The 2010 scientific strategic plan of the Global HIV Vaccine Enterprise

The Council of the Global HIV Vaccine Enterprise[1]

An important moment in HIV vaccine research

HIV/AIDS remains one of humanity's greatest challenges. Since 1981, it has claimed over 25 million lives and is currently responsible for over 2.5 million new infections worldwide each year[1]. Although progress has been made in preventing new HIV infections and in lowering the annual number of AIDS-related deaths through comprehensive prevention programs and increased access to antiretroviral therapy, the number of people living with HIV—now over 33 million—continues to grow[1]. Currently, only two out of five people who need treatment receive it, and even this modest level of progress in treatment is in jeopardy, as the availability of donor funds plateaus or declines[2]. Whereas universal access to treatment is an ambitious goal, the annual accrual of newly infected individuals who require treatment testifies to the urgent need for more effective prevention strategies. Vaccines are the primary public health intervention for dozens of infectious diseases worldwide; they are easy to administer and yield lasting effects. As one of the most powerful tools for preventing infection against other infectious diseases, a safe, effective, accessible HIV vaccine is therefore one of our greatest priorities—and one of science's greatest challenges.

The unique ability of HIV to evade and suppress the immune response, its extraordinary genetic diversity, the properties of its envelope glycoprotein and the ability to establish systemic infection within days and to induce dysfunction and death of the immune cells needed to mount a protective response have posed unprecedented challenges for vaccine development[3]. Nonetheless, although a highly effective HIV vaccine remains elusive, we have never been closer to the target. Among the most visible achievements of the past five years were the results of RV144, the trial conducted in Thailand, that showed that a poxvirus-protein prime-boost combination provided modest (31%) protection against HIV acquisition[4]. These results represent the first-ever demonstration of any level of efficacy in preventing HIV acquisition in humans by a vaccine. Although many questions remain, the results of the RV144 trial have brought renewed energy to the field and created a new lens through which to evaluate future priorities and set strategic directions.

There have been other key advances in HIV vaccine research over the past five years. They include a growing understanding of the role of the mucosa as a barrier to sexually transmitted HIV infection[5], descriptions of the earliest immunological responses in humans after acute HIV infection[6], the demonstration that HIV infection in humans is usually initiated by one or a very small number of founder viruses[7,8], the development of computational algorithms to inform the design of unique mosaic immunogens to address the challenge of viral sequence diversity by achieving maximum epitope coverage while preserving natural antigen expression and processing[9], new insights into the immunological and genetic basis for the ability of some people to control the virus or prevent virus acquisition (so-called 'elite controllers' and 'exposed but uninfected persons', respectively)[10,11], the first proof of substantive simian immunodeficiency virus control by $CD8^+$ effector memory T cells induced through vaccination[12], the isolation of new antibodies with broadly neutralizing activity from HIV-infected subjects[13–15] and appreciation of the possible role of non-neutralizing antibodies in protection[16–18].

Progress in other areas of biomedicine, including the development of faster and cheaper DNA sequencing, high-throughput and computational technologies, will increasingly affect the progress of HIV vaccine research and development. Last, although two large-scale human efficacy trials—STEP and Phambili—failed to confer protection[19], further analysis of these trials has influenced current thinking about the direction of HIV vaccine design, development and clinical evaluation[20,21].

It is now incumbent upon the field to translate the opportunities created by these developments into a safe and effective HIV vaccine suitable for use in populations with markedly different epidemiological, social, genetic and behavioral characteristics. This next stage in HIV vaccine research requires a strengthened global strategy that incorporates current efforts and encourages new and existing partners from high-, low- and middle-income countries to embark on a shared scientific agenda.

The Global HIV Vaccine Enterprise

In 2003, recognizing that a more collaborative global approach was needed to address the scientific and public health challenges of HIV vaccine development, a group of 24 leaders in the field proposed the creation of the Global HIV Vaccine Enterprise[22], an alliance of independent organizations committed to accelerating the development of an HIV vaccine through a shared scientific strategic plan, increased resources and greater collaboration.

The Enterprise Scientific Strategic Plan articulates the commitment of Enterprise partners to work toward aligning relevant aspects of their own strategies and activities with the goal of contributing to the realization of a shared vision. The Plan sets out to define crucial roadblocks and opportunities that would benefit from increased global cooperation, complementing and building on the research

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efforts and discoveries of individual scientists. In so doing, the Plan puts forward priorities and strategic considerations of the Enterprise Council, informed by discussions among Enterprise partners and by the recommendations of the Enterprise Science Committee and its Working Groups.

The Enterprise's first Scientific Strategic Plan[23], published in 2005 and supplemented with two updates[24,25], called for increased collaboration and coordination of partners dedicated to HIV vaccine research and development and identified six priority areas for vaccine development.

The Plan's overall impact was evaluated in 2009 and progress was reviewed on two levels: progress against the six identified priorities (detailed below) and commitment of resources and development of programs that align with the vision of the 2005 Plan (**Table 1**).

Impact of the 2005 Plan: a more collaborative global research environment. The Plan helped encourage dialogue and coordination among funders and scientists and was the impetus for the commitment of new funding for the establishment of collaborative initiatives in priority areas, complementing the essential work of individual investigators (**Table 1**).

