

Considerations for a Pan-African HIV Vaccine Development Agenda

Meeting Report

16 – 17 March 2015, Kigali, Rwanda

Introduction

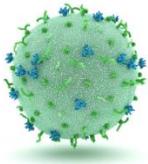
The Global HIV Vaccine Enterprise and partners, with financial support from IAVI, held a meeting on 16-17 March in Kigali, Rwanda on “Considerations for a Pan-African HIV Vaccine Development Agenda.” The diverse range of vaccine strategies, including subtype-neutral designs for global use, provided an opportunity to review and discuss the vaccine pipeline, the burden of disease in various African regions, African cohorts with high enough disease incidence for future efficacy trials, and strategies to determine how broad or narrow protection will be.

With only 5% of the world’s population, Eastern and Southern Africa are home to half of the world’s population living with HIV. The African continent continues to be the epicenter of the HIV/AIDS epidemic, with 48% of the world’s new HIV infections among adults and 55% among children. Multiple HIV-1 subtypes are prevalent on the African continent. Subtypes A and D are stable in East Africa; C in Southern Africa; A, G, CRF02_AG, and CRF06_cpx in Western Africa; and subtype B and CRF02-A in Northern Africa. This diversity in HIV-1 subtypes as well as multiple viral variants and recombinant viruses have presented a challenge for vaccine development. The development of a safe and effective HIV vaccine for prevention of AIDS is a global public health priority and the best chance for ending the epidemic.

The main objective of the meeting was to discuss how to support development of a pan-African HIV vaccine agenda and facilitate strategic planning to ensure that vaccine strategies address all populations in need. The meeting involved discussions about the optimal design of initial efficacy trials and potential bridging studies to ensure that HIV vaccine candidates include regions that did not participate in a successful efficacy trial. This is necessary to expedite widespread use when deployable results are obtained. In addition, the group discussed the need for a united African research voice that advocates research capacity in Africa to ensure accelerated development and rollout of an effective HIV vaccine.

The concept of this Timely Topic arose when a small group of leading African researchers and advocates met in Cape Town at the International Conference on AIDS and Sexually Transmitted Infections in Africa to discuss the future of African HIV vaccine research. This group was then expanded to create a larger [organizing body](#) for advice on the organization and [agenda](#) of this meeting.

The meeting was attended by 60 [researchers, advocates, regulators, and funders](#) representing all African regions as well as international partners and chaired by Pontiano Kaleebu, MRC/UVRI Uganda Research Unit on AIDS and Sabin Nsanzimana, Rwanda Biomedical Center. Dr. Agnes Binagwaho, minister of health of Rwanda, opened the meeting by welcoming all to Kigali and emphasizing Rwanda’s commitment to HIV prevention research. Summaries of the discussion and key recommendations raised during the meeting follow.

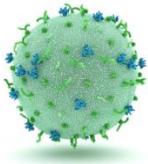


Diversity of the Epidemic in Africa

Moderated by Thumbi Ndung'u and Etienne Karita

The extraordinary genetic diversity of HIV-1 strains worldwide is arguably the greatest challenge in HIV-1 vaccine development, a hurdle that must be overcome by paradigm-shifting design or vaccination strategies. If a vaccine is to be effective in Africa, it must take into account the multiple HIV-1 groups, subtypes, and recombinants circulating within the continent. The group agreed on several key issues that require further investigation, including the extent of viral diversity within sub-Saharan Africa, the evolution of diversity as the epidemic spreads, and the impact that this diversity may have on vaccine design strategies and the generation of protective immune responses by candidate vaccines.

