The complex challenges of HIV vaccine development require renewed and expanded global commitment

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Linda-Gail Bekker, Roger Tatoud, Francois Dabis, Mark Feinberg, Pontiano Kaleebu, Mary Marovich, Thumbi Ndung'u, Nina Russell, Jeremiah Johnson, Maureen Luba, Anthony S Fauci, Lynn Morris, Giuseppe Pantaleo, Susan Buchbinder, Glenda Gray, Johan Vekemans, Jerome H Kim, Yves Levy, Lawrence Corey, Robin Shattock, Michael Makanga, Carolyn Williamson, Carl Dieffenbach, Maureen M Goodenow, Yiming Shao, Silvija Staprans, Mitchell Warren, Margaret I Johnston

Introduction

Despite substantial progress in understanding and treating HIV/AIDS, existing tools have not effectively controlled the epidemic, and the potential threat of resurgence looms as the largest cohort of young people in history enters early adulthood.[1] Treatment alone will not end the epidemic.[2–4] The International AIDS Society–*Lancet* Commission[1] recommends that global treatment efforts should be complemented with stronger investments in primary prevention, including research to accelerate the development of a preventive vaccine. Indeed, even a partially effective vaccine could help to change the course of the HIV epidemic and have a substantial public health impact.[5–8]

Developing a safe and effective preventive HIV vaccine has proven to be an exceptional challenge. After more than 30 years of HIV vaccine research and development, the possibility of an efficacious vaccine is now tangible, with multiple efficacy trials underway and with novel HIV vaccine concepts in the pipeline. However, the field is unprepared for the challenges that follow testing in trial settings. For example, for an efficacious vaccine candidate in a high-burden, resource-constrained setting (eg, sub-Saharan Africa) with little or no financially sustainable market, there are substantial resource and operational challenges associated with process development, manufacturing scale-up, and deployment. This situation reflects, in part, a paucity of corporate and other partners who are willing to make large investments at a high risk of a low financial return. The mix of cautious optimism and measured realism presents a timely and pivotal opportunity to reflect on key issues and challenges in HIV vaccine development, and to call attention to the crucial importance of expanded investment and stronger collaboration across geographies, sectors, and disciplines.

Challenges and needs in the HIV vaccine field

HIV vaccine research and development efforts are hindered by numerous challenges.[9] Primarily, to ensure rapid follow-on in the event of an efficacious vaccine, substantial investment is required now, before any efficacy trial results and from as yet unidentified sources.[10] Additionally, there is a persistent need for increased funding across all aspects of HIV vaccine research and development. In this Viewpoint, we provide an overview of key priority issues in the HIV vaccine field.[9]

The time to plan for success is now

The HIV vaccine field is undergoing an unprecedented level of late-stage clinical activity, with three vaccine efficacy trials underway in southern Africa.[11] HVTN 702 (Uhambo; NCT02968849) is a phase 2b/3 trial evaluating the safety and efficacy of the so-called prime-boost ALVAC-HIV vaccine plus bivalent gp120 protein adjuvanted with MF59 regimen in 5400 adult men and women in South Africa. The safety and efficacy of another prime-boost regimen, Janssen's (Beerse, Belgium) Ad26-mosaic vaccine plus a gp140 protein vaccine, is being assessed in the phase 2b Imbokodo study (HVTN 705/HPX2008; NCT03060629) in 2600 adult women in South Africa and other sub-Saharan countries. A second efficacy trial of this strategy in men who have sex with men is also about to start (HVTN 706/HPX3002/Mosaico; NCT03964415). Both HVTN 702 and HVTN 705 are expected to be completed in 2022, with HVTN 706 soon after. Another phase 2b study, PrEPVacc (NCT04066881), underway in sub-Saharan Africa, will assess the combination of an HIV vaccine (DNA, modified vaccinia Ankara Virus, and Env protein plus adjuvant) and pre-exposure prophylaxis using an adaptive trial design.[12–17]

