Report

of the

WHO-UNAIDS Vaccine Advisory Committee (VAC)

and

Scientific Briefing on the biomedical HIV/AIDS prevention landscape and consequences for HIV vaccine development

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Contents

Introduction & Background 2

PART ONE (Scientific Briefing)
1. Biomedical prevention of HIV by non-vaccine approaches 4
2. The vaccine trial landscape 5
3. Implications for HIV vaccine trials 7
4. Combining interventions 10
5. Developing a global advocacy roadmap for HIV prevention 13

PART TWO (VAC Report) 15
Conclusions and Recommendations 22
Introduction

This report is a summary record of the WHO/UNAIDS HIV Vaccine Advisory Committee (VAC) meetings on 1-3 May 2012, including the scientific briefing on the biomedical HIV/AIDS prevention landscape and consequences for HIV vaccine development.

In addition to summarizing the scientific presentations and discussions, this report also reflects the VAC efforts to formulate a related WHO workplan for 2012-2013. This includes building consensus about the main issues, and demonstrating to Member States the important role WHO has in HIV vaccine development and the added value that WHO has in this endeavour.

Finally, this report puts forward a list of recommendations for action drawn from the proceedings.

The report is structured in two main parts: (1) the scientific presentations in plenary on the first and second days of the meeting; and (2) the VAC closed session on the third and final day in which those presentations and discussions, augmented by further presentations from representatives of invited groups and networks, formed the basis for shaping the workplan and producing recommendations.

Background

Almost thirty years after HIV was first identified, the virus still ravages the world. Nearly three million new HIV infections still occur annually with about 1.8 million deaths from AIDS-related causes. UNAIDS has set a target of zero new HIV infections, zero discriminations and zero AIDS-related deaths (for when?). These goals, though attainable, will require greater innovation from all stakeholders.

Although HIV presents extraordinary barriers to vaccine development, advances in knowledge about the virus and the immune system, and in technologies for vaccine design and development, are producing steady results. There is growing recognition that an effective HIV vaccine is feasible. In 2009, the RV144 phase III trial conducted in Thailand, and involving over 16,000 volunteers, showed that people who had received the test vaccine were 31% less likely to be infected with HIV than those who received the placebo 3 ½ years after vaccination. At one year after vaccination, the efficacy was 60% (although not statistically significant) and rapidly it waned over the following months.

Although this result may appear modest, it is a foundation for optimism. It proves that an HIV vaccine is possible, and has inspired new vaccine development efforts. As of July 2011, there were some 50 trials of 42 HIV vaccine candidates taking place worldwide. Many researchers now agree that the development of an AIDS vaccine is a matter of when, not if.

Because the heaviest burden of HIV still rests on Africa, the participation of Africa in the search for an effective HIV vaccine cannot be over-emphasized. Regional initiatives such as the African AIDS Vaccine Partnership (AAVP) strive to ensure that HIV vaccine research and development remains a top priority in HIV prevention, both in Africa and globally. But HIV in Asia is also a major concern, as the work of the AIDS Vaccine for Asia Network (AVAN) also illustrates.
Against this background the Vaccine Advisory Committee was given a series of expert scientific presentations related to the most urgent issues in HIV vaccine development. The essence of these was then taken into the closed meeting of the committee with the aim of shaping the future directions for WHO/UNAIDS on related biomedical and ethical issues.
PART ONE

*Scientific briefing on biomedical HIV/AIDS prevention landscape and consequences for HIV vaccine development*

1. Biomedical prevention of HIV by non-vaccine approaches

Dr Catherine Hankins, Deputy Director, Science, Amsterdam Institute for Global Health and Development, and Honorary Professor, London School of Hygiene and Tropical Medicine, opened the session. Her presentation examined non-vaccine combination approaches to prevention of HIV sexual transmission, with a review and discussion of a range of trials and their results; post-trial access and implementation; and future research challenges. Combination prevention is evidence-based, tailored, prioritized, and integrated.

Prevention of HIV sexual transmission through non-vaccine methods of preventing HIV sexual transmission include: male circumcision; treatment of STIs; male and female condoms; HIV counselling and testing; behavioural intervention; treatment for prevention; post-exposure prophylaxis (PEP); oral pre-exposure prophylaxis (PrEP); and microbicides.

Opportunities for preventing sexually-transmitted HIV infection to HIV negative individuals independent of coitus (male circumcision, vaccines, injectable long acting PrEP, daily PrEP); pre-coitally or coitally (topical microbicides, intermittent PrEP, condoms); or post-coitally, (therapeutic vaccines, post-exposure prophylaxis - PEP), or for those infected. (treatment of HIV).

Randomised controlled trials in Kenya, Uganda, and South Africa provided compelling evidence that medical male circumcision confers almost 60% protection, with effects persisting for up to five years post-trial.

Antiretroviral therapy for HIV-positive persons reduce onward transmission by 96% (HPTN052), while oral PrEP reduced HIV acquisition in MSM by 44% (IPREX) and by 75% in serodiscordant couples 73% (Partners PrEP) and microbicides reduced transmission by 39% (CAPRISA 004).

Dr Ying-Ru Lo, of the WHO HIV/AIDS Department, reviewed WHO activities on antiretroviral treatment (ART) including: the evidence for WHO guidelines on ART as prevention; ongoing research and the knowledge gaps in ART as a prevention method; and WHO meetings with stakeholders and mathematical modellers.

She gave numbers from the end of 2010 showing 34 million people living with HIV, 2.7 million annual new infections and 6.6 million people on ART. For every person starting ART, two others are newly-infected.

She described WHO activities on ART as prevention, from the “3 by 5” initiative in 2003 up to the flagship priority in 2012 of the strategic use of ART for treatment and prevention. WHO had also provided guidance on ART for treatment and prevention in serodiscordant couples, including a programmatic update on updates on treatment as prevention and rapid advice on PrEP for demonstration projects.
The key questions for decision-makers were:

- What is the magnitude of the ART prevention benefit in the local epidemiological context?
- How can results be translated into effective programmes - at scale and at what additional cost?
- In which settings and for what populations should ART prevention be used to have the greatest impact?
- What is the best mix of prevention interventions to optimize impact?
- What are best ways to deliver and achieve retention?