1. Viral diversity within sub-Saharan Africa: The HIV-1 epidemic is unevenly spread within the African continent, with East Africa, West Africa, and Southern Africa being the most heavily affected regions. The circulating viral strains and subtypes in these regions differ, and country-specific and within-country differences have also been noted.
 - a. East Africa: Analyses of gp120 and full-length sequences from East Africa have shown that the epidemic is predominantly composed of subtypes A, C, D, and their recombinants. However, there are country-specific differences—65% of the epidemic in Kenya consists of A1 and A1/D recombinants; in Uganda, A1/D recombinants and D comprise 68% of circulating strains; in Tanzania, nearly 60% is composed of C and A1/C recombinants; and in Rwanda, A1 comprises approximately 75% of published sequences.
 - b. West Africa: Using Cameroon as a case study to investigate the diversity of HIV-1 in West Africa, Gag and Nef sequencing data showed that CRF02_AG was the most dominant strain, comprising nearly 50% of the epidemic; however, the CRF02_AG represents only 8% of global HIV-1 strains. The HIV-1 epidemic in Cameroon is also genetically diverse. Only 15% of sequences represent pure subtypes; the rest are recombinants, including unique recombinant forms. Sequences from Cameroon include many highly divergent outliers that cannot be classified under the currently defined HIV-1 M group subtypes. Analysis of CD8+ T cell responses of infected persons from Cameroon using consensus and potential T cell epitope (PTE) reagents designed based on consensus group M Gag sequences demonstrated that the PTE reagents were more frequently recognized than their consensus sequence counterparts. In contrast, Nef PTE and consensus M epitopes were equally recognized. Overall, both sets of reagents often failed to induce responses compared to highly immunodominant peptides that were common within the population, likely driven by viral and host genetic differences. These data underline the need to better understand the virology and immunology of the highly diverse HIV-1 epidemic in West Africa for an optimal vaccine design, along with assay development to track immune responses.
2. Impact of HIV-1 diversity on antibody response: Speakers presented three studies on how HIV diversity affects antibody response. In the first, pre-seroconversion HIV-1 subtype C viruses were less susceptible to neutralization by serum, derived from a pool of chronically infected participants, compared to post-seroconversion viruses. However, there was no difference in neutralization when considering a panel of broadly neutralizing antibodies (bNAbs) targeting conserved epitopes such as CD4, V2, and MPER epitopes, but the viruses were less susceptible to PGT128. The N332 glycan (linked to PGT128 recognition) was under-represented in pre-seroconversion viruses, but that only partially explained the



increased resistance.

A second study demonstrated that the increase in viral diversity over the past 10 years is associated with an increase in neutralization resistance. This resistance is evident for some broadly neutralizing epitopes, such as 4E10 and V2, but not for others such as the CD4 binding site and some epitopes in the V2 and V3 loops.

Finally, a third study demonstrated that coverage of clade C acute/early viruses by monoclonal antibodies can theoretically reach 94% if more than one antibody is present, suggesting that the impact of intra-clade diversity could be overcome by targeting at least two broadly cross-neutralizing epitopes. Taken together, these data indicate that within clade C, diversity has increased over the past decade, giving rise to variants that are harder to neutralize and hence may require induction of at least two bNAbs through vaccination for neutralization. More needs to be done to understand the implications of the increasing diversity on antibody responses and how best to target vaccine design to achieve maximum protection and prevent breakthrough infections given intra- and inter-clade diversity.

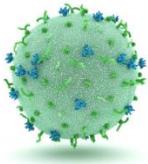
3. Role of viral fitness on transmission: A Zambian study showed that transmission of a particular variant during a heterosexual encounter is not simply stochastic, but involves selection for more consensus-like, fitter viruses. Selection is greatest in female-to-male transmission, less in male to female, and in female to males with ulcers or inflammation. Females were more likely to be infected by less fit viruses than men, consistent with the lower early viral load in females. In a follow-up study, high viral replicative capacity was characterized by elevated inflammatory cytokines early in infection and aberrant CD8 and CD4 T cell phenotypes, including increased levels of cellular activation, exhaustion, and proliferation. Higher replication capacity was also linked with increased viral burden in naïve and memory CD4+ T cells. Overall, this presentation emphasized the need to understand the nature of the infecting virus and the impact it may have on subsequent immune responses.

The conclusion from this session was that the extensive viral diversity in Africa matters in terms of approaches to vaccine design. We need to better understand this diversity, the factors that drive diversity, and the subsequent implications for pathogenesis and vaccine design strategies. Data suggest that vaccines will need to induce bNAbs to more than one conserved epitope to be efficacious and that the reach of the evolving diversity needs to be considered when designing clade-neutral vaccines because clade-specific vaccines will likely not work in countries with the diversity of Cameroon, for example.