In parallel with these ongoing vaccine studies, the Antibody Mediated Prevention programme is testing passive antibody immunity in two phase 2b trials. HVTN 703/HPTN 081 (NCT02568215) is testing the regimen in women in seven countries in sub-Saharan Africa whereas HVTN 704/HPTN 085 (NCT02716675) is being done in men who have sex with men and transgender women and men in the USA, Peru, Brazil, and Switzerland. Broader and more potent antibodies are rapidly entering the pipeline, alone and in combination, and evaluation of a more practical delivery route is being planned. If the Antibody Mediated Prevention approach proves to be effective, the development of broadly neutralising antibodies will continue, but will also face challenges related to large-scale manufacturing and delivery.[18,19]

The Chinese Center for Disease Control and Prevention team are also moving vaccine products towards efficacy trials following early phase (ChiaCTR-PRC-10001287; NCT01705223) studies of a DNA prime and replication competent recombinant vaccinia Tiantan vector booster regimen (ChiCTR1900021442).[20]

The path to market for HIV vaccine candidates

Despite the pipeline of promising vaccine candidates, gaps in late-stage development need to be addressed.

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The Desmond Tutu HIV Centre (Prof L-G Bekker MD) **and Division of Medical Virology, Faculty of Health Sciences** (Prof C Williamson PhD), **University of Cape Town, Cape Town, South Africa; Bridge HIV, San Francisco Department of Public Health, San Francisco, CA, USA** (Prof S Buchbinder MD); **Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (Prof L Corey MD); **France Recherche Nord and Sud Sida-HIV Hépatites, Paris, France** (Prof F Dabis PhD); **National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA** (C Dieffenbach PhD, A S Fauci MD, M Marovich MD); **International AIDS Vaccine Initiative, New York, NY, USA** (M Feinberg PhD); **The Office of AIDS Research, National Institutes of Health, Bethesda, MD, USA** (Prof M M Goodenow PhD); **South African Medical Research Council, Cape Town, South Africa** (Prof G Gray MD); **Treatment Action Group, New York, NY, USA** (J Johnson MPH); **Medical Research Council/Uganda Virus Research Institute and The London School of Hygiene & Tropical Medicine Uganda Research Unit, Entebbe, Uganda** (Prof P Kaleebu PhD); **International Vaccine Institute, Seoul, South Korea** (Prof J H Kim MD); **Vaccine Research Institute, Creteil, France** (Prof Y Levy PhD); **INSERM U955, University Paris-Est Créteil, Créteil, France** (Prof Y Levy); **AIDS Vaccine Advocacy Coalition, New York, NY, USA** (M Luba BPA, M Warren BA); **European and Developing Countries Clinical Trials Partnership, The Hague, Netherlands** (M Makanga PhD); **National Institute for Communicable Diseases of the**

National Health Laboratory Service, Johannesburg, South Africa (Prof L Morris PhD); **Center for the AIDS Program of Research in South Africa** (Prof L Morris) **and Africa Health Research Institute, HIV Pathogenesis Programme** (Prof T Ndung'u PhD), **University of KwaZulu-Natal, Durban, South Africa; Medical Research Council Antibody Immunity Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (Prof L Morris); **Service of Immunology and Allergy and Swiss Vaccine Research Institute, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland** (Prof G Pantaleo MD); **Bill & Melinda Gates Foundation, Seattle, WA, USA** (N Russell MD, S Staprans PhD); **State Key Laboratory for Infectious Disease Prevention and Control, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Beijing, China** (Y Shao PhD); **Department of Medicine, Imperial College London, London, UK** (Prof R Shattock PhD); **International AIDS Society, Geneva, Switzerland** (R Tatoud PhD, M I Johnston PhD); **and World Health Organization, Geneva, Switzerland** (J Vekemans PhD)

Correspondence to:
Prof L-G Bekker, The Desmond Tutu HIV Centre, University of Cape Town, Cape Town 7925, South Africa
linda-gail.bekker@hiv-research.org.za

Recent events in the malaria vaccine field starkly exposed the immense challenges that the HIV vaccine field will face. Since partial efficacy of the multidose malaria vaccine RTS,S was shown in 2014, GlaxoSmithKline (Brentford, UK) and its partners have been navigating complex regulatory and implementation planning processes, resulting in multiple, multiyear pilot studies, the first of which started in 2019 in Malawi and Ghana.[21] Widespread roll-out of the vaccine is years away and will need further funding, even if the outcomes of pilot studies are favourable.

