Recommendations for the Future Utility of the RV144 Vaccines to the Thai Ministry of Health

Report on Meeting in

Bangkok, Thailand

March 16–18, 2010

Recommendations developed and written by the participants at the March meeting in Bangkok, Thailand (Appendix 1), including

Dr. Catherine Hankins (Chair); *Public Health and Future Access*
Dr. Ruth Macklin (Chair); *Ethical, Regulatory and Community Issues*
Col. Nelson Michael (Chair); *Science and Vaccine Development*
Dr. Donald Stablein (Chair); *Clinical Trial Design and Statistics*

Executive summary

The purpose of this report is to summarize recommendations concerning the steps that should be undertaken following the first-ever report of a limited degree of protection against HIV acquisition in a preventive HIV vaccine efficacy trial in humans (RV144; ClinicalTrials.gov number NCT00223080). The recommendations, which will be presented to the Thai Ministry of Public Health, were developed at a meeting of international experts that took place in Thailand on March 16–18, 2010. The meeting was co-sponsored by the Global HIV Vaccine Enterprise, WHO-UNAIDS, the Thai Ministry of Public Health, and the U.S. Military HIV Research Program. It was organized following a request from the Thai Ministry of Public Health (MOPH) just after the RV144 trial results were announced in September 2009.

The 22 recommendations developed by the meeting participants are broad in scope, ranging from those that relate directly to the RV144 trial to the information needed to support public health decisions regarding future introduction of new preventive HIV immunization programs. The recommendations spanned four broad areas, reflecting the thematic mandates of the four working groups: *Public Health and Future Access; Ethical, Regulatory and Community Issues; Science and Vaccine Development;* and *Clinical Trial Design and Statistics*.

1. The Thai Ministry of Public Health, researchers, and sponsors have no obligation at this point in time to offer the RV144 vaccine regimen to the placebo group in the trial.

2. Re-vaccination of a small subset of HIV-uninfected RV144 vaccine recipients with ALVAC-HIV [vCP1521] and AIDSVAX B/E, alone and in combination. This study should comprehensively assess the effect of such late boosting on immune responses.

3. A separate immunogenicity study of HIV-uninfected volunteers should be conducted to further characterize the immune responses induced by the RV144 vaccine regimen.

4. Consideration should be given to comparing the RV144 vaccines with related vaccines in intensive immunogenicity studies.

5. Efforts should be made to improve and extend the results of the RV144 trial.

6. Discussions for future HIV vaccine efficacy trials should begin within the global context of HIV vaccine development.

7. The use of a placebo control in future HIV vaccine trials is warranted and ethically acceptable.

8. It is not currently necessary to include the RV144 vaccine regimen in a prevention package.

9. Future vaccine protocols should anticipate and explicitly state benchmarks (such as the level of efficacy) and also describe the strategy that will be used for un-blinding of the trial and vaccination of the control group.

10. Future phase III or later-stage trials should maintain individual HIV infection control observation periods for at least 2 years after initiation of the vaccine sequence with duration examined for at least 1 year after the last vaccination.

11. Improved and standardized methods for characterizing transmission route in infected participants should be included in future trials.

12. Multi-arm studies must be designed with incidence rates in mind, and are probably not applicable in low incidence, general-risk populations in Thailand.

13. The Thai Ministry of Public Health in its capacity of overseeing research in Thailand should ensure that researchers "consult communities through a transparent and meaningful participatory process, which involves them in an early and sustained manner in the design, development, implementation, and distribution of results of biomedical HIV prevention trials."

14. More intensive studies of increased risky behavior post-vaccination would be valuable, and consideration could be given to inclusion of the RV144 placebo group participants in such studies.

15. Improved data collection methodologies and validation measures should be developed to improve accuracy of behavioral risk assessments.

16. Several modelling teams should be encouraged to estimate the cost and impact on the HIV epidemic of vaccine regimens with varying efficacy and durability (including a 31% efficacious general population vaccine with 1-year duration of protection).

17. Better estimates are needed of what will happen in the Thai population when preventive HIV vaccines are introduced, including the acceptability of these vaccines.

18. Public health decisions related to preventive HIV vaccines must start with a focus on the current context of public health prevention and care and treatment.

19. The pathways to licensure for preventive HIV vaccines in general should be defined and the role of regulatory bodies, both national and other bodies, explored.

20. A plan should be developed to ensure access to preventive HIV vaccines post-licensure.

21. The Thai Ministry of Public Health, in its capacity of overseeing research in Thailand, should seek to ensure that vaccine trial results and implications are communicated to the public in clear and understandable language.

22. There are compelling scientific and ethical reasons to continue further vaccine research that may benefit the Thai people.

Given the contribution of Thailand in undertaking this trial and the potential benefit for this population, meeting participants stated there are compelling scientific and ethical reasons to continue further vaccine research that may benefit the Thai people. The Thai Ministry of Public Health should encourage continued interpretation and expansion of the results of the RV144 trial in Thailand. It should also encourage all efforts to pursue the development of new vaccine concepts that may be beneficial to the Thai population, particularly the segment of the population at higher risk of HIV exposure.

