Global HIV Vaccine Enterprise
IAS

Global HIV Vaccine Enterprise

Annual Stakeholders' meeting

Meeting report

Accelerating early-phase HIV vaccine clinical research

17 November 2022

Meeting Report - 19 December 2022

roger tatoud IAS Consultant

Background

Biomedical prevention interventions have helped reduce the number of new HIV aquisitions and are saving lives. However, a decline in HIV incidence remains far from the 95-95-95 UNAIDS target.

A safe and effective HIV vaccine remains a necessity to achieve durable control and an end to the HIV pandemic.

Although there are only two vaccine efficacy studies ongoing, there is a rich pipeline of promising products, platforms and strategies for the development of an HIV vaccine.

However, progressing products on the development path remains a slow process marred by operational, clinical and funding challenges.

There is a particular need to accelerate clinical testing of promising products and platforms currently at a preclinical stage of development. Concurrently, new clinical testing strategies, such as experimental medicine, offer opportunities for speeded-up iterative product testing.

The Global HIV Vaccine Enterprise at IAS – the International AIDS Society – is in a unique position to bring together the scientific community with other stakeholders involved in HIV vaccine R&D to explore how to accelerate early clinical research for products and platforms.

Consistent with its strategic objectives, the Enterprise convened HIV vaccine research and development (R&D) stakeholders with the aim of building a consensus on efficient ways to prioritize and advance vaccine product development that encompasses design, clinical testing and funding to accelerate the development of an HIV vaccine.

Agenda

4:00-4:02 PM	**Welcome** – Elena Moreno, Senior Project Manager, IAS, Switzerland
4:02-4:05 PM	**Opening** – **Susan Buchbinder**, Vaccine Enterprise Advisory Group Chair – Bridge HIV at the San Francisco Department of Public Health, USA
4:05-4:20 PM	**An overview of the pipeline of products ready to enter, or already in, early-phase clinical testing** Kundai Chinyenze – IAVI, Kenya
4:20-4:35 PM	**Promises and challenges of new early-stage clinical testing strategies** Bart Haynes – Duke University, USA
4:35-4:45 PM	**HIV vaccine R&D in context – A community perspective: Who needs an HIV vaccine when long-acting PrEP is around the corner?** Maureen Luba – Cooper Smith, Malawi
4:45-5:25 PM	**Panel 1 discussion: What will it take to test an array of strategies simultaneously to pursue answers and accelerate timelines?** • Chair: Gavin Churchyard – Aurum, South Africa • Bart Haynes – Duke University, USA • Glenda Gray – South African Medical Research Council (SAMRC) • Jim Kublin – HVTN, USA • Johan Vekemans – IAVI, USA • Nandi Luthuli – AVAC, South Africa • Yves Levy – VRI, France
5:25-6:00 PM	**Split rooms**

	Room 1	Room 2	Room 3
Facilitator	Gabriella Scarlatti	Jim Kublin	Linda-Gail Bekker
Rapporteur	Susan Barnett	Sandhya Vasan	William Kilembe
	Prioritization of products, platforms and strategies informed by science	**Design of iterative processes and studies to progress product development**	**Infrastructure and mechanisms to accelerate iterative clinical research**

6:00-6:15 PM	**Break**
6:15-7:00 PM	**Report back and open guided discussion** Facilitator: Roger Tatoud – IAS consultant
7:00-7:55 PM	**Panel 2 Discussion: Supporting changing research approaches to accelerate early-phase HIV vaccine R&D** • Chair: Stacey Hannah – AVAC, USA • Carl Dieffenbach – NIAID, USA • Carey Hwang – Vir Biotechnology, USA • Margaret McCluskey – USAID, USA • Pervin Anklesaria – BMGF, USA • Roger Le Grand – CEA, France
7:55-8:00 PM	**Closing and what's next** - Susan Buchbinder

Introduction to the meeting

Susan Buchbinder

This is an exciting time in HIV vaccine research. There are new tools, such as mRNA, that can accelerate our ability to iterate product testing faster and a robust scientific agenda with hypotheses about how best to create vaccines that will generate broadly neutralizing antibodies (bnAbs), as well as T-cell-based vaccines.

However, the field is facing operational, regulatory, clinical and funding challenges that can slow the pace of HIV vaccine R&D. The Global HIV Vaccine Enterprise convened this stakeholders' meeting to identify and address some of these challenges and help chart a path forward for accelerating the experimental medicine portfolio of studies.

The audience of this meeting is broad and diverse. The format is to facilitate a productive discussion on how to accelerate HIV vaccine R&D, how to ensure that the most promising approaches move forward swiftly, and how to identify and address the biggest challenges the field is facing in achieving these goals.

Presentations

00:03:56-**An overview of the pipeline of products ready to enter, or already in, early-phase clinical testing. Kundai Chinyenze** – IAVI, Kenya

00:20:09-**Promises and challenges of new early-stage clinical testing strategies. Barton Haynes** – Duke University, USA

00:35:34-**Who needs an HIV vaccine when long-acting PrEP is around the corner? Maureen Luba** – Cooper Smith, Malawi

Panel discussion 1: What will it take to test an array of strategies simultaneously to pursue answers and accelerate timelines?

