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EXPANDING RESEARCH CAPACITY AND ACCELERATING AIDS VACCINE DEVELOPMENT IN ASIA

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Abstract. According to the Joint UN Program on AIDS (UNAIDS), an estimated 4.9 million adults and children are living with HIV in Asia and the Pacific. Refinement and development of existing and new prevention and treatment technologies - including safe, effective, and accessible AIDS vaccines - are urgent public health priorities. The Asian region faces several challenges for AIDS vaccine development. There are multiple genetic variants of HIV-1 driving the epidemic in the region and too few vaccine candidates in the pipeline targeting those subtypes. Low HIV incidence throughout the region means that trial sites must recruit larger numbers of volunteers and shift their focus to higher-risk populations where incidence is higher. Also, the cultural, economic, and political diversity of the region may render collaboration very complex, but also beneficial at a regional level. Recognizing that collaborating as a region could foster and accelerate AIDS vaccine development, participants at the Sapporo International Consultation recommended that an AIDS Vaccine Asian Network (AVAN) be created to facilitate interactions between donors and funding opportunities, increase regional clinical trial and production capacity, support region-specific advocacy and communication strategies, contribute to the Global HIV Vaccine Enterprise Scientific Plan, prepare a regional approach for future vaccine deployment, and develop a regional platform for clinical trials including harmonized legal, regulatory, and ethical frameworks.

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BACKGROUND AND THE NEED FOR REGIONAL STRATEGIES IN ASIA

In 1998, the UNAIDS, World Health Organization (WHO), and the Japanese National Institute of Infectious Diseases (NIID) met to discuss needs and opportunities for AIDS vaccine research in Asia. The meeting concluded that "the future success of AIDS vaccine development hinges on: establishing and maintaining a healthier pipeline of candidate vac-

cines; developing international collaborations that cut across sectors; conducting parallel phase III efficacy trials of the most promising candidate vaccines in different populations, especially in those with the highest need of a vaccine; and ensuring that, once a successful vaccine is identified, it is rapidly assessed, modified as necessary, and widely used to meet worldwide needs (Esparza, 1999).

Today, the development of an AIDS vaccine remains one of the most difficult challenges confronted by the biomedical research (Emini and Koff, 2004; Letvin, 2006; Berkley and Koff, 2007). More than 160 phase I and II vaccine trials have been conducted since 1988. A phase III trial is still on going in Thailand. A phase IIB test-of-concept (TOC) although now stopped for futility has been implemented in the Americas, Australia and South Africa (WHO/UNAIDS/IAVI International Expert Group, 2007). Additional phase IIB TOC trials are planned, with the muticlade DNA and Adenovirus 5 in a prime-boost regimen by the US National Institutes on Health's Vaccine Research Center in multiple sites.

Other prevention technologies that can help slowing the spread of HIV are making progress and the results from ongoing studies will continue to influence the way AIDS vaccines are studied. Results of microbicide and retroviral drug interventions (post- and pre-exposure prophylaxis), circumcision, and sexually-transmitted infection (STI) prevention and treatment trials may soon impact AIDS vaccine trial protocol designs and raise complex ethical questions in terms of the standards, access, priority, and care and treatment.

While the AIDS vaccine field has reached new levels of complexity, it has also opened new avenues for collaboration. The Global HIV Vaccine Enterprise was proposed in 2000 to speed up the development of an effective AIDS vaccine (Klausner *et al*, 2003). The Enterprise model represents a new way of behaving as a

global community of problem-solvers, striking a balance between collaboration and competition to drive scientific discovery.

A more collaborative model for vaccine research is reflected in new, cross-cutting research consortia, such as those supported by the Bill and Melinda Gates Foundation's Collaboration for AIDS Vaccine Discovery (CAVD) and the United States National Institutes on Health (NIH) Center for HIV/AIDS Vaccine Immunology (CHAVI). Together, these research consortia support 245 AIDS vaccine researchers with nearly US\$600 million in funding over ten years.

With much of the global AIDS vaccine research focused on Africa, WHO began working with African countries in 2000 to create a regional initiative for vaccine research in Africa. The African AIDS Vaccine Program (AAVP) is a network of African AIDS vaccine stakeholders committed to AIDS vaccine development for Africa, through research, advocacy, partnership, and contribution to capacity strengthening and policy development.

A regional network is now being proposed in Asia to accelerate the region's AIDS vaccine research and development efforts. Efficacy trials remain the bottleneck of vaccine development in Asia, despite the demonstrated ability to generate excellent safety and immunogenicity results in phase I and II trials (Excler and Beyrer, 2000; Esparza and Burke, 2001). Because efficacy trials are required for licensure, the implementation of efficacy trials in Asia will likely require a regional strategy to establish multiple vaccine trial sites, coordinated platforms for efficient testing, and vaccination strategies designed specifically for the Asia and the Pacific region (Excler JL, *et al*, 2008, in press). The Sapporo consultation, "Expanding Research Capacity and Accelerating AIDS Vaccine Development in Asia" (2006) aims to intensify and expand regional collaboration, networking, and initiatives in support of AIDS vaccine research and development in Asia.

HIV PANDEMIC AND RATIONALE FOR THE DEVELOPMENT OF A REGIONAL PLATFORM FOR AIDS VACCINE EFFICACY TRIALS IN ASIA

By the end of 2007, UNAIDS estimated that 2.5 million people worldwide became newly infected with HIV and 2.1 million people died from AIDS. The total number of people living with HIV is estimated to be near 33.2 million people, with almost two-thirds living in Africa. In Asia and the Pacific, a total of 4.9 million adults and children are estimated to be living with HIV (UNAIDS, 2007a). Although HIV prevalence is still relatively low in the general population, due to larger populations the absolute number of people living with HIV/AIDS in the Asia and the Pacific region remains high, accounting for about 7% of the global total.