Background

In 2009, for the first time, vaccination was shown to reduce the risk of acquisition of HIV infection in humans in a preventive HIV vaccine trial (RV144; ClinicalTrials.gov number NCT00223080).[1] This phase III, double-blind, placebo-controlled trial tested the effect of four priming injections of a *Canarypox* vectored vaccine (ALVAC-HIV [vCP1521]) and two booster injections of a recombinant envelope glycoprotein rgp 120 subunit vaccine (AIDSVAX B/E) on preventing HIV infection. Over 16,000 healthy 18- to 30-year-old Thai men and women, primarily at low heterosexual risk for HIV, were recruited and randomized into two equal groups. One group received the vaccine regimen and the other group received placebo injections. The volunteers were tested for HIV infection before and during the six-month vaccination period and every six months thereafter for a period of three years. If HIV infection was detected, the amount of HIV virus (viraemia) and the number of $CD4^+$ T cells in the blood were measured. Vaccine immunogenicity was assessed by measuring cellular and humoral immune responses in samples taken from the volunteers.

At the end of the study, when the results of all volunteers who underwent randomization were analyzed (excluding 5 individuals from the vaccine group and 2 individuals from the placebo group who subsequently had been found to be infected with HIV at baseline), a modest (31.2%), but statistically significant, lower rate of HIV infection was observed in the group who received the vaccine regimen as compared to those who received the placebo. Vaccination, however, did not reduce viraemia or preserve $CD4^+$ T cells in volunteers who became infected with HIV during the study. Antigen-specific binding antibodies and lymhoproliferation were significantly elevated in the vaccinated group when measured one year after vaccination, indicating that the vaccine regimen had induced HIV-specific immune responses.

The encouraging RV144 trial results were discussed at a meeting of the Global HIV Vaccine Enterprise Coordinating Group on October 1, 2009[2]. The Group agreed that the results raised several important research questions and created new opportunities. At the conclusion of the meeting, Dr. Supachai Rerks-Ngarm, of the Thai Ministry of Public Health and the principal investigator of the study, requested that a meeting of international experts be convened to develop recommendations concerning the next steps that should be undertaken for the future utility of the vaccines used in the RV144 trial.

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[1] Rerks-Ngarm, S. *et al.* Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. N. Engl. J. Med. 2009; 361(23):2209-2220.

[2] Global HIV Vaccine Enterprise. (2009, December 1). *Meeting of the Enterprise Coordinating Group – October 1, 2009.* Retrieved from http://www.vaccineenterprise.org/content/meeting-enterprise-coordinating-group-october-1-2009.

To this end, the Global HIV Vaccine Enterprise, WHO-UNAIDS, the Thai Ministry of Public Health, and the U.S. Military HIV Research Program co-sponsored an international expert group meeting in Bangkok, Thailand, on March 16–18, 2010. Over 50 experts attended the meeting, including HIV and vaccine researchers, clinical trial experts, ethicists, public health professionals, industry representatives, clinicians, community members, and representatives from nongovernmental and governmental organizations. (See Appendix 1 for the List of Participants and Appendix 2 for the Meeting Agenda.)

After welcoming remarks from the co-sponsors and an update on the RV144 trial, presentations concerning the questions and key issues arising from the RV144 trial were made by the Chairs of the meeting's four working groups:

- *Public Health and Future Access* – Dr. Catherine Hankins (Chair);
- *Ethical, Regulatory and Community Issues* – Dr. Ruth Macklin (Chair);
- *Science and Vaccine Development* – Col. Nelson Michael (Chair); and
- *Clinical Trial Design and Statistics* – Dr. Donald Stablein (Chair).

Meeting participants then gathered in the working groups to develop recommendations addressing the questions and issues that had been raised. During the course of the meeting, participants came together at daily plenary sessions to share the outcomes of their discussions and to solicit comments from participants in other groups, thereby allowing the groups to set a common ground for discussions, avoid duplication and get an input and different perspective from members of other working groups and thus further refine their recommendations.

The recommendations developed by the meeting participants were broad in scope, ranging from those directly related to the RV144 trial to those related to the eventual implementation of preventive HIV immunization programs. The recommendations are presented below together with the rationale, questions, and issues that were discussed and taken into consideration. The recommendations, in the form of this report, will be presented to the Thai Ministry of Public Health in May 2010.