Opening, Gavin Churchyard

The rapidly changing HIV prevention landscape is making stakeholders rethink how HIV vaccine R&D is being done with respect to product development, clinical testing and capacity building. New strategies and platforms are being developed, particularly the mRNA platform that allows to accelerate the development of HIV vaccines. The question is, therefore: what will it take to test these strategies to pursue answers and accelerate timelines?

Barton Haynes discussed the benefits and limitations of the mRNA platform. Using protein-based immunogens takes too long compared with mRNA. Data shows that mRNA may be better based on their processing and that of the protein they encode intracellularly before being expressed on the surface of cells. mRNA may also be better for selecting rare mutations, particularly those that are needed for binding to the protein glycans. The problem is that the LNP, the cationic ionizable nanoparticle,

is part of the "magic" of the mRNA. These are very good adjuvants inducing a high level of IL-6 and other chemokines, but in higher doses, they can be reactogenic, which raises the issues of side-effects. There are also rare anaphylactic reactions thought to be related to the polyethylene glycol (PEG) used in the LNP. However, COVID-19 vaccines have been given to billions of people and their safety profile remains acceptable, which is encouraging for HIV vaccines.

Jim Kublin raised the operational challenges of clinical trial designs to iterate clinical testing more quickly. Defining the most strategic and effective designs for getting the laboratory analyses out of these clinical trials is needed to make tactical decisions to move forward with the next study. For example, it could be that a multivalent vaccine targeting the MPER region, CD4 binding site and V2/V3 loop would be required. Optimizing each of these components will require work on each individually before they can be combined into a multivalent functional antibody immunization strategy. Current trial designs are focused on individual antigens and getting the clinical trials launched and implemented as quickly as possible. Laboratory assays and data analysis must be completed as quickly as possible to make critical decisions about moving forward with the next iterative study. To manage its portfolio of experimental medicine trials, HVTN has looked at how to best optimize each step of its operations.

Johan Vekemans described how experimental medicine can contribute to product development, with long-term perspectives. With the goal in mind, it is important to understand the complexity of the undertaking on the one hand and end users' expectations on the other. IAVI has been thinking about its operational pathway to ensure that there are clinical trial avenues to support rapid progress of iterative trials. It is important to be very transparent with affected communities, those considering hosting a trial and trial volunteers, and to communicate that this is a lengthy upstream research process. Initial investigations focus on science generation, not on meeting licensure expectations. Creating a consensus with regulators that allows for the rapid iteration of clinical trials is also extremely important. It is possible to create a clinical trial platform with an overarching study protocol that can host the modular introduction of individual immunogens or the testing of immunization schedules changes in a way that will accelerate decision making and implementation of new trials. This will avoid having to go through lengthy reviews each time a new immunogen is tested or there is a change in a study schedule. COVID-19 has shown that with political will and the ability to change our ways of working, there is clearly capacity to accelerate clinical research.

Glenda Gray shared her perspectives on some of the regulatory challenges with doing experimental medicine trials. Discussion to reach a consensus with the regulators is necessary because we have to decide how much preclinical work, including animal studies, is required before conducting first-in-human studies and whether a generic approach to certain platforms that do not require each product to go through preclinical testing is possible. Some of the issues are around overall toxicity and the type of immunogenicity needed. Adjuvant studies with proteins are also relevant to the mRNA approach as they are critical to direct the immune response in certain ways.

Gray said that we have to identify bottlenecks and gaps in protein manufacturing to speed up the process. There is also a need to speed up recruitment of trial participants. Overall, we should look at all the bottlenecks and find ways that give the regulators and ethics committees comfort to advance into human studies with minimal preclinical data. Gray stressed the importance of involving sub-Saharan Africa, which has experience of the burden of the disease and of recruiting participants and where there is an appetite to speed up the research. All areas from discovery to application should be looked at to get rid of all the wastage we currently see.

Gray also pointed to the need to think about vertical transmission and the work done with Barton Haynes looking at inducing bnAbs in babies to prevent breast-milk transmission. This may be relevant to the advancement of the research.

Nandi Luthuli spoke about the key partnerships that will accelerate early phases of clinical trials. Bringing communities along in the journey is fundamental. Research literacy has supported communities' understanding of the importance of the research and how to engage in the research. Currently, implementation research is taking place at the same time as experimental medicine. This is an opportunity to discuss how products get approved, implemented and rolled out. It is not only about what the trial is about or what kind of study one can join, but also the trade-offs between being in a study and being given the opportunity to access a proven product. As much as we need an HIV prevention vaccine, researchers should understand that communities are grappling with the idea of accessing prevention tools here and now. It is crucial to involve and work with the community, civil society and advocates to inform them of how we move forward.

Yves Levy discussed the requirements to accelerate early-phase clinical trials as there are now multiple strategies and candidate vaccines. There is a need for go/no-go criteria based on practical studies to move products and strategies forward, as well as a generic protocol and laboratory assays to inform decisions to discard or select products. Good progress has been made in evaluating the immune response and tracking what we want from the immune response. Problems remain with the multiplicity of candidates, the design of studies, go/no-go criteria and the manufacture of products. Defining the iterative process to select and test different combinations is critical. Currently, different candidates are tested separately although there would be a benefit in doing combination and comparative studies, which is possible by pulling in resources.

