

HIV vaccine clinical trials: An overview

Jackline Odhiambo

HIV Vaccine Trials Network
Cape Town, South Africa

Correspondence to:

Jackline Odhiambo
Hutchinson Centre Research Institute
of South Africa (HCRISA)
First Floor, Wembley Square 3
McKenzie Street, Gardens
Cape Town 8001, South Africa
+27 76 302 5393
jodhiamb@hcrisa.org.za

Abstract

More than 30 years after the discovery of the human immunodeficiency virus as the agent that causes AIDS, an effective vaccine against this deadly disease has yet to be developed. The pathway to the development of a vaccine has been riddled with challenges, many unique to HIV itself. As a result, advocates, scientists, and funders have had to move away from a “home run” philosophy that had anticipated early success. Nonetheless, much has been learned along the way about the genetic diversity of the virus, the limitations of animal studies, and the cultural infrastructure and regulatory challenges involved in testing HIV vaccines. The application of coordinated approaches to face the difficulties outlined in this article is a logical way forward in developing a vaccine. Then even more progress can be made, in spite of all the uncertainties, toward the achievement of a successful vaccine.

A vaccine is a substance that teaches the body's immune system to recognise and defend against harmful viruses or bacteria by stimulating the production of specific antibodies and thereby producing immunity to a disease.¹ Vaccines are prepared from the disease pathogen or its products, or from synthetic substitutes that act like antigens without inducing disease; vaccines are typically administered through injections, orally, or by aerosol.

Vaccines are the most safe and cost-effective way to prevent and eliminate infectious diseases, disability, and death. Preventive/prophylactic vaccines given before exposure to a disease enable the body to build protective mechanisms against infection when one is still healthy, therefore averting future illness. Examples include vaccines against meningitis, influenza, polio, smallpox, measles, rubella, and hepatitis. A vaccine against the human immunodeficiency virus (HIV) would be no exception in terms of impact in the fight against this pandemic.¹ A therapeutic vaccine (which treats disease in individuals who are infected by stimulating the immune system to target diseased cells, thereby improving immune response and enabling the body to curb or exterminate a pathogen) would also have an impact against HIV by reducing the infectiousness (viral load) of those already infected.

HIV, the pathogen that causes AIDS, can be transmitted when a person's body fluids (blood, genital secretions) come into contact with those of an infected person, through sexual contact (the main way the disease spreads) or by needle-sharing amongst intravenous drug users. HIV impairs the immune system over time leading to AIDS. When the body's white blood cells are destroyed, the ability to fight off other diseases is compromised. Active treatment with anti-retroviral (ARV) drugs, which help to maintain or restore immune function, can keep people healthy for years. To manage and end the spread of HIV, a variety of highly effective preventive strategies, best used in combination, is required. A comprehensive toolkit to prevent HIV transmission would include the use of ARVs (antiretroviral therapy as prevention (TAsP) to minimize the infectiousness of HIV-infected persons, Pre-Exposure Prophylaxis (PrEP), Post-



Exposure Prophylaxis (PEP)), behavioural changes, male circumcision, microbicides, needle/syringe exchange programs, and a vaccine, among other strategies.² If inoculation with a HIV vaccine reduces the number of people who become infected with HIV, there will be a significant decrease in the number of people in the population who can pass the virus on to others. By preventing future infections, spread of the disease can be halted, and in the process, save millions of lives. Even if the vaccine were of low efficacy and with limited coverage, the effect would still be significant from a public health perspective.³ Vaccines are the only prevention modality that do not rely on sustained behaviour modification.⁴

Although researchers have been working for many years to develop a vaccine that would treat or prevent HIV infection, little headway has been made. Many potential vaccines have been developed in the past, but none have been good enough for approval. (For information on past and current preventive HIV vaccine trials, see <http://www.iavi.org/trials-database/>). This is because of numerous challenges experienced in creating a successful HIV vaccine, including the fact that this lentivirus mutates much faster than other viruses, thereby making it difficult to target.⁵ Another reason is that HIV targets the immune system, which is the very thing a vaccine would try to trigger to elicit protection, so

developing a vaccine to activate the immune system without adversely affecting it like the virus would is not an easy task.⁵ The issue of waning immunity over time after receipt of a vaccine is another challenge.⁴ In short, for an HIV vaccine to be considered successful, it would have to substantially affect acquisition of infection (if preventive), progression of disease among the already infected, or the infectiousness of the infected (if therapeutic).⁶

HIV vaccine development and trials

The process of HIV vaccine development, testing, and regulation follows much the same pathway as that of other vaccines, with the stages outlined in Table 1.