Priorities 1 and 2 emphasized the importance of continued investments in discovery research and the need for standardization of laboratory assays. In response, there have been advances in our understanding of virus-host interactions, including characterization of the transmitted viruses derived from recently infected individuals, description of the earliest cellular and humoral responses to HIV infection, isolation of new broadly neutralizing antibodies, greater understanding of the structural motifs of the HIV envelope protein and new insights into mucosal and innate immunity[6,8,13–15,26]. There has also been progress in lab standardization, including greater access to clinical trial specimens for immunological analysis, common reagents and validated assays for studying vaccine responses. These advances have been facilitated in large part by the establishment of the Center for HIV-AIDS Vaccine Immunology (CHAVI) by the US National Institute of Allergy and Infectious Diseases (NIAID) and the Collaboration for AIDS Vaccine Discovery (CAVD) by the Bill & Melinda Gates Foundation as well as key collaborative research initiatives by International AIDS Vaccine Initiative (IAVI), the French National Agency for Research on AIDS (ANRS) and the European Commission.

Priority 3 proposed the establishment of coordinated, dedicated product development and manufacturing capacity to support HIV vaccine trials. This recommendation has largely gone unfulfilled. Production needs have been met through the available global capacity, although no substantive efforts have been made to ensure coordinated access to manufacturing resources.

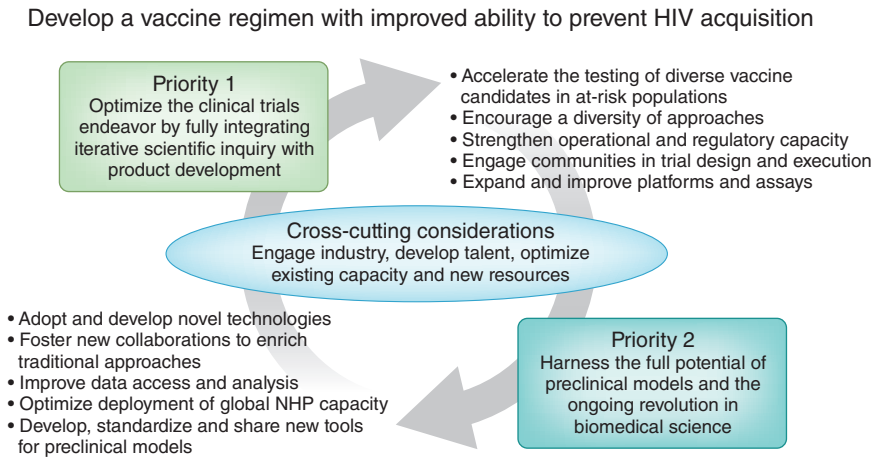

Figure 1 The interconnected priorities and cross-cutting considerations of the Enterprise 2010 Plan.

Priority 4 called for increasing the quantity and quality of sustainable clinical research facilities, and expanding access to well-defined populations at risk of HIV infection. Overall, HIV trial capacity in low- and middle-income countries has improved, with clinical sites supported by many agencies, and the development of research capacity at trial sites has been enabled through different training initiatives. Challenges remain in retaining clinical trials staff, ensuring that working at clinical trial sites remains an attractive career choice and strengthening research capacity in low- and middle-income countries to enable substantive contribution to the HIV vaccine research effort.

Priority 5 called for regulatory capacity building and greater exchange of information needed to facilitate regulatory decision-making and address institutional review board (IRB) issues. Examples of progress include the establishment of the African Vaccine Regulatory Forum to support national regulatory authorities in assessing clinical trial applications, monitoring trials and evaluating clinical data and the publication and subsequent updates of ethical and good participatory practices for biomedical HIV-prevention trials[27,28].

Priority 6 called for an intellectual property framework to stimulate early-stage research by increasing scientific freedom and the sharing of data and reagents. Although the complexity of intellectual property issues necessitates greater effort, progress has been made by NIAID, IAVI and others to support public-private partnerships in HIV vaccine development.

Although the 2005 Plan had a positive impact on the field, three key objectives were not fully reached. First, with notable exceptions, the 2005 Plan had limited success in mobilizing funding from new partners for HIV vaccine research. Second, further effort is required to align clinical research efforts with product development to capitalize fully on the contributions of Enterprise partners to clinical trials infrastructure, regulatory innovation, intellectual property, manufacturing expertise and private sector resources. Finally, the success of Enterprise-inspired collaborative initiatives has helped to highlight gaps that persist, particularly between basic and clinical research, and between the HIV vaccine field and other areas of biomedicine.

Development of the 2010 Plan. In January 2009, the Enterprise Council initiated a process to update the 2005 Plan to reflect the anticipated challenges and opportunities affecting HIV vaccine research over the next five years. The Enterprise Science Committee identified five key areas for discussion: (i) immunogens and antigen processing, (ii) host genetics and viral diversity, (iii) new approaches to HIV vaccine research and development, (iv) bridging the gaps between fundamental, preclinical and clinical research and (v) challenges faced by young and early-career investigators.

The Working Groups formed around each of these five themes prepared reports with recommendations[29–33]. The development of the Enterprise 2010 Scientific Strategic Plan (2010 Plan) was then informed by these reports.