The growing epidemics in China and India dominate the region even though official prevalence figures for both countries remain low. Vietnam and Indonesia have low prevalence and incidence, with epidemics concentrated among injecting drug users (IDUs) and sex workers, however, the virus appears to be spreading beyond the high-risk groups into the general population (Brown and Peerapatanapokin, 2004; Ruxrungtham *et al*, 2004). Myanmar, Cambodia and Thailand have HIV epidemics that have already moved beyond high-risk groups, but both Cambodia and Thailand have been able to slow the spread of HIV through targeted prevention and treatment efforts. In Papua New Guinea (PNG) the HIV epidemic has been rising in Port Moresby by about 60% per annum over the past 10 years. This rise, if sustained, would infect 10% of the adult population of PNG in about 10 years (Caldwell and Isaac-Toua, 2002).

The dynamic of the Asian HIV epidemic is different from Africa. In Asia, groups at higher risk for HIV infection, including female sex workers (FSW), injecting drug users (IDU) and men-who-have-sex-with-men (MSM), interact and

overlap with the general population through their partners and clients, allowing HIV to spread to lower-risk males and females.

AIDS vaccine efficacy trials are often conducted in populations with high HIV-1 incidences because they require much smaller sample sizes, thus shortening the duration of the trial, speeding the availability of results, and lowering the cost of the trial. The design of community-based efficacy trials with heterosexual transmission in Asia remains extremely difficult, costly, and far too long to implement with such a low incidence level. The efficacy trials that have been implemented in Thailand illustrate this point well. The first one was among IDUs in Bangkok with HIV incidence of 5.6% at baseline and 2,500 volunteers enrolled. The second one is being implemented in the general population of two provinces with HIV incidence of less than 1.0%, enrolling more than 16,000 volunteers.

There is still potential in the region for efficacy trials among high-risk groups. China has shown through various cohort studies that HIV incidences observed in IDUs in Yunnan, Xinjiang, and Sichuan range from 3.1% to more than 8% per year (Ruan *et al*, 2005). Men-having-sex-with-men (MSMs) represent an important and hidden epidemic in several Asian countries (van Griensven *et al*, 2005); however, incidence data in MSMs are currently unavailable. Data on discordant couples in Asia are similarly lacking.

There are several challenges to working with populations with high HIV incidence rates. These populations are not infinitely expandable and conceivably may shrink in the future. When Cambodia (Charles, 2006) and Thailand implemented national HIV control and prevention programs, the number of new infections fell significantly. Similarly, substantial declines in injection risk behavior have been observed after risk reduction counseling during cohort studies with IDUs (Choopanya *et al*, 2003; Vanichseni *et al*, 2004; Kawichai *et al*, 2006).

These promising behavioral prevention and treatment programs among high-risk groups will intensify and diversify as more interventions, harm reduction programs and the results of new preventive research become available, including *Herpes simplex* suppression, circumcision programs, and the development and testing of microbicides (Simon *et al*, 2006). Another challenge of working with high-risk groups is that they often belong to local minorities, and are subject to stigma and discrimination. They will therefore deserve the greatest attention for their participation in HIV prevention trials. An additional factor that may make efficacy trials among high-risk groups more challenging is the possibility that AIDS vaccines and microbicides trials may need to access to and even compete for the same populations for efficacy trials.

A regional approach to vaccine development may help overcome this issue through the implementation of multi-country and multi-site trials (Excler, 2006) and preparatory cohort studies (Fast *et al*, 2007).

Another issue that differentiates the HIV epidemic in Asia from other regions is the variety of HIV-1 subtypes circulating throughout Asia, often shared across national borders. HIV-1 strains are classified into different genetic subtypes (A through K) and up to 24 circulating recombinant forms (CRFs). While most subtypes found in Southeast Asia are CRF01_AE, there are also large areas where B', C, and recombinant AE/B dominate. In China, a significant portion of the population is infected with subtype B' and C/B' (Su *et al*, 2003; Zhang *et al*, 2004; Liu *et al*, 2005) but recombinant CRF01_AE has become increasingly prevalent (Zhang *et al*, 2006). Similarly, increasing complexity in HIV-1 genotypes has also been observed in Taiwan Province, China (Lin *et al*, 2006). About 91% of AIDS in India is caused by subtype C strains; however B' and recombinant B/C have been found along the border with Myanmar and some A/C re-

combinants are occurring in the state of Maharashtra (Ruxrungtham *et al*, 2004). Subtypes B and C drive the epidemic through heterosexual transmission in Papua New Guinea (Curry *et al*, 2005; McBride, 2005; Ryan *et al*, 2007).

Although superinfection has been described in HIV-infected humans (Fultz, 2004), scientists do not yet know if or how the genetic subtype will impact preventive AIDS vaccine's effectiveness (Brown *et al*, 2005). Ample evidence of cross-clade immune responses are now described suggesting that vaccines may overcome the genetic variability of HIV (Cao *et al*, 2000; Ferrari *et al*, 2001; Coplan *et al*, 2005; Pantophlet and Burton, 2006). It is likely that AIDS vaccine phase IIB TOC and efficacy studies may need to be conducted with appropriate circulating strains in a given region, although HIV genotype-mismatched trials may be considered. The phase IIB TOC Merck trial in South Africa was designed to address cross-clade immune responses issue. Certain subtypes shared across borders offer an opportunity for countries to collaborate on the development of a single vaccine candidate.

The extreme political, social, cultural and economic diversity in the Asian region may render collaboration and cooperation particularly important, but also probably more complex. While the diversity of skills, experience, and infrastructure can be seen as an advantage, harmonization of approaches in regulatory processes, operational methodology, and technical aspects of clinical trial preparedness and implementation will require effective regional collaborative and cooperative mechanisms and commitments.

Each of these factors emphasizes a need for a regional approach to AIDS vaccine development that would establish coordinated technical platforms and multiple vaccine trial sites for testing specific vaccine candidates designed for the region.

THE CURRENT EFFORTS AND GAPS IN AIDS VACCINE DEVELOPMENT IN ASIA

Five countries in Asia; Thailand, China, India, Australia, and Japan, are currently involved at some stage of AIDS Vaccine Research and Development. Table 1 gives an overview of the AIDS vaccine development effort in Asia.