Questions from the audience

- *RNA vaccines, in addition to having an adjuvant effect, have the property of delivering proteins in a more prolonged manner. Is this property, which mimics natural infection, necessary for the induction of broadly neutralizing antibodies?*

Haynes responded by saying that the adjuvant effect is one component of the answer, but mRNA processing is also important. mRNA appears to be better at selecting for the right kind of mutations and at giving rise to antibodies that can

either bind completely to glycans or bind to glycans and the polypeptide backbone. It may be possible that glycosylations differ between RNA processed within cells and RNA given to an individual.

- *Most of the Phase 1 studies are conducted in the US. Good clinical trial infrastructure exists in Africa, which also bears the burden of disease. Should more studies be conducted in Africa and other continents?*

Gray said that discussions with communities and regulators are needed to debate the rationale for doing, or not doing, first-in-human studies or experimental medicine studies in high-burden countries. South Africa has done vertical transmission studies before doing studies in adults. It is necessary to engage with regulators, communities and ethics committees to address concerns about first-in-human trials in certain parts of the world. In the past, it might have been imperialism or neo-colonialism or fear that there was experimentation on more vulnerable people. It is important to find out about today's barriers to conducting these trials in places where they would not have been done first; this is not the case in South Africa because these studies have already been done successfully.

Beatriz Grinsztejn said that it is important to put Latin America back on the map. There is good local capacity to conduct clinical studies and there is also a high incidence in very vulnerable populations (trans women).

- *What are the opportunities for local manufacturing?*

Haynes said that there are many big challenges to manufacturing products locally, including the supply of raw materials. In addition, the necessity for toxicity studies and other regulatory requirements, which are farmed out and take time, could lead to severe delays (there is a saturation). Duke University is committed to global access and has shared mRNA know-how with Afrigen in South Africa, for example. Not-for-profit hubs have also been created to conduct the work collaboratively. It is important to share knowledge to get a robust local production up and going.

Gray agreed that manufacturing is a major obstacle, and that in-house production may be needed to get around delays, which are major hurdles, to iterate faster.

Levy said that discussions with regulators, like those for COVID-19 where the same platform was used but only the insert changed, would accelerate research. However, he added that the regulators may not yet be ready to follow the same path with HIV vaccines.

Vekemans commented that product development has to be considered from an end-to-end perspective. It is not just about manufacturing and access to products, but also about creating an environment that is supportive of vaccine development capacity, from discovery to access. It's very good that there is an expanding platform of mRNA technologies, but there is a very low number of players that can provide access to their technology for research. It would be much better to have a broader panel of accessible platforms in the future.

- *How do we address IP issues affecting technology transfer?*

Kublin said that it is critical to engage with industry and demonstrate the potential of bnAbs via passive immunization, as well as providing concrete evidence of how their induction can be accomplished via active immunization. Moderna and BioNtech have talked about how they can be engaged individually as production entities. If there are IP issues that are critical to protect there should be incentives for these partners to be engaged with academics in anticipating production scale up, even for Phase 2- and 3-type studies that are hopefully coming in the not-too-distant future. This is a complicated negotiation about technology transfer and agreements if we are serious about transferring some of this technology to the countries most impacted by the HIV pandemic. Many of the people who attended this meeting are committed to ensuring that this happens.

Breakout room and rapporteurs' summary

	Room 1	Room 2	Room 3
Topic	Prioritization of products, platforms and strategies informed by science	Design of iterative processes and studies to progress product development	Infrastructure and mechanisms to accelerate iterative clinical research
Facilitator	Gabriella Scarlatti	Jim Kublin	Linda-Gail Bekker
Rapporteur	Susan Barnett	Sandy Vasan	William Kilembe

Room 1: Prioritization of products, platforms and strategies informed by science

- Good science is critical to motivate industry's engagement in HIV vaccine R&D and for non-industry researchers to deliver on the best HIV vaccine approaches.
- Build on learnings from decades of HIV R&D and develop multiple approaches, besides bnAbs and Tier 2 neutralization.
- Consider comprehensive approaches that include both B- and T-cell responses, as well as innate immunity.
- Exploit biomarkers defined by previous proof-of-concept trials in humans.
- Take a more industrial approach to move concepts along the clinical path, including strict go/no-go criteria for advancing products from early clinical trials through clinical development.
- Adopt a mindset where bad vaccine concepts that have low probability of success are discarded earlier rather than later.
- Take the totality of the data, preclinical and clinical data, and optimize the clinical models we have at our disposal to down-select the most promising approaches.
- Be very critical of ourselves along the product development pathway.

Room 2: Design of iterative processes and studies to progress product development

- Conduct experimental medicine and first-in-human trials in low- and middle-income countries.
- Educate regulators in different countries about new concepts so that these are better received when submitted for approval.
- Rely more on standardized adaptive trials wherever possible to minimize the time required to approve new protocol development and allow for plugging of experimental products into the same platform. Use of similar backbone may help speed up approval, keeping in mind that switching pathogens may require additional studies (for example, from COVID-19 to HIV).
- Develop and agree on common safety standards to facilitate approval, especially when using the same platform with different inserts.
- Develop volunteer registries to facilitate and speed up recruitment and enrolment.
- Open Phase I trials to participants who are not at low risk of HIV acquisition, keeping in mind the potential impact of VISP.
- Develop capacity for laboratory assays globally and a commonality of assays to allow comparison between different trials. However, some experimental medicine trials may require specific assays and, therefore, capacity building may have to be prioritized. The value of conducting trials in two countries may remain due to the complexity of the assays.
- Expand local manufacturing capacity, especially for mRNA, with the caveat that there is no guarantee of quality for the protein.