The 2010 Plan's two scientific priorities

Recognizing the importance of pursuing a diverse range of vaccine concepts and approaches, the 2010 Plan prioritizes two main drivers key to the next phase of HIV vaccine

research and development that specifically require global collaboration.

First, the Plan recognizes that clinical trials and human clinical investigation present an unequalled opportunity to obtain important information about the human immune system and its response to vaccine candidates and that they are pivotal to advancing both vaccine discovery and vaccine development. Human efficacy trials are essential to defining the ability of vaccines to prevent infection or disease and for the discovery of vaccine-induced correlates and signatures of protection, which would ultimately accelerate the development or improvement of HIV vaccines for future licensure and public health use. This scientific imperative—made possible by major advances in laboratory and computational techniques that have opened up complex biological systems, including the human immune system, to rigorous and rapid scientific analysis[34]—underpins the importance of clinical efficacy trials to advancing vaccine discovery and development.

Second, the Plan recognizes that trials must be linked to and build upon the tools and concepts of basic biomedical science, including genomics and computational biology, immunology, virology and model systems, to optimize both vaccine design and information on vaccine biology in humans. A strengthened clinical trials effort must therefore be accompanied by sustained, strong support for fundamental vaccine discovery research. In pursuing an increasingly science-driven clinical trials effort, the field will advance promising candidates toward vaccine licensure and, at the same time, contribute fundamental scientific insights that will improve future vaccine design, product development and clinical trials.

The 2010 Plan is therefore predicated on a multidisciplinary approach that bridges the lab and the clinic, entrenching human research as intrinsic to the discovery process, and mobilizing the collaborative efforts of basic, preclinical and clinical scientists in highly iterative vaccine design and testing.

To accelerate the development of a highly efficacious vaccine, two interlinked priorities form the core of the 2010 Plan (**Fig. 1**).

2010 Priority 1: optimize the clinical trials endeavor by fully integrating iterative scientific inquiry with product development. One of the greatest barriers to the design, prioritization and refinement of vaccine concepts is the absence of an established correlate of vaccine-induced protection. Notwithstanding our growing understanding of HIV pathogenesis and immunity, we lack proven immunological markers to guide fully rational vaccine design and predict vaccine protection in humans. Ultimately, the clinical relevance of immunological assays (breadth, depth, kinetics and location) can only be understood in the light of a clear efficacy signal. But beyond the search for a correlate, and beyond the success or failure of a given vaccine candidate, clinical studies produce valuable biological and sociobehavioral data essential to future vaccine development. Trials designed to maximize this learning opportunity will ensure that the contributions and expectations of trial volunteers are effectively translated into improved, more efficient product development efforts.

Therefore, Priority 1 takes the view that clinical efficacy trials should not be perceived as the culmination of a series of basic science experiments but rather as an integral part of the discovery process. To that end, teams of investigators, with complementary scientific, clinical, behavioral and ethical interests and technical skills, must form highly integrated teams to address new concepts in vaccine design and product development. The field would benefit from clinical research consortia where hypotheses are generated, debated and tested, new trial designs that accelerate the research effort are optimized and implemented and multidisciplinary teams dedicate themselves to executing trials that simultaneously advance both discovery and product development objectives. Clinical research consortia that fulfill this dual mandate have the potential to transform clinical trials.

Speedier execution of clinical trials is essential if we are to capitalize on scientific advances, expedite further clinical and laboratory evaluation of promising candidates and drive future vaccine development. Improvements may be achieved by implementing a series of process efficiencies, including accelerating protocol development and funding, facilitating ethical and regulatory approvals, exploring new approaches to trial design and ensuring timely manufacture and availability of 'good manufacturing practice' material. Reducing the timeframe will also require that the field be more nimble about acquiring, analyzing and rapidly sharing laboratory data through advanced planning and by capitalizing on new technologies and widely accessible databases.

Future clinical trials will be shaped by the evolving landscape of the epidemic. Decreasing incidence rates within populations historically at higher risk of HIV exposure will require larger trials, whereas recruitment—which is already a rate-limiting factor in most large-scale trials—may be further slowed by the need to explain increasingly complex trial designs to regulators, policy-makers, communities, potential volunteers and other research stakeholders. Moreover, the results of clinical testing of other prevention strategies, such as microbicides, preexposure prophylaxis or 'test-and-treat' approaches, will become available in the near future (http://www.avac.org/ht/d/sp/i/398/pid/398/). If the results of these trials lead to the implementation of new prevention strategies, vaccine trials may become larger, more complex (for instance, combination prevention studies) and more costly. The vaccine development effort, therefore, must be informed by and informative to other prevention studies to ensure that HIV vaccine research is integrated within the overarching goal of preventing HIV infection and transmission. Social, behavioral and ethical research, as well as a robust community engagement strategy, will increase in importance as the prevention armamentarium embraces new behavioral, biomedical and policy strategies.