Should an HIV vaccine warrant consideration for licensure, several issues will need to be addressed to ensure vaccine access. The potential public health benefits, feasibility, and costs need to be understood, especially for a multidose regimen. Regulatory requirements, manufacturing scale-up, and deployment of an efficacious vaccine need to be tackled.[22] Given the perceived relatively small commercial opportunity associated with developing an HIV vaccine for high-incidence countries compared with industrialised countries, new solutions will be necessary. Resource-intensive requirements include process development, bridging studies, and large-scale manufacturing. New manufacturing capacity and technology transfer to third parties, potentially in Asia or sub-Saharan Africa, might be required. Engagement of existing adjuvant vaccine manufacturers from developing countries, which supply 70% of the world's global health vaccine needs, or creation of new manufacturing capacity in high-burden countries, will necessitate the development of a strong business case to make this an attractive endeavour.

Successful vaccine access and delivery will hinge on extensive stakeholder engagement and careful planning. The multidose, multicomponent regimens in development, and the shortage of existing health-care programmes that target many of the populations that are likely to be prioritised to receive an HIV vaccine, pose a substantial challenge. The identification of target populations, development of workable delivery channels, and estimating demand is crucial. Determining the optimal target populations will be likely to depend, in part, on the level of observed efficacy and availability of doses.[23]

A potential way forward for the RTS,S malaria vaccine and similar vaccines is to conceptualise a full public health value proposition for vaccines.[24] Consensus at the level of institutions, such as WHO, on such a proposition for vaccines could provide the necessary incentives for commercial entities to invest in vaccine research and development, as well as encourage country government buy-in. Diverse stakeholders, including health-care providers, community representatives, disease modellers, health economists, vaccine developers, funders, and decision makers across government departments, are all needed at the table.[25] The role and timing of engagement of organisations such as Gavi, the Vaccine Alliance, and the Strategic Advisory Group of Experts on Immunization, needs to be defined.

A multistakeholder meeting hosted by WHO in 2018 sparked discussions towards an HIV vaccine target product profile and made clear that additional consensus conversations are needed now. In addition to WHO prequalification, local regulatory capacity for licensing an HIV vaccine in high-burden countries will be essential. A joint review sponsored by WHO and the Dengue Vaccine Initiative allowed early adopter countries to review the Sanofi dengue vaccine dossier with regulators from WHO, consultants and advisors from the US Food and Drug Administration, and the UK-based Medicines and Healthcare products Regulatory Agency.[26] Although regulatory strategies are being explored by individual vaccine sponsors, this precedent shows how stakeholders can work together to support regulators in sub-Saharan Africa, or to build on other initiatives in the area.[27,28]

Innovative trial designs

Future efficacy trials will be challenged by the evolving nature of the HIV epidemic.[29] The combined effect of greater treatment coverage and new prevention modalities has led to the welcome, but difficult, problem that reduced incidence plays in efficacy trial design. A conference hosted by the Fred Hutchinson Cancer Research Center in November, 2018, raised discussion points on ethical considerations, and the need for more affordable and feasible trial designs that still meet regulatory requirements.[30]

Strengthening the pipeline

Dozens of early-stage HIV vaccine candidates are largely guided by one or more of three general immune system targeting strategies, namely: stimulating the production of broadly neutralising antibodies, eliciting non-neutralising anti-HIV antibodies, and achieving T-cell-mediated control or clearance of HIV.[31] Moreover, clinical efficacy data will be crucial for the identification and validation of immune correlates of protection, which would catalyse the rational design of new candidates and accelerate clinical development.[13,32]