Factors to consider for HIV vaccine studies

Developmental strategy complexities

HIV vaccine development is a challenging, complex, and lengthy process, scientifically and operationally. The number of participants in vaccine clinical trials is usually greater than in non-vaccine drug trials because vaccines are generally tested more thoroughly, and scrutiny by approval bodies is more intense.⁹ The time and cost resource requirements of testing these vaccines deters investment in vaccine development by manufacturers; such investment is

perceived as risky,¹⁰ even more so for HIV.

Successful development of effective HIV preventive and/or therapeutic vaccines requires that many different candidate vaccines be studied simultaneously in different populations around the world. Research is currently underway on different HIV immunisation concepts/modalities for efficacy based on non-human primate studies and results from earlier trials, as summarised in Table 2.

Additionally, in Africa, the region hardest hit by the epidemic, HIV vaccine clinical trials face unique community, ethical, political, regulatory, and scientific challenges.¹⁶ These challenges include weak or vaccine research-inexperienced national regulatory authorities (RAs), inadequately resourced institutions, undeveloped clinical and laboratory infrastructure, and sub-standard participant recruitment strategies that may exploit communities with high rates of illiteracy.

Given these considerations, no entity can single-handedly overcome the hurdles associated with HIV vaccine development. Indeed there is an urgent ethical need for global support, political will, and collaboration to find a HIV vaccine. This necessitates significant international cooperation over time, drawing on partners from various health sectors, intergovernmental organisations, government, research institutions, industry, and affected populations.⁴ Countries with scientific expertise and resources must assist countries that lack infrastructure and regulatory and ethical capacity to conduct trials.

Infrastructure and oversight needs

Research sites with insufficient infrastructure often need time to develop facilities (clinic, laboratory, and human capacity), which can take some years to achieve – something to be factored in while building developmental strategies to ensure host countries and communities can meaningfully participate in vaccine development, ensure scientific and ethical conduct of vaccine studies, and function as equal partners with other stakeholders in a collaborative process. To facilitate timely approvals of research, regulatory expertise may also need to be strengthened. Regional regulatory harmonisation could hasten the process and enable a wide knowledge-sharing base. The WHO-supported African Vaccine Regulatory Forum (AVAREF) is one such



Table 1. HIV vaccine development pathway

Stage	Description	Additional Notes
Exploratory ⁵	<ul style="list-style-type: none"> ● Basic laboratory research conducted by academic or government researchers ● Discovery of natural or synthetic antigens that might help prevent HIV or modify effects of the virus. ● Antigens may include virus-like particles (made in the lab for preventive vaccines), or other substances derived from HIV. ● Duration: 2 to 4 years. 	
Pre-clinical studies ^{4,5}	<ul style="list-style-type: none"> ● Conducted by biopharmaceutical companies. ● Tissue-/cell-culture systems used to assess safety/potential toxicities of candidate vaccine &, crucially, its immunogenicity (ability to induce an immune response). ● Extensive animal testing (challenge studies) also done, involving NHPs, or non-human primates (monkeys), and other animals. Usually shed some light on cellular responses that might be expected in human beings (though protection using these models of prediction has been particularly difficult with candidate HIV vaccines so far). ● May test for safe starting dose for next phase of research & a safe way to administer the vaccine. Injections, including biojectors (needle-free injections) and infusions have been tested. ● Duration: 1 to 2 years. ● Successful candidate vaccines proceed to clinical studies. 	<ul style="list-style-type: none"> ● Adjuvant (substance that enhances magnitude & durability of immune responses elicited by vaccine) may be added to potential vaccine to make it more effective. ● Prime-boost technique of vaccination is being studied, where booster doses are given following vaccination with primary vaccine to prolong durability of protection (peak immunogenicity) to counteract inadequacy of primary vaccination alone (waning effect). ● Many candidate vaccines flop at this stage as they do not induce desired immune response.⁴
Clinical development ^{5,6,7,8}	<ul style="list-style-type: none"> ● Does not involve vaccinating human subjects & then intentionally exposing them to HIV. ● Starts with Investigational New Drug (IND) application by study sponsor (typically a private company) to a Regulatory Authorities (RA) of country(ies) in which vaccine may be marketed. ● Study also subject to ethical review. ● Vaccine, like other drugs, undergoes a series of clinical trials, Phase I to IV: <p><i>Phase I</i></p> <ul style="list-style-type: none"> ● Involves a small number of adult participants (20-80) who are at low risk for HIV acquisition. ● Conducted to assess safety in humans (tolerability, dose ranges) & determine immunization regimens. ● Follow-up for adverse effects and/or vaccine reactogenicity (local or systemic signs & symptoms post-vaccination like pain, swelling, redness at injection site, fever, malaise etc.). ● Blood samples also drawn to estimate preliminary immunogenicity (type and extent) to HIV elicited by vaccine. ● Responses may or may not be protective against HIV; larger trials needed to determine this. ● Promising results lead to next testing phase. 	<ul style="list-style-type: none"> ● Information about experimental vaccine, risks and benefits of study participation, participant rights & responsibilities is given before seeking consent from potential participants, & throughout trial participation. ● IND application includes: description of the vaccine manufacturing & testing processes, summary of the laboratory reports, and clinical study proposal. ● Study must have both ethical & regulatory approvals prior to commencement. ● The nature of each adverse event is defined in a standardised manner e.g. Injection site pain. ● Immunogenicity analysis include measurements of antibody levels & cell-mediated immunity. ● Studies may be blinded or open-label.