Implementing Priority 1 would be accelerated by a coherent global effort to maximize the effective use of resources, infrastructure and

Box 1 Targets for Priority 1

Qualitative targets for achieving the objectives of Priority 1:

- Strengthening existing or creating new clinical research structures that engage basic researchers as crucial partners in the design, execution and analysis of clinical efficacy trials
- Implementing process improvements and exploring new trial design strategies to increase the number, efficiency and speed of clinical trials
- Implementing a robust pipeline of diverse vaccine strategies for testing in innovative human trials (with a focus on phase 2b efficacy trials)
- Ensuring comparability of trial data, regardless of sponsor
- Strengthening global ethical, legal and regulatory frameworks to allow for the efficient conduct of trials
- Maintaining appropriate and flexible research capacity and intensity in high-incidence countries
- Strengthening community engagement to ensure that communities and individual volunteers are engaged as true partners in the clinical trials endeavor, understand the broad goals of trials and are involved throughout trial design and implementation

Box 2 Targets for Priority 2

Qualitative targets for achieving the objectives of Priority 2:

- Developing and rapidly disseminating new technologies applicable to HIV vaccine design and testing
- Creating opportunities for multidisciplinary collaborations with HIV vaccine investigators and scientists from other fields
- Seeking consensus and implementing the principle of rapid sharing of research data within the global research community while ensuring the rights of volunteers
- Developing the necessary infrastructure for depositing, annotating, accessing and analyzing research data
- Developing collaborative programs to maximize the efficient use of resources and to increase the relevance of the NHP modelD
- Promoting research on the earliest events after both vaccination and infection in NHP
- Standardizing protocols, assays and reagents used in NHP research

partnerships throughout all stages of clinical vaccine discovery and development. Six elements should also be considered: trial design, regulatory and operational capacity, community engagement, research platforms, databases for sharing trial data globally and an insistence on pursuing diverse hypotheses. Many of these considerations were identified in the 2005 Plan and remain priorities in the context of a scientifically intensified global HIV vaccine trials endeavor. With a view to advancing iterative, scientifically integrated product development trials that rapidly generate laboratory results and achieve definitive clinical results over a shorter trial horizon, the field should do the following (**Box 1**):

1. Accelerate the clinical testing of promising vaccine candidates while maximizing opportunities to advance scientific discovery. Scientifically coordinated, multidisciplinary clinical research endeavors, with a particular focus on phase 2b efficacy trials, would consist of teams of clinical, preclinical and basic scientists capable of pursuing a hypothesis-driven scientific program in the context of product development efforts that might lead to future licensure; scientifically justified and IRB-approved clinical sampling, extensive lab work and the availability of specimens to address key questions in vaccine immunology; manufacturing of clinical-grade materials for clinical trials, including process development, production and formulation of immunogens and adjuvants; and access to formulations and adjuvants, including those from the private sector, for the testing of combination vaccine regimens. Because these studies may entail a higher cost per trial, available resources will need to be increased, used more efficiently or both. Multidisciplinary teams will therefore be needed to design and implement the most informative trials.

2. Support a diversity of approaches to vaccine research and trial design. A strengthened clinical trials endeavor is predicated on the development, testing and systematic comparison of a diversity of vaccine concepts that explore different mechanisms to achieve effective and sustained protection against HIV. Diversity is best fostered by encouraging new ideas and new players and introducing process improvements so that more trials can be carried out. To reap the full benefit of a diverse clinical trials portfolio, it is crucial, as noted in point 5 below, that data generated in different trials be comparable, regardless of the sponsor.

3. Strengthen regulatory and clinical trial capacity to expedite the review, approval and execution of trials. The field, including national regulatory authorities, UNAIDS and World Health Organization (WHO), should continue to strengthen regional, national and global regulatory processes for trial design ethical review and data analysis to facilitate innovative trials. Integrating scientific discovery and product development objectives should be clearly presented so that the long-term benefits to volunteers and communities are discussed and understood. The establishment and maintenance of trial sites and cohorts should be optimized, with due consideration to the development of sustainable, versatile sites that can be adapted to other health priorities.

4. Engage concerned communities, including volunteers, advocates and community leaders, in the design and implementation of scientifically robust and ethically sound trials. HIV vaccine trials cannot succeed without substantial community engagement, particularly given the need to involve large numbers of healthy volunteers at risk of acquiring HIV. Therefore, as trial design and trial objectives become more complex, it will be important to engage communities in dialogue about the scientific and clinical value of the increased clinical sampling required by discovery-oriented trials and to set realistic expectations with respect to future licensure pathways and access to prevention alternatives. Strengthening the clinical trials endeavor will therefore require a concerted effort to build on existing community advisory efforts to increase participation from the trial design phase throughout the trial life cycle, eliciting the contributions of affected populations in appraising trial conduct and maximizing the value of research for volunteers. It will be especially important to ensure that trial protocols are appropriate, sensitive and well understood, that communities are fully engaged in respectful dialogue about the scientific purpose and expectations of trials, and that communities, nongovernmental organizations, media and policy-makers have the necessary scientific literacy. To this end, we should build on the recent publications containing guidelines and advice on these issues[27,28,35]. Where appropriate, the context-specific frameworks for community engagement that have been developed by WHO and UNAIDS, ANRS, the European & Developing Countries Clinical Trials Partnership (EDCTP), NIAID Human Vaccine Trials Network (HVTN), IAVI, US Military HIV Research Program (MHRP) and others should be adapted. Crucial to community engagement efforts will be the strengthening of local researchers' leadership opportunities and the development of context-specific skills, expertise and tools at the country and local levels.