Recommendations

Because there was certain overlap among the recommendations from the different working groups, the recommendations have been combined. They are organized starting from those that stem directly from the RV144 trial to those that are broader in nature. *(Note that the recommendations are not necessarily listed in order of priority and may not reflect the opinion of all participants or their respective organizations.)*

Following up on the RV144 trial

- ***Should the placebo recipients in the RV144 trial now be offered the RV144 vaccine regimen?***

This question was discussed by three of the four working groups. It was noted that the level of efficacy demonstrated in the trial was low, the confidence interval was wide (ranging from 1% to 52%), and that active vaccine regimen recipients may alter behavior offsetting modest protective effects. As well, the vaccine regimen did not reduce viral burden in the volunteers who became

infected with HIV following vaccination. Meeting participants noted that the Roadmap adopted during the trial (a guiding document for post-RV 144 activities based on the four predetermined clinical scenarios of efficacy >50%; efficacy <50% with no viral load effect; only a viral load effect; neither efficacy nor a viral load effect) for anticipated efficacy that would justify the provision of the vaccine regimen to the placebo group was set at 50% of efficacy in reducing risk for acquisition of HIV infection, which appeared to be higher than the real 31.2% observed in the trial. There were also concerns about the insufficient data to support a conclusion about the durability of the efficacy effect induced by the RV144 vaccine regimen. Other participants noted that providing the RV144 vaccine regimen to the placebo group may make them ineligible for any possible benefits resulting from their participation in other future trials. A possibility of rare risks from the vaccine that could not have been detected in the RV144 trial, and the possibility of increased risk behavior, could not have been ruled out either. Taken together, these reasons led the *Ethical, Regulatory and Community Issues,* the *Clinical Trial Design and Statistics,* and the *Public Health and Future Access* working groups to recommend that:

The Thai Ministry of Public Health, researchers, and sponsors have no obligation at this point in time to offer the RV144 vaccine regimen to the placebo group in the trial. **# 1**

The *Ethical, Regulatory and Community Issues* working group also recommended that the volunteers who were in the placebo group for the RV144 trial should be given priority in the future for access to the RV144 vaccine regimen, or new iterations of the RV144 vaccine regimen, should it prove to demonstrate sufficiently high level of efficacy in future trials. Even if future trials show sufficient level of efficacy only in specific high-risk groups, there may be a presumption that the RV144 vaccine regimen could be similarly efficacious in a lower risk group, and therefore, appropriate for provision to the placebo group in the RV144 trial.

- ***Can the duration of the RV144 vaccine regimen efficacy be extended by giving additional vaccine boosts?***

There is some evidence consistent with the interpretation that protection from HIV infection observed in the RV114 trial appeared to diminish after the first year following vaccination. In addition, some of the immune responses to the vaccine antigens, particularly gp120-binding antibodies, also declined around this time. This decline might have been responsible for the short duration of the observed protection from HIV infection, although the correlate(s) of protection still remain unknown (see below). It is important, however, to determine whether the efficacy of the RV144 vaccine regimen could be extended with additional vaccine boosts. To address this question, the *Science and Vaccine Development* working group recommends:

Re-vaccination of a small subset of HIV-uninfected RV144 vaccine regimen recipients with ALVAC-HIV [vCP1521] and AIDSVAX B/E, alone and in combination. This study should be able to comprehensively assess the effects of such late boosting on immune responses. **#2**

To maximize the chance to gather the most useful information, re-vaccinations should take place in 2010, otherwise the opportunity to rapidly follow up on the immunogenicity results of the RV144 trial will be reduced.

Future studies with ALVAC-HIV [vCP1521] and AIDSVAX B/E vaccines

- ***What are the correlates of protection in the RV144 vaccine recipients?***

Because of the encouraging results of the RV144 trial, there is now considerable scientific interest in a more comprehensive characterization of the immune responses induced by the RV144 vaccine regimen. While an intensive effort is under way to determine correlate(s) of protection using samples taken from the volunteers during the RV144 trial, the quantities and type of samples are limited. Therefore, the *Science and Vaccine Development* working group recommends that:

A separate immunogenicity study of HIV-uninfected volunteers should be conducted to further characterize the immune responses induced by the RV144 vaccine regimen. **#3**

Outstanding scientific questions include a fuller evaluation of immune responses in blood, genital, and gastrointestinal compartments; the relative contribution of the individual prime-boost vaccine components to these immune responses; and the impact of additional vaccine boosts (see previous recommendation). Volunteers in these immunological studies will need to be informed that large volumes of blood samples, multiple blood draws, and invasive mucosal sampling will be required. The results will inform the design of improved vaccine regimens for future HIV efficacy trials in Thailand and globally.

- ***How do the vaccines in the RV144 trial compare to other vaccines in development?***

The RV144 vaccines included a poxvirus vector prime (ALVAC-HIV [vCP1521]) and a recombinant protein subunit boost (AIDSVAX B/E). It is possible that other vaccines that are currently in development could improve upon the modest level of protective efficacy observed in the RV144 trial. For example, consideration is being given to the use of related pox virus vectors (e.g., NYVAC) in combination with a recombinant protein subunit boost in future HIV vaccine efficacy trials in multiple parts of the world. Alignment of vaccine development in Thailand with activities performed in other parts of the world will accelerate the development of a globally effective HIV vaccine. To this end, the *Science and Vaccine Development* working group recommends that:

Consideration should be given to comparing the RV144 vaccine regimen with other promising prime-boost combinations of related vaccine candidates in intensive immunogenicity studies. **#4**

The advantage of performing an immunogenicity trial instead of an efficacy trial is that fewer participants and less time would be needed to complete the trial. To be able to relate immunogenicity to efficacy, however, it would be critical to have an understanding of the correlate(s) of protection in RV144. If the vaccine products are available, the group recommends performing a comparative trial within the intensive immunogenicity trial described in Recommendation #3.