Thailand

In collaboration with partners, Thailand has developed over the last thirteen years an impressive clinical and laboratory research infrastructure, community interaction mecha-

nisms, and has gained considerable experience running all phases of clinical trials and conducting epidemiological cohort studies. The country has been involved in laboratory research on HIV molecular epidemiology since 1996 and now has almost 2,000 HIV-1 nucleotide sequences database of Thai viruses available in the National HIV Repository Bioinformatic Center (Chantapong *et al*, 2006). Thailand has also been involved in efforts to develop subtype E-specific vaccines in collaboration with Japan (Warachit, 2006), the US Military HIV Research Program (Sandstrom *et al*, 2006) and clinical trials of AIDS vaccines,

Table 1
AIDS vaccine platforms in the development pipeline in Asia.

Country	Vaccine	Sponsor	Subtype	Phase
Australia	DNA + fowlpox	NIH grant	B	I
China	DNA + MVA China	China	B'/C	I
	DNA + MVA	ADARC/China	C	I (preparation)
	DNA + replicative Tiantan	China/CDC	B'/C	Preclinical
	DNA + non-replicative Tiantan	China/CDC	B'/C	Preclinical
	Anthrax-derived fusion protein	China/CDC	B'/C	Preclinical
	NYVAC, MVA	EU	C	I (Europe)
	India	Adeno-associated virus	IAVI	C
Japan	MVA	IAVI	C	I
	DNA + MVA	IAVI	C	I (preparation)
	DNA + attenuated vaccinia (DI)	Japan	A/E	Preclinical
Thailand	DNA + chimeric Ad5/35	Japan	NA	Preclinical
	BCG	Japan	A/E	Preclinical
	Sendai	DNAVEC/IAVI	A	Preclinical
	V3 peptides	UBI	Multiclade	I
Thailand	DNA	USMHRP	B	I
	gp120	Vaxgen	E, B, B'/E	I/II, III
	gp160	Chiron	E	I/II
	Canarypox + gp140/120	USMHRP	B/E	I/II
	Canarypox + gp120	USMHRP/NIH	B/E	III
	Adenovirus type 5	Merck	B	I/II
	DNA + fowlpox	HIVNAT	A/E	II

ADARC: Aaron Diamond AIDS Research Center; EU: European Union; IAVI: International AIDS Vaccine Initiative; NIH: US National Institute of Health; USMHRP: US Military HIV Research Program; UBI: United Biochemical Inc; HIVNAT: The HIV Netherlands Australia Thailand Research Collaboration.

NA: Not available

including two phase III efficacy trials with rgp120 B/E AIDS VAX candidate vaccine (Pitisuttithum *et al*, 2006) and a prime-boost regimen using ALVAC-HIV and AIDS VAX B/E (Rerks-Ngarm *et al*, 2006).

The current gaps in AIDS vaccine development in Thailand include a decline in funding and political commitment. The new Thai AIDS Vaccine Communication Network, for example, does not have funding for next year despite the inroads it has made with policy makers, media, and investigators. Another gap is the path to licensing. The National Regulatory Authority (Thai FDA) just established an Investigational New Drug (IND) department but needs infrastructure and capacity strengthening to be able to move products from non-clinical studies to clinical trials and from phase III results to licensure. At the manufacturing level, there is limited national capacity to receive technology transfer and there is no production plant or GMP facility available. Human resources are also limited, as scientists in Thailand lack incentives and a career path. At the global level, there appears to be a lack of interest among the scientific community to develop a subtype E vaccine or multi-clade vaccine. Although the scientific community is interested in "missing cohorts," no funding has been granted to look into a multi-center trial involving IDUs, CSWs, and MSM.

China

China has expressed its strong and growing political interest in developing an AIDS vaccine by developing impressive infrastructures including state-of-the-art laboratories, clinical evaluation units, primate facilities, manufacturing capacity, and offering opportunities through grant mechanisms to young generations of scientists while opening the door to international collaboration. In 2005, China conducted a DNA-MVA clinical trial in Guangxi Province. The phase I trial was recently completed and the data demonstrated a good safety profile of the vaccina-

tion strategy. A phase II trial is now being prepared. Another Phase I trial has recently been initiated with an attenuated replication-competent Chinese TianTan Vaccinia vaccine candidate. Other trials are under consideration with other candidate vaccines including adenovirus non-replicative TianTan Vaccinia and DNA. Between 2000 and 2005, the industry grew by 30% annually to \$3 billion, compared with a 19% annual growth rate for the pharmaceutical industry as a whole (Frew *et al*, 2008). The Chinese government has been a strong promoter of innovations for both biotechnology and pharmaceutical industries. In more recent Government's Eleventh Five-Year Plan (2006-2010), programs that support the national science and technology agenda include: the 973 Basic Research Plan; the 863 High-Tech R&D Program (863 Program); and the National Science Support Plan, and the Technology Resource and Platform Construction.

These programs aim at promoting and encouraging technology innovations, prioritizing and reconstructing platforms necessary for innovation, focusing on the development of training programs, promoting international collaborations, encouraging publications in international journals, improving research ethics guidelines, updating IP protection and regulatory mechanisms, etc. In the meantime major multi-national and research-based pharmaceutical companies have either initiated or increased significantly their R&D investment in China in recent years. These investments will surely stimulate China's R&D growth and innovations.

However, it is equally critical for better coordination among the major players in China to be synergistic rather than isolated and separated. Challenges for China's AIDS vaccine development efforts also come with a limited definition of a streamlined national policy, regulatory or implementation strategy, and stable financial support. This has made international

collaboration in HIV/AIDS vaccine development more difficult while highly needed.