5. Expand and improve laboratory platforms and assays to analyze immunological responses to vaccination. A robust clinical trials endeavor requires improved method-

Box 3 Targets for industry engagement

Qualitative targets for achieving the cross-cutting consideration on industry engagement:

- Exploring models of collaboration between academia and the private sector that build on precedents from other areas of research and that satisfy the needs of all the partners in the collaboration, including the public
- Achieving a substantial increase in the number of companies (small and large) actively involved in HIV vaccine research and development
- Developing and adopting an intellectual property– and data-sharing framework that balances the needs of industry with the global access principles of the Enterprise

Table 1 Progress of the HIV vaccine field toward the vision set out in the 2005 Scientific Strategic Plan

Element	Progress
Funding	
Encouraging funders to complement and reinforce each other's efforts and provide a framework for bringing in new funders.	• **Increased dialogue and cooperation among funders:** the 2005 Plan encouraged funders to come to the collective table, raising the level of discourse to a broader planning horizon and resulting in several joint initiatives, establishing a precedent and mechanism for greater communication and coordination among existing partners and with new funders in the future. • **Attraction of new funding:** NIH and the Bill and Melinda Gates Foundation provided new funding for the establishment of CHAVI and CAVD; the government of Canada, in partnership with the Bill and Melinda Gates Foundation, pledged new resources toward Plan priorities; the Swiss Vaccine Research Institute was launched; China has launched the Chinese AIDS Vaccine Initiative and Enterprise partners pursued programs aligned with Plan priorities.
People	
Creating a culture of global collaboration and coordination.	• **Promoting collaboration:** collaboration has been accelerated within and between large-scale consortia (CAVD encompasses 103 institutions in 20 countries; CHAVI consists of 43 institutions in nine countries) and increasingly in the field at large. The Canadian HIV Vaccine Initiative, IAVI, the HVTN, the European Commission through Europrise and the EDCTP and WHO-UNAIDS have taken steps to share resources and promote collaboration. Although the field is more collaborative, global efforts would benefit from stronger ties outside North America and Europe, particularly with low- and middle-income countries and emerging scientific and economic powers. • **Developing human capacity:** attracting new talent and strengthening career paths have begun to be addressed through a growing number of training and funding opportunities offered by ANRS, CIHR, NIAID's joint HVTN-CHAVI program and the Wellcome Trust. Efforts must continue in a more concerted manner to ensure that fresh ideas from scientists in low- and middle-income countries are brought into the field and supported.
Processes	
Enabling a meeting of minds to address the major roadblocks to a vaccine and reach consensus on the best path forward.	• **Communication between scientists and funders and alignment of research vision:** the process of developing the 2005 Plan catalyzed a spirit of dialogue between scientists and funders, which has persisted through Enterprise structures and activities. Moreover, there is a broader awareness of unpublished and planned research, reducing unnecessary duplication and creating new opportunities for collaboration. Nonetheless, there is room for more dialogue to ensure that best practices are disseminated, data are shared rapidly and resources and infrastructure are efficiently and effectively used. • **Endorsement of the Enterprise as a collective vision that shepherds the global effort toward development of an effective HIV vaccine:** the 2005 Plan helped establish a common understanding of priorities for the field and enabled the Enterprise to bring together diverse stakeholders for more focused dialogue, for instance around the STEP/Phambili and RV144 trial results. Timely communication of information to the lay public and support of advocacy efforts remain imperative.

ologies for measuring the human immune response, techniques for assessing mucosal and innate immunity after vaccination, and high-throughput assays to develop and verify signatures of protection. As the repertoire of assays used to measure the immune response to vaccination expands and becomes more sophisticated, assay harmonization and standardization, and broad dissemination of laboratory platforms to countries where trials are being conducted will be increasingly important.

2010 Priority 2: harness the full potential of preclinical models and the ongoing revolution in biomedical science. Fundamental questions about the mechanisms that underlie pathways to immune protection and govern vaccine efficacy remain unanswered. We lack basic insights into the nature, quality and quantity of immune responses needed for protection and how to induce them through rationally designed vaccine concepts. Moreover, the field is just beginning to understand the window of opportunity during the first few days of infection, when vaccine-induced immunity might arrest systemic dissemination and the establishment of chronic infection. Detailed insights into these events, especially at mucosal barriers[5,24], are essential to drive the design of preventive vaccines that focus on blocking infection. It is also crucial that we deepen our understanding of the genetic underpinning of the interplay between host defenses and viral evolution that leads to such drastically variable phenotypes as, for example, exposed uninfected, long-term nonprogressors and rapid progressors[36–38]. Fundamental research, driven by an appropriate mix of funding to individual and teams of investigators, will continue to play a major part in HIV vaccine research.

We now have an opportunity to pursue intensive strategies that exploit the potential of model systems and harness ongoing advances from other disciplines of biomedicine to explain clinical phenomena and advance our understanding of the pathways to immunity. Vaccine development would benefit substantially from having access to the best models, technologies and data to answer fundamental questions about the prevention of HIV infection and transmission.

