 2010).

FUTURE TRENDS IN HIV VACCINE RESEARCH AND DEVELOPMENT

There are a variety of interventions for prevention and treatment of HIV to reduce new infections. Potential methods that would prevent infections include microbicidse, pre-exposure prophylaxis (PrEP), circumcisions, behavior changes, and eventually possibly vaccines. Strategies for use after exposure include post-exposure prophylaxis (PEP), anti-retroviral treatment, and eventually possibly therapeutic vaccines. These interventions could lead to aborted infection, lowering the viral load set point, or stopping the progression of the disease. These interventions need to be coordinated with future HIV vaccine trials. The results of the ALVAC HIV vaccine priming and AIDSVAX boosting trial (RV144 trial) showed a 31% lower risk of contracting HIV among a low risk heterosexual population (Rerks-Ngarm *et al*, 2009). The efficacy appeared early but was not durable on post hoc analyses. This could imply booster dose(s) may be necessary to improve durability and potency.

Further studies will be built on the results of the RV144 trial by the US Military HIV Research Program (MHRP) for developing a regional vaccine with the proposal of two small phase II trials, a phase IIb efficacy trial with the ALVAC/AIDSVAX or similar vaccine with an additional boost or shorter follow-up among three populations: a heterosexual risk Thai population, a MSM Thai population, and a high risk heterosexual population in the Republic of South Africa.

PERSPECTIVES ON THE STRENGTH OF THE AVAN

AVAN has the potential to accelerate all aspects of HIV vaccine research and development in the region. These include increasing the number of vaccine candidates suitable for Asia by establishing and maintaining collaboration between Asian researchers and industry with global part-

ners. AVAN's role in research coordination is critical to coordinate regulatory and ethical frameworks to comply with international standards and regional vaccine production. AVAN will help to engage public and private sectors to establish political and financial support for vaccine research and development, including licensing and future access. AVAN will provide a framework for implementing phase IIb proof-of-concept, phase III and adaptive design trails.

Vaccines being developed in Asia include: DNA vaccines (China), Tiantan vaccinia (China), Vaccines expressing CD40 ligand (Canada), Envelop trimers (Australia), Nanoparticles (Australia), BCG vectors (Japan), Influenza vectors (Australia) and Sendai virus vectors (Japan/China). There are opportunities in Asia to incorporate prevention technologies with vaccine initiatives. Those include: participating in pre-exposure prophylaxis (PrEP) trials or testing PrEP/Vaccine combinations which may be more effective than vaccine alone. There are concerns about the challenges relating to PrEP/vaccine trials. These include drug sourcing, national and international guidelines that constrict the scope of such trials, the new skills and procedures needed to monitor vaccine recipients on PrEP, adherence to PrEP among populations targeted for the AIDS vaccine trial, and gathering data regarding HIV seroconversion/viral load patterns from PrEP trials.

Expanding trials to include high-risk groups, such IDU, will be important. In Asia there are more than 4.5 million IDU. IDU have the highest HIV prevalence of any population in Asia. Regionally, 16% of IDU are estimated to be infected with HIV. However, involving IDU in clinical trials poses ethical, regulatory, legal, logistical, social, and structural challenges. There are issues around recruitment and retention of participants, issues specific to the standard of prevention, to care and treatment, and issues related to special populations, such as women, adolescents and those in closed facilities.

There is an urgent need for specific rights-based evidence-informed research guidance that addresses the challenges and implications of working with IDU. The role of AVAN here is to facilitate the development of these guidelines in collaboration with UNAIDS and the WHO.

OUTCOMES OF THE WORKING GROUPS

The Pattaya AVAN meeting included six working groups to discuss current activities, gaps, challenges and proposed recommendations to help AVAN formulate an action plan for HIV vaccine development. The topics discussed by the groups and their recommendations are shown in Table 1.

Working group 1: Clinical trials and regulatory issues

The testing of potential vaccines should be as efficient as possible. There were concerns about ethical issues, intellectual property (IP) rights, and sharing data and specimens. The group recommended the establishment of a network of existing clinical trial sites in the region for the exchange of knowledge, sharing protocols and clinical data, developing multiple cohorts, standardizing procedures per GCP or GLP guidelines, and manufacturing vaccines according to WHO guidlines. There is a need to organize regional consultations to harmonize regulatory measures; it was agreed these should be presented as an international agenda.