Room 3: Infrastructure and mechanisms to accelerate iterative clinical research

- Implement learnings from the COVID-19 experience, especially the three Cs: communication, coordination and collaboration.
- De-risk HIV vaccine R&D with a well-thought-out pipeline for product development, manufacture, scale up and IP management.
- Give all strategies and products equal attention.
- Test candidate vaccines simultaneously. There should be more basic immunology and a better understanding of HIV immune responses.
- Develop platforms and frameworks to ensure that data and information are shared to accelerate regulatory approvals and strategic decision making.
- Explore the potential of using common DSMB, endpoints, correlates of protection and inclusion/exclusion criteria from the outset.
- Broaden inclusion in studies to different key populations to facilitate vaccine development and enable the comparison of datasets from different areas.
- Engage and involve community stakeholders from an early stage and develop new and better approaches to community engagement and involvement right from the design stage of clinical trials.
- Increase collaboration across different regions.
- Enhance capacity building for laboratory science, particularly where the burden of the epidemic is highest.
- Build consensus around the characteristics of the desired vaccine to allow everyone to work towards that goal.
- Develop strategic plans and roadmaps. These should be housed at the Global HIV Vaccine Enterprise.

- Proactively engage with the industry. The Enterprise should initiate engagement and educational activities with industry to anticipate barriers to engagement.

Group discussion

The following topics were discussed:

- **Sustainable funding**

Roger Le Grand raised the issue of sustainable funding for HIV vaccine R&D, at least for European researchers. Strong advocacy is needed to raise politicians' awareness that the current short-term EU funding strategy is not suitable for the conducting of the research.

- **Learning from COVID-19**

Le Grand emphasized the need to learn from COVID-19 vaccine R&D. Many of the successful COVID-19 vaccine platforms have been de-risked by academics or small biotechs conducting HIV vaccine R&D. HIV vaccine R&D provided innovation, and academic research brought these products up to pre-industrial levels. This means that many things have been de-risked because there were preclinical, toxicology and clinical trials done with these platforms and the bioproduction processes had already been improved. We should improve the capacity for a very agile and organized R&D pipeline, from antigen design to production of vaccine products accessible to academics rapidly. This is a matter of technology, science and management and organization. Readily available contracts and agreements will facilitate moving quickly from the preclinical to the clinical stage and, supported by bioproduction systems, into clinical trials. It is necessary to engage sooner with private companies. If the industry can be convinced that its investment in very challenging vaccines will benefit the development of other types of vaccines, then it may see a return in the development of vaccine platforms for different purposes.

- **Go/no-go criteria**

John Hural said it may be difficult to establish go/no-go criteria. Measures of success may not translate into standardized go/no-go criteria for different studies with different primary objectives. For example, B-cell immunogen studies may have to induce a specific germline as primary objective, other studies may need to drive a specific lineage or to induce neutralizing responses. Therefore, the go/no-go criteria have to be tailored to the specific product or regimen.

Susan Barnett agreed that this is true from a trial perspective, but questioned whether it is possible at portfolio level for go/no-go criteria to be driven by the knowledge of the breadth and potency of the antibodies that the approach is trying to induce by vaccination.

Yves Levy said that a vaccine candidate should not be discarded because it does not induce a response it was not designed to induce and is induced by other candidates. Since we do not know what the correlates of protection are, should we discard a vaccine that induces T-cell responses and anti-V1V2 antibodies and not

neutralizing antibodies (Tier 2)? Levy said that after the failure of the Step trial, it was said that we should return to hypothesis-driven and proof-of-concept studies and capitalize on promising research of the past and try to reproduce it.

Jim Kublin said that parallel programmes are focused on the induction of bnAbs through different approaches and we are getting to a point where some agreement on what go/no-go criteria could be used for moving products forward. There is also synergy to be gained from both passive and active immunization strategies that will inform what level of bnAbs, induced through various pathways, is required to prevent HIV acquisition.

- **Capacity building**

Linda-Gail Bekker said that it is possible to overcome the "mythological" thinking that clinical trials cannot happen in low- and middle-income countries where, typically, basic science is not necessarily happening or because it is not acceptable. Taking the science, there is one way to overcome this and it is already appening with the mRNA technology being transferred to Afrigen in South Africa. It is important to do this urgently as it will facilitate increasing manufacturing capability, improve clinical trial acceptance and improve the acceptability of new products in many parts of the world.

Hural said that capacity building is also required in high-income countries where there is a saturation of laboratories, with several clinical studies running concurrently. It is important to be able to conduct assays in real time for a fast iterative process.

Legrand added that there is a bottleneck in bioproduction, preventing going into trial faster. Also, the capacity to produce different types of experimental vaccines must be improved, which is challenging.