She outlined WHO’s technical and policy leadership on ART for 2012-2013. The guidance focus on ART treatment as prevention for 2012-2013 has six main elements. The first five of these are in for 2012, and the sixth for 2013:

1. Guidance on couples HIV testing and counselling and ART as prevention in serodiscordant couples;
2. HIV/TB collaborative policy;
3. Programmatic update on operational aspects of prevention of mother-to-child transmission prevention (PMTCT);
4. Treatment-as-prevention technical/programmatic update;
5. PrEP rapid advice;
6. WHO Consolidated guidance will combine all ARV related guidance.

There were three priority areas of work: to develop norms and standards; inform programmatic and operational decisions; and define metrics for monitoring and evaluating impact of treatment as prevention.

Her conclusions:

- Consolidated guidelines will include formal recommendations for ART as prevention beyond serodiscordant couples.
- Countries are moving towards introducing ART for prevention in serodiscordant couples and beyond.
- PrEP guidelines for demonstration projects will follow.
- HIV vaccine researchers will have to consider these developments in the design of their trials.

2. The vaccine trial landscape

This session consisted of three presentations, by Dr Alan Fix, of the Division of AIDS (DAIDS), National Institute for Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), Bethesda, United States of America; Dr Nelson Michael, of the Walter Reed Army Institute for Research, also in Bethesda, and Dr Frances Priddy, of the International AIDS Vaccine Initiative (IAVI), USA.

Dr Fix reviewed HIV vaccine candidates in NIAID-supported clinical trials, and current products and concepts, including DNA, vectors (adenovirus, pox, VSV), protein boost and adjuvants. He discussed Phase I research trials, current Phase II trials, and elements in the DAIDS Vaccine Research Programme’s HIV vaccine pipeline in the near-term and longer
term. He provided an overview of protocols supported by the Programme that were either active or anticipated in 2012 VRP/DAIDS-supported protocols. He described the Pox-Protein Public Private Partnership (P5), whose members include the Bill & Melinda Gates Foundation (BMGF), NIH DAIDS, the HIV Vaccine Trials Network, the U.S. Military HIV Research Programme (MHRP), and Sanofi and Novartis. The Partnership has important linkages to the Pantaleo Poxvirus T Cell Vaccine Discovery Consortium (PTVDC) of the BMGF-supported Collaboration for AIDS Vaccine Development (CAVD), and host country representatives.

The Partnership’s goal is to substantiate and extend the RV144 vaccine result. Its strategy is aligned with five key drivers of product development and impact. This strategy aims to:

- Substantiate and extend RV144 results;
- Continue to build public-private partnerships critical for success;
- Achieve timely public health impact;
- Work with host countries to support a flexible regulatory strategy in target populations and regions;
- Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.

The strategic objective is to increase RV144 vaccine efficacy from 30% to > 50%. Achieving vaccine efficacy of 50% for three years would offer a significant public health benefit for regional epidemics. Population modelling data for Benin and rural Zimbabwe suggest that a vaccine with VE >30% could significantly reduce the number of new infections. Potential efficacy trials in the next few years would be in South Africa and southern Africa, Thailand, and the Americas.

Dr Michael surveyed the vaccine trial landscape from the perspective of the U.S. Military HIV Research Programme. He explained its HIV vaccine incremental strategy. The first part of this was building on RV144 with a regional vaccine strategy to improve on RV144 and verify correlates. Here, the approach is to have an efficacy trial with an additional boost, aimed at (a) heterosexual risk, in Thailand; (b) males having sex with males, in the Thai population; and (c) high-risk heterosexuals in South Africa.

The second part of the incremental strategy is diversifying the portfolio through a global vaccine strategy – diverse approaches towards a globally-effective vaccine. The approach in this case was to pursue multi-clade efficacy testing, increase CD8 immunogenicity and prime for potent and durable antibody responses. The global strategy would be mutually reinforcing and amplify global impact and regional relevance. Coordination of proposed trials provided the strongest regulatory strategy for filing in target markets.

Short-term development objectives were to characterize vaccine immune responses, using samples collected (in sufficient amounts, at the right times and from systemic as well as mucosal sites) and to improve magnitude and durability of vaccine-induced responses.

The pathway to a global HIV vaccine, based on RV144 data, led from the Phase I trial for safety and immunogenicity in 2011 (of a mosaic vaccine?), through Phase IIa in 2013 (for epitope and clade breadth and magnitude of immune response), to Phase IIb in 2015 (two or three-arm efficacy trial with a common placebo group). A successful outcome would yield a mosaic or multi-clade vaccine effective in high-risk populations. But commercial partners had yet to be identified, and might restrict development and access to products.
Dr Priddy presented the International AIDS Vaccine Initiative portfolio, with a history of IAVI’s clinical trials dating from 2000 (DNA candidates, MVA candidates, DNA+MVA candidates; ADARC DNA and MVA candidates; AAV candidates; and adeno-based candidates. The milestones between now and 2016 were to advance current candidates through clinical trials; advance the next generation of improved vector candidates; and, develop candidates to elicit broadly neutralizing antibodies.

The near-term objective was to see the Adenovirus 35 vector-based platform advance to efficacy trials. It was the ability of IAVI’s to foster broad partnerships linking government, academic and private-sector expertise with clinical collaborators in Africa that enabled clinical testing. The medium-term objective was to advance the next generation of improved replicating vector candidates. IAVI was filling the translational gap in the field through its links with the biotechnology industry and others to accelerate work on replicating vectors.