The Vaccine Pipeline

Moderated by Pat Fast and Hannah Kibuuka

Vaccines developed earlier in the epidemic, some of which are in clinical testing, were often designed with immunogens and inserts derived from a particular HIV clade with the expectation that they would elicit a protective immune response against viruses from that clade. However, many of these approaches proved ineffective in controlling intra-clade viral diversity. Presentations and discussions in this session revolved around promising vaccine candidates in the pipeline and how to overcome HIV diversity to develop vaccine candidates suited to African human genetic background, risk factors, and transmission routes. In addition, speakers discussed general considerations for vaccine trial design, including standards of care, combination prevention trials, and consequences of implementing prevention technologies such as male circumcision and pre-exposure prophylaxis (PrEP).



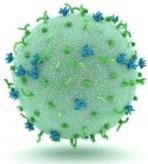
T-cell vaccines induce cytolytic or inhibitory T cells with exquisite specificity. Changing the target epitope by one or two key amino acids can result in an escape mutant and allow the virus to replicate unchecked. Recently, computational analyses have been used to optimize epitope sequences to represent as many key epitopes as possible. In general, two such optimized epitope versions are produced that complement each other.

- **Mosaic vaccine insert:** A computational algorithm is used to create synthetic sequences that encode composite full-length HIV-1 proteins that optimize coverage of potential T-cell epitopes. A vaccine using this approach in combination with a gp140 immunogen is being developed by Janssen in collaboration with Harvard University and partners and is currently in phase 1 trials.
- **Conserved mosaic vaccine insert:** Only the most conserved portions of the HIV genome are selected and optimized. This reduces the chances of viral escape because the conserved portions of the genome are unlikely to change without negatively affecting the replicative capacity of the virus. A first-generation vaccine using this approach is being developed by Oxford University and partners and is currently in clinical trials.

Most immunogens fail to induce strong neutralizing antibodies even against a matched virus, but polyclonal sera and monoclonal antibodies derived from people with HIV demonstrated that at least some are capable of producing antibodies with broad potency and reach. Efforts to create immunogens or vaccines that can induce those bNAbs include producing envelope proteins with native configurations, synthesizing molecular mimics of the native structure, or using mosaic approaches for immunogen design.

The group provided the following recommendations:

1. **Designing and testing vaccines:** As more candidate vaccines designed to have global coverage move into clinical trials, past approaches to conducting regional efficacy trials should be reconsidered. Designers/manufacturers should select vaccine candidates that have the potential to be efficacious in global settings, and components of several clades or regions should be included in the first efficacy trials(s). African scientists (or those from other affected regions) and clinicians should be involved in designing and selecting vaccines to advance as well as in evaluating safety and immunogenicity. Evaluating vaccine immunogenicity in several African countries early will provide an understanding of how the vaccines might work in different African populations. Although not specific to Africa, the group thought that vaccine candidates should be tested in human studies (phase 1 or experimental medicine trials) faster. In addition, the group agreed that a rational process for prioritizing vaccine candidates that move into later stage testing would be ideal—considering broad coverage, safety and immunogenicity, and plausibility based on preclinical and in vitro data. Although no such process currently exists, both public funding for HIV vaccine testing and the availability of forums such as the AIDS Vaccine/HIV R4P meeting can help to provide a means to openly discuss existing approaches in the pipeline and select the best candidates for advancement. The [immune space concept](#), developed by the Enterprise and an ad hoc group of clinical trials collaborators, was also mentioned for consideration on how to define what should advance into the clinic.
2. **Plan bridging studies:** Bridging studies to address broadness of a vaccine candidate, transmission routes, risk factors, and human genetics should be planned early. The group suggested holding strategic consultations for advanced candidates to discuss what the best strategy for the first and the follow-up



studies should be to ensure that effective vaccines can be deployed quickly to all regions in need and ensure that vaccines are effective for all populations.

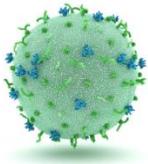
3. Examining correlates of immunity: Laboratory scientists should design assays that will apply to HIV variants from around the globe (preferably creating these reagents in advance and making them widely available).

Assays and Laboratory Endpoints

Moderated by Omu Anzala and Muhammad Bakari

There is substantial laboratory capacity in sub-Saharan Africa, with a significant number of laboratories working under Good Laboratory Practice (GLP) or Good Clinical Laboratory Practice (GCLP) accreditation. The discussion in this session focused around four main topics: laboratory accreditation, training, local clinical trial immunogenicity assays, and next-generation research assays.