Over the coming years, concerted research will be needed to further test existing and new immune strategies. For example, deciphering the mechanisms associated with the generation of broadly neutralising antibodies and exploring how their generation can be recapitulated by vaccination is important.[33] Ongoing efficacy studies will elucidate whether non-broadly neutralising antibody binding antibodies can provide substantial protection from HIV infection. Identification of strategies that improve the durability of anti-envelope antibodies is another recalcitrant challenge and evidence that gut and vaginal microbiomes play key roles in HIV risk is also emerging.[34] Ongoing and planned human clinical trials will help us to understand the predictive value of preclinical mouse models[35] and non-human

primate models in protection.[36,37] Qualifying immune response measurements to be used in correlates of protection studies is another area that needs to be addressed.[38]

The HIV vaccine research and development field has benefited from the establishment of large, global, and highly collaborative research and clinical networks funded in the USA. Examples of these include the Collaboration for AIDS Vaccine Discovery, Centers for HIV/AIDS Vaccine Immunology & Immunogen Discovery, Consortia for HIV/AIDS Vaccine Development, and ADVANCE (Accelerate the Development of Vaccines and New Technologies to Combat the AIDS Epidemic). Examples from Europe include the European HIV Alliance and European AIDS Vaccine Initiative 2020. AIDS vaccine initiatives in Africa and Asia, such as the African AIDS Vaccine Programme and AIDS Vaccine Asian Networks, are also important given the high HIV burden in these regions.[39] In addition to these and other initiatives, increased information sharing and exchange of vaccine materials would assist collaborative efforts across networks and with researchers in Africa, Asia, and other regions, while recognising the importance of country ownership. At the same time, increasing awareness and knowledge of product development and access challenges, knowledge gaps, and risks will help ensure that stakeholders—even at a basic research level—share a focus on developing an HIV vaccine for populations in need.

New approaches and models

HIV vaccine research and development requires a substantial level of sustained resources and support from diverse partners. Unfortunately, funding for HIV vaccine research and development has declined since 2010, with approximately 85% of funding coming from only two sources: the US Government and the Bill & Melinda Gates Foundation (figure).[40,41] The Chinese Government has scaled up funding since 2006. Some governments have been reluctant or unable to fund HIV vaccine research and development because of competing priorities or structural constraints (such as difficulty integrating HIV vaccine funding within broader HIV or infectious disease funding portfolios).[10] Governments in emerging economies should be encouraged to support vaccine research and, if possible, commercial entities from these countries should be considered in the production of sustainable, low cost vaccines.

International development agencies are often focused on community-based programme delivery and might not have the latitude or appropriate mechanisms, such as product development partnerships, to invest in HIV vaccine research and development. Most industry players have stepped away from substantial investments given the scientific challenges and uncertainty for success combined with the absence of commercially viable models. Janssen's pursuit of a global vaccine designed to