Neutralizing antibodies had the highest potential impact; the challenge was to develop candidates that elicit broadly neutralizing antibodies. The goal was to have first-generation immunogen in Phase I trials by 2015. The rationale was that most licensed vaccines elicit neutralizing antibodies - they attach onto the virus and prevent infection. Since HIV is highly variable, a vaccine needs to elicit broadly neutralizing antibodies. However, at present, no candidate vaccine in the pipeline elicits broadly neutralizing antibodies against HIV.

3. Implications for HIV vaccine trials

3a. Trial design

Dr Glenda Gray of the University of the Witwatersrand, Republic of South Africa, presented on the use of adaptive and other novel designs in HIV vaccine trial design. In 2009–2010, the HVTN developed a Phase 2b efficacy trial design with an eye toward implementation in South Africa. The design was discussed by clinical trials experts (especially statisticians) at a workshop sponsored by NIAID in January, 2010, and published in 2011 together with commentaries from workshop participants.

The adaptations proposed for HIV vaccines include group sequential monitoring; adaptive two-stage vaccine efficacy design; the use of one, two or three vaccine regimens with shared placebo (efficiency); staggered start/rolling phase-in design; correlates/sieve analysis; and use of non-HIV vaccines for surrogates of protection. The adaptations follow FDA guidance principles (Adaptive Design Clinical Trials for Drugs and Biologics, FDA, February 2010).

Dr Gray summarized the research design under consideration for South Africa, including licensure design, additional design considerations, and the use of non-HIV vaccines as surrogates. Potential complicating issues related to (1) product development time-lines: What if it were not possible to start all vaccine regimens simultaneously in the research design? (2) HIV incidence: What if it was lower than projected? (3) Immune correlates assessment: How to ensure inclusion of the best possible immune variables and deliver answers in a timely manner?

Related to these, (1) staggered-start design increases the sample size, enrolment period, and likely trial duration relative to concurrent starts, but not as much as two separate trials. It
substantially reduces power for head-to-head comparisons of vaccines. Staggered-start designs may be viewed on a continuum from no staggering (original research design) to complete staggering (separate trials). With only a minor delay, staggered start design clearly is more efficient than two separate trials. There is continuing research to determine the tipping point where the delay is long enough to abandon the staggered start design in favour of separate trials.

(2) If HIV incidence is moderately lower than what was projected, then the plan may provide a straightforward way to expand accrual to ensure reaching the needed endpoints. If HIV incidence is much lower, then the plan provides a way to halt the trial as soon as it is evident that a timely answer cannot be obtained. At each DSMB meeting the closed statistical report provides the estimated distribution of the time to reaching the needed number of events (based on trial data on accrual, infections, and dropout). Operational futility stopping guidelines based on these estimates are specified, leading to decisions on whether to continue with no changes; expand accrual; or halt.

(3) Following RV144 model, an open process is needed where the field is invited to perform their assays on pilot samples to qualify for the immune correlates study. In the planned designs, pilot studies are initiated if and when a vaccine reaches Stage 2, leaving 18 months until the vaccine reaches its full evaluation out to 36 months. Pilot studies occur during Stage 2 of the trial, enabling the case-control results to be reported shortly after the trial. Strong leadership and coordination are required to keep the pilot process on track over 18 months.

3b. Standard of prevention and ethical landscape for HIV vaccine trials

Dr Jonathan Jay of Georgetown University Law Centre, USA, demonstrated that the vaccine trial landscape is also an ethical landscape. He gave an overview of the standards of prevention in recent and continuing prevention trials; developments in ARV modalities, and the potential consequences for vaccine trials; and discussed an ethical framework for the design of HIV vaccine trials.

The development of ARV-based prevention modalities presents a potential challenge for HIV vaccine trials: well-accepted ethical norms would require that at some point in the development of ARV-based modalities, researchers should provide these to participants in vaccine efficacy trials. However, these norms do not clearly identify the point at which an ARV-based modality becomes ethically required, or the trial populations which must receive the modality. Additionally, there is controversy among these guidelines as to the appropriate role of scientific considerations in modifying an otherwise appropriate standard of care.

Dr Jay’s presentation offered a framework for analyzing these critical issues in standards of prevention, based on work from an ongoing project involving Glenda Gray, Ian McGowan, Kenneth Mayer and Hannah Burris. They argue that a new modality should be included once it has been validated for clinical use, unless modification is methodologically necessary to serve a compelling public health need. The presentation explained factors involved in making these key determinations.

Regarding concern that providing oral Truvada in the background package of a preventive HIV vaccine trial might make it methodologically impossible to achieve meaningful results, Dr Jay suggested that the prospective population for receiving oral PrEP might be
significantly smaller than the population of prospective vaccine trial participants, based on the likelihood that oral PrEP will be focused among those with a specific, high level of risk, whereas vaccine trials can accommodate a relatively low level of risk (as evidenced by the extremely low incidence and large sample size in the RV144 trial). Dr Robin Shattock later pointed out that the efficacy of Truvada in other trials was not so high as to generate a significant methodological obstacle; however, a higher efficacy rate, such as might be expected from longer-acting PrEP (ring or injectables) could generate such an obstacle.

Dr Jay examined the relevant standards currently influencing ethical issues, including the Declaration of Helsinki, originally adopted in 1964 and revised six times since (the latest was in 2008), often amid heated controversy and debate; and the UNAIDS-WHO Ethical considerations document of 2007, which he said also contained ambiguities. According to this document, when a new ARV modality is added, researchers or sponsors should ensure “appropriate counseling and access to (1) all state of the art HIV risk reduction methods”; new methods should be added based on (2) consultation among all stakeholders, including the community as (3) scientifically validated or (4) approved by relevant authorities.