1. Accreditation: Laboratory accreditation, a process of independent evaluation of a laboratory's quality, performance, reliability, and efficiency, provides many benefits including high-quality assays, assurance that results are internationally comparable, standardized laboratory practices, and reduced cost. However, maintaining accreditation is resource intensive—laboratories must be reaccredited every 2 years, standard operation procedures developed and continuously reviewed, quality assurance and safety guidelines instated, key performance indicators monitored, and personnel developed and retained. Given these requirements and current resources across Africa, the group discussed what standards laboratories in the region should aim for. They agreed that laboratories that are or will be involved in clinical trials should aim for GCLP standards, whereas laboratories doing basic science should get accredited if they have the available resources to maintain that status.
2. Training: Another key priority discussed during this session was building African capability to contribute from basic research to vaccine and clinical trial design to performing the trials and analyzing the samples collected. Because many laboratories in Africa have access to samples from clinical trials and other studies, the group strongly agreed that this provides a good platform to train the early-career researchers and technicians. The challenge is to balance availability of samples for safety and other clinical trial tests and training purposes. The session moderators highlighted the importance of discussing sample acquisition and quantity with regulators and ethic committees to ensure that samples can be assigned appropriately, including for new immunogenicity and research assays.
3. Performing clinical trial immunogenicity assays locally and introducing next-generation research assays: There has been a lot of progress in developing capacity to perform clinical trial immunogenicity assays locally, but it is not always necessary that every laboratory have the expertise to perform every assay. It will sometimes be more efficient to have a central laboratory perform assays for all sites. However, exploratory and research assays should be performed locally on a subset of samples and clarifying sample needs ahead of time will be required.
4. Assay selection: The group also discussed choosing assays for use in various clinical trials, among the validated, standardized and exploratory assays, and tying in the choice of assay with the go/no-go criteria for each vaccine candidate. Although the choice of assay would depend on the vaccine trial, focusing on assays that assess functionality of the immune response elicited would be a priority. In particular, the group discussed the need to improve mucosal sampling techniques and assays to better



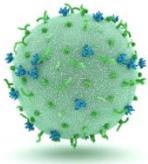
understand what occurs at the mucosal points of HIV entry, focusing again on functionality of the response to tease out whether a vaccine is protective.

Cohorts and Capacity in Africa

Moderated by Gaudensia Mutua and Fred Sawe

This session focused on the importance of HIV cohorts in the African region in preparation for HIV vaccine trials. Presentations in this session focused on cohort work in key populations, including female sex workers (FSW) in Nairobi, men having sex with men (MSM) in Nairobi and Nigeria, fisher folk communities around Lake Victoria in Kenya and Uganda, and discordant couples. Despite the fact that the FSW and MSM activities are illegal in many African countries and stigmatized, researchers have been able to work with these communities to not only collect information such as HIV epidemiology, but also to provide comprehensive HIV treatment and prevention services. These services were provided as much as possible at the research facilities or by referral to other locally available services through the Ministries of Health, the military, or local hospitals. The consortiums around fisher folk community near Lake Victoria and MSM cohorts in East Africa demonstrate how developing these cohorts based on shared experience and objectives will ensure that platforms are set up to address important interventions and research questions in the future. Some additional recommendations follow:

1. Maintaining key population cohorts: Maintaining cohorts is expensive and labor intensive. Whereas some have been in place for a long time, it is uncertain how long they can be sustained in readiness for HIV vaccine and other prevention research. The vaccine pipeline needs to be actively pushed forward to take advantage of the opportunities, working arrangements, and trust that have been built between researchers and these key populations.
2. Providing prevention services to trial participants: The combination prevention services provided to study participants should be of the best achievable standards, which may exceed the local standard of care. The decision on which mix of combination prevention interventions to provide may be based on the per-capita income expenditure on health in each country and the highest attainable standards. At minimum, the services provided to the participants should include HIV testing and counseling, couple counseling, condom provision, voluntary medical male circumcision, prevention of mother-to-child transmission, and treatment for sexually transmitted infections. Where possible, it is advisable to provide PrEP to those in a discordant sexual relationship.
3. Feasibility of trials in key populations: The above key populations have very high HIV prevalence, and incidence that is likely to remain high enough to support HIV vaccine research despite HIV transmission prevention interventions. Providing combination prevention intervention services can be challenged by inadequate infrastructure and limited resources available to the general community.
4. Changing HIV incidence in cohorts: When participants first enroll in high-risk cohorts, the incidence of HIV is initially high but can rapidly decrease after approximately 3 to 6 months; in some cases, by over 30%. This decrease in incidence may be attributable to the combination prevention interventions that are provided. However, the impact of enrollment on incidence is hard to predict and is shown to be non-significant in some cohorts. Changing HIV incidence in cohorts needs to be estimated and tracked when designing HIV vaccine studies, in particular for sample size calculations and study duration.
5. Other key populations to consider: Additional efforts are needed to focus on other underrepresented high-risk populations, such as young girls and adolescents and intravenous drug users.

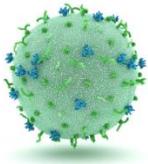


Regulatory Considerations

Moderated by Thomas Nyirenda and Dean Smith

This session focused on sponsor and principal investigator (PI) engagements with African national regulatory authorities (NRAs), exploring how NRAs are dealing with the challenge to provide timely clinical trial review and appropriate oversight of approved trials, as well as issues related to product approvals with sufficient safety and efficacy demonstrated through clinical trials. The group also considered regulatory issues within the countries hosting clinical trials, and in countries that would depend on trial data generated outside their jurisdiction. There was the general acknowledgment that pre-submission meetings are a mutually beneficial confidence-building exercise, resulting in an efficient review of the submission and thus meeting relevant regulatory group(s) as early as possible and as frequently as necessary was encouraged. Pre-submission meetings enable regulators to gain insight into the scientific and technical expertise behind a Clinical Trial Application (CTA) and learn specific submission details; similarly, the sponsor/PI can directly communicate the more complex elements of their trial and clarify specific issues of concern to the NRA. Participation of local investigators is critical to provide local context. Additional discussions revolved around four key areas:

1. Joint review by collaborating NRAs: The group encouraged the use of joint reviews through the platform established by participating members of AVAREF, which is supported by the WHO and can draw upon expertise from external agencies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Health Canada (HC). WHO devised a joint review of CTA concept that brings together NRAs and ethics committees in countries targeted for a multi-site vaccine clinical trial to jointly review the CTA with the assistance of expert regulators (often from the country of origin of the candidate vaccine) in the presence of the sponsors/manufacture and clinical investigators. Successful joint review experience with other vaccines, including the recent Ebola vaccine trials, was discussed, as was the extension of these approaches through AVAREF to future HIV clinical trials and potential vaccine approvals. Some of the efficiencies and advantages of joint reviews discussed include:
 - The process is especially useful for multi-center CTAs, where the NRAs representing the host countries for the trials collaborate to review the file(s). Although each NRA controls the decisions within its jurisdiction, the joint review can facilitate a more robust and efficient process.
 - AVAREF can provide an assisted review for countries with less regulatory experience to strengthen the regulatory capacity of the host NRA.
 - Joint reviews were also seen as an excellent means to foster best review practices within and between agencies and to reduce the technical dependency of less experienced NRAs on a CTA sponsor, which could lead to conflicts of interest.
2. Roles and responsibilities of NRAs and ethics/expert committees: There is a need for clear roles and responsibilities within and between NRAs and ethics/expert committees, and the lack of a single entry point for sponsors to communicate with an NRA contributes to miscommunications and can slow the review process. The group voiced concern that sponsors and PIs can get caught in loops in which two levels provide conflicting advice, or situations in which protracted exchanges unfold among different groups within the review units. Some NRAs have strict review deadlines (generally 30 days) to achieve the review targets, which require agencies to be well organized and focused on key questions in the submission, such as safety. Such tight review timelines also highlight the value of the pre-CTA meetings with sponsor/Pis to help clarify key issues that might otherwise delay or prevent an approval. The



review times within African NRAs are country dependent, and a collaborative approach to best review practices and timelines would benefit everyone.