India

In a context of sustained political support, India has developed a collaborative agreement for AIDS vaccine development with three major partners: International AIDS Vaccine Initiative (IAVI), Indian Council of Medical Research, and the National AIDS Control Organization in the Ministry of Health and Family Welfare. Centers of excellence have been developed at the National AIDS Research Institute in Pune and the Tuberculosis Research Center in Chennai. These centers comprise state-of-the-art immunology, virology and safety laboratories, as well as a clinical unit (Gilmour *et al*, 2007). Support services include a reliable medical referral system and access to HIV care and treatment. They have developed in collaboration with IAVI a preparedness framework and robust mechanisms for community involvement and mobilization (Excler *et al*, 2008, in press).

India has implemented two phase I vaccine trials using an adeno-associated virus type-2 subtype C construct (AAV2) vaccine (Clumeck *et al*, 2006; Van Lunzen *et al*, 2007; Mehendale *et al*, 2008) and recombinant MVA subtype C vaccine (Ramanathan *et al*, 2007). A third phase I trial consisting in a DNA and MVA subtype C prime-boost regimen is being prepared. The regulatory and ethical clinical trial approval process is well defined, although lengthy. There is an urgent need to document more broadly the HIV incidence in various high-risk populations in the country in order to assess the feasibility to conduct efficacy trials and justify a need to expand an AIDS vaccine development program in India.

In order to capitalize on the strong innovative capacity of emerging countries like India, IAVI in collaboration with the Department of Biotechnology, Ministry of Science and

Technology, has initiated partnerships with leading private and public institutions (India Institute of Science, Bangalore; International Center for Genetic Engineering and Biotechnology, New Delhi) for the initiation of a program of medicinal chemistry and vaccine immunogen design.

Australia

Australia is currently involved in all stages of AIDS vaccine development, including assay development, basic research, product development, clinical trials, and preparedness cohorts. Various vaccine candidates are being developed in Australia including SAVINES and Kunjin vectors, various envelope constructs for neutralizing antibodies, co-stimulatory molecules, and mucosal vaccines. A phase I trial with DNA prime followed by Fowlpox boost (subtype B-based product tested in Australia and CRF01_AE-specific tested in Thailand) (Kelleher *et al*, 2006).

Japan

Japan is mostly involved in AIDS vaccine pre-clinical research. Japan's most advanced candidates include a recombinant BCG-based (BCG Tokyo strain) vector prime and non-replicating vaccinia (DI) boost (Ami *et al*, 2005) and a Sendai virus-based vector vaccine (Matano *et al*, 2004). The latter vaccine candidate is being developed in collaboration with IAVI. The major gap in Japan's AIDS vaccine development effort is structural. The current governmental support for AIDS vaccine R&D is mostly for basic research, not for clinical development. A UNAIDS guidance document recommends that sponsor countries support larger scale trials in host countries, and a regional network may be effective in stimulating the Japan's Overseas Development Agency (ODA) to adjust its position in this area (UNAIDS, 2007b). The participants felt while the ODA currently prioritizes concrete public health procedures over vaccine R&D, a comprehensive response to the epidemic is a de-

velopment issue. This response includes everything from condoms to development of new prevention technologies. Because of the growing costs for continued antiretroviral therapy, international donors must invest in new prevention technologies and provide capacity to develop regulatory authorities and research capacity. Participants recommended that a working group help developing a rationale for countries to support AIDS vaccine research.

Other efforts

Other countries in the region have vaccine development or clinical trial experience that could be expanded. The Philippines, for example, has good vaccine development and manufacturing capacity (BCG vaccine) and phase III clinical trials experience, but no experience with AIDS vaccines. Vietnam has major DPT, measles, JE, and hepatitis B vaccine production facilities, ethics committees, and a national regulatory authority, but limited clinical and laboratory facilities, particularly at the provincial level. Vietnam and Cambodia are both involved in therapeutic drug trials in collaboration with Agence Nationale de Recherche sur le SIDA (ANRS). Other countries not represented at the meeting (Myanmar, Indonesia, Malaysia, Singapore, for example) have additional assets and experiences they could offer to a regional vaccine development strategy. To document the full range of expertise, infrastructure, and capacity throughout the region, an Asian network could conduct a more thorough needs and capacity assessment so that opportunities for collaboration can be identified more efficiently.

NEED FOR INFRASTRUCTURE AND CAPACITY BUILDING IN PREPARATION FOR VACCINE EFFICACY TRIALS

As AIDS vaccine development progresses beyond phase I and II trials into larger and lengthier phase IIB and III trials, there is an urgent need to build clinical trial capacity and

infrastructure throughout the world, including in Asia.

The PAVE Survey

In 2003, the NIH Partnership for AIDS Vaccine Evaluation (PAVE) conducted a survey of US-funded, non-US-based clinical trial sites to inventory trial site capacity and identify opportunities where shared resources or training materials could achieve better efficiency and improve consistency between sites (These sites include the NIH Division of AIDS, Dale and Betty Bumpers Vaccine Research Center, HIV Vaccine Trials Network, AIDS Vaccine Research Working Group, Centers for Disease Control and Prevention, US Military HIV Research Program, US Agency for International Development, and IAVI). PAVE ranked specific areas of capacity by importance and grouped them into five categories: country-level issues, HIV testing and care, phase IIB/III clinical infrastructure, laboratory infrastructure, and data management.

Country level issues. Required elements under the PAVE ranking include a National HIV Vaccine Plan, in-country institutional review board (IRB) with Federalwide Assurance, and a process to review phase IIB/III trials. Sites also have to be able to develop an in-country biosafety committee within 12 months of a trial. Valuable, but not necessary elements include a national AIDS control program and national vaccine regulatory body.

HIV testing and care. Required elements under the PAVE ranking include voluntary counseling and testing, HIV care and treatment, antiretroviral drugs and opportunistic infections (OI) prophylaxis, TB treatment guidelines and drugs, and sexually-transmitted disease (STD) treatment guidelines and drugs.