Continued on next page

HIV vaccine clinical trials – an overview – Odhiambo

Table 1. (Continued)

Stage	Description	Additional Notes
Exploratory ⁵	<p><i>Phase II</i></p> <ul style="list-style-type: none"> ● Involves up to several hundred participants. May include some individuals at higher risk for HIV acquisition. ● Purpose is to collect more safety data and more detailed assessment of immune responses. ● In Phase IIb studies, more emphasis placed on estimating efficacy. ● Randomized, double-blind, placebo-controlled, parallel group design is mostly used. ● Successful candidate vaccines move on to larger trials. 	<ul style="list-style-type: none"> ● Dosing data is collected; best immunisation schedule is determined. ● Best method of vaccine delivery also investigated.
Approval and Licensure ^{5,7}	<ul style="list-style-type: none"> ● After successful phase 3 trial proving efficacy, the vaccine would go through an approvals process for licensure. ● Sponsor submits a Biologics License Application [BLA] to the Regulatory Authorities (RAs). ● RA will conduct an inspection of the vaccine’s manufacturing facility and approve the product labelling of the vaccine following usability testing. 	
Post-Marketing Surveillance ⁵	<ul style="list-style-type: none"> ● Similar to other drugs/vaccines, various systems would be used to monitor the licensed HIV vaccine: <ul style="list-style-type: none"> ● adverse event reporting system & database that health care providers and consumers can report a suspected side effect into (pharmacovigilance). ● continuous inspection of the HIV vaccine manufacturing facilities by RAs. ● review or conduct of batch tests by RAs to ensure the vaccine is consistently safe for public use, unadulterated and efficacious. ● phase IV trials. <p><i>Phase III</i></p> <ul style="list-style-type: none"> ● Large trials involving thousands of people (high risk participants). ● Usually a public-private partnership. ● Incidence data in regions where vaccine will get tested is gathered when designing study, to inform sample size calculation & duration of follow-up, e.g. with an incidence of HIV of 1.5% per year in a population, ~5,000 volunteers would be needed to adequately power the study. ● HIV infection in the population is 1.5% per year ● Tests whether experimental vaccine: <ul style="list-style-type: none"> ● provides any protection against HIV infection, i.e. vaccine efficacy (VE), ● delays progression to AIDS should one get infected (by checking viral load or CD4 count), ● causes production of antibodies to HIV or other types of immune responses. ● Also assesses HIV vaccine safety in a large group of people for rare adverse effects. ● Randomised, double-blind, placebo-controlled, parallel group trial design. ● Study follow-up usually for 2 to 3 years. Participants receive regular HIV testing & risk reduction counselling. That the vaccine is experimental and not yet proven effective is emphasized to study participants. ● The questions of whether, and how well, the vaccine works should ideally be answered by a well-designed, well-planned, well-executed and well-controlled efficacy trial, with a statistically significant result. However, reality with HIV vaccines is that may need to do more than just one phase III trial with the same candidate. <p><i>Phase IV</i></p> <ul style="list-style-type: none"> ● Vaccine license-holder might elect to conduct these studies once vaccine is approved and in the market. ● Purpose would be to continue to test for vaccine safety, efficacy & other potential issues. 	<ul style="list-style-type: none"> ● Key beneficial effects of an HIV vaccine may not be realized directly to vaccinees directly, but at a population level through indirect effects (e.g. reduced infectiousness of infected vaccinees), which are not captured by typical efficacy trial endpoints. ● Higher the incidence, lower the number of participants and/or shorter the follow-up period.⁵ ● Assumption is that most participants will be exposed to HIV (unprotected sex, needle sharing) during follow-up in study. ● VE evaluated by comparing rate of HIV infection in active vaccine study arm with that in placebo arm. Differences detected, are further analysed to investigate whether due to chance or attributable to vaccine. Normal saline solution or some other inactive substance may be used as placebo.