Harnessing advances from other areas of science. Rapid adoption of new ideas and technologies from different areas of science is central to a science-driven clinical trials endeavor, where the potential of research in humans is, in part, defined by available assays and systems and the ease with which specimens and data can be transferred to researchers with relevant expertise. With this in mind, the field should do the following (**Box 2**):

1. Continue to develop and adopt new technologies. The field would benefit from looking outward more in its search for new tools and ideas, embracing technologies and approaches arising from other areas of biomedical research. Examples include imaging technologies for studying mucosal immunity and the trafficking of viral or vaccine antigens and immune effectors, genomic technologies to better understand host factors that regulate the immune response, high-throughput screening methodologies for optimizing vaccine components and vaccination regimens, and new immunogen-design and gene-delivery technologies.

2. Foster collaboration with researchers from disciplines that have the potential to transform current approaches to HIV vaccine discovery and development. For example, systems biology provides a promising approach for the integrative analysis and modeling of large data sets that could drive improvements in vaccine design, vaccine delivery strategies and methods for sustaining responses[39–42]. Globally accessible databases, coupled with the com-

putational power for the systematic analysis of large data sets and for cross-database queries, would greatly facilitate these approaches. Potential mechanisms to promote increased interaction with researchers from other areas of science include funding strategies to encourage researchers to form new multidisciplinary groups around important scientific questions in vaccine design, organizing joint scientific conferences on topics of mutual interest, inviting new investigators into existing collaborative structures and actively encouraging new investigators from other areas of science to enter HIV vaccine research.

3. Seek consensus on the principle of rapid access to data and develop the infrastructure to annotate, deposit and analyze large amounts of data. Data are the foundation of biomedical research. Over the next several years, the amount of data from HIV vaccine research will markedly increase as a result of increases in the number and complexity of trials and the increased application of high-throughput and systems-biology approaches. Realizing the full value of these data requires deployment of the newest computational technologies and rapid data access. Funders, researchers and community representatives need to agree on a shared set of principles for data access and a global approach to develop the necessary infrastructure[43].

Integrating preclinical models. Progress in HIV vaccine research will continue to depend on a variety of preclinical models, in particular nonhuman primate (NHP) and humanized mouse models that can be used to explore new approaches to engineer the immune system and to evaluate vaccine immunogenicity. It is generally accepted that the immune system of NHPs most closely approximates the human immune system and therefore provides an *in vivo* model in which many aspects of virus infection and immunity can be explored. Recently, the NHP field has recognized that repeated low-dose mucosal challenges more closely approximate the mechanisms of sexual transmission of HIV and hence may increase the relevance of the model for HIV vaccine design and testing[44].

We identified two areas of focus for NHP research: enhancing our understanding of viral-host interactions, including virus vulnerabilities to immune effector mechanisms triggered by different vaccine concepts and the relationship between the innate and the adaptive immune responses in viral containment, and dissecting the earliest events after infection at the mucosa, an immunological window that cannot be easily addressed in humans. However, the utility of the NHP model as a translational bridge in HIV vaccine design and development has been limited by the lack of standardized methodologies and the continued use of a variety of challenge models that differ from each other and from the human situation, by the high costs associated with NHP research that have underpowered many studies, and by the relative paucity of shared reagents, tools, technologies and infrastructure to optimize the model and enable closer coordination with clinical studies.

The NHP model cannot serve as a gatekeeper for the advancement of candidates to clinical trials. Nevertheless, the availability of a uniformly accepted model or models would enable the standardized testing and comparison of vaccine concepts to inform hypothesis-driven clinical trials. To capitalize on the potential of the NHP model, the field should do the following (**Box 2**):

1. Make better use of global NHP infrastructure and enhance current capacity to support appropriately powered experiments. As a consensus in the field develops around repeated low-dose challenge studies, larger numbers of animals will be required. This will put additional strain on primate facilities and increase the costs of experiments. Therefore, it will be essential to explore ways of lowering the costs of NHP studies by maximizing the use of available resources and by increasing the level of collaboration, for example by the creation of multidisciplinary consortia.

2. Develop, standardize and share tools and technologies to support NHP studies. The field should strive to develop and use comprehensive standardized *in vitro* and *in vivo* immunological, virological and genomic assays and reagents, as well as mechanisms for sharing data among investigators. Collaborative, multidisciplinary consortia are one way to encourage the standardization and sharing of reagents, protocols and data. Efforts underway in this regard include the European Primate Network, a recent initiative funded under the EU Framework, which aims to bring together researchers and breeding centers to standardize processes and optimize the use of NHP models, and the Institute for Laboratory Animal Research, which is leading the development of an international primate plan, including characterization of NHP genetics and the development of global informatics to share information on animal tissue and diagnostics.

Box 4 Targets for the cross-cutting consideration on people

Show progress in the following:

- Expanding opportunities for active participation and leadership roles by researchers in countries highly affected by the epidemic in the research effort
- Expanding sustainable research partnerships between developing countries and Enterprise members to strengthen institutional capacity and increase the contributions of scientists and clinical personnel from low- and middle-income countries
- Strengthening career development opportunities for young and early-career investigators through appropriate funding programs (such as transitional grants, leadership roles in team and consortia grants and start-up salary support), high-quality mentorship, expanded multidisciplinary training opportunities, conference presentations and leadership, and the creation of an online community for young and early-career investigators

Cross-cutting considerations

Developing a framework that better integrates the clinical trials endeavor with discovery research requires strengthening and/or establishing additional enabling structures and processes. The following three cross-cutting considerations are essential to achieve the field's scientific priorities (**Fig. 1**).