Stacey Hannah briefly described the Matrix project funded by USAID to advance the R&D of innovative HIV prevention products for women. The ProJet is testing the next generation of PrEP products in parallel in sub–Saharan Africa and the global North. There is a growing body of first-in-human trials taking place outside of the US or the global North. The first trial will start in 2023 and most of the portfolio is in preclinical stages, but thinking is ongoing on how to prioritize products.

Katrina Pollock described the public and participant involvement and engagement activities conducted by the Lymph Node Single-Cell Genomics Ancestry (LEGACY) Network, a collaboration between the University of Oxford, Imperial College London and the UVRI, in the UK and Uganda. Engagement in the design stage was particularly successful. Finding out from people willing to participate in the research what they expected from it contributed to a design that met their needs. Feedback was very important for the recruitment of participants and the sustainability of research programmes in those areas.

- **Strategic plans and roadmaps**

Pervin Anklesaria suggested creating a roadmap to help guide vaccine research. The roadmap should prioritize key approaches eliciting bnAbs and cellular CD8 T-cells currently being tested. Other promising immunization strategies that combine strategies that elicit cellular and humoral (bnAb) responses should be tested. Resources are not infinite, and with other biomedical prevention options now available or soon to be available, conducting efficacy studies will require creative clinical study designs, which should be discussed early to gain acceptance by regulators and community members.

Roger Tatoud reported on a recent meeting of European stakeholders, including EU funders, where it was said that funding for HIV vaccine research will benefit from having a roadmap to ensure that requests for funding are aligned with a global plan.

Bill Snow said that making a strategic plan agreeable to the whole field is time-consuming and that science is often moving faster than committees. We are at a juncture where it makes sense to have some broader discussions about the big picture, but Snow was not sure how to do this effectively and efficiently.

Vekemans said a plan is necessary and possible. Go/no-go criteria may be detracting from the fact that some decisions are somewhat qualitative. Articulating turning points, key assays and milestones would bring visibility and help create a consensus between stakeholders that should engage in collaborative work. This will also support sustainable funding, discussions with regulators and engagement with industry. A strategic plan should indicate avenues for product combinations, how to host an increasing complexity in a first stage and then how to simplify a product development pathway.

- **Intellectual property**

Tatoud raised the question of intellectual property and how it has been and remains a barrier to technology transfer and local manufacture for COVID-19 vaccines. He asked what the role of the scientific community and community stakeholders is to ensure that IP does not get in the way of research moving forward faster.

Carey Hwang said IP is the difficult part and that it always takes a lot of time to put the necessary agreements together. Voluntary licencing and other strategies are being developed. Hanke said that companies have their own agendas, which are not always compatible with HIV R&D, and that he had a rather negative experience in this area.

Panel 2 - Supporting changing research approaches to accelerate early-phase HIV vaccine R&D

Overview of funder perspectives and directions

- Carl Dieffenbach – NIAID

The NIH remains wholly committed to the development of a safe, effective and durable HIV vaccine. The two major remaining challenges in the HIV field are a vaccine and a cure; some interesting activities are under investigation, including bnAbs. Now is the time for the field to step back and reassess where we are. The NIH supports high-priority investigator-initiated and other forms of studies that it solicits for HIV vaccines and cures.

- Carey Hwang, Vir Biotechnology

Vir Biotechnology is an immunology biotech focused on immunology platforms to treat and prevent serious infectious diseases. The company works with the Bill & Melinda Gates Foundation (BMGF), the HVTN and other funders to facilitate the development of its CMV-HIV vaccine programme. Initial data from the VIR-1111 trial were recently presented at the 2022 CAVD meeting, and additional trials are planned for that platform. Partnerships are critical to move programmes forward and leverage the expertise of the different partners. Hwang is Co-Chair of the IAS Corporate Partnership Programme HIV Vaccine Industry Partnership with Linda-Gail Bekker; the newly formed group is engaging different parts of industry, including diagnostics, manufacturing and traditional types of pharmaceutical companies, to facilitate this work going forward. The HIV Vaccine Industry Partnership was recently launched, and a first event on biomarkers of vaccine efficacy took place on 15 November 2022.

- Margaret McCluskey, USAID

USAID has been working in the HIV vaccine space since 2001 with valued partners, such as IAVI for research and AVAC for advocacy and communication. USAID does not generally invest in basic research and development, although the agency has been investing for years in the contraception, microbicides, malaria vaccine and HIV vaccine spaces. The mission of USAID is to build a world that is safer, healthier and more prosperous for people everywhere. In the R&D space, the agency invests in people and product development. USAID recognizes the importance of traditional partners, including those that are based in the United States, but the agency is shifting towards non-traditional, underutilized local partners with whom it is eager to engage.