Phase IIB/III clinical infrastructure. Required elements under the NIH ranking include clean water, electricity, fuel, internet access, email, international phone lines, approval for import/export of biologicals, and data on HIV

incidence, prevalence, or clade distribution. Within 12 months of a trial, a site also needs to have a Community Advisory Board (CAB), nitrogen generators, AIDS vaccine communications plan, administrator, shipping for import/export of biologicals, trained staff in good clinical practice (GCP) and standard operating procedures (SOPs), research pharmacist, SOPs for adverse events and investigational new drug (IND) agents, and a pharmacy with backup power, security, and refrigeration.

Laboratory infrastructure. PAVE guidelines require proficient availability of HIV rapid tests, HIV serology, hematology, chemistries, and STD diagnostics. Within 12 months, sites also need capacity for CD4 counts, viral load, peripheral blood mononuclear cells (PCMB) separation and freezing, storage for serum and cells, good laboratory practices (GLP)-compliant laboratory procedures, and participation in multicenter quality assurance and quality control.

Data management. According to the PAVE guidelines, data management must be Title 21 Code of Federal Regulations part 11 compliant (validated and auditable) within 12 months of the start of a trial. SOPs and record maintenance for source documents, and SOPs for case report forms must also be in place.

Experiences from Thailand

In 1991, Thailand was selected as one of four countries to be strengthened for AIDS vaccine development by WHO. By 1993, Thailand had developed its first HIV Vaccine Development Plan to help find a safe, effective, affordable and accessible AIDS vaccine for Thai people. Since 1993, 10 AIDS vaccine trials have been implemented in Thailand, including one phase III trial now completed and a second phase III trial underway.

Thailand remains the pioneer in AIDS vaccine development among resource-limited countries worldwide and in Asia (Pitisuttithum, 2005; Thongcharoen *et al*, 2007). Over the

past 10 years, Thailand in close collaboration with several partners has built up a remarkable clinical and laboratory research infrastructure and know-how capacity to run all phases of clinical trials (Morgan *et al*, 2003; Saengdidtha and Rangsin, 2005). Thailand is currently conducting several phase I/II trials and is the only country to have conducted two efficacy trials (Pitisuttithum *et al*, 2006), one of which is on going.

In the Thai experience, much of the physical infrastructure for trial preparation reflects the findings of the PAVE survey. Clinical infrastructure for the current phase III trial includes 47 health centers (screening sites) and 8 district hospitals (clinical sites), with a vaccine storage and distribution center covering clinical sites. The existing EPI cold rooms and transportation networks support the trial. Specimens are processed and stored at the Health Promotion Center in Chon Buri Province. Nearly 800 personnel work on the trial, including 200 community outreach workers and almost 100 counselors, 40 clinical researchers, 16 pharmacy nurses, and 24 research assistants. All were trained on GCP, counseling, SOP, emergency response, record keeping, vaccinology, and communications skills. Laboratory capacity in Thailand includes HIV serology, hematology and flow cytometry, and a molecular laboratory. Thai personnel were also trained to conduct advanced laboratory procedure. Laboratories are required to process 99% of specimens within six hours. Both Thai and international Data Safety and Monitoring Boards oversee data management. A data management unit, staffed by teams in Thailand, acted as a minor database for the first phase III trial and has been the primary database for the current prime-boost trial.

In addition to these elements, the Thai trials have offered important lessons in the areas of cohort development, advocacy, community engagement, and post-trial access.

Cohort development for the current trial evolved from searching for areas with high prevalence to finding areas with high incidence that were also suitable for the location of vaccine trials. Ultimately, military recruits in Chon Buri and Rayong Provinces were identified. This cohort had 3.7 to 7.8% prevalence (incidence was 0.68/100 per year) among ANC attendees during 1990s. The two adjacent provinces also had existing physical infrastructure that could be applied to the trial. The prospects of conducting further efficacy trials in Thailand in the general population are limited because of the low HIV incidence (<1%) observed (Rerks-Ngarm *et al*, 2006). However, HIV incidence is still high in groups such as IDUs (2.7-3.9%) (Xiridou *et al*, 2007). The HIV epidemic in Thai MSM has recently been described as rampant, although HIV incidence data are not available yet and the willingness to participate of this community in vaccine clinical trials is unknown (van Griensven *et al*, 2005; Mansergh *et al*, 2006).

Another key lesson learned has been the importance of advocacy, particularly at the political level. The Thailand's first vaccine plan was developed by the National AIDS Commission, which was initially chaired by the Prime Minister of Thailand. This level of political support allowed Thailand's clinical trial capacity and expertise to expand quickly.

In the area of community outreach, the Thai trial enlisted help from supportive AIDS-related nongovernmental organizations (NGOs) and community service organizations (CSOs), as well as local community leaders. Their communications links and credibility among community members proved invaluable.

One of the major lessons learned from phase III trials is the need for vaccine provision, vaccine licensure and manufacturing capacity. These are not necessarily in place in Thailand, but they are the crucial next steps following a successful phase III trial.

Experiences from the STEP Study

Merck, the National Institutes of Allergy and Infectious Diseases and the HIV Vaccine Trials Network (HVTN) recently launched a phase IIB TOC trial with an replication-incompetent adenovirus subtype 5-based vaccine (MRK-rAd5), known as the "STEP Study," involving 3,000 people, 34 sites, and 7 countries. The STEP Study was halted on September 19, 2007 for futility when the interim data reviewed by the Data and Safety Monitoring Board indicated that the MRK-rAd5 HIV vaccine was not preventing HIV infections and was not reducing the HIV viral load in participants who became HIV-infected. Although not conducted in Asia, trial organizers shared early lessons learned in the areas of regulatory and ethical approval, community engagement, and enrollment (Robertson *et al*, 2006), lessons that may be useful to consider for further large-scale trials in Asia.

Regulatory reviews and IRBs. In the STEP Study, as with the Thai trials, regulatory reviews were lengthy and multilayered. For example, in South Africa, the protocol needed approval from the site and the national regulatory authority (NRA) each time when there were changes. IRBs at each site also indulged in lengthy negotiations and reviews. Merck & Co had one central IRB, which made their reviews much more efficient—an element that might be considered for future trials.