Consideration 1: industry engagement. Industry expertise and resources, including technologies, research platforms, vaccine components and formulations and production capacity are essential to moving promising vaccine candidates from research and development to licensure and distribution. At the same time, publicly funded academic research has focused on upstream discovery and on developing the infrastructure necessary for trials, including trial sites and relationships with volunteer communities. There is, therefore, a clear complementarity of expertise and a compelling public health imperative for industry and academia to explore innovative approaches to collaboration. Despite this complementarity of strengths and shared interests, it has been challenging for industry to justify sustained, upstream, high-risk investment in HIV vaccine research. As a result, these collaborations typically form on an *ad hoc* basis, involve a single company with an academic group and have short-term objectives. The field's challenge and opportunity now is to explore systematic, strategic approaches that maximize the scientific value of such partnerships, minimize risk for industry, and allow

for more open, nonexclusive arrangements, especially for precompetitive areas of research. The urgency and opportunity, together with the risks and cost of HIV vaccine research, require that we explore the following multipronged strategy to strengthen partnerships and engagement with industry (**Box 3**):

1. Explore innovative models for collaborations with pharmaceutical and biotechnology companies, public funders and researchers. The field should explore innovative models of partnership that build on either existing arrangements in the health and other sectors or new collaborative models specific for HIV vaccine development. For example, IAVI, in partnership with the Bill and Melinda Gates Foundation, has established an Innovation Fund that proactively surveys the commercial biotech universe to identify and finance innovative technologies offering the potential for breakthroughs in HIV vaccine discovery and development.

2. Develop working arrangements to protect intellectual property while ensuring maximum public benefit. With the multidisciplinary product development endeavor proposed in the 2010 Plan, there is urgency in developing a globally accepted intellectual property framework that supports open practices and the freedom to operate while judiciously protecting industry interests. As articulated in the 2005 Plan, the field should explore new mechanisms of sharing the results of precompetitive research while safeguarding the intellectual property of industry partners and protecting further downstream discoveries and at the same time working to ensure that future vaccines are available to all populations in need. There is an increasing number of examples of innovative public-private partnerships that could be looked at as starting points for discussion. In addition, Enterprise members should consider committing to principles such as the recent Statement of Principles and Strategies for the Equitable Dissemination of Medical Technologies (http://www.autm.net/source/Endorsement/) endorsed by the NIH and over a dozen major universities and, where possible, should improve and harmonize material transfer agreements and develop grant terms that mandate the sharing of resources.

Consideration 2: people. The path forward will rely heavily on the application of new and diverse approaches to build a vaccine pipeline driven by multidisciplinary clinical and scientific investigation. This long-term effort must be sustained by reinforcing current research and development efforts with fresh talent, including individuals from areas most affected by the epidemic and from early-career investigators who bring fresh perspectives, enthusiasm and creativity. To attract the brightest minds to the field and provide them with the training and support needed to cross disciplines and platforms to navigate basic, preclinical and clinical domains, the field should do the following (**Box 4**):

1. Establish, support and sustain global research excellence. The global clinical research effort requires a strategic commitment to developing and sustaining talent in low- and middle-income countries by expanding training opportunities, providing mentorship (locally and globally, and in clinical and basic research domains), ensuring protected research time and salary support for basic and preclinical researchers and clinician-scientists pursuing independent research programs, developing attractive career pathways for clinical trial staff, and providing opportunities for meaningful contribution and leadership within the global research effort. To this end, the imminent relocation of the African AIDS Vaccine Partnership offices to Africa provides an opportunity to further mobilize efforts across the African continent. Similarly, the AIDS Vaccine for Asia Network is providing a facilitative mechanism for strengthening and coordinating vaccine research and development activities in Asia. Building on the programs of EDCTP, IAVI, the Wellcome Trust, the NIH Fogarty International Center and individual academic institutions, capacity building would benefit from coupling local financial and organizational contributions from host country governments with sustainable funding commitments from development agencies and international partners. Moreover, emerging scientific and economic powers where HIV is a public health concern have an important stake in the HIV vaccine research effort and should be actively encouraged to contribute their knowledge-based workforces and scientific resources to the goals of the Enterprise.

2. Attract and mentor young and early-career investigators. Despite their importance to progress in science, young and early-career investigators in both developed and developing countries face serious obstacles to establishing their careers, securing independent funding, developing multidisciplinary expertise and achieving visibility and recognition, particularly in the context of large collaborative initiatives. Strategies are needed to strengthen and clarify career paths for early-career investigators through mentorship, training and leadership opportunities and to increase the availability of funds to pursue unique approaches to vaccine research.