initiative to build regulatory capacity where there is limited framework to approve vaccine studies. WHO also supports the Developing Country Vaccine Regulatory Network (DCVRN) in strengthening national RAs in low- and middle-income countries where vaccines are manufactured.^{4,5,17,18}

Community engagement

Local communities are often keen to be credible partners in HIV vaccine research efforts. To ensure sound ethics, scientific quality, relevance, and acceptability of the proposed research in the affected community, local representatives should be approached early; their involvement in the design, development, implementation, and distribution of results of HIV vaccine research should be sustained throughout. Community support on all these fronts is crucial.^{17,19}

Post-trial access

When developed, HIV vaccines should be made available and affordable to the population in need. Thus, when the research protocol is developed, it should include scientific justification of the selected population, a balance between risk to study participation and potential benefits to that population, and safeguards from potential harm (medical or social) to participants and exploitation of that community. HIV stigma, human rights discrimination (against women, users of injectable drugs, men who have sex with men, and sex workers). Limited healthcare options, limited

ability to understand the study and consent processes, legal factors, weak regulatory framework, and other factors may increase risk of harm to participants, and hamper the accessibility to potential participants.¹⁸

Institutional and regulatory oversight of recombinant DNA research

Institutional Biosafety Committees (IBCs) are responsible for reviewing research that involves recombinant DNA, RNA, other potentially infectious material, and transgenic animals, to provide recommendations on control of biohazards associated with the use of microbiological agents. Since HIV vaccines fall in this category because they could consist of substances derived from HIV or other viruses such as the canarypox, adenovirus, or cytomegalovirus vectors, IBCs must review and approve these studies, in addition to the usual regulatory and ethics permissions. IBCs represent the interests of the local community in terms of public health and the environment.²⁰

For similar reasons a HIV vaccine may be subject to approval for use as a genetically modified organism (GMO) product in some countries. For instance, in South Africa yet another layer of approval is required by the Department of Agriculture, Forestry and Fisheries (DAFF) for “intentional introduction of GMOs into the environment”.²¹

Vaccine manufacturing capacity

It is vital that a test HIV vaccine for an efficacy trial have consistent batch-to-batch production, with defined, reproducible specifications.¹⁸ It takes time to formulate a fully characterised vaccine, including stability and data regarding immunogenicity (its ability to provoke an immune response). Capacity to produce such a vaccine in large quantities over a certain period is another factor to consider. Adenovirus vector vaccines are popular as vaccine platforms as they satisfy all the above factors.²²

Local communities are often keen to be credible partners in HIV vaccine research efforts.