Table 1
Proposed plan, gaps, challenges and timeline for AVAN action plan.

Working Group 1: clinical and regulatory issues

Issues	Proposed	Gaps/challenges
Strengthen networking	- For improving networking, training of investigators and sharing of data for clinical sites in different countries. - Training can be conducted for GCP, GLP or exchanging protocols and/or other documents. - List of funding strategies.	- Training needs to be standardized, identifying "centers of excellence" for various subjects. - Tech transfer (data fax). - Sharing data may present a problem.
Improving regulatory measures	- Harmonizing the regulatory framework with research activities. - To utilize the existing regulatory networks.	- Countries will have their own rules and regulations.
Production of clinical trial lots	- Plan for the GMP production of clinical trial lots through WHO pre-qualification. - Identify GMP facilities by country (consider listing vaccine trial sites by country). - Early involvement of authority to inspect GMP production sites. - OECD practice in Japan is an example of production of clinical trial lots. - Regional consultations. - Clinical trial authorization needs to be standardized.	
Advocacy	- Need to make advocacy for policy makers both country wide and region wide. - Make recommendations for harmonization of regulatory measures and GMP production at APEC meeting.	
Sharing specimens and vaccine constructs	- Specimen sharing starts where it is most feasible. - Sharing of vaccine products with different clades within Asian members.	- Specimen sharing among Asian countries has some limitations due to sensitivity regarding ownership and IP.

Working group 2: Laboratory research and vaccine development

The vaccine under development in the region were reviewed (Table 2). The issue of the availability of different vectors for NHP studies and the need for large co-

Working group 2: Laboratory research/vaccine development in the region

Issues	Proposed	Gaps/challenges
Research - Studies already underway and list of vectors available. - Safety/immunogenicity/ efficacy trials in animal models. - Variability of prevailing subtypes across the region. - Lack of subunits as inserts for vaccine production. - Work on neutralizing antibodies.	- Regional meeting to discuss preclinical and clinical studies to compare vectors available. - Propose to conduct clinical trials as a follow-up to RV 144. - AVAN-develop cohort for vaccine study in the region. 1. Look for resources and approach the NIH or CHAVI. 2. Establish acute infection cohort, especially for the AE/BC subtype epidemic region. 3. Involve at risk populations a. IDU, b. IDU + heterosexual cohort to see if results are same between the groups. - Standardized protocols among sites so analysis and data management become easier.	- Cohort development-standards of care vary by country and site. - Cohorts cannot be maintained for long periods. - Issues of intellectual property rights/ownership issues have to be dealt with.
Infrastructure/resource center	- Establish regional laboratory network and collaboration able to carry out: 1. virus isolation and characterization in the region; 2. create a database of the circulating virus subtypes; 3. matching the international standard in the repository - Training in cryopreservation - Training for sample collection/ laboratory techniques (focusing on young scientists) 1. Training for characterization of virus group; 2. Immunoassays; 3. Cohort development in collaboration with regional and international resources	

horts to test efficacy were discussed. There were concerns about potential duplication of efforts and resources. The group recommended efforts to create a data base for the vaccines being studied in the region and of cohort development activities for comparatives studies. The establishment of a central laboratory (or laboratories) to serve as reference laboratories was also recommended.

Working group 3: Community and ethical considerations on HIV vaccine research and clinical trials