- ***What future efficacy trials based on the RV144 vaccine regimen should be conducted?***

The RV144 trial was the first demonstration of any degree of protection against HIV infection. In order to develop a highly effective preventive vaccine for public use, however, it is imperative to improve upon the modest level of protective efficacy observed. Results from the research described in Recommendations #2 through #4 will lay foundation to help accomplish this task. The protective effect of the RV144 vaccine regimen should be further confirmed. Additionally, it is essential to extend the evaluation of efficacy to key populations at higher risk of HIV exposure (e.g., men who have sex with men). The *Science and Vaccine Development* working group recommends that:

Efforts should be made to improve and extend the results of the RV144 trial. **#5**

Thailand is uniquely positioned to undertake this type of trial given the country's involvement in the RV144 trial. However, the timeline for initiating efficacy studies is long and includes multiple stakeholders, thus the group also recommends that:

Discussions for future HIV vaccine efficacy trials should begin within the global context of HIV vaccine development. **#6**

Design of future preventive HIV vaccine trials

Since the RV144 trial was "rigorously designed and well conducted,"[3] the knowledge gained and lessons learned will help to inform the design of future preventive HIV vaccine trials. In fact, several recommendations made by meeting participants relate to the design of future trials.

- ***Should a placebo-control group be included in future preventive HIV vaccine trials?***

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the WHO, "[t]he use of a placebo control arm is ethically acceptable in a biomedical HIV prevention trial only when there is no HIV prevention modality of the type being studied that has been shown to be effective in comparable populations."[4] Given the uncertain infection protection results of the RV144 regimen, the lack of the vaccine's effect on viral burden in the volunteers who became infected with HIV, and for all of the other reasons discussed along with Recommendation #1, both the *Clinical Trial Design and Statistics* and the *Ethical, Regulatory and Community Issues* working groups recommend that:

The use of a placebo control in future HIV vaccine trials is warranted and ethically acceptable. **#7**

- ***Should the RV144 vaccine regimen be included in a prevention package in future HIV prevention trials?***

[3] Dolin, R. HIV vaccine trial results – An opening for further research. N. Engl. J. Med. 2009; 361(23):2279-80.

[4] UNAIDS/WHO. Ethical considerations for biomedical HIV prevention trials: guidance document. Geneva: Joint United Nations Programme on HIV/AIDS, 2007, Guidance Point 15, Control Groups.

UNAIDS and WHO have provided guidance concerning whether new HIV risk reduction methods should be included in a prevention package. According to their guidelines, "[r]esearchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling and access to all state-of-the-art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial. New HIV risk-reduction methods should be added . . . as they are scientifically validated or as they are approved by relevant authorities."[5] The *Ethical, Regulatory and Community Issues* working group discussed whether the RV144 vaccine regimen should be included as part of a prevention package in future HIV prevention trials. The Group concluded that, for the reasons discussed along with Recommendation #1, the RV144 vaccine does not meet the necessary requirements for inclusion at this time. Therefore they recommend that:

It is not currently necessary to include the RV144 vaccine regimen in a prevention package. **#8**

However, if after future trials, this vaccine regimen is approved by the national regulatory authority as a HIV risk-reduction method, it should be provided in a prevention package for any future HIV prevention trial in Thailand.

A related issue that was discussed by the *Public Health and Future Access* working group was the possibility that tailored prevention strategies might become standard in the future. For example, Pre-Exposure Prophylaxis trials (PrEP) in different risk populations are currently testing whether providing HIV-negative people who inject drugs with antiretroviral prophylaxis will protect them from acquiring HIV. If these trials were to demonstrate sufficient level of efficacy (see also Rec. No. 9), the approach might become the standard of prevention in high-incidence populations of people who inject drugs. This may preclude these populations at higher risk of HIV from future vaccine trials.

What other factors should be considered when designing future vaccine trials?

Efficacy levels

The criterion for offering the immunization regimen to the placebo group when the RV144 trial was already under way was an efficacy level at 50%. This meant that if a vaccine efficacy of 50% or greater had been observed in the trial, the placebo recipients would have been offered the vaccine. Meeting participants concluded that the level of efficacy and other benchmarks should be set during the protocol design phase and explicitly stated in the protocol and in the consent form. In addition, strategies for un-blinding of the study and vaccination of the control group should be developed in advance. Others argued that it was extremely difficult to set these benchmarks ahead of time. In spite of these objections, the *Clinical Trial Design and Statistics* and the *Ethical, Regulatory and Community Issues* working groups recommend that:

Future vaccine protocols should anticipate and explicitly state benchmarks (such as the level of efficacy) and also describe the **#9**

[5] UNAIDS/WHO. Ethical considerations for biomedical HIV prevention trials: guidance document. Geneva: Joint United Nations Programme on HIV/AIDS, 2007, Guidance Point 13, Standard of Prevention.

strategy that will be used for un-blinding of the trial and vaccination of the control group.