Dr Jay related these points to the issue of when is the obligation to participants triggered, and the need for stakeholder negotiation throughout the process. There was no international consensus on whether there was an absolute duty to provide or when a duty is triggered. He proposed a three-part framework. The first question to be asked was whether an obligation to participants had been triggered. If so, the second question was whether methodological considerations prohibited the optimal prevention package. If that was also the case, the third question to be asked was whether there was a compelling public health consideration for a lesser prevention package. Dr Jay examined the key issues surrounding each of these questions and proposed an approach in which (1) general populations should be excluded from vaccine trials; (2) populations with elevated HIV risk should be recruited for trials and also screened for PrEP eligibility; and (3) those with the greatest need for PrEP should be offered a link to treatment.

Dr Punnee Pitisuttithum of the Faculty of Tropical Medicine, Mahidol University, Thailand, also examined some of these issues in her presentation on HIV/AIDS and standard prevention in HIV vaccine trials in Thailand. Implementation of this standard prevention follows the country’s national guidelines, and are within the context of the national AIDS prevention strategies and solutions 2012 – 2016, which have the following goals to be reached by 2016:

- No new infections (new HIV infections reduced by two-thirds; vertical transmission eliminated)
- No deaths due to AIDS (Equal access to quality treatment, care and social services support for all people living with HIV and their households; TB deaths among people living with HIV reduced by half)
- No stigma and discrimination. (rights protection mechanisms for key affected populations functioning in all provinces; removal of all laws and policies which block effective responses).

Dr Pitisuttithum gave a range of examples of programmes and initiatives based on the prevention strategies related to these 2016 goals, including risk reduction; STIs screening and treatment; promoting HIV disclosure to partner; promoting partner HIV testing; promoting ARV adherence; and family planning to prevent unwanted pregnancy.
4. Combining interventions

Dr Robin Shattock of the Faculty of Medicine at Imperial College, London, presented on the subject of combined interventions. He proposed a combined research strategy for biomedical interventions, ranging across time from pre-exposure to post-exposure as likely to provide the fastest, most tangible impact on HIV transmission.

The pathway to reversing the epidemic, in which prevention research/funding is viewed as a continuum, would begin with male circumcision, followed by treatment for prevention, ARV PrEP (oral, microbicide), a partially-effective vaccine, and a highly-effective vaccine, underpinned throughout by positive promotion of behavioural and structural interventions to provide a comprehensive package of prevention options.

Possible biomedical prevention combinations included:

- Combined use of oral PrEP and microbicides for intermittent dosing– optimal systemic and local drug levels (steady state and bolus)
- PrEP (oral, topical) for women combined with circumcision + oral PrEP for men
- T4P combined with ARV PrEP (microbicide or oral for women, oral for MSM) for the HIV-negative partner.
- Vaccines plus ARV PrEP
- T4P combined with ARV PrEP (microbicide or oral for women, oral for MSM) for the HIV-negative partner.
- Vaccines plus ARV PrEP

A combination of vaccine and PrEP might deliver better protection in the following ways:

- Providing protection during the immunization period
- Reducing infectious challenge and primary foci of infection
- Increase eclipse phase prior to systemic dissemination providing an extended opportunity for adaptive immunity to respond
- Boosting local immunity (virus/antigen)
- Broadening localized immunity through protected exposure to prevalent virus.
- Converting high risk (or frequency) challenge to low risk challenge (RV144)
- Coverage between potential re-vaccination campaigns as immunity wanes
- Providing immunological coverage of intermittent PrEP adherence, break through virus and resistance evolution.

Potential challenges to combination trials included:

- Increased sample size, trial complexity and cost
- Potential for adaptive design
- Additional visits for safety, HIV testing, etc
- Risk compensation and adherence may vary according to perceived efficacy of the individual components of any combination
- Issue of informed choice becomes more complex
- Open-label trials may be the best way to assess concerns about risk compensation while learning about implementation.
4a Modelling

Epidemiological: Potential impact of an RV144-like HIV vaccine in diverse epidemic settings

Dr Robert Chen of the Centers for Disease Control and Prevention, Atlanta, USA, discussed the outcome of a modelling consortium established by CDC and UNAIDS in early 2010 after the publication of the RV144 trial results. Independent groups of mathematical modellers were invited to join and adapt their pre-existing models to assess the impact of a modestly effective HIV vaccine with waning efficacy (similar to that observed in RV144 vs. hitherto purely hypothetical efficacy) on the HIV epidemic in select countries (Thailand, South Africa, United States, and Australia).

The consortium presented its preliminary results at the AIDS Vaccine Conference in Atlanta in September, 2010 and these were published in a special issue of Vaccine in August 2011.

The modellers identified a clear reference case to facilitate model comparisons:
- Single vaccination campaign with waning efficacy
- Vaccination of adult population: 30% or 60% coverage
- Modeled outcome: proportion of HIV infections averted over 10 years

Additional optional analyses included:
- Periodic booster vaccinations, assuming restoration
- Effect of behavioural risk compensation
- Cost-effectiveness

All other modelling assumptions and parameters were allowed to vary between groups.

Dr Chen provided a summary of the results (10-year outcomes with 60% coverage) and listed the lessons that had been learned.

- Model-based analyses were broadly consistent, despite widely different assumptions
- One-time vaccination averts approximately 10% of new HIV cases
- If effective, periodic booster vaccinations substantially improve infections averted
- Bi- or tri-annual boosters prevent 20-27% of cases
- Annual boosters prevent 35-58% of cases
- Prioritization to groups at higher risk of HIV improves programme efficiency
- Can prevent 80% as many infections, with 10% of required vaccinations, compared to universal adult vaccination.
- Vaccination with partially-effective HIV vaccines can be cost-effective
- (At $100 per regimen, vaccination in South Africa costs $2,700/case averted, or $10,000/life-year gained; at $500 per regimen, vaccination in USA costs $100,000/QALY gained).
- Behavioural risk compensation post-vaccination does not eliminate vaccination benefits
- Rate of efficacy decline affects short- and long-term epidemic outcomes.
The key remaining questions were:

- What is the rate of efficacy decline and duration of protection?
- How does efficacy differ among individuals at higher risk of HIV infection?
- What is the role of a vaccine in a portfolio of interventions?
- What is the immunological impact of vaccine boosters?
- Is there evidence of behavioural risk compensation post-vaccination?