Issues	Proposed	Gaps/challenges
Community engagement (CE)	- Stakeholder mapping and analysis. - Listing of CE guidelines and best practices. - Review CE practices by research community. - Forum for community stakeholders.	- Lack of information about community stakeholders. - Limited awareness of available resources about CE.
	- Stakeholder training, education, strengthening, empowerment (research literacy and community literacy/social competence). - Strengthening CE infrastructure (CAB, CAF, etc), possibility of National CAB as "super-CAB" - Thai AIDS Vaccine CAB, training, develop a manual. - Linkage with international advocacy (AVAC), and international organizations (WHO-UNAIDS), for advocacy and technical support. - Advocacy support from community stakeholders for AIDS vaccine research in AVAN member countries.	- Conceptual gap about CE among stakeholders. - Lack of mechanism for dialogue and partnership. - Gap in sharing lessons learned and regional/ international advocacy.
Research ethics	- Mapping research ethics infrastructure (institutional, national, and regional levels) and frameworks (guidelines, laws and regulations). - Identification of gaps with regional, international guidelines, laws and regulations. - Situation analysis, identification of strengths and weaknesses. - Developing of ethical guidelines for research in vulnerable populations, *eg*, IDU - Build on RV 144 experience and Bangkok meeting in March 2010 on post-trial obligations and benefits for trial participants (low efficaciousness of vaccine) to placebo group and community.	- Lack of information on who is involved, and how they operate, what ethical frameworks are used.
	- Engagement of other disciplines in research ethics (philosophy, anthropology, law, civil society, other). - Training, strengthening research ethics (formal and informal settings). - Plan for step by step process towards standardization and harmonization of ethical practices. - National guidelines for biomedical research, guidelines for protocol submission and review. - Mechanism for reviewing performance, auditing ethical infrastructure. - Assessment of available standards of care and treatment, and prevention package offered to trial participants in AVAN member countries (and publish).	- Lack of formal ethics education in some regions. - Limited coordination (recognition of other ethical practices, multi-site studies). - Lack of national guidelines.

Working group 4: Vaccine research and development; non-human primates/NHP

Issues	Proposed	Gaps/challenges
Preclinical studies/ new vaccines	- Inventory labs working in HIV vaccine research. - Inventory experimental systems. - Satellite to international meeting (AIDS meeting in Bangkok in 2011). - Web-based list of researchers and expertise. - Inventory of early stages of development. - Develop opportunities for feedback to speed pathways for development.	- Limited sources. Existing international linkage is helpful but costly for investigators.
	- Training for young investigators and provide regional mentorship. - Regional consultative forum for (young) investigators to assist in preclinical development of novel HIV vaccine concepts. - Link with young investigator program.	- Many good HIV vaccine concepts come from unusual sources. - Engaging investigators with emerging concepts could be difficult.
Primate centers	- Inventory primate centers in the region: type of facility (breeding, research), size, type of monkeys, genetic background, cost, type of models used, other new/existing resources (reagents, adjuvants). - Inventory challenge models in region. - Begin to forge stronger links with US primate centers and OAR/NIH.	- Lack of harmony of existing primate centers. - Lack of information on primate centers: where are they, what models are used, what expertise, what primates (Japan, China, Australia, Indonesia, Singapore).
	- Stronger regional network. - Regular meetings may be in conjunction to international meetings (start with small forum in conjunction with Bangkok AIDS meeting in 2011). - Consider identifying one of the yearly US NHP/AIDS conferences to promote attendance by Asian NHP/AIDS investigators. - Share facilities in region and try to link centers in order to get robust study results (*eg*, sufficient numbers of animals).	- Will need to stimulate robust network. Linkages across groups will be important.
Technology transfer (lab assays, reagents, people) within the region.	- Inventory existing relationships and training opportunities. - Inventory resources available to support technology transfer (local resources within labs, international resources).	- Funding the exchange of young researchers. - Planning for ongoing success not easy.
	- Develop funding pathways for investigators to learn assays and technologies.	- Identifying young investigators staying in field of HIV vaccine research. - Potential legal problems (MTAs etc) with transfer of reagents.

Working group 5: Young investigators program

Issues	Proposed	Gaps/challenges
Recruitment	- AVAN to co-sponsor workshop as platform for recruitment of new scientists. - Establish website for sharing information. (AVAN website a likely resource). - Advocacy for AVAN.	- The nature of vaccine research is competitive, complex and needs special knowledge. - Insufficient funding for young investigators. - Limited opportunities for young investigators for decision making or leadership. - Logistic and institutional challenges. - Hierarchy.
Training	- Mapping existing opportunities in the region. - Mentorship. - Networking and exchange programs. - Manuscript writing. - Grant writing. - General and specific training programs. - Allocated time for scientific work.	
Career path for the future	- Mapping existing COE. - Scholarships. - Recognition of competency of work. - Attend and present works at regional conferences and AIDS vaccine scientific conferences. - Starting grants. - Protocol and grant reviews.	