Duration of the observation period
In the RV144 trial, HIV infection was monitored for three years after the end of the vaccination period. Analyses of the RV 144 trial suggested the possibility of reduced levels of protection beyond the first year of vaccination. Participants in the *Clinical Trial Design and Statistics* working group discussed the minimum length of time that volunteers in a preventive HIV vaccine trial should be followed in the future. The group recommends that:

Future phase III or later-stage trials should maintain individual HIV infection control observation periods for at least 2 years after initiation of the vaccine sequence with duration examined for at least 1 year after the last vaccination. **#10**

Characterizing HIV transmission route
Some of the volunteers in the RV144 trial were subsequently diagnosed with HIV after the start of the vaccination period (51 out of 8,197 in the vaccine group and 74 out of 8,198 in the placebo control group). Given the considerable interest in identifying the correlates of protection of the vaccine group, it would have been useful to have had information concerning the infection route in both groups, but this information was not gathered from the volunteers at the time of their HIV diagnosis. Therefore, the *Clinical Trial Design and Statistics* working group recommends that:

Improved and standardized methods for characterizing transmission routes in infected participants should be included in future trials. **#11**

Implementation of this recommendation could involve questioning infected volunteers about risk behaviors they might have engaged in before diagnosis.

Multi-arm studies
It is possible that future preventive HIV vaccine trials will include multiple arms in which, for example, the two components of the RV144 regimen alone or in combination will be tested, or perhaps the RV144 vaccine regimen will be compared to another type of preventive HIV vaccine. In order to detect the differences between the multiple groups in the study, while keeping the size of the study manageable, it will be essential to conduct trials in groups with higher HIV incidence, such as groups at high risk for becoming infected with HIV. Therefore, the *Clinical Trial Design and Statistics* working group recommends that:

Multi-arm studies must be designed with incidence rates in mind, and are probably not applicable in low incidence, general-risk populations in Thailand. **#12**

Community participation
The importance of engaging the community in biomedical HIV prevention trials is critical and should be strengthened. This helps to "ensure the ethical and scientific quality and outcomes of proposed research, its relevance to the affected community, and its acceptance by the affected

community."[6] Participants in the *Ethical, Regulatory and Community Issues* working group agreed that enhanced community participation should occur in all vaccine trials. They recommend that:

The Thai Ministry of Public Health in its capacity of overseeing research in Thailand should ensure that researchers "consult communities through a transparent and meaningful participatory process, which involves them in an early and sustained manner in the design, development, implementation, and distribution of results of biomedical HIV prevention trials."[3] **#13**

Studies/information to support future vaccine trials and to aid public health decisions

- ***Does vaccination increase high-risk behaviors?***

In the RV144 trial, all volunteers were assessed at several stages for behaviors that put them at risk of becoming infected with HIV. As well, HIV prevention counseling was provided during each vaccination and post-test counseling visit. In order for vaccine trial experts, public health officials, and governments to make decisions about the efficacy of vaccines and whether to immunize populations, it is important to know whether vaccination may increase risk behaviors, and if so, by how much. Therefore, the *Clinical Trial Design and Statistics* and *Public Health and Future Access* working groups recommend that:

More intensive studies of increased risky behavior post-vaccination would be valuable, and consideration could be given to inclusion of the RV144 placebo group participants in such studies. **#14**

- ***What are the best methods to assess risk behavior?***

There are several methods that can be used to assess whether individuals may engage in risk behaviors. These include questionnaires, interviews with trained counselors, and automated counselor interviews. Both the *Clinical Trial Design and Statistics* and *Public Health and Future Access* working groups discussed these approaches and recommend that:

Improved data collection methodologies and validation measures should be developed to improve accuracy of behavioral risk assessments. **#15**

This could include direct comparison of alternative methods in preliminary studies to prepare for streamlined performance in large trials.

- ***What are the costs and benefits of HIV immunization programs?***

[6] UNAIDS/WHO. Ethical considerations for biomedical HIV prevention trials: guidance document. Geneva: Joint United Nations Programme on HIV/AIDS, 2007, Guidance Point 2, Community Participation.

Decisions about whether to immunize the general population or specific high-risk groups rely on mathematical modeling predictions of the costs and impact of the immunization program. The *Public Health and Future Access* working group recommends that:

Several modelling teams should be encouraged to estimate the cost and impact on the HIV epidemic of vaccine regimens with varying efficacy and durability (including a 31% efficacious general population vaccine with 1-year duration of protection). **#16**

The teams should be convened to discuss their results and refine their models. Models should also take into consideration behavioural risk enhancement/compensation scenarios. Related to this, standard parameters from the RV144 trial to apply to mathematical models should have been agreed to by modelers and RV144 trial researchers beforehand.