**4b Economic: Economic analysis for future HIV vaccines**

**Dr Raymond Hutubessy** of the Initiative for Vaccine Research (IVR) at WHO, discussed cost-effective analyses (CEA) of future HIV vaccines. IVR’s core functions on vaccine and implementation research are setting the research agenda and scanning the horizon of innovative vaccines and related technologies, supporting vaccine development and evaluation, and implementing research and evidence for policy.

The presentation also explained the functions, membership, meetings and operational procedures and Immunization and Vaccines-related Implementation Research (IVIR) Advisory Committee (formerly known as QUIVER). The IVIR committee recommends on modelling methods among others. Due to the complexity of vaccine modelling, IVIR underlines the importance of not relying on one single model for decision-making.

This presentation made the following key points:

- No vaccine will be 100% effective – an HIV vaccine should complement other prevention practices and could reach populations where other existing efforts have been insufficient.
- A partially-effective HIV vaccine should be assessed as a stand-alone intervention as well as in combination with other therapeutic and preventive interventions against HIV/AIDS.
- Wide public health perspective is needed. Ultimately, sector-wide priorities needs have to be set, given the limited resources available.

Examples were given of a range of CEA models, and cited the work of modelling groups to assess CEA in RV144-like vaccines with same vaccine scenarios/parameters (efficacy, duration, booster, etc.) in South Africa, Thailand, and the USA, in 2011, and the earlier work of the WHO-UNAIDS collaborative group on cost-effectiveness, delivery and future access to HIV vaccines (AIDS, 2005).

The limitations of incremental cost-effectiveness analysis (iCEA) were examined. Current practice versus new intervention always requires comparison with a range of other options. iCEA does not allow examination of whether current practice should have been done in the first place. Incremental analysis is not generalizable, e.g. expanding coverage of immunization depends on the existing coverage rate which varies across different regions. Therefore, iCEA may be too narrow and broader, generalized CEA (GCEA) may be needed to capture combined synergistic effects of partially-effective HIV vaccines and other preventive interventions.
The key conclusions of the ad-hoc WHO consultation (in Montreal, Canada in July 2010) on the assessment of cost-effectiveness tools to support introduction decisions for human papillomavirus (HPV) in low- and middle-income countries, and the lessons learned, could also be applied to HIV vaccines:

- Many countries face a lack of capacity to interpret results of economic models, and require guidance from WHO.
- It is important not to rely on a single model for decision making. It is most useful to provide countries with a “menu” of tools rather than to recommend a single model.
- The strengths and limitations of different kinds of models need to be understood before their results are used for decision making at local level.

5. Developing a global advocacy roadmap for HIV prevention

Dr Mitchell Warren Director, described the work of AVAC (Global Advocacy for HIV Prevention), founded in 1995, which uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of AIDS vaccines, male circumcision, microbicides, PrEP and other emerging HIV prevention options as part of a comprehensive response to the pandemic. AVAC is dedicated to:

- Translating complex scientific ideas to communities and translating community needs and perceptions to the scientific community.
- Managing expectations.
- Holding agencies accountable for accelerating ethical research and development.
- Expanding international partnerships to ensure local relevance and a global movement.
- Ensuring that policy and advocacy are based on thorough research and evidence.
- Building coalitions, working groups, and think tanks for specific issues.
- Developing and widely disseminating high-quality, user-friendly materials.

AVAC currently focuses on:

- Building and sustaining a global coalition of civil society and community-based organizations, research agencies, and networks that supports and facilitates HIV vaccine and prevention research;
- Developing and advocating for policy approaches to facilitate the expeditious, ethical development, introduction, and use of vaccines and other HIV/AIDS prevention technologies and to ensure that prevention research and development efforts strengthen HIV/AIDS programmes;
- Monitoring the vaccine and broader prevention research field and mobilizing political, financial, and community support for prevention research as part of a comprehensive response to the epidemic; and
- Developing and sustaining a system for global delivery of advocacy resources and information to the array of stakeholders who must work together to ensure that the rights and interests of trial participants, eventual users, and communities are fully represented and respected in the scientific and product development processes.
Since 1997, there have been HIV vaccine trials in 16 countries, involving a total of 69 000 volunteers. Investment in 1997 was US$ 186 million and US$ 821 in 2012. About 75% of the current amount (US$ 614 million) comes from the USA; US$ 97 million from philanthropic organizations; US$ 54 million from European countries; US$ 40 from other governments; and US$30 million from industry.

Despite this, the general trend in funding has been downwards, no doubt due in some part to the global economic crisis; but there was also a lack in the general sense of urgency, and HIV could no longer be discussed outside of the context of other diseases. He proposed a three-part agenda for ending AIDS: Deliver (test, treat, circumcise); Demonstrate (proven tools for immediate impact, PrEP, microbicides) and Develop (long-term solutions).
PART TWO

The WHO-UNAIDS HIV Vaccine Advisory Committee

Dr Uli Fruth reviewed HVI-VAC past and planned activities. On the Adaptive Trial Design publication, an editorial committee had completed a draft which VAC members have received and to which they could provide editorial comments. He proposed publication of the document in *AIDS* or *Vaccine* with the names of the editorial group membership "on behalf of the WHO/UNAIDS HIV Vaccine Advisory Committee".

At the VAC 2012 scientific pre-meeting on opportunities for collaboration among the HIV, TB and malaria vaccine development “communities”, a number of potential areas of common interest were identified, including prime boost strategies, vectors, vector delivery systems and adjuvants, potential assay harmonization and shared use of trial sites or trial site network, to name a few. As a first concrete outcome of these recommendations, WHO and the US-NIAID have organized a workshop on heterologous Prime-Boost Vaccine Strategies for HIV, Malaria and TB, in Rockville, Maryland, in April 2012, and the lessons learned.