3. Develop and sustain strong institutional capacity. Scientific and medical personnel from low- and middle-income countries face special challenges. To retain highly trained professionals and enable them to make maximal use of their expertise, strong scientific and healthcare institutions are essential. Without strong institutions, individual capacity building will result in the emigration of highly qualified personnel from the countries that need them most. Aid and scientific agencies have an opportunity to expand current efforts to build long-term partnerships with countries and institutions in low- and middle-income countries to develop the institutional support that is a necessary element for both HIV vaccine research and capacity development more broadly.

Consideration 3: funding and resources. The current global level of funding for HIV vaccine research (about $850 million in 2008) is a substantial sum[45]. However, when placed in the context of the financial response to the global epidemic that has reached tens of billions of dollars annually, it represents a comparatively small investment of global AIDS resources. If we are to bring the epidemic under control and mitigate the burden of this disease, we must sustain and fortify our quest for a vaccine.

The 2010 Plan puts forward an ambitious program of research and development. Clinical trials are expensive, especially the large, scientifically rich efficacy trials called for in the 2010 Plan. Moreover, a strengthened clinical trials endeavor that includes a marked increase in the number and complexity of clinical efficacy trials will require a major increase in support. The 2010 Plan recognizes that resources are scarce and that most financial commitments have been made by a handful of organizations[45]. Therefore, a first priority must be to ensure that existing resources are prioritized, sustained and optimized. However, it is unlikely that more efficient use of current resources will be suf-

Box 5 Targets for cross-cutting consideration on funding and resources

Show progress in the following:

- Improving the use, prioritization and sharing of global research resources
- Mobilizing new funders and new investments in HIV vaccine research and development that align with the 2010 Plan

ficient to achieve the priorities and targets laid out in the 2010 Plan. Rather, new sources of investment are needed to exploit recent scientific progress and to match the world's investments in HIV vaccine research with the urgency, size and cost of the epidemic. To this end, it will be important to do the following (**Box 5**):

1. Use existing resources more efficiently through increased coordination and sharing of global capacity and expertise. Having taken major steps over the past few years toward coordinated HIV vaccine research efforts, the field must now take stock of available resources (facilities, platforms and policies) across the globe to harness their full potential, avoid redundant investments and foster a more coordinated research effort. For instance, the field should ensure that the contributions of volunteers in cohort studies and clinical trials are maximized by the efficient use and sharing of existing resources (for example, clinical trials sites) before developing new ones. Similarly, the sharing of high-quality primate facilities around the world should be maximized. Enterprise partners should work together to identify and facilitate opportunities for cost sharing.

2. Diversify and increase funds. Implementing the Priorities and Cross-cutting Considerations in the 2010 Plan requires new investments. Only a small number of funding organizations provide the majority of funds devoted to HIV vaccine research[43]. This situation is less than desirable for the following reasons: first, relying so heavily on a small number of funding partners places the global HIV vaccine research agenda at risk if even one of those funders changes priorities or cuts back their investments; second, it compromises a priority articulated in the Plan for a diversity of approaches to vaccine development; and third, it limits the possibility of new funds if the same small number of funders are repeatedly asked to invest more. Put simply, the global HIV/AIDS challenge requires a global effort that is commensurate with the size of the challenge. Therefore, Enterprise partners should articulate an implementation strategy that makes it clear for other organizations where new investment and expertise is needed.

Conclusions and next steps

The creation of the Global HIV Vaccine Enterprise and its emphasis on a shared Scientific Strategic Plan represents an unprecedented response by the international scientific community to the scientific, public health and humanitarian challenges posed by HIV/AIDS. Enterprise stakeholders have a shared commitment to fulfill three essential functions: conducting regular assessments of scientific priorities and updating them to reflect lessons learned, new opportunities and the influence of new scientific findings and new technologies, establishing global processes to address priority areas and establishing a culture of mutual accountability for effective implementation of the Plan by funders and investigators. These commitments remain imperative to the fulfillment of the 2010 Plan in driving progress in the field.

Over the past 18 months, major scientific advances have signaled the beginning of an important new phase in HIV vaccine research. At the same time, there is increasing evidence that the epidemic is in danger of spinning out of control[46]. It is our collective responsibility to ensure that this moment is not lost. Continued progress in the field urgently requires that funders, aid agencies, researchers, industry, regulatory agencies, advocates and civil society commit to working together as an open and collaborative global community. Until a deployable, efficacious vaccine is developed, that objective will be the only and ultimate goal of the Global HIV Vaccine Enterprise.

Note: Opinions reflected in this manuscript do not necessarily reflect the official policies of the agencies represented by Council members.

ACKNOWLEDGMENTS

The 2010 Scientific Strategic Plan of the Global HIV Vaccine Enterprise was developed through a broad process of consultation. Thanks are given to the co-chairs of the various Enterprise Working Groups (A. Aderem, B. Autran, D. Barouch, L. Corey, R. King, J. Mascola, F. McCutchan, A. McMichael, T. Ndung'u, L. Picker, B. Pulendran, R. Rappuoli and R. Steinman), to Working Group members and to the Enterprise Science Committee for their invaluable insights and recommendations that have informed the development of this document. R. Lackman, R. Wiley and B. Snow provided much appreciated assistance and advice. Special thanks to A. Manrique and Y. Voronin for their invaluable support, input and suggestions at all stages during the process of developing the Plan.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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