There are also opportunities to learn about how populations respond to immunization programs. The *Public Health and Future Access* working group recommends that:

Better estimates are needed of what will happen in the Thai population when preventive HIV vaccines are introduced, including the demand and acceptability of these vaccines. **#17**

Studies to address this recommendation could, for example, assess information gathered following the publication of the Pre-Exposure Prophylaxis for HIV Prevention (PrEP) trial results later this year or data collected following the introduction of the immunization programs against *Human Papillomavirus*.

The *Public Health and Future Access* working group noted that public health decisions should be informed by scientific evidence, human rights principles, political/economic/social issues, and other factors. With this principle in mind, the group recommends that:

Public health decisions related to preventive HIV vaccines must start with a focus on the current context of public health prevention and care and treatment. **#18**

It is critical to update the information about HIV epidemiology (e.g., the overall incidence and mode of transmission, dynamics, and geospatial aspects of the epidemic). This information will assist in targeting appropriate health measures to specific groups and areas. Models of the cost-effectiveness of HIV immunization programs must use the most recent information available. For example, the new WHO guidelines concerning the recommended $CD4^+$ T-cell counts at which to begin antiretroviral treatment of HIV-infected individuals have recently been raised to ≤ 350 cells/mm^3 from ≤ 200 cells/mm^3. When these guidelines become part of national treatment plans, the cost to treat those already infected with HIV will increase. These enhanced costs as well as number of averted infections due to reduced transmission should be included in cost-benefit models.

It is also important for public health officials to take into consideration the current coverage of the existing HIV prevention services and to identify areas where there are gaps. (This

information will be available in the UNGASS report that is due March 31, 2010.) In addition to coverage, consideration must be given to the effectiveness of the existing prevention methods and opportunities to improve strategies to combine prevention approaches to reduce HIV incidence in the absence of a vaccine. Public health decisions regarding preventive HIV vaccines should also take into consideration the Thailand universal health care context; current adult vaccine delivery mechanisms; Thailand's commitment to biomedical HIV prevention trials; and Thailand's National HIV Vaccine Plan.

Vaccine licensure and future access

While there was no strong view among meeting participants that the RV144 vaccine regimen should go through for licensure at present, participants in the *Public Health and Future Access* working group, acknowledging the encouraging results of the trial, recommend that:

The pathways to licensure for preventive HIV vaccines in general should be defined and the role of regulatory bodies, both national and other bodies, explored. **#19**

This will involve determining the regulatory processes and criteria for licensing in Thailand; defining future trials that will be needed to support licensure; and exploring the potential for multiple licensing routes (e.g., FDA Thailand, European Medicines Agency [EMEA], etc.). The timeline for assembling the data for licensing will depend on the number and duration of proposed future trails.

The *Public Health and Future Access* working group also discussed access considerations for the future when a preventive HIV vaccine is licensed. They recommend that:

A plan should be developed to ensure access to preventive HIV vaccines post-licensure. **#20**

This recommendation includes taking into consideration manufacturing and technology transfer; security of the vaccine supply; demand forecasting and pricing strategies; equity of access (e.g., migrant populations, non-Thai groups); importance of monitoring evolving epidemic dynamics to best target the vaccine; delivery strategies; budget implications and financing alternatives; impact on other public health services; and post-marketing surveillance strategies. A figure showing the relationship between Recommendations #18 through #20 that was developed by the *Public Health and Future Access* working group is presented in Appendix 3.

Other considerations

Given the complexity of the RV144 trial results, the *Ethical, Regulatory and Community Issues* and the *Public Health and Future Access* working groups recommend that:

The Thai Ministry of Public Health, in its capacity of overseeing research in Thailand, should seek to ensure that vaccine trial results and implications are communicated to the public in clear and understandable language. **#21**

In addition, researchers should engage communities in consultation and dialogue throughout all stages of vaccine trials in accordance with the UNAIDS/AVAC Good Participatory Practice Guidelines for Biomedical Prevention Trials.[7]

As the RV144 trial was the first to suggest that a vaccine to prevent HIV infection is possible, and given the contribution of Thailand in reaching this result, the *Ethical, Regulatory and Community Issues* working group recommends:

There are compelling scientific and ethical reasons to continue further vaccine research that may benefit the Thai people. **#22**

This recommendation is based on the principle of "justice as reciprocity." To address this recommendation, the Thai Ministry of Public Health should encourage continued interpretation and expansion of the results of the RV144 trial in Thailand. It should also encourage all efforts to pursue the development of new vaccine concepts that may be beneficial to the Thai population, in particular, the segment of the population at higher risk of HIV exposure.

Conclusion

The expert recommendations presented in this report address the new questions and opportunities arising from the Thai RV144 preventive HIV vaccine trial. Acting upon these recommendations will speed the development of a highly effective preventive HIV vaccine that will be suitable for use in Thailand, the South East Asia region, and, ideally, the rest of the world.