Community engagement. In hindsight, the outreach should have started earlier in the process to create awareness and generate a positive public perception for recruitment. Recruitment itself was much costlier, time-consuming and logistically challenging than originally thought. Centrally purchased advertising and strategic use of the internet were helpful in recruitment. Local NGOs through the established relationships with high-risk groups were also helpful in building trust and credibility during the recruitment phase.

Enrollment. Although some sites had experience with high-risk groups and/or with vaccines, most sites found it more difficult to recruit and retain HIV negative populations, as compared to treatment trials in HIV positive volunteers, noting that HIV negative populations have different expectations and motivations for participating in the trial.

Working with vulnerable populations also made recruitment and retention much more complex. Poor, disadvantaged communities have multiple needs and problems (*eg*, drugs, mental health, clothing, food, and general health care). In addition, they are highly mobile and hard to track down. Retention strategies need to include relationship building with enrollees to motivate them to continue with the trial.

The biggest challenge now is the rate of pregnancies among high-risk populations in the STEP Study – an issue that needs to be addressed and accounted for in efficacy trials.

Several participants suggested that guidelines for clinical trial preparation be aligned and standardized, so that any trial site can follow one set of guidelines for adequate preparation. PAVE has tried to do this with the US-government funded agencies and partners, but ultimately looks to the Enterprise to make their efforts more international. Similarly, there is a need to harmonize assays to objectively assess trials.

Given the resources and energy required to develop a site, participants noted the need to discuss multifunctional sites. For example microbicides and AIDS vaccine trials, which are currently competing for the same populations, could be done at multifunctional sites. Sites could also be designed to do different kinds of trials. For example, although the Philippines do not have AIDS vaccine experience, it has other vaccine experience that is valuable and can be adapted for AIDS vaccine trials.

PERSPECTIVE FOR MANUFACTURING CAPACITY

Industry perspective for manufacturing capacity

From the perspective of industry, vaccine development is time-consuming and extremely capital-intensive process. There is a very complex supply chain for vaccine development where a company that produces vaccines against 20 different diseases must be able to produce about 150 different antigens that are formulated differently (pediatric, adult, dose differences, labeling, packaging), resulting in upwards of 1,500 different individual products. These products are developed using an aseptic process as clean as a surgical theater, and require storage in a cold chain.

The typical timeline for vaccine development is between six to eight years for clinical development. During this time, a decision must be made about whether to scale production in anticipation of licensure. Developing this additional capacity can take about five years (two years for packaging, four years for lyophilization, five years for a new facility). The average timeline for production is between 9 and 22 months. With GMP conditions becoming more stringent every year, these are usually incompressible steps that are almost impossible to accelerate.

Investment hurdles for AIDS vaccine development are equally complicated. Even after proof of concept in humans, there is a need to agree on milestones and navigate very complex partnerships. The traditional access model for developing countries is unacceptable for AIDS vaccine. Given the urgent need for the vaccine, industry, public sector, NGOs and donors need to work on parallel tracks, in partnership. All partners need to make accommodations, including guarantees of purchase, regulatory harmonization, financial incentives for industry, and greater access to technology to eligible countries or regions with capacity. If these agreements are not in place

when a vaccine is discovered, it will take time to put them in place, further delaying vaccine development.

The discussion focused on the role of industry on producing pilot lots of vaccine for clinical trials. It is unlikely that global manufacturers would play this role, making it a potentially important role for smaller biotechnology companies. The Enterprise may also consider establishing a manufacturing facility to produce pilot lots—not to compete with industry, but to support new vaccine concepts in a field where few manufacturers are able to produce pilot lots.

Participants were reminded that the African AIDS Vaccine Strategy is only a part of a global AIDS vaccine strategy. It is important, therefore, to discuss whether the African strategy is appropriate for Asia. Because incidence rates observed in Asia are much lower than in Africa, there may be a need to access much larger populations for efficacy trials. There may be a need to establish a manufacturing facility in Asia. China has capacity to produce pilot lots, including adenovirus- and vaccinia-based vaccine candidates. The technical issue is that China has different GMP standards that would need to be internationally standardized, perhaps with the help of WHO. Also, China SFDA regulation stipulates that for any vaccine that enters the Chinese market, all clinical phases must be done in China. This is similarly true for India.

ETHICAL AND REGULATORY CHALLENGES

Regulatory challenges

The purpose of clinical trial regulations is to ensure safety (protect human subjects), quality (stability, purity, reproducible, validated manufacturing process), and scientific validity. While every country has its own regulatory process and set of ethical review committees, many countries in the region are facing similar

challenges, particularly as multiple collaborators from multiple countries must meet different requirements for reviews and respond to multiple directives for modifications. Not only is there an increased probability of communication issues and different understandings of regulations, in some countries, infrastructure for research and health care delivery can be weak and decision making systems and experience can be limited.

A good example is the current phase III trial in Thailand where eight different collaborating institutions, representing industry, academia and multiple government departments from multiple countries were required to review and approve research protocols. With no oversight ethical or regulatory body, all amendments had to be submitted to all bodies, usually taking between six and eight months for each review.

Clinical trials in India have confronted similar challenges. While the approval process in India is a well-defined, mandatory, and transparent pathway, some institutional review committees are less experienced and/or understaffed, requiring numerous meetings to address concerns. There appeared to be some distrust among certain committees for private agencies, especially imported contract research organizations.

Overcoming these challenges required that presentations from investigators and sponsors be simple and coherent, allowing committee members to absorb technical information while considering ethical or regulatory issues. Investigators had to make themselves available for questions and answers, and address concerns promptly, even if the concerns were not scientifically valid. It was helpful to work with local agents and experts wherever possible and be highly sensitive to cultural differences.