- Pervin Anklesaria, BMGF

The BMGF has an end-to-end strategy to accelerate the reduction of HIV incidence. A highly efficacious and durable HIV vaccine will have an important role in reducing the overall incidence. Learnings from past clinical studies indicate that an HIV vaccine will require a potent, durable, broad humoral and cellular response to overcome viral diversity. This remains a key challenge. Thus, it will be important to test multiple vaccine concepts that an effective vaccine will need to prevent acquisition and/or at least stringently control viral replication or kill infected cells at the site of entry to terminate the primary infection. New concepts being tested include the promising elicitation of cross-reactive potent neutralizing antibodies or

CD8 T-cell responses. Based on current data from structural studies, molecular dynamic simulations and biochemical and biophysical information, there is a better understanding of how to precisely design immunogens. A robust preclinical pipeline with precisely designed priming and boosting immunogens which, given sequentially, can elicit cross-reactive neutralizing Abs, is an important step in immunogen selection and generating proof of principle for bnAb-eliciting vaccines. Testing these selected immunogens iteratively in clinical studies will provide critical data to identify immunogens as components of an efficacious HIV vaccine. It is critical to start development of a single regimen that can stimulate both a broad humoral and cellular response.

- Roger Le Grand, CEA

The work of the two large EU-funded consortiums on developing an HIV vaccine under the H2020 funding framework is coming to an end. There is no sustainable mechanism for funding long-term vaccine development in Europe; this requires further discussion. It has been possible to continue developing an HIV vaccine in France because there is a dedicated agency (ANRS|MIE). However, funding is not sufficient to support efficacy studies. With limited resources for research, it is necessary to maintain a top-down approach. Developing a roadmap, although it could be overwhelming, will be important to advocate for funding and research. Another challenge is that early-career investigators are distracted from HIV research by new and more attractive vaccines or programmes. HIV vaccine R&D must be made more attractive to early-career investigators.

Discussion

The following topics were discussed:

- **Working towards a roadmap for an HIV vaccine**

Le Grand said that an agile continuum of research and development accessible to academics is needed so that products can be brought to production level and tested in clinical studies quickly. This requires coordination and facilitation and could be a role for the Enterprise.

Anklesaria said that it will be critical to engage and support efforts of scientists from across the globe, particularly in communities where the vaccine will have the most impact. Developing a vaccine should include consideration of the needs of end users. This is central to vaccine development activities. New ideas with clear hypotheses should be considered, and she urged all to engage in finding practical solutions for potentially complex regimens that may be part of an efficacious HIV vaccine.

Dieffenbach added that great ideas know no country borders. Innovation, new approaches and new ideas are needed, and we should be willing to take some risks. We should look at new ideas coming forward and be willing to step outside our comfort zones and support truly novel mechanisms. The NIH has programmes designed for which no new data is required. The NIH has also been exploring the

manufacturing issue and has helped investigators making GMP material. He emphasized the importance of ongoing dialogue and partnership with industry and referred to the collaboration between Dan Barouch and Janssen Vaccine Prevention as a strong successful partnership that the NIH and BMGF were able to support.

From an industry perspective, Hwang said that as we think about moving forward with different development programmes, we should consider programmes with different risk/reward ratios. Manufacturing is a persistent challenge, even for industry. Manufacturing capacity worldwide to generate the amount of material needed for clinical trials, including the availability of raw materials, is a challenge. One potential way is to invest in manufacturing capacity or have some organizations invest in the manufacture of earlier phases or smaller manufacturing plants that can make products faster, at least for Phase 1.

- **Inclusiveness in research and development**

McCluskey said that political challenges are not small matters; these are in addition to the biological and scientific challenges of finding an HIV vaccine. This includes having domestic resources added to the pool of resources from each country where HIV remains an epidemic, including scientists from low- and middle-income countries. It is necessary to widen the space for colleagues who have been working very hard testing existing products and ensure that their ideas are heard to help design products. USAID is working towards changing who is included in the "we", striving for more inclusion of low- and middle-income country researchers in scientific decision making and leadership in a more genuine way so that these colleagues are taking some of the decisions and leading some of the discussions and innovation.

Anklesaria endorsed USAID's inclusive approach, added that the BMGF is supportive of that action plan and emphasized that it is important to have community input and user-centred research with users from across the world, not just from high-income countries.

- **De-risking platforms**

Hwang said that de-risking platforms is complicated. Once there is proof of concept in one disease, there is the potential of moving the platform into another disease areas – although it may not work – and toxicology studies and Phase 1 studies may be needed to ensure safety. Each situation will be different.

Dieffenbach said that novel ideas and methods are needed and that these could go into platforms. Following the failure of the most recent HIV vaccine efficacy trials, we should step back and consider what else is available. The CMV vector remains an interesting strategy that requires further iterations. We have to understand why approaches don't work and what can be done to either tweak, improve or modify them in a way that will move this field along. It is necessary to create a sense of urgency for new ideas so that we have a robust, innovative pipeline.

- **Access to products**

Anklesaria said that products developed in collaboration with industry collaborations should be rapidly deployed in low-income countries within a few months, if not immediately, once regulatory approval is given. This is critical as communities in these countries have contributed to the development of these products. Not having them immediately available, as we have seen with COVID-19, creates significant inequality. Global access must be built in early in agreements and collaborations with industry.

Stacey Hannah asked about the steps that can be taken now to ensure equitable and fast access globally.

Anklesaria described the BMGF staged approach, with global access agreements as a product progresses further along the development pathway. This includes discussions on pricing and identification of countries that will benefit most. **McCluskey** said that USAID invests only in products that will be accessible and affordable in low- and middle-income countries.