Other elements of his report included:

Adaptive Trial Design: a draft meeting report of a meeting on adaptive trial design, hosted by IAVI in February 2011, has been completed by an editorial committee. The draft was shared among VAC members for comments. Publication of the document in “AIDS” or “Vaccine” was proposed, authored with the names of the editorial group membership "on behalf of the WHO/UNAIDS HIV Vaccine Advisory Committee” and other meeting participants.

VAC should consider how to continue the monitoring and distribution of HIV subtypes and recombinants, to estimate the global and regional HIV subtype distribution in the period 2008-2012 Comparative data for the periods 2000-2007 and 2008-2012 will be analysed to detect significant changes in the HIV subtype distributions between these periods.

WHO-UNAIDS Guidelines for HIV Isolation and Characterization: Procedures were last updated in 2002 and should be extended with up-to-date knowledge tests for different aspects of HIV-specific cryotechnology. A meeting on this is planned for 18-19 June 2012 at the Fraunhofer Institute in Sulzbach, Germany.

On written and physical standards: Dr Fruth proposed for VAC to take a lead in identifying standardization needs, both for written standards ("regulatory guidance") and physical (measurement) standards. This consensus-building effort within the broader "community" would provide the first step for development of the standards by the QSS (Quality Safety and Standards) team in IVB. Furthermore he mentioned that HVI was currently investigating how to better structure its support to strengthening capacity of developing country regulators and ethical bodies and a report to VAC was planned for 2013.

VAC review of scientific session and workplan discussion

The committee discussed the scientific presentations which had revealed a new climate where vaccines might be somewhat overshadowed by other developments in prevention and treatment. These, particularly pre-exposure prophylaxis (PrEP) had clearly emerged as one of
the most significant issues. In constructing a workplan, VAC had to define its role for the next 12 months and decide its priorities.

Among these, the most important was how to keep HIV vaccine research at the top of the Global Health agenda. The challenges here were that there was a long time to wait before a vaccine would be available; and at the same time, a growing sense in some parts of the world that the AIDS crisis was already solved. Combined, these two factors would make fund-raising for vaccine research more difficult. More broadly, there was a growing tension between advance planning in vaccine research and the need to adapt to the very dynamic pace of change in the field.

Meanwhile, there was still a huge gap among countries in the implementation of preventive methods, which lead to ethical as well as practical dilemmas. One PrEP, Truvada, was licensed for use in the USA, but not in African countries. What were the obligations of an investigator in Africa receiving US funding? If standards varied between countries, whose standards should apply in PrEP studies? These were questions for lawyers as well as researchers. The availability of PrEP would change how candidate vaccines could be tested in many populations; it would probably not be possible to conduct trials in high-risk groups of serodiscordant couples.

VAC represented WHO and as part of its workplan had a responsibility to its Member States and regulators to provide solid, evidence-based advice as clearly as possible, and to clarify where there was confusion over some issues. Countries, particularly developing countries, were looking to WHO for guidance and VAC’s role was to facilitate the work between researchers in developing countries and developed nations.

At the same time, there was a funding plateau for HIV vaccine research just when more trials were required. WHO should lobby (advocate?) for more funding. VAC could strongly recommend much more work on prevention standards of care related to vaccine research, with a rapid WHO response as trial results are announced and a role in stimulating new partnerships.

The VAC-WHO workplan should contain an important convening function, tracking progress, as well as performing a normative role. A central element of the workplan was to help develop evidence-based policy and translate it into practice, to foster capacity-building and advocacy.

In developing the workplan, there was now an opportunity for closer collaboration between VAC and a range of WHO-linked groups and networks. These opportunities were reflected in the following presentations by invited representatives.

**AIDS Vaccine for Asia Network (AVAN)**

**Dr Yiming Shao** of the Chinese Center for Disease Control and Prevention, Beijing, People’s Republic of China, presented on behalf of the AIDS Vaccine for Asia Network (AVAN). Its vision is to develop a safe and effective HIV vaccine and ensure its access as a part of a comprehensive public health strategy for the control of new HIV infections across the region, where more than 500 million people are at-risk for HIV infection. More than 5 million people are already infected with HIV, although the epidemic is highly variable across different
countries within the region. The epidemic is driven mainly by unsafe sex and injecting drug use and is spreading to the general population.

AVAN is a group of concerned investigators across the region committed to assisting regional and global HIV vaccine efforts. It is developing a regional strategy to accelerate the research and development of an AIDS vaccine, suitable for use in Asia. The region has the capacity to do HIV vaccine research and development. Several countries of the region, especially Thailand actively participate in many international vaccine trials. Others include Australia, China and India. It seeks international support from WHO, the European Union, the Bill and Melinda Gates Foundation, among others.

**The Strategic Advisory Group of Experts (SAGE)**

**Dr Philip Duclos** of the WHO Department of Immunization, Vaccines and Biologicals (IVB) described SAGE as the principal advisory group to WHO for vaccines and immunization: from research to delivery of immunization and linkages with other health interventions - all vaccines, all ages. It reports directly to WHO’s Director-General, providing vaccine policy recommendations, and involves all relevant WHO departments. SAGE was restructured in 2005 in context of Global Immunization Vision and Strategy. Its 15 members are appointed on the basis of their individual capacity and expertise and geographical representation.

SAGE has a “watching brief” on the HIV vaccine research agenda, providing updates when new findings arise. On behalf of WHO and together with UNAIDS, it fosters international consensus and provides technical guidance to WHO Member States on technical, regulatory, ethical and community participation issues.

WHO shapes the global research agenda and has an increasingly important role in coordinating the growing number of players. It was required to adapt to the new political climate and demonstrate global leadership. If an international organization like WHO were created today, it would be unlikely to be given the same powers that WHO currently holds. Consequently, while remaining true to its normative and bold vision of health for all, the WHO must adapt to a new political climate, demonstrate global leadership, and deliver results.