3. Insurance as a barrier to clinical trials: Pls raised the concern that in some African jurisdictions (eg, Kenya), NRAs require sponsors to obtain insurance coverage for clinical trial participants, but there is no such insurance available in the country. While this issue is generally beyond the scope of a review agency, higher levels of an NRA have worked with public health and other branches of government to address issues related to indemnification when this type of problem has occurred in special situations in North America. Such an approach may be useful where this is a problem in specific African countries.
4. Legal frameworks to support regulatory collaboration: NRAs such as the FDA, EMA, and HC have specific regulatory and legal frameworks in place that provide the basis for memorandums of understanding to share proprietary and trade secret sponsor information among the agencies. As joint reviews are developed in Africa, it is essential for countries to establish similar regulatory/legal frameworks. Several of the more experienced African NRAs with such frameworks may be able to assist other NRAs to do the same. Countries within the East African community were cited as one example of such regulatory/legal frameworks, but examples within Africa are not limited to East African community member states.

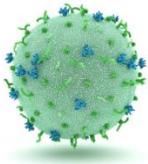
Closing Session Summary

In the closing session, the group discussed strategies to ensure that African researchers are fully engaged in the HIV vaccine development process. The group thought that the lack of a cohesive African voice among researchers prevented Africans from fully participating in the global HIV vaccine. Therefore, much of the discussion revolved around ways to bring African researchers and other players in HIV vaccine development, such as communities, civil societies, and advocacy groups, together to foster more interaction and cohesion. There was a call for a sustainable African network that would not rely too heavily on external funding. In particular, the group thought that it was important to ensure that African researchers are involved from conception and design of clinical trials to data analysis, which requires investing in training and development of young researchers.

As a guide for a future African scientific networking, the group discussed the successes and shortcomings of the African AIDS Vaccines Program (AAVP). Although they agreed that they did not want to reinstate the AAVP, the group did think it was worthwhile to assess the lessons learned and determine which aspects of the AAVP are valuable to reestablish going forward. Toward this goal, the group decided to elect a core group to bring suggestions, ideas, objectives, and priorities of such a network to the larger group for further discussion.

Key recommendations discussed during the closed session included:

- **Establish a virtual network for African researchers:** A virtual network is more sustainable and would require less external funding than a physical institute. The group agreed that with any new structure, the objectives and topics need to be clearly defined from the outset.
- **Advocate for more funding from within Africa:** Much HIV vaccine funding still comes from outside of Africa. While the group recognized that external funding is currently necessary, they stressed that commitment from African governments and organizations is essential to empower African researchers to drive the vaccine research agenda.



- **Involve community and advocacy groups:** The group felt that the vaccine development field has not done an effective job of engaging the community, pointing to recent successes within the microbicide and PrEP movements. They called for identifying opportunities to bring researchers and community advocates together, perhaps via the virtual network discussed above.

Increase Research Capacity and Capability in Africa

Throughout several sessions of this meeting, capacity development was a key discussion point. Attendees were concerned that capacity development is not uniform and that African researchers are more involved in processing and shipping samples than in conducting research locally. In an effort to increase capacity, the group recommended the following:

- **Increase training for African researchers:** The group called for continued efforts to train African scientists to be integral members of the clinical trial team from protocol development to trial design and implementation involving young African scientists early in many of the activities recommended here. Because it can be difficult to train students within a GCP/GCLP environment, the group suggested setting up biobanks and laboratories that can run in parallel to clinical trial sites so that students can train and conduct research on the samples being collected. As part of this initiative, young investigators should be encouraged to speak at and attend conferences.
- **Create an HIV vaccine laboratory network:** The group recommended creating an HIV vaccine laboratory network so that African researchers can be involved in designing protocols for clinical trials. In addition, this could help researchers become more involved in moving products into clinical trials and deciding which products should move forward. Building capacity so that Africans are involved in designing trials and asking research questions will also help to ensure that African researchers are a leading voice of the vaccine development agenda.
- **Ensure that African researchers are recognized in publications:** The group expressed concern that African researchers are not always recognized as equal contributors to research and may be left off publications. The research and policy guidelines of the Rwandan government were provided as a possible model to emulate.

Next steps: the group agreed that creating an advisory committee, initially led by Pontiano Kaleebu, to develop a proposal on what the scope, structure and goals of the virtual network should be would be a good first step. This proposal would then be reviewed and approved by the larger community.