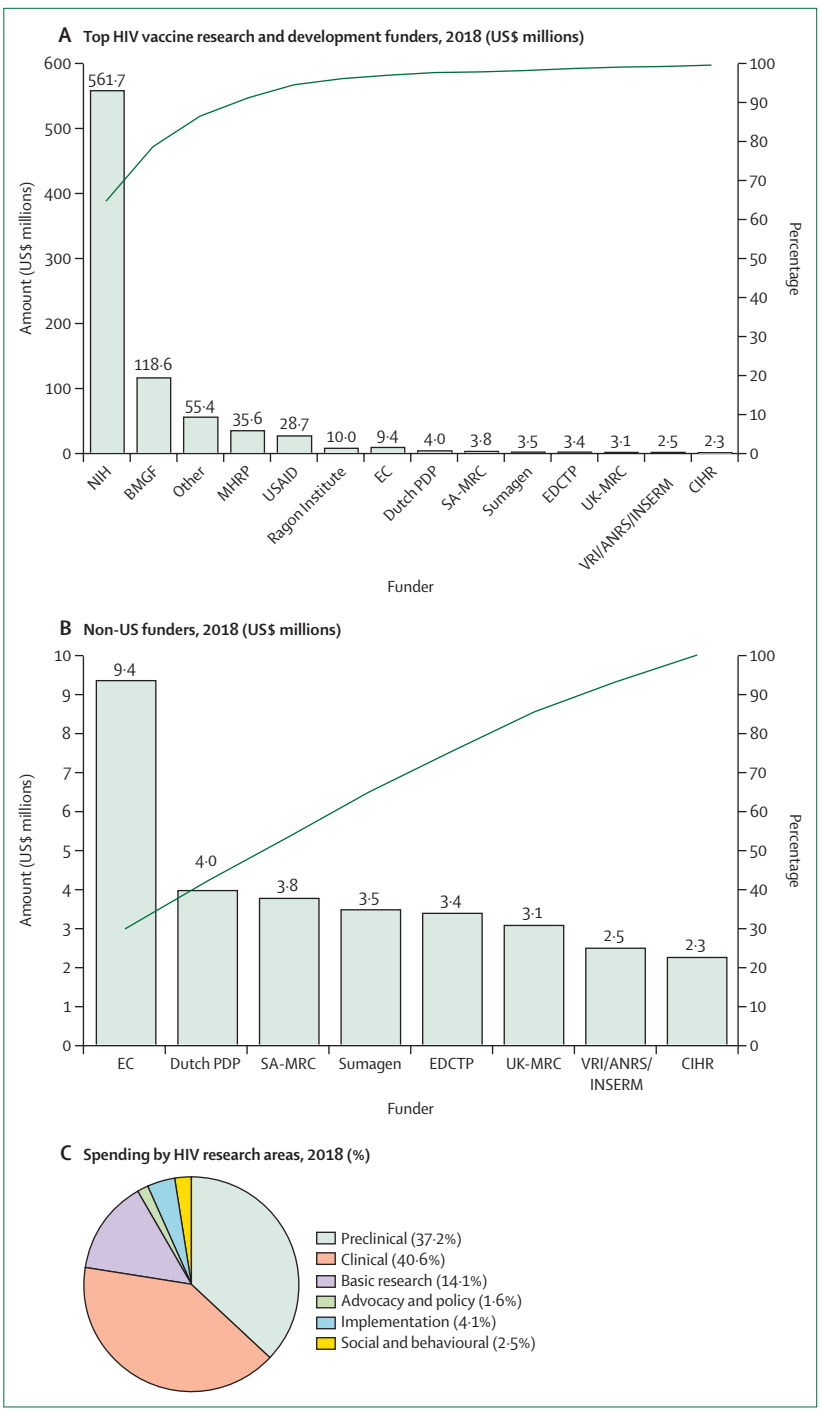

Figure: **Top preventive HIV vaccine research and development funders (A, B), and proportion of spending on HIV vaccine research areas (C)**

ANRS=French National Agency for Research on AIDS & Viral Hepatitis. BMGF=Bill & Melinda Gates Foundation. CIHR=Canadian Institutes of Health Research. Dutch PDP=Dutch Product Development partnership. EC=European Commission. EDCTP=European and Developing Countries Clinical Trials Development partnership. INSERM=French National Institute of Health and Medical Research. MHRP=US Military HIV Research Program. NIH=National Institutes of Health. USAID=US Agency for International Development. SA-MRC=South African Medical Research Council. UK-MRC=UK Medical Research Council. VRI=Vaccine Research Institute.