[7] UNAIDS/AVAC. Good participatory practice guidelines for biomedical HIV prevention trials. Geneva: Joint United Nations Programme on HIV/AIDS, 2007.

Appendix 1: List of Meeting Participants

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Dr. Prasert Thongchareon, Ministry of Public Health, Thailand
Mr. Nimit Tienudom, AIDS-Access Foundation
Dr. Paijit Warachit, Ministry of Public Health, Thailand
Dr. Carol Weiss, U.S. Food & Drug Administration
Dr. Bruce Weniger, U.S. Centers for Disease Control and Prevention
Dr. Ryan Wiley, SHI Consulting

Appendix 2: Meeting Agenda

16 March, 2010

0530 – 0830 Breakfast at your leisure

Moderator: ***Dr. Alan Bernstein***

0830 – 0900 Welcome Remarks (Plaza Athenee Hotel, Star room 29 on the 29th Floor)
- Dr. Alan Bernstein
- Dr. Catherine Hankins
- Col. Jerome Kim
- Dr. Saladin Osmanov
- Dr. Paijit Warachit

0900 – 0930 Update on RV144
- Col. Jerome Kim

0930 – 1000 Discussion/Q&A

1000 – 1015 Break (Plaza Athenee Hotel, Star room 29 on the 29th Floor)

1015 – 1030 Statement of Meeting Objectives, Review of Meeting Format and Procedures, and Introduction of Breakout Group Chairs
- Dr. Supachai Rerks-Ngarm

1030 - 1200 Introductory Presentations by Breakout Group Chairs
Includes a broad presentation of the issues to be addressed by each group, general implications of the Thai Trial for the area of focus, and questions to be answered over the course of the meeting.
- Dr. Catherine Hankins (Public Health and Future Access)
- Dr. Ruth Macklin (Ethical, Regulatory and Community Issues)
- Col. Nelson Michael (Science and Vaccine Development)
- Dr. Donald Stablein (Clinical Trial Design and Statistics)

1200 - 1300 Breakout Groups Meet
- Public Health and Future Access (Plaza Athenee Hotel, Atheneum 1 on the 6th floor)
- Ethical, Regulatory and Community Issues (Plaza Athenee Hotel, Atheneum 2 & 3 on the 6th floor)
- Science and Vaccine Development (Plaza Athenee Hotel, Atheneum 7 on the 6th floor)
- Clinical Trial Design and Statistics (Plaza Athenee Hotel, Atheneum 6 on the 6th floor)

1300 - 1400 Lunch (Plaza Athenee Hotel, Rain Tree Cafe on the ground floor)

1400 – 1500 Breakout Groups Meet

1500 – 1515 Break (Plaza Athenee Hotel, Star room 29 on the 29th Floor)

1515 – 1800 Report on Group Discussion and Proposed Way Forward For Group
The objective of this plenary discussion is for each group representative to share the output of their discussion and to solicit comments from participants of other groups.
(Plaza Athenee Hotel, Star room 29 on the 29th Floor)

- Public Health and Future Access Group Representative
- Ethical, Regulatory and Community Issues Group Representative
- Science and Vaccine Development Group Representative
- Clinical Trial Design and Statistics Group Representative

1800 - 1900 Break

1900 Dinner (Plaza Athenee Hotel, The View Restaurant on the 4th floor)

17 March, 2010

0530 – 0830 Breakfast at your leisure (complimentary for hotel guests; Rain Tree Cafe, Plaza Athenee Hotel)

Moderator: ***Dr. Saladin Osmanov***

0830 – 0900 Recap of Key Points from Day 1 and Review Objectives for Day 2 (Plaza Athenee Hotel, Star room 29 on the 29th Floor)

- Dr. Saladin Osmanov

0900 – 0920 Presentation of RV144 Cost Utility Analysis Findings

- Health Intervention & Technology Assessment Program, Thailand

0920 – 1035 Breakout Groups Meet

1035 – 1055 Break (6th floor)

1055 – 1250 Breakout Groups Meet

1250 – 1350 Lunch (Plaza Athenee Hotel, Rain Tree Cafe on the ground floor)

1350 – 1520 Breakout Group Recommendations and Presentation Development

1520 – 1535 Break (Plaza Athenee Hotel, Star room 29 on the 29th Floor)

1535 – 1820 Report on Group Discussion and Proposed Way Forward For Group
The objective of this plenary discussion is for each group representative to share the output of their discussion and to solicit comments from participants of other groups.
- Public Health and Future Access Group Representative
- Ethical, Regulatory and Community Issues Group Representative
- Science and Vaccine Development Group Representative
- Clinical Trial Design and Statistics Group Representative

1820 – 1900 Break

1900 Dinner (Plaza Athenee Hotel, the View restaurant on the 4th floor)

18 March, 2010

0530 – 0830 Breakfast at your leisure (complimentary for hotel guests; Rain Tree Cafe, Plaza Athenee Hotel)