**Joint Technical Expert Group on Malaria Vaccines**

**Dr Vasee Moorthy** of the Initiative for Vaccine Research at WHO explained the role of JTEG, which was jointly constituted in April 2009 with the WHO Global Malaria Programme and IVR, and with the involvement of the WHO Regional Office for Africa (AFRO).

JTEG advises WHO on the clinical trial data necessary and desirable for evaluation of the public health impact of a malaria vaccine in malaria endemic countries, and the design, analyses and interpretation of Phase 2, Phase 3 and Phase 4 malaria vaccine trial data.

In its constitution, JTEG co-opted public health/clinical malariology expertise from the existing upstream MALVAC committee. The Global Malaria Programme designated experts in malaria control and malaria programmes. AFRO nominated the head of the Extended Programme on Immunization (EPI). JTEG and its Chair have strong malaria and vaccine biostatistics expertise, and strong African representation, given its target group.
It is an important part of the pathways for WHO recommendations on malaria vaccine use, providing input to and responding to requests for evidence reviews from SAGE (see above) and MPAC. JTEG guides the approach to interpretation of multiple efficacy analyses and requests for additional analyses for public health/policy perspective. It serves as the WHO malaria vaccine expert pool when requests are made by external agencies, and communicates WHO’s processes and likely timings. JTEG reviews WHO’s external communications related to Phase III trial results, allows a solid basis for WHO technical briefings internally and externally, and provides background papers and draft policy recommendations for consideration by SAGE and MPAC.

In its role in the assessment of cost-effectiveness status for malaria vaccines, JTEG has conducted assessments using the JTEG (malaria vaccine) and QUIVER (modelling/cost effectiveness) joint subgroup models. This has allowed an assessment of model structure, assumptions, data gaps and uncertainties, and predictions. It has also enabled WHO to provide guidance to modelling groups about further work needed on cost-effectiveness.

Dr Moorthy said the JTEG mechanism has enabled it to communicate clear timings for the first WHO malaria vaccine policy position. A WHO position on use will reflect SAGE and MPAC recommendations in 2015. This allows other agencies and partners to fulfil their role, and potentially accelerates timelines.

Dr Sergio Nishioka of IVB/QSS at WHO, summarized initiatives developed and/or supported by WHO HQ and Regional Offices, focusing mainly on vaccine clinical trials and not including NRA strengthening activities that were part of the NRA assessment conducted by WHO HQ.

The traditional view of regulators from developing countries was that for drug registration/licensure/MA they should rely on previous assessments made by a developed country regulatory agency. For clinical trial authorization, developing countries should limit themselves to evaluate clinical trial protocols from the ethical perspective (ethics committees). Regulators should authorize the import of investigational products (e.g. vaccines) for use in clinical trials.

The current situation worldwide was that vaccines or drugs under development were targeting diseases prevalent only in developing countries. Clinical trials were to be conducted only in developing countries, and products were to be licensed or registered first in developing countries, and the use of “old” products was to be continued only in developing countries. New products (e.g. combination vaccines) were to be developed from products manufactured in developing countries (technology transfer).

Dr Nishioka described the Pan American Health Organization (PAHO) regional initiative of 2003, and the subsequent series of regional meetings with Latin American country regulators. This built an inventory and better understanding of clinical trial evaluation processes in the region, developed capacity-building and triggered the introduction of a new rotavirus vaccine to be introduced in the region for the first time worldwide.

He also described several networks, as follows:

*The Developing Country Vaccine Regulators’ Network (DCVRN)*, launched in September 2004. It aims to promote the strengthening of the procedures for evaluating clinical trial
protocols and clinical data, and involved nine countries: Brazil, China, Cuba, India, Indonesia, Korea (must check whether the Republic of Korea or the Democratic People’s Republic of Korea), the Russia Federation, the Republic of South Africa, and Thailand. DCVRN discussed vaccines or candidate vaccines related to a range of diseases including HIV, tuberculosis and malaria.

The Pan American Network for Drug Regulatory Harmonization (PANDRH), an initiative of the national regulatory authorities within the American Region and PAHO, which supports the processes of pharmaceutical regulatory harmonization in the Americas, within the framework of national and sub-regional health policies and recognizing pre-existing asymmetries. PANDRH has a number of working groups, including one on vaccines.

The African Vaccine Regulatory Forum (AVAREF), involving 19 countries, has representatives from national regulatory authorities and ethics committees, and has the regulation of vaccine clinical trials within its scope. It is an effective initiative to stimulate progress towards regulatory harmonization of clinical trials, and a channel of communication among African regulators and with regulators from developed countries. It had created confidence, strength and willingness to harmonize processes. Model regulatory procedures developed and adopted by many countries

The ASEAN/PPWG/Vaccine Chapter identified training needs relevant to clinical trials and had a communication strategy to identify representatives to meetings and course candidates. It had a workshop on regulatory pathways for clinical trials of dengue vaccines.

The Regional Alliance for National Regulatory Authorities in the Western Pacific Region was the latest network, established in 2011, and meeting in Canberra, Australia, at the end of May 2012 to discuss issues including technical and financial support and to meet with donors on resource mobilization.

The benefits of collaboration between NRAs included comparisons of their strengths and weaknesses and the sharing of information. This helped strengthen some NRAs, but not all. Collaboration could accelerate or delay the availability of new vaccine; delay of access to these vaccines was not necessarily a disadvantage. Strong NRAs pushed local manufacturers to raise their standards.

The HIV vaccine backup plan or pipeline strategy

Dr José Esparza, from the Bill & Melinda Gates Foundation, opened a discussion on this issue by asking whether there was sufficient diversity for VAC to consider not just what was currently fashionable, but to also consider new concepts. Very few candidate vaccines were likely to reach Phase III trials in the next five years. VAC should try to help the rapid entry of candidates for clinical trials; this was a critical time and a more strategic approach to them was required in order to keep the pipeline flowing.