- **Reimagining HIV advocacy for an HIV vaccine**

Hannah said that there has been strong support from stakeholders for an HIV vaccine from the beginning. However, it may be necessary to retell the story with new messages about why we still need an HIV vaccine, especially with the shift from product development (leading to efficacy trials) toward experimental medicine and testing of hypotheses, rather than possible products. **Tatoud** commented that we are working in a bubble and HIV is no longer perceived as a problem outside this bubble. The HIV vaccine advocacy movement is not at the level seen for other prevention tools and he wondered how to reimagine advocacy to bring back HIV vaccines in the HIV prevention conversation.

Francois Dabis said that HIV vaccine research should not be considered to be a separate field of research. He pointed to the WHO Global Vaccine Market Report, which aims to support vaccine development as part of pandemic prevention, preparedness and response efforts. He added that WHO should be at the table discussing HIV vaccines.

Le Grand said that from a European perspective, HIV should not be disconnected from the applications of vaccine development in other diseases. This is very important for advocacy. Going forward, there is a need to go beyond the impact on public health to illustrate that investment in this kind of challenging innovation is an investment in capacity for doing clinical trials, in production of vaccines and in the industrialization of Europe, creating an economic ecosystem that can develop by itself.

McCluskey said that the question of urgency must be reconsidered. Unless we can reach those hard-to-reach populations, there will be a resurgence of the epidemic. She wondered whether the word *urgency* is no longer as relevant as the word *essential* in the current situation where there is an expanding toolkit for HIV prevention. The question is: where does an HIV vaccine fit in this toolkit? We must

continue in the pursuit of a vaccine because it is potentially the most effective, cost-effective and efficient tool that does not require taking pills.

Final panellist remarks

Panellists were asked what their big bet for the vaccine field is in the next five to 10 years.

- Carl Dieffenbach – NIAID

We require strategies based on the design of very specific, very targeted immunogens that precisely engage B-cells and then precisely engage mature B-cells. An HIV vaccine must be better than natural immunity.

- Carey Hwang, Vir Biotechnology

Much was learned from COVID-19 on how to accelerate clinical trials and platforms. Finding a way to integrate the learnings and different strategies will improve progress in developing HIV vaccines.

- Margaret McCluskey, USAID

As the various innovative approaches to a safe and effective HIV vaccine continue emerging, it is essential to have the right people at the table, not only because it is morally the right thing to do, but because we need to think about end users. If they are not involved in the effort, along with the scientific community, it will be difficult for studies to be conducted and for products to be effectively used.

- Pervin Anklesaria, BMGF

For a highly efficacious HIV vaccine, the different arms of the immune system must work in a coordinated and comprehensive way to prevent and/or rapidly control HIV acquisition. It is important to continue community engagement. Strengthening regulatory, clinical and laboratory services are critical to ensure equitable global participation.

- Roger Le Grand, CEA

We require investment in early-career investigators with "good brains" to build long-term HIV vaccine R&D programmes that they can take charge of.

Closing

Susan Buchbinder thanked all participants, adding that the meeting had been an opportunity for a very rich conversation covering many different issues, including what the products should be, how we decide what to move forward, who is at the table, where and how the trials are done, how to engage regulators, and how to truly engage with communities.

Key messages

Strategy for HIV vaccine R&D

- Rethink HIV vaccine R&D in a fast-changing HIV prevention landscape.
- Be critical and focus on "good science".
- Start thinking about an HIV vaccine at a higher strategic level.
- Comprehensive approaches are needed (B- and T-cell + innate immunity).
- RNA allows faster iteration, but will not be enough on its own.
- Give attention to a range of products and approaches.
- Test products in combination and in parallel.
- Learn from previous studies, especially about immunology.
- Adopt an "industry mindset": product characteristics; development plans and roadmaps; stricter product selection; identify go/no-go (at portfolio level); end-to-end perspective; and put learning from COVID-19 into practice. This will contribute to de-risking platforms and products.

Clinical research

- Identify and address bottlenecks from start to finish.
- Speeding up clinical testing is in part an operational challenge with improvements needed at all steps (product manufacture, regulatory approvals, recruitment, laboratory assays, data sharing and IP management).
- Consider an overarching "plug and test" protocol.
- Manufacture products and conduct research in countries bearing the burden of epidemics.
- Improve speed and agility of product manufacturing (technology transfer, production capacity and legal agreements).
- Create platforms for data and information sharing to support rapid strategic decision making.
- Agree on standards for preclinical work and safety to facilitate regulator reviews and approvals.

Engagement, collaboration and partnership

- Engage early and meaningfully with community stakeholders.
- Raise research literacy among a range of stakeholders (such as communities and regulators).
- Increase global collaborations.
- Ensure that the right people are at the table and that they are heard and contribute to the research.
- Engage with the industry, connecting HIV vaccines to other applications.
- Reinvent advocacy for an HIV vaccine.