Impact of non-vaccine prevention measures on HIV incidence

Current and future efficacy trials for HIV-1, the most common and infectious type, face practical challenges as effective or partially effective non-vaccine prevention programs²³ with agents such as oral PrEP, are projected to decrease the incidence of HIV-1. This requires consideration during sample size calculation and other study design matters. If there is a decreased incidence of HIV-1, larger cohorts would be needed to power the studies sufficiently for demonstration of efficacy while also assessing safety of the vaccine, so there needs to be a way of monitoring uptake of the prevention programme. Depending on uptake or other events, there may need to be design adjustments

Table 2. HIV vaccine concepts currently under study for efficacy in humans

<p>Broadly neutralizing monoclonal antibodies (bnmAbs)</p>	<ul style="list-style-type: none"> ● Discovered from persons who were able to control the virus naturally without the use of ARVs for over 15 years, where antibodies bind to the CD4 cell site that HIV targets.¹¹ ● From in vitro studies, it is hoped that bnmAbs like VRC01 can be used to design reasonably efficacious preventive vaccines that give passive immunity in humans against different HIV strains.¹²
<p>Vaccines targeting specific HIV-1 strains^a</p>	<ul style="list-style-type: none"> ● Progress made from the Thai prime-boost trial (RV144).¹³ ● Different HIV-1 subtypes (clades) are found in different regions of the world, e.g. HIV-1 subtype C, found in the Southern Africa population, which is the target for the vCP2438 and Bivalent Subtype C gp120/MF59 prime-boost vaccine regimen.¹⁴
<p>Global vaccine targeting multiple HIV-1 strains</p>	<ul style="list-style-type: none"> ● Immunogens (proteins) assembled from natural sequences of different prevalent HIV-1 subtypes (collectively known as a mosaic antigen) to increase the range of immune responses for improved coverage (worldwide).⁹ ● Initial proof of concept study with the Ad26.Mos4.HIV (Ad26 vaccine) and Clade C gp140 (protein vaccine) prime-boost regimen, is initially being tested in young women at high risk of HIV infection.¹⁵

^aHIV-1 is one of the two types of HIV and the most common. The other type, HIV-2, is relatively uncommon, is less infectious, and has a lower mortality rate.

or modification of endpoints for ongoing studies.

Local reviewing bodies need to be aware of what is considered the standard of HIV prevention in their country, communities, or study populations in order to assure that sponsors address these issues in their trials with stated aims; appropriate ethical standards must also be upheld.⁴

Deficit of appropriate pre-clinical animal models

Several experimental HIV vaccine approaches in pre-clinical studies have elicited varying degrees of efficacy in non-human primates (chimpanzees, monkeys). Many of these approaches fail in clinical testing, underscoring the fact that although animal models are valuable in various ways, they are yet to be predictive of protection in humans. Therefore, we can then only truly obtain such information from human trials. This limitation should be considered by regulators when reviewing trial applications. As clinical trials are costly (human, financial, materials, laboratory resources), improvement on animal models is warranted.^{4,8}

Unknown immunological correlates of HIV/AIDS protection

While immunogenicity data or a probable mode of action should be provided to justify conducting a HIV vaccine trial, not enough is known currently in the field about the candidate vaccines/regimens/amount of immunogenic response to make rational go/no-go decisions with vaccine development. With most other diseases that can be prevented with vaccines, there is a correlation between the natural or vaccine-induced immune response and the protection against infection/disease. With HIV, a wide range of immune responses are seen when one becomes infected with the virus. Furthermore, these responses do not eradicate all of the infection in the body or prevent progression to AIDS. So not only is there no known reliable correlate of protection, but even the immunological mechanism is still unknown whereby a vaccine might protect, either by preventing the acquisition of disease or by modulating it. Lack of clear scientific criteria to support advancement into efficacy studies is a challenge. An option would be to submit a trial application without these correlates and use the proposed study to identify them. Current HIV vaccine develop-

ment strategies target the induction of both humoral immunity (antibody-mediated protective response involving B lymphocyte cells that recognize pathogens in blood or lymph) and cell-mediated immunity (protective response for pathogen-infected cells, tumor cells, or transplanted cells, following activation of antigen-sensitized T lymphocyte cells).^{4,8}

Genetic variation of HIV

The classification of HIV isolates from different geographical areas into genetic sub-types (clades) has enabled mapping of the epidemiological spread of infection, which has led to the rationale of selecting local isolates from trial sites as the basis of immunogens to be used in vaccine trials, for example subtype B in the Americas, subtype C in Africa, subtype E in Thailand. This heterogeneity in HIV lies particularly in the genes that encode for the gp120 and gp41 proteins. Unique circulating forms can also result from recombination among the different HIV subtypes. Despite this knowledge, it remains unclear what the relationship is between this genetic variability of HIV and any vaccine-induced protection observed. Trial investigations with experimental mosaic vaccines (that use proteins assembled from natural sequences of different prevalent HIV subtypes) may shed some light on this.^{4,8,18}

Vaccine-induced seropositivity

Whereas creating an antibody response is the goal of an HIV vaccine, such a response may lead to a reactive result if a vaccine recipient were to undergo routine HIV testing since these tests usually detect antibodies to HIV in the blood, and not the virus itself. This phenomenon is called vaccine-induced seropositivity (VISP).²⁴ VISP detection and duration rates vary greatly, depending on the product's potency, durability, dosing, and type of the test being used.