To streamline the regulatory process in the future, the Global HIV Vaccine Enterprise is working on harmonized regulatory ap-

proaches and tools and a forum where multiple stakeholder can collaborate more closely. New solutions to regulatory issues might include regional approaches for regulatory reviews and recommendations, capacity building support, risk/benefit evaluations in the context of a specific country's needs and resources (so that risk/benefits decisions are not based on US populations), removing scientific impediments to regulatory decision-making, and addressing ethical issues that relate to regulatory issues.

Ethical challenges

There are several important ethical challenges to address in the context of large-scale clinical trials, particularly when working with vulnerable populations. These relate to informed consent, perceptions of risk/benefit, seropositivity, and provision of care and treatment. While there is no clear consensus on these, many have been tackled in the Thai trials, which could provide a starting point for regional discussions.

Vulnerable populations (*ie*, IDUs, MSMs, sex workers, adolescents) need to be included in trials because their risks are different, their response to vaccines may be different, and they are often most in need of the benefits of an AIDS vaccine. Certain vulnerable populations have been historically excluded from trials for many reasons. When not overtly excluded, these populations may face significant barriers, such as lack of empowerment or decision-making authority, social isolation, discrimination, pregnancy, stigma, inability to meet trial enrollment criteria, and concerns about confidentiality and informed consent.

Informed consent. One of the guiding ethical principals for enrolling volunteers in trial is that the participant has full autonomy. Those with diminished autonomy are entitled to special protection in the informed consent process, which has led several trials to include representatives of vulnerable populations in the

composition of the IRB. The HIV Vaccine Trial Unit in Thailand, for example, developed a community outreach unit, adolescent working group, and IDU working group to help reduce barriers to participation while protecting their autonomy and specific needs. Beyond that, informed consent documents are always prepared in Thai (instead of being translated from English); participants are given enough time for decision-making; they are required to re-consent when their status changed; and participants need to pass a test of understanding before becoming eligible for the trial.

Risk-benefit equation. Basic principals for ethical clinical trials include the need to minimize risks and maximize benefits for trial volunteers and communities involved in trials. To balance risks and benefits in Thailand, all trial volunteers are offered voluntary counseling and treatment, confidential AIDS test results, referral of HIV cases to routine care services, follow-up on breakthrough infections and free ARV when required until the end of the project. Risks are mitigated through condoms and behavioral risk reduction counseling as well as reminders at every visit that the vaccines are under study and there is the possibility of getting placebo. Participation impact events are also explored and addressed at every visit.

Seropositivity. The issue of seropositivity was raised as another major concern, particularly in Asia because of stigma and discrimination. In Thailand, volunteers participate in a laboratory-based workshop to explain false positivity; they are also advised not to do HIV tests outside of the trial. Blood donors cannot donate when they are seropositive, so this issue is explained during enrollment. If participants need documentation, they can get a free test showing whether or not they are infected.

Provision of care and treatment. The question of access to care and treatment in a clinical trial is an ethical issue that has been debated for nearly a decade without clear answers or

consensus. The current UNAIDS guidance document on ethical considerations in HIV prevention research does not provide an answer to the question of access to care and treatment. Instead, it offers a minimum and a maximum, which is still hotly debated at all levels. WHO convened several consultations to solicit practical guidance on provision of care and treatment in clinical AIDS vaccine trials. The aim of these consultations were to review ethical principals and guiding documents, map out scenarios from the field to determine what kind of care and treatment to provide, develop a process for formulating care and treatment plans, and identify potential solutions and recommendations (Tarantola *et al*, 2007).

Criteria to consider include normative regulations existing in the country, factual evidence of what is actually offered in the country, evaluative information of expectations and effectiveness of policies structures and services and feasibility, and prospective considerations for sustainability and availability of resources. It may be helpful to consider these questions within an Asian framework and create guidelines for AIDS vaccine trials in Asia.

The few trials that have confronted this challenge, namely the phase III trials in Thailand and the STEP trial could provide a starting point for these discussions. In Thailand, all participants receive screening and voluntary counseling and testing, risk reduction counseling, free condoms, confidential HIV test results, and referral to routine services. ARV therapy, available under the national health program in Thailand, is provided to volunteers who breakthrough for the lifetime of the patient. There is also a trust fund, administered by the Thai government to pay for ARVs for patients that cannot access the national scheme for any reason. Volunteers in the STEP trial are offered a similar package. In each country, they are first referred to national programs for ARV therapy. The trial also set up an ARV fund (supported by developers and some donors) for break-

through infections among participants who cannot access national services.

The discussion revolved around the issue of access to care and treatment, revealing a wide spectrum of opinions on the issues. For example, one participant stated that there should be no reason to treat non-trial participants. Another participant responded that countries participating in trials are grappling with this issue frequently, especially as whole communities are suffering from the disease. Another participant suggested that the focus should not be on treatment as an ethical issue in the context of trials, but as an ethical issue on its own. The next question is, who will pay? Trial sponsors do not necessarily need to pay for all medical care. As treatment rolls out, services are becoming available in more and more countries. Because HIV is linked to behavior, there is a risk that participants may change their behavior in a study. These risks are not only medical, but are also related to stigma and discrimination. Therefore, trials need to ensure access to care and treatment for participants, particularly when there is not something already available. In the Thai trial, ARV provision is guaranteed for volunteers, but this was not mentioned in initial recruitment in case participants saw it as an inducement. Whatever a trial decides to provide, it must be clear and agreed prior to the start of the trial. In the next five years, there will be a huge need to care for individuals who develop a resistance to Tenofovir. This needs to be taken into consideration.

COMMUNITY CONSIDERATIONS AND NEEDS FOR POLICY DEVELOPMENT

Global advocacy strategy for sustained research and development of new HIV prevention tools

AIDS vaccine research has truly gone global, which presents both opportunities and challenges for the field. With each new country participating in AIDS vaccine research comes a set of new political leaders and new

communities that need to learn about and grapple with issues related to clinical trials. Fortunately, there is a wealth of experience available to these countries, often from within the region.