Moderator: ***Dr. Supachai Rerks-Ngarm***

0800 – 0815 Recap of Key Points from Day 2 and Review Objectives for Day 3 (Plaza Athenee Hotel, Star room 29 on the 29th Floor)
- Dr. Saladin Osmanov

0815 – 0915 Public Health and Future Access: Presentation of Recommendations and Discussion
- Dr. Catherine Hankins

0915 – 1015 Ethics and Regulatory Issues: Presentation of Recommendations and Discussion
- Dr. Ruth Macklin

1015 – 1030 Break (Plaza Athenee Hotel, Star room 29 on the 29th Floor)

1030 – 1130 Science and Vaccine Development: Presentation of Recommendations and Discussion
- Col. Nelson Michael

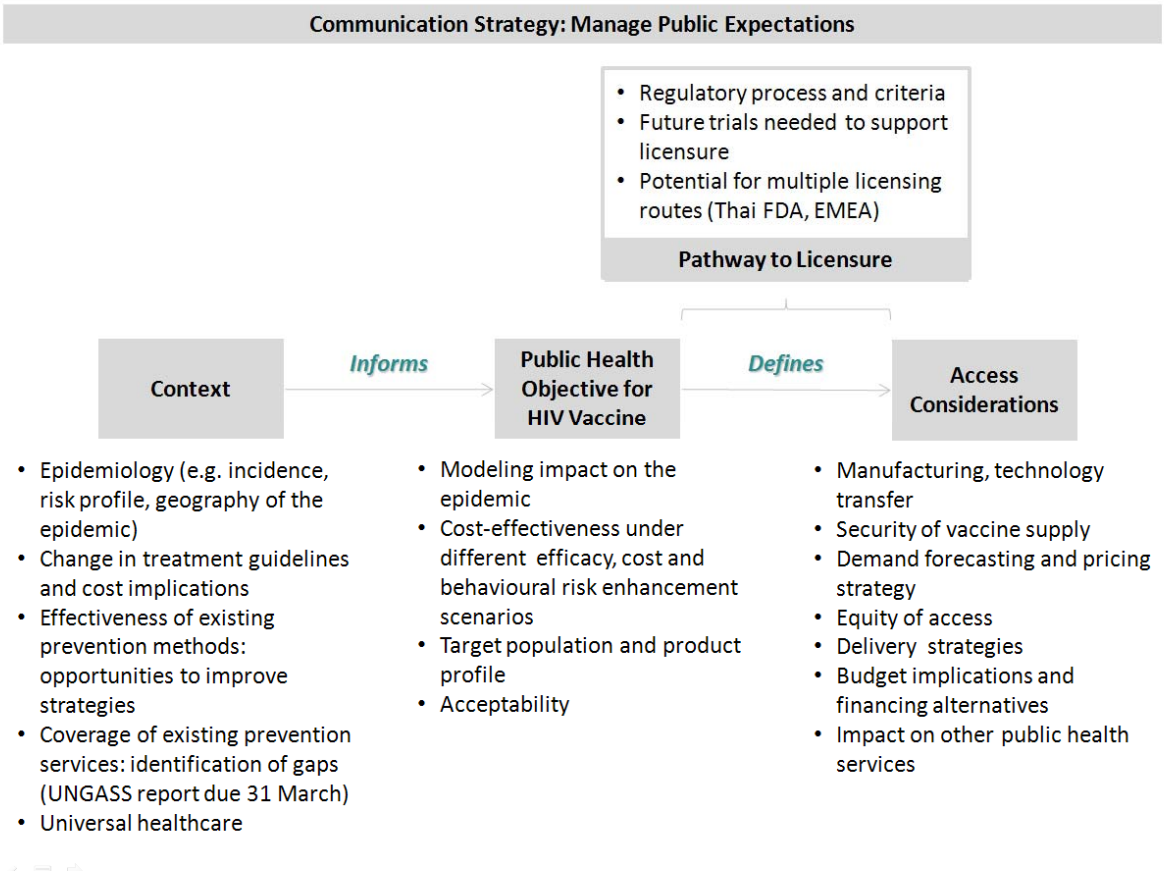
1130 – 1230 Clinical Trial Design and Statistics: Presentation of Recommendations and Discussion
- Dr. Donald Stablein

1230 – 1330 Lunch (Plaza Athenee Hotel, Rain Tree Café on the ground floor)

1330 – 1445 Outline Next Steps
- Col. Jerome Kim

1445 – 1500 Closing Remarks
- Dr. Supachai Rerks-Ngarm

Appendix 3: Public health and future access considerations related to the implementation of a preventive HIV immunization program*



*This figure was developed by the *Public Health and Future Access* working group.

Acknowledgments

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Mr. Bruce Merrell

Meeting Note-takers:

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Dr. Bilal Ahmad Rahima
Ms. Laura Sadowski
Ms. Elizabeth Shoaf
Dr. Wai Lin Htun

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Dr. Michelle French