Working group 3: Community and ethical issues relating to HIV vaccine research and clinical trials

Community involvement in HIV vaccine research is critical. There may be informal or formal consultation with the trial community. One example is the formation of a community advisory board (CAB) which serves as a link between the community and investigators in some countries such as Thailand and India. Lack of knowledge among community stakeholders, community advocacy groups, and the different national ethical frameworks impose great challenges for conducting research. Strengthening of community involvement by providing communities with adequate information about trials, standardization and harmonization of ethical practices. The involvement of other disciplines, such as anthropology and philosophy,

Working groupn 6: Public private partnerships

Issues	Proposed	Gaps/challenges
Mapping funding agencies	Identify funding agencies in the region (*eg*, ADB) and globally, including in country and regional economic development funds and other non-traditional mechanisms.	Economic crisis limits potential contributors.
How to start	- Advocacy for the establishment of PPP for AIDS vaccine research and development. - Identified vaccine research and development expertise that can assist member countries and facilitate the formation of PPP by engaging relevant partners (*eg*, workshops). - Assist AVAN members in identifying resources for development of high priority projects. - Mapping potential institutions that have fund raising experience and have them as a partner in the establishment of early partnerships.	- Finding willing partner(s). - Determine and establish agreements on who owns results, etc. IP licensing rights (AVAN as neutral broker).
Public and private fund contributions	Secure funding from AVAN members to support its activities to promote PPP.	Political sensitivities and mobilization.

in research ethics could help improve community involvement. Participants emphasized the need to develop ethical guidelines for research in vulnerable populations.

Working group 4: Basic laboratory HIV vaccine research and studies among non-human primates (NHP)

Advanced preclinical evaluation of HIV vaccine candidates is critical and under-utilized in the region due to lack of awareness of such facilities. However, the region has excellent primate centers, particularly in Japan, China, Australia, Indonesia, Singapore, and India, with a diversity of species (macaques, rhesus subspecies, cynomolgus subspecies, pig-tail macaques, and others) with strong expertise in preclinical research. The group recommended an inventory of existing laboratories, technology transfer (assays, reagents, and people) between primate centers in the region and building collaboration by organizing regional meetings, all of which help speed HIV vaccine development.

Working group 5: Young investigator program

Recruiting talented young investigators into the field will be crucial in sustaining the HIV vaccine effort. There are some challenges identified, such as linguistic barriers, lack of adequate communication and writing skills and lack of information regarding career paths for the young professionals to entering in the field of research. It was proposed to create an inventory of existing expertise and research resources as well as centers of excellence in the region. National and

Table 2
List of vaccines in clinical trial in Asia.