***Panel:* Steps to be taken following the completion of HIV vaccine efficacy trials*†**

1 The vaccine is provided to placebo recipients and effectiveness, regimen optimisation, and bridging studies are initiated
2 A full public health value of vaccine analysis with business investment case is made available to potential manufacturers, the WHO Strategic Advisory Group of Experts (SAGE), Gavi, the Vaccine Alliance, regulators, and other stakeholders (including national immunisation technical advisory groups of early adopter countries)
   - Doing so requires knowledge of target population and the delivery platform with modelling for demand
3 The vaccine manufacturer starts scale-up of production, assuming that lot-to-lot consistency and bridging studies after any necessary licensing and technology transfer has occurred
4 An application is made for approval by the National Regulatory Authority (NRA) of the manufacturing country (eg, European Medicines Agency, US Food and Drug Administration, Drug Controller General of India)
5 A prequalification application is made to WHO (after approval by the NRA)
6 WHO prequalifies the vaccine, allowing purchase by UN agencies (eg, UNICEF)
7 Gavi supports the creation of a stockpile, then subsidises or eliminates the cost to lowest income countries
8 The WHO SAGE gives a strong recommendation for deployment
9 National immunisation technical advisory groups with political support add the vaccine to the national immunisation programme

*Assuming an efficacy of >80% (the HVTN 702 study is powered for a primary endpoint of >50% at 3-year follow-up).
†The steps in this panel could occur concurrently.

have cross-clade efficacy, which could prove suitable for both resource-rich and resource-constrained countries, has the potential to shift thinking and influence greater investment from industry.

The funding situation—both in terms of total resources invested and the ongoing collaborative structures—is no longer sufficient to address all essential HIV vaccine development priorities, especially late-stage activities such as process development, manufacturing scale-up, and preparing markets for vaccine uptake and health systems for vaccine delivery. Entities that could address these and other vaccine related funding gaps are not positioned to serve some very high-need markets, exemplified in the ineligibility of particular countries such as South Africa for Gavi funding. This mismatch between resource needs and funding vehicles will need new or modified funding solutions.

Ensuring that a safe and effective HIV vaccine will be approved in multiple countries and rolled out as expeditiously as possible necessitates substantial at-risk investment in downstream activities—preferably beginning before efficacy signals are reported. Investing in planning activities could be more cost-effective if applicable to HIV vaccine development generally, independent of platform or regimen. An ideal set of downstream activities are highlighted in the panel. In parallel, the field must maintain, if not increase, support for early-stage research to propel the pipeline of new vaccine candidates. Support for the harmonisation of regulatory capacity in developing countries is an important step to prepare for vaccine successes. Finally, new vaccine initiatives will need to align with—and leverage when possible—research and development programmes, partnerships, and resources for other diseases (eg, tuberculosis and emerging pathogens), and integrate with the broader global health agenda.[1]

Addressing important challenges

The challenges of developing and deploying an HIV vaccine are many and the approaches needed to tackle those challenges will depend on greater coordination, collaboration, and increased and diverse resources. Maintaining the status quo will result in a substantial delay or forfeit of the health, social, and economic effect that an effective vaccine would bring, as has been the case with other much needed public health vaccines.

Since 2005, the Global HIV Vaccine Enterprise (the Enterprise) has supported the field as a neutral convener and facilitator, committed to identifying gaps and mobilising stakeholders to accelerate HIV vaccine development.[39] We have supported the development of, and enthusiastically endorse, the Enterprise's new strategy (2018–23) and new home within the International AIDS Society.[9]

As results from efficacy-stage studies are eagerly awaited (as soon as 2021–22), all possible outcomes must be anticipated. The downstream stages of vaccine development must be swifty supported and the possibility that efficacy levels or durability might not be sufficient to warrant deployment must be recognised. The possibility of less than full success underscores the crucial importance of a diverse pipeline of next-generation candidates. Activities that galvanise efforts and investment across the field—through the Enterprise and other key players—are essential to the development of an HIV vaccine that will help change the course of the epidemic and will have a substantial effect on global public health.

Contributors
L-GB, MIJ, and RT wrote the first draft. All authors contributed to content and finalisation of this Viewpoint. All authors signed off the final version.

Declaration of interests
We declare no competing interests.

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RT is employed by the International AIDS Society as the enterprise progamme director and MIJ as a senior advisor to The International AIDS Society. L-GB, SB, LC, FD, CD, MF, GG, JHK, MM, NR, RS, MMG, ML, and JV all serve on the external advisory group of the Global HIV Vaccine Enterprise.

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