There is also a wealth of experience outside of the field that can help the AIDS vaccine field anticipate outcomes and questions that will arise from ongoing and future trials. There are multiple new, partially efficacious technologies, for example, that will complicate ethical issues and standards of prevention in vaccine trials. In the next few years, a number of trials may unveil around male circumcision, diaphragms, risk-reduction interventions which may make enrollment and implementation more difficult.

The message for people at risk will be different when partially efficacious products are part of the package of standard care. To communicate this message effectively means that we must go beyond community advisory boards (CAB) to ensure that communities are well engaged. Trial participants are not isolated—immediate family, their communities, regional and national identities, and a global community surrounds them. Neglecting one layer can jeopardize the smooth, efficient running of a trial.

The advocacy challenge for today is to build research literacy, particularly on partial efficacy and test-of-concept trials while also delivering existing technologies (condoms, HPV, HSV-2) and being honest and realistic about timelines and expectations. In just a few years, the context for conducting prevention trials may be dramatically different from what it is today, but there will still be a need for a safe, effective and affordable vaccine as part of a comprehensive prevention package. Advocacy is needed to generate political commitment throughout the world, mobilize resources, create an enabling policy environment, ensuring meaningful community involve-

ment, and determine how to rapidly get a vaccine to people who need it most.

CHALLENGES AND OPPORTUNITIES FOR REGIONAL NETWORKS, CAPACITY BUILDING, AND POLICY DEVELOPMENT

Tapping into the depth and complexity of expertise in the region, a regional AIDS Vaccine Asian Network (AVAN) can advocate for more vaccine work in the region while also accelerating the global agenda.

The Asian region currently faces several challenges to AIDS vaccine development, including too few vaccine candidates in the pipeline, need for site strengthening, very wide diversity of capability, resources, and infrastructure in Asia, low incidence in huge general populations, under explored HIV epidemic in terms of prevalence and incidence in some population subgroups such as men MSM, the prevalence of multiple HIV-1 subtypes and CRFs in the region.

There has been a general lack of focus on AIDS vaccine development in the last five to seven years, but this is something a regional network might be able to address, as the region also possesses several strengths.

Strengths in the Asian region include, experience in clinical development and in particular efficacy trials, access to population subgroups at higher risk for HIV infection and experience working with IDU populations in the context of efficacy trials, unique disease dynamics driven by social and behavioral factors, advanced vaccine development and manufacturing capability in the region (Japan, Australia, Thailand, China, India), extensive R&D capability, innovation and discovery, laboratory infrastructure, mature regulatory systems in some countries, and relatively strong human resource capacity and social infrastructure (through the Expanded Program on Immunization and National Immunization Days) that can be leveraged for the benefit of the region.

Table 2
List of participants.

Participants	Dr Alash'le Abimiku, Maryland, USA; Dr Susan W Barnett, Emeryville, CA, USA; Dr Rossana A Ditungco, Metro Manila, Philippines; Dr Xiao-Ping Dong, People's Republic of China; Dr Jose Esparza, Seattle, USA; Dr Jean-Louis Excler, New Delhi, India; Dr Nguyen Tran Hien, Hanoi, Viet Nam; Dr Tony Kelleher, Darlinghurst, Australia; Dr Denny Kim, Washington DC, USA; Dr Jerome Kim, Bangkok, Thailand; Dr Katherine Kripke, Bethesda, MD, USA; Mrs Heidi Lasher, Bozeman, MT, USA; Professor Yves Levy, France; Testuro, Matano, Tokyo, Japan; Dr Bonnie Mathieson, Bethesda, MD, USA; Dr Kazuhiro Matsuo, Tokyo, Japan; Dr Chhi Vun Mean, Cambodia; Dr Thi Hien Thanh Nguyen, Ha Noi, Viet Nam; Dr Remigio M Olveda, Metro Manila, Philippines; Dr Chansy Phimpachanh, Lao PDR; Prof Punnee Pitisuttithum, Bangkok, Thailand; Dr Supachai Rerks-Ngarm, Bangkok, Thailand; Professor Yiming Shao, Beijing, People's Republic of China; Dr Hiko Tamashiro, Sapporo, Japan; Dr Sombat Thanprasertsuk, Nonthaburi, Thailand; Dr Mean Chhi Vun, Phnom Penh, Cambodia; Mr Mitchell Warren, New York, NY, USA; Dr Naoki Yamamoto, Tokyo, Japan; Dr Taro Yamamoto, Tokyo, Japan; Dr Shudo Yamazaki, Japan; Dr Linqi Zhang, Beijing, People's Republic of China.
Overall chairpersons	Saladin Osmanov, Jean-Louis Excler, Hiko Tamashiro.
Moderators/chairs	Naoki Yamamoto, Catherine Hankins, Linqi Zhang, Jerome Kim, José Esparza, Yves Levy, Saladin Osmanov, Mitchell Warren, Jean-Louis Excler, Hiko Tamashiro.
Chief Rapporteur	Heidi Lasher.

The purpose of the network would be to promote the development of a vaccine for Asia – not necessarily a global vaccine and not necessarily a country-specific vaccine. Specifically, the network would: 1) Create forums to facilitate interactions between funders and funding opportunities; coordinate funding streams and funder capabilities; 2) Facilitate linkage between R&D, innovation and discovery in particular in emerging countries with strong innovation capacity such as India and China, and clinical trial capacity and production; 3) Provide a forum for coordination of regional expertise, capacity building, and technical assistance; 4) Provide advocacy and communication support for region-specific strategies; develop communication for a new vaccine paradigm; and advocate directly among scientists, politicians, community, media and regulators; 5) Contribute to and promote the implementation of the Scientific Stra-

tegic Plan of the Global HIV Vaccine Enterprise; 6) Prepare for future deployment of a vaccine by discussing a regional approach to access, delivery capacity, demand, epidemiology, vaccine characteristics, and strategies for delivery; and 7) Create a regional harmonization or regional authority for regulatory interactions, including regional licensure and review and regional ethical committees with an initial "core" working group. The next workshop is scheduled in late 2008 will be hosted by China and will examine the different facets of the network implementation.

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