Type of vector	Name	Group studying	Clade	Insert	Comment
Replicating virus vector	Tiantan vaccinia	Y Shao, X shen, China CDC/ Natl Sera vaccine Inst (NSVI)	CRF-07, B'C (CN54)	Gag, Pol, gp 140	Phase I,2007Phase II plan 2010/2011 (Shao *et al*, 2008)
	Tiantan vaccinia	Y Shao, China CDC	B',A/E	Gag, Pol, gp 140	Phase I (Shao *et al*, 2009)
	Modified Tiantan vaccinia	Z Chen, L Zhang Hong Kong/Tisinghua Unit	B'/C	Gag, Pol, gp 140	(Personal communication)
	Modified Tiantan vaccinia	Y Shao,China CDC	B'/C CRF-07, CN54 strain	Gag,Pol gp 140, Tat. Nef, Rev	(Personal communication)
Non-replicating vectors	MVA-CMDR	MHRP, Thailand	A/E	Gag,Pro,Env	Phase I (Currier *et al*, 2010)
	MVA	W Kong Changchun Baiko Co	CRF08, B'/C	Gag,Pol, ΔV2 env,tat,and nef	Phase II (Kent *et al*, 2010)
	ALVAC-Canarypox	Sanofi Pasteur,Thai group	E	Gag, Pro, A/E gp 120 B gp41 tm	Phase III (Rerks-Ngarm *et al*, 2009)
	MVA-Therion strain	NARI/TRC India	C	Env,gag, rev,nef and pol	Supported by IAVI (Personal communication)
	Nyvac-Vaccinia	Eurovacc/	CRF-07, B/C CN54 strain	Gag,Pol,Nef Env	Phase I (Bart *et al*, 2008; Excler *et al*, 2008), Phase II Available at end of 2010
	Nyvac-Vaccinia	Eurovacc/	B/E		(Personal communication)
	DNA	B Felber, USA	B/C	Gag,env	Expression optimized (Personal communication)
	Sendai	Y Zeng China CDC	B/C	Env,Gag,Pol	(Personal communication)
	DNA	W Kong ChangchunBaiko Co	CRF08,B'/C	Gag,Pol, Env	Phase II (Kent *et al*, 2010)
	DNA	Y Shao,China CDC	B'/C,CRF-07, CN54 strain	Gag,Pol, gp140,Nef	Phase I (Shao *et al*, 2009) Phase II plan 2010/2011
Previously studied but not for further development	AAV				Studied in India, limited immunogenicity (Mehendale *et al*, 2008)
	Fowlpox	D Cooper, S Kent *et al* Australia/P Phanaphak Thailand	A/E	Gag,Pol,Env	Studied in Phase I in Thailand, limited Immunogenicity (Kelleher *et al*, 2006; Excler *et al*, 2008; Kent *et al*, 2010)

Table 3
List of 2010 AVAN participants.

Name	Affiliation	Country
Dr David A Cooper	National Centre in HIV Epidemiology and Clinical Research, Sydney	Australia
Dr Denise Hsu	The National Centre for HIV Epidemiology and Clinical Research, Sydney	
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Dr Vonthanak Saphonn	National Institute of Public Health (NIPH), Phnom Penh	Cambodia
Prof Yiming Shao	National Center for AIDS/STD Control and Prevention, China CDC, Beijing	China
Dr Zhang Mei-yun	AIDS Institute, Li Ka Shing Faculty of Medicine, The University of Hong Kong	
Prof Nirmal Kumar Ganguly	National Institute of Immunology, New Delhi	India
Mr Rajat Goyal	International AIDS Vaccine Initiative (IAVI)	
Dr Budiman Bela	Department of Microbiology, University of Indonesia, Jakarta	Indonesia
Dr Dyah Erti Mustikawati	Ministry of Health, Indonesia, Jakarta	
Dr Diah (Atie) Ishkandriati	Primate Research Centre at Bogor University, Jakarta	
Prof Hiko Tamashiro	Department of Global Health and Epidemiology Division of Preventive Medicine Hokkaido University, Tokyo	Japan
Dr Kazuhiro Matsuo	BCG Laboratory	
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Dr Van Kinh Nguyen	National Institute of Infectious and Tropical Diseases	Vietnam
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Dr Bonnie Mathieson	Office of AIDS Research, National Institutes of Health, Bethesda, MD	
Ms Amapola Manrique	Global HIV Vaccine Enterprise, New York	
Dr Jerome Kim	US Military HIV Research program (MHRP)	
Dr Jose Esparza	Bill & Melinda Gates Foundation, Seattle, Washington	
Dr Alan Bernstein	Global HIV Vaccine Enterprise, New York	
Dr Edward Karamov	Laboratory of Molecular Biology of HIV, Institute of Immunology, Moscow	Russia
Dr Rodney Hoff	Regional Emerging Diseases Intervention Centre	Singapore
Dr Eric Sandstrom	Department of Infectious Diseases, Karolinska University Hospital, Stockholm	Sweden
Dr Jean-Louis Excler	International AIDS Vaccine Initiative (IAVI)	Switzerland
Dr Saladin Osmanov	WHO-UNAIDS HIV Vaccine Initiative (IVR/HVI), Geneva	
Prof Punnee Pitisuttithum	Faculty of Tropical Medicine, Mahidol University, Bangkok	Thailand
Dr Michael Benenson	US Military HIV Research Program, AFRIMS, Bangkok	
Dr Mark De Souza	US Military HIV Research Program, AFRIMS, Bangkok	
Dr Joseph Chiu	US Military HIV Research Program, AFRIMS, Bangkok	
Dr Viseth Ngauy	US Military HIV Research Program, AFRIMS, Bangkok	
Ms Nusara Thaitawat	US Military HIV Research Program, AFRIMS, Bangkok	
Dr Sorachai Nitayaphan	AFRIMS, Bangkok	
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Table 3 (Continued).