For study participants who receive a VISP-positive result, this can sometimes lead to incorrect diagnoses, which can cause stress and unnecessary complications such as challenges with insurance, military service, blood/tissue donation, immigration, and pregnancy (a false positive antibody test could lead to unnecessary ARV treatment of a baby). Testing outside the study can also lead to unblinding of the participant. This scenario can occur if a "positive" result is obtained during routine testing

conducted outside of the study, followed by in-study HIV-negative test results. When this occurs, it can compromise study data if the participant changes risk behaviour, even if unintentionally. It is therefore necessary for VISP education to emphasise to all participants the importance of getting all HIV testing done through the study or research site until their VISP is no longer detectable. A VISP registry to verify previous study participation and receipt of HIV vaccine product, to promptly facilitate further HIV testing, is indicated.

Reactogenicity data collection

The collection of data on specific adverse reactions (reactogenicity) after vaccine administration is a study process that must be implemented well. This would usually be in the form of diary cards, which are used to collect participant-recorded data on temperature, injection site reactions such as swelling or redness, among other solicited symptoms. These data contribute to the safety endpoints of vaccine studies, therefore participants need to be well trained on completing and returning the tool (keeping in mind recall bias and varying levels of cognitive abilities among participants) such that accurate and complete data are collected.

Sufficient time for antibody development

It takes time for sufficient antibodies to develop in the body such that the full protective picture is elicited and can be evaluated. This contributes to the length of time required for trial participant follow-up. If the study is conducted in a population at high risk of acquiring HIV, where more events could occur in a shorter timeframe, this period could potentially be 3 years; the time could be lessened if the sample size is very large. Correlates analyses should be planned prospectively in efficacy trial designs. Timing and frequency of collection of the appropriate specimens post-vaccination and post-infection (serum, plasma, blood cells, mucosal cells), as well as the handling and storage of specimens, must be considered. All HIV infections that occur during prevention trials should be characterized by subtyping and sequencing. Impact of any ARVs (if started) on viral load should be factored in. Of course, all of this need for data should be weighed against the operational costs and logistics of collection (participant study visits, risky or invasive sampling, and sample processing).⁴

Considerations regarding regulatory bodies

Statistical analysis plans submitted to approvers should be clear from the beginning on various issues including analysis of overall efficacy and subgroup results, timing of unblinding for analysis purposes, modified intention-to-treat analysis (if results are discordant, attention should be paid as to why).

The Informed consent process should relay the paradoxical potential risk to harm, rather than protect (greater risk of infection through risky behaviour or of disease progression in those who become infected), and referral to care if seroconversion occurs.^{4,18}

Conclusion

With HIV vaccine development, what is most important is not whether trials are in a particular phase but rather that studies are designed and carried out in a manner that supports the practice of sound and ethical science. That, ultimately, is what is needed to progress toward the goal of an approved HIV vaccine.⁴

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by her employer. or EMWA.

Conflicts of interest

The author declares no conflict of interest.