Participants/speakers	Country	Affiliation
Natalia Laufer	Argentina	Instituto de investigaciones biomedicas en retrovirus y sida
Gerald Voss	Belgium	TBVI
Beatriz Grinsztejn	Brazil	The Oswald Cruz Foundation (FIOCRUZ)
Morgan Bomsel	France	Inserm
Mireille Centlivre	France	VRI/IMSERM
Francois Dabis	France	ANRS | Maladies infectieuses émergentes
Laurent Hanot	France	Inserm
Roger Le Grand	France	ANRS | Maladies infectieuses émergentes
Jean-Daniel Lelievre	France	Vaccine Research Institute
Yves Levy	France	Vaccine Research Institute
Rodolphe Thiebault	France	Universite de Bordeaux
Ralf Wagner	Germany	Universitaetsklinikum Hamburg-Eppendorf (UKE)
Andrea Cara	Italy	Istituto Superiore di Sanità (ISS)
Gabriella Scarlatti	Italy	Ospedale San Raffaele, OSR
Tetsuro Matano	Japan	AIDS Research Center, National Institute of Infectious Diseases
Kundai Chinyenze	Kenya	IAVI
Gaudensia Mutua	Kenya	Kenya AIDS Vaccine Initiative
Juan Sierra-Madero	Mexico	Instituto Nacional de Ciencias Médicas y Nutrición Dr. Salvador Zubirán
Juan Vicente Guanira	Peru	Investigaciones Medicas en Salud, Lima, Peru
Maureen Luba	Malawi	Cooper Smith
Gavin Churchyard	South Africa	Aurum
Linda-Gail Bekker	South Africa	Desmond Tutu HIV Centre
Glenda Gray	South Africa	South African MRC
Nandi Luthuli	South Africa	AVAC
Ansuya Naidoo	South Africa	IAVI
Wim Vandevelde	South Africa	GNP+
Ntando Yola	South Africa	Desmond Tutu HIV Centre
Jose Alcami	Spain	Instituto de Salud Carlos III
Christian Brander	Spain	IrsiCaixa AIDS Research Institute
Beatriz Mothe	Spain	IrsiCaixa AIDS Research Institute
Song Ding	The Netherlands	EuroVacc Foundation (EuroVacc)
Maria Pau	The Netherlands	Janssen Vaccines & Prevention B.V
Rogier Sanders	The Netherlands	Academisch Medisch Centrum bij de Universiteit van Amsterdam (AMC)
Daniel Stieh	The Netherlands	Janssen Vaccines & Prevention B.V
Gus Cairns	UK	AIDSMap
Tomas Hanke	UK	University of Oxford

Participants/speakers	Country	Affiliation
Carolina Herrera	UK	Imperial College of Science, Technology and Medicine (Imperial)
Sarah Joseph	UK	Imperial College of Science, Technology and Medicine (Imperial)
Debbie King	UK	Imperial College of Science, Technology and Medicine (Imperial)
Roger Peabody	UK	AIDSMap
Katrina Pollock	UK	Imperial College London
Johan Vekemans	UK	IAVI
Margaret Ackerman	USA	Dartmouth
Julie Ake	USA	MHRP
Erica Andersen-Nissen	USA	HVTN
Pervin Anklesaria	USA	BMGF
Pervin Anklesaria	USA	BMGF
Susan Barnett	USA	BMGF
Iris Benhayoun	USA	Worcester HIV Vaccine
Cesar Boggiano	USA	NIAID/NIH
Susan Buchbinder	USA	San Francisco Department of Public Health
Trevor Crowell	USA	MHRP
Carl Dieffenbach	USA	NIAID
Dazon Dixon Diallo	USA	Sister Love, Inc
Deborah Donnell	USA	U. Washington
Daniel Driffin	USA	Fred Hutch
Patricia D'souza	USA	NIAID
Nicole Frahm	USA	Gates MRI
Maureen Goodenow	USA	NIAID/NIH
Vinay Gopan	USA	NIAID/NIH
Kyle Gordon	USA	Fred Hutch
Stacey Hannah	USA	AVAC
Barton Haynes	USA	Duke
John Hural	USA	HVTN
Carey Hwang	USA	Vir Biotechnology (Co-chair Industry Vaccine Group-CPP IAS)
Holly Janes	USA	HVTN
Peggy Johnston	USA	Independent
Jim Kublin	USA	HVTN
Shuying Liu	USA	Independent
Shan Lu	USA	University of Massachusetts Medical School
Paolo Lusso	USA	NIAID, NIH
Matshidiso Malefo	USA	HVTN

Participants/speakers	Country	Affiliation
Mary Marovich	USA	NIH
Kenneth Mayer	USA	Fenway Community Health Center
Margaret McCluskey	USA	USAID
Zoe Moodie	USA	HVTN
Thandi Onami	USA	BMGF
William Snow	USA	Independent
Devin Sok	USA	IAVI
Rasmi Thomas	USA	MHRP
Frank Tomaka	USA	Janssen Vaccines & Prevention B.V
Georgia Tomaras	USA	Duke
Tina Tong	USA	NIH
Jan van Lunzen	USA	ViiV Healthcare
Sandhya Vasan	USA	MHRP
Stephaun Wallace	USA	HVTN
Peng Zhang	USA	NIAID/NIH
William Kilembe	Zambia	Zambia Emory HIV Research Project (ZEHRP)

IAS	Country	Affiliation
Marlene Bras	Switzerland	IAS staff
Elena Moreno	Switzerland	IAS staff
Asli Heitzer	Switzerland	IAS staff
Julieta Firmat	Switzerland	IAS staff
Roger Tatoud	France	IAS- consultant