Name	Affliation	Country
Dr Yupin Lawanprasert	FDA, Ministry of Public Health Thailand, Bangkok	Thailand
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Prof Ruengpung Sutthent	Department of Microbiology, Faculty of Medicine Siriraj Hospital, Bangkok	
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Dr Thira Sirisanthana	Research Institute for Health Sciences, Chiang Mai University, Chiang Mai	
Dr Pathom Sawanpanyalert	National Institute of Health of Thailand, Bangkok	
Dr Prasit Palittapongarnpim	Faculty of Science, Mahidol University, Bangkok	
Dr Pokrath Hansasuta	Faculty of Medicine, Chulalongkorn University, Bangkok	

international programs should provide information about training, employment and career opportunities as a way of attracting young investigators into the field of vaccine research.

Working group 6: Role and importance of public-private partnerships (PPP) in the development and implementation of AVAN

Limited funding sources and the global economic crisis prompted the working group to call for involvement of governments of member countries. The identification of other funding sources for research and development, including nontraditional agencies, with the help of experienced international fund raisers is an important priority.

THE AVAN SECRETARIAT

China, under the direction of Dr Yiming Shao, was selected as the site for the permanent AVAN secretariat office. This proposed structure of the AVAN secretariat received strong support from the China Ministry of Health and China AIDS Vaccine Initiative (CAVI). There will be Collaborating Centers, which would have different tasks and responsibilities established in various countries. These would consist of training (Japan, Thailand, Australia), resources (China, Thailand, India, and Japan), clinical trial and ethical centers (Thailand), regional laboratories (Australia, Thailand) and Primate centers (China, India, Malaysia). The proposed functions of the secretariat include facilitating collaborative research, serving as a liaison to international organizations, such as WHO/UNAIDS, conducting fund-raising in partnership with its counterparts, coordinating resource centers, promoting knowledge sharing, promoting training of young scientists and providing support to AVAN working groups. An AVAN task force website (www.avan.asia) has been developed and maintained for team discussions and resource sharing.

CONCLUSION

The development of an effective AIDS vaccine is important. Due to the inherently

challenging nature of the disease and the virus, calls for increased collaboration of efforts among researchers across the region have been made to sustain the momentum of developing a vaccine. This AVAN meeting detailed the gaps and challenges that HIV vaccine research faces in the region and recommended improvement and standardization of the facilities, coordination and harmonization of all the activities and technology transfer. Further strengthening of the AVAN network is planned to occur for the AIDS Vaccine 2011 conference in Bangkok in September 2011.

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REFERENCES

Bart PA, Goodall R, Barber T, *et al*. EV01: A phase I trial in healthy HIV negative volunteers to evaluate a clade C HIV vaccine, NYVAC-C undertaken by the EuroVacc Consortium. *Vaccine* 2008; 26: 3153-61.

Buchbinder SP, Mehrotra DV, Duerr A, *et al*. Efficacy assessment of a cell- mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomized, placebo-controlled, test-of-concept trial. *Lancet* 2008; 372: 1881- 93.

Currier JR, Ngauy V, de Souza MS, *et al*. Phase I safety and immunogenicity evaluation of MVACMDR, a multigenic, recombinant modified vaccinia Ankara-HIV-1 vaccine candidate. *PLoS One* 2010; 5: e13983.

Excler JL, Pitisuttithum P, Rerks-Ngarm S, *et al*. Expanding research capacity and accelerating AIDS vaccine development in Asia. *Southeast Asian J Trop Med Public Health* 2008; 39: 766-84.

Kelleher AD, Puls RL, Bebbington M, *et al*. A randomized, placebo-controlled phase I trial of DNA prime, recombinant fowlpox virus boost prophylactic vaccine for HIV-1. *AIDS* 2006; 20: 294-7.