References

- Hiv.gov. HIV Vaccines. 2017 [cited 2017 Nov 11]. Available from: <https://www.hiv.gov/hiv-basics/hiv-prevention/potential-future-options/hiv-vaccines>.
- Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities. *Current HIV/AIDS reports*. 2011;8(1):62–72.
- Stover J, Bollinger L, Hecht R, Williams C, Roca E. The impact of an AIDS vaccine in developing countries: a new model and initial results. *Health Aff*. 2007;26(4):1147–58.
- Sheets RL, Zhou T, Knezevic I. Review of efficacy trials of HIV-1/AIDS vaccines and regulatory lessons learned: a review from a regulatory perspective. *Biologicals*. 2016;44(2):73–89.
- The History of Vaccines: An Educational Resource by The College of Physicians of Philadelphia. Vaccines for Sexually Transmitted Diseases. 2017 [cited 2017 Nov 11]. Available from: <https://www.historyofvaccines.org/content/articles/vaccines-sexually-transmitted-diseases>.
- Follmann D, Duerr A, Tabet S, Gilbert P, Moodie Z, Fast P, et al. *J Acquir Immune Defic Syndr*. 2007;44(1):49–60.
- HIV/AIDS vax - An IAVI Report Bulletin. Understanding Vaccine Trials: How are AIDS vaccines tested? 2003;1(1):4. Available from: The Bulletin on AIDS Vaccine Research. <http://www.vaxreport.org/vax-1-1-august-2003/869-understanding-vaccine-trials>.
- Esparza J. An HIV vaccine: how and when? *Bull World Health Organ*. 2001;79(12):1133–7.
- The History of Vaccines: An Educational Resource by The College of Physicians of Philadelphia. Vaccine Development, Testing, and Regulation. 2017 [cited 2017 Nov 04]. Available from: <https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation>.
- Black S. The costs and effectiveness of large Phase III pre-licensure vaccine clinical trials. *Expert Rev Vaccines*. 2015;14(12):1543–8.
- Wu X, Wang C, O'Dell S, Li Y, Keele BF, Yang Z, et al. Selection pressure on HIV-1 envelope by broadly neutralizing antibodies to the conserved CD4-binding site. *J Virol*. 2012;86(10):5844–56.
- AMP Study. About AMP: What is the AMP Study? 2017 [cited 2017 Nov 30]. Available from: <https://ampstudy.org.za/about>.
- U.S. Military HIV Research Program. RV144 Trial. 2017 [cited 2017 Dec 02]. Available from: <https://www.hivresearch.org/rv144-trial>.
- Uhambo: A Journey of Hope to Prevent HIV. What is HVTN 702? 2017 [cited 2017 Nov 30]. Available from: <http://www.uhambo.org.za/about>.
- Imbokodo: Stand up to HIV. What is Imbokodo? 2017 [cited 2017 Nov 30]. Available from: <https://www.imbokodo.org.za/about>.
- Vardas E, Buttò S, Glashoff R, Malnati MS, Poli G, Clerici M. Preparing for phase II/III HIV vaccine trials in Africa. *Microbes Infect*. 2005;7(14):1436–44.
- UNAIDS Guidance Document: Ethical considerations in HIV preventive vaccine research. 2000
- Scientific considerations for the regulation and clinical evaluation of HIV/AIDS preventive vaccines: report from a WHO-UNAIDS Consultation 13-15 March 2001, Geneva, Switzerland. *AIDS*. 2002;16(10):W15–25.
- Okpokoro E, Osawe S, Datong P, Yakubu A, Ukpogon M, Orhii P, et al. Preparing for HIV vaccine trials in Nigeria: building the capacity of the community and national coordinating, regulatory and ethical bodies. *J AIDS Clin Res*. 2013;4(12):260.
- National Institute of Environmental Health Sciences. Institutional Biosafety Committee. 2017 [cited 2017 Dec 03]. Available from: <https://www.niehs.nih.gov/about/boards/ibc/index.cfm>.
- Department of Agriculture, Forestry and Fisheries: Republic of South Africa. Biosafety Notifications. 2017 [cited 2017 Dec 03]. Available from: <http://www.daff.gov.za/daffweb3/Branches/Agricultural-Production-Health-Food-Safety/Genetic-Resources/Biosafety/Biosafety-Clearing-House>.
- Barouch DH, Picker LJ. Novel vaccine vectors for HIV-1. *Nat Rev Microbiol*. 2014;12(11):765–71.
- Excler JL, Michael NL. Lessons from HIV-1 vaccine efficacy trials. *Curr Opin HIV AIDS*. 2016;11(6):607–13.
- HIV Vaccine Trials Network. Getting the Right Test for HIV. [cited 2017 Nov 30]. Available from: <http://www.hvtn.org/en/participants/visp-hiv-testing.html>.

Author information

Jackline Odhiambo, B. Pharm, MSc. Clinical Trials, has held various roles in clinical research since 2009, including quality management. She is a project manager at the HIV Vaccine Trials Network, working with protocol chairs to support study operations and implementation.