Other participants in this discussion said the goal of a universal HIV vaccine had not been lost sight of, and VAC had a role to play in keeping the focus on subtypes globally, and taking account of modes of HIV transmission. VAC should be ready to confront concerns that were arising in developing countries. WHO was a powerful influence worldwide, and VAC should be part of the process of responding increasingly to the concerns of Member States.
VAC had a responsibility to be a good steward of the vaccine portfolio, and to address Member States’ concerns so that there was communication among stakeholders. VAC could advise whether there were redundancies in some approaches or whether others were being ignored. VAC could be more alert to suggestions from the global community.

**The Global HIV Vaccine Enterprise**

Bill Snow, Director, introduced the Enterprise, which supports a global approach to the challenge of HIV vaccine research and development that transcends individual funders, countries, researchers, and civil society. Its partners include HIV vaccine researchers and programmes, advocacy and policy groups, governments, international organizations, multilateral agencies and community and outreach groups. (I will leave to Bill to clarify that the Enterprise is not an association of concerned individuals, but one of major funders and implementers).

In terms of coordination, the Enterprise shares information on strategies, current and planned activities, and budget; it identifies priority issues where collective effort is required; and it identifies new, unmet priority areas where additional resources are needed. In terms of collaboration, it promotes more efficient, faster ways for funders and researchers to share findings and avoid duplication of efforts; it engages new implementing organizations to the field and convenes the scientific community to share information and data. Mobilization is directed towards maximizing existing resources and bringing in additional resources and new funders.

**The African AIDS Vaccine Partnership (AAVP)**

Dr Chidi Victor Nweneka of Entebbe, Uganda, representing AAVP, said that while advocating primarily for HIV vaccines, AAVP also works within the context of HIV prevention in general and fully supports work on other HIV prevention tools. AAVP is a partnership with a three-pronged approach: advocacy, communication and coordination. Its vision is an HIV-free Africa, and its mission is to accelerate HIV vaccine research and development and eventual access for Africa through strategic partnerships. Its strategic goal is to provide a voice for HIV vaccine R&D in Africa. What AAVP needs most is a strategic, mutually-beneficial partnership.

It adds value to the work of VAC by assisting in the implementation of strategies and plans related to Africa agreed at VAC meetings and similar forums; providing policy advocacy support to VAC at the highest ministerial level in Africa; and in future, assisting with identifying new funding sources in Africa to assure consistent funding for HIV vaccine R&D. In return, VAC can add value to AAVP by providing advice on strategic issues and direction; highlighting priority areas for AAVP to address, such as challenges and new gaps; giving opportunities for access to latest HIV vaccine related information; endorsing AAVP strategies, plans and programmes to relevant stakeholders, thus speeding up their implementation; and providing any other assistance, within its remit, to make AAVP truly the African Voice for HIV vaccine R&D.

With specific regard to ethics and regulatory issues, Dr D Wassenaar, who is responsible for the AAVP resource center for ethics, law and human rights, presented two useful resources: 1) An ongoing online project mapping all research ethics committees and regulatory authorities in Africa (with rapid uptake also from Latin America) and 2) free, substantive,
online research ethics training resources via the TRREE\textsuperscript{ii} website which hosts a growing number of country-specific modules and a growing number of topical modules. A module on ethical issues in HIV prevention trials is currently being drafted, funded by the UKZN Fogarty MEPI programme.

\textsuperscript{i} \url{http://www.researchethicsweb.org/}
\textsuperscript{ii} \url{http://elearning.trree.org/}
Conclusions and recommendations

The VAC scientific presentations and discussions in this three-day meeting amounted to a comprehensive review of the current HIV vaccine landscape, bringing out both the progress that is being made towards a vaccine, and the barriers obstructing its achievement in the next few years. The following recommendations resulted from these deliberations:

1. Foster international consensus on standards of prevention in HIV vaccine trials, in light of the several recent breakthroughs in biomedical (non-vaccine) prevention research, but in particular oral pre-exposure prophylaxis.

2. Foster international consensus on the relevance for future HIV vaccine trials of the finding of an “immune correlate of risk” during the analysis of the Thai RV14 clinical trial results.

3. Initiate closed interaction with SAGE, submitting an annual report and updates on key developments, such as efficacy results and other breakthroughs. VAC should adopt the approach of JTEG as a template for this interaction.

4. Assist and promote rapid entry of candidates into clinical trials. Develop a more strategic approach to keeping the pipeline filled with innovative products.

5. Help strengthen the capacity of national regulatory authorities and ethical bodies, facilitating the exchange of information between NRAs and ethical groups and supporting international NRA networks such as those who contributed presentations to the Committee. The question of changing standards of prevention will require specific clear guidance to RECs and NRAs.

6. Perform an update of the WHO-UNAIDS Guidelines for HIV Isolation and Characterization Procedures (last updated in 2002) in view of numerous technology innovations over the last 10 years.

7. Initiate consensus-building within the HIV (vaccine?) development "community" on the need for defining international standards to guide HIV vaccine development, including written standards (regulatory guidance) and physical (measurement) standards. Moreover, organize a meeting between the “Quality Standards & Safety” team and.

8. Quickly finalize the draft Adaptive Trial Design document and go forward with its publication in a journal such as AIDS or Vaccine.

9. Continue, for the time being, to monitor global distribution of HIV subtypes, with the results published in a report.

10. Seek collaboration with organizations such as the Global HIV Vaccine Enterprise, in support of a global approach to encounter the challenges of HIV vaccine development.

11. Continue support to the African and Asian HIV vaccine networks, AAVP and AVAN.
12. Develop a coordinated approach on the integration of future HIV vaccines into existing preventive interventions, encouraging working together rather than having each proponent acting individually and seeking individual funding.

13. WHO should continue to assert itself as an important, valuable partner in HIV vaccine development, by demonstrating WHO’s added value and by giving Member States a clear sense of direction, i.e.: WHO firmly believes HIV vaccines are possible and that Member States should be encouraged to invest in them.