Kent SJ, Cooper DA,Vun MC, *et al*. AIDS vaccine for Asia network (AVAN): Expanding the regional role in developing HIV vaccine. *PLoS Med* 2010; 7: 1- 6.

Mehendale S, van Lunzen J, Clumeck N, *et al*. A phase 1 study to evaluate the safety and immunogenicity of a recombinant HIV type 1 subtype C adenoassociated virus vaccine. *AIDS Res Hum Retroviruses* 2008; 24: 873-80.

Pitisuttithum P, Gilbert P, Gurwith M, *et al*. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. *J Infect Dis* 2006; 194: 1661-71.

Pitisuttithum P, Choopanya K, Rerk-Ngnam S. HIV-vaccine research and development in Thailand: evolution and challenges. *Vaccine* 2010; 28S: B45-9.

Ramanathan VD, Kumar M, Mahalingam J, *et al*. A Phase 1 study to evaluate the safety and immunogenicity of a recombinant

HIV-1 subtype C modified vaccinia Ankara virus vaccine candidate in Indian volunteers. *AIDS Res Hum Retroviruses* 2009; 25: 1107-16.

Ramanathan VD, Mehendale S, Sahay S, *et al*. Safety and immunogenicity of DNA prime and modified ankara virus HIV subtype C vaccine boost in Indian volunteers. *AIDS Res Hum Retroviruses* 2010; 26: A-1-A-184.

Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, *et al*. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009; 361: 2209-20.

Rerks-Ngarm S, Pitisuttithum P, Ganguly N, *et al*. Defining the objectives of the AIDS vaccine for Asia network: report of the WHO-UNAIDS/Global HIV vaccine enterprise regional consultation on expanding AIDS vaccine research and development capacity in Asia. *Curr Opin HIV AIDS* 2010; 5: 435-52.

Shao Y, Li T, Shen X, *et al*. The safety and immunogenicity of the replicative Tiantan vaccinia HIV vaccine in phase I clinical trial. [Poster No P13-18]. Cape Town: AIDS Vaccine, 13-16 October 2008.

Shao Y, Li T, Wolf H, *et al*. The safety and immunogenicity of HIV-1 vaccines based on DNA and replication competent vaccinia vector in phase I clinical trial. [Poster No P14-15LB]. Paris: AIDS Vaccine, 19-22 October 2009.

Shao Y. AIDS epidemiology update in China. [Report]. Pattaya, Thailand: AIDS Vaccine for Asia Network Meeting, 29-30 June 2010: 1-20.

Shida H. Replication competent vaccines: rBCG/VVm8Δ: Update of epidemic & prevention in Japan. [Report]. Pattaya, Thailand: AIDS Vaccine for Asia Network Meeting, 29-30 June 2010: 1-20.

Tee KK, Pybus OG, Li XJ, *et al*. Temporal and spatial dynamics of human immunodeficiency virus type 1 circulating recombinant forms 08_BC and 07_BC in Asia. *J Virol* 2008; 82: 9206-15.

The Council of the Global HIV Vaccine Enterprise. The 2010 scientific strategic plan of the global HIV vaccine enterprise. *Nat Med* 2010; 16: 981-9.

UNAIDS. AIDS epidemic update. Geneva: UNAIDS, 2009.

UNAIDS. AIDS epidemic update. Geneva: UNAIDS, 2010.

United Nations General Assembly Special Session (UNGASS). Country progress report: Thailand. New York: UNGASS, 2010. [Cited 2011 Apr 2011]. Available from: URL: http://www.unaids.org/en/dataanalysis/monitoringcountry progress/2010progressreportssubmittedbycountries/thailand_2010_country_progressreport_en.pdf

Yamamoto N, Nakasone T, Izumi Y, *et al*. Prime-boost vaccination with recombinant *Mycobacterium bovis* bacillus Calmette-Guerin and vaccinia strain DIs elicits protective immunity against pathogenic SHIV infection in macaques. [Abstract 434a]. Boston, Mass: 10th Conference on Retroviruses and Opportunistic Infections, 10-14 February 2003.