I. About the Disease and Pathogen

Basic information on pathogen, including transmission, estimated global disease burden for those at risk, for morbidity and for mortality, including uncertainties/data gaps, geographical distribution, economic burden if available, age groups affected and target groups for vaccination. Existing preventive, diagnostic and treatment measures and their limitations.

Since the identification of HIV as the cause of AIDS, the pandemic has caused extensive global morbidity and mortality. In 2010, HIV was the 5th leading global cause of disability adjusted life years (DALYs), and the leading cause of DALYs in 21 countries[1]. In 2012 alone, UNAIDS estimates that 35.3 million persons are living with HIV, with 2.3 million new infections and 1.6 million deaths annually[2]. HIV remains a major global killer, with sub-Saharan Africa continuing to bear the greatest burden of disease. Transmission of HIV occurs through sexual intercourse, injection of blood or blood-derived products, and from mother-to-child during pregnancy, at delivery or through breast-feeding. Despite significant advances in HIV anti-retroviral development and delivery and new prevention technologies, development of a safe and effective HIV vaccine for prevention and control of AIDS remains a global public health priority and the best hope for eventually ending the AIDS pandemic.

II. Overview of Current Efforts

A. Biological feasibility for vaccine development

Where there are no vaccines available, this section should focus on the evidence that vaccine development is biologically feasible including from development of naturally acquired immunity, from vaccine development for related pathogens, from animal models or in vitro data

Unlike many infectious diseases, HIV infection does not generally result in protective immunity against subsequent exposure. While some individuals remain uninfected despite multiple exposures to HIV-1, immune-mediated correlates of protection have not been conclusively identified. However, adaptive immune responses do contribute to controlling HIV infection in a subset of infected persons termed elite controllers. Gag-specific CD8+ responses in many elite controllers can inhibit HIV-1 replication in ex vivo-infected cells, a phenotype not observed in HIV-1 progressors [3]. The contribution of cellular immunity to controlling infection has also been observed in rhesus macaque studies of simian immunodeficiency virus (SIV) challenge, although the correlates of protection are not well understood. Preclinical studies with genetically modified cytomegalovirus vectors have demonstrated the potential to elicit CD8+ effector memory cells restricted by both MHC-class I and MHC-class II, and control SIV to undetectable levels in approximately 50% of macaques immunized with CMV-SIV vaccines [4]. These studies are providing clues towards understanding how best to elicit cellular immune responses, to control and possibly abort HIV infection.

Most effective vaccines prevent infection by stimulating development of neutralizing antibodies. About 5% of HIV+ subjects develop potent neutralizing antibodies against HIV-1 Envelope (Env) that effectively neutralize a broad range of HIV-1 isolates in vitro [5]. A number of these broadly neutralizing monoclonal antibodies (bnAbs) have been isolated and characterized in detail. In vitro, combinations of such bnAbs can prevent infection of human CD4+ T cells by virtually all HIV isolates. In animal models, passive transfer of several different bnAbs can prevent infection at antibody concentrations that should be achievable by vaccination [6]. The activity and specificity of bnAbs is generating vaccine design hypotheses with the goal of eliciting broad neutralizing activity to prevent infection,
B. General approaches to vaccine development for this disease for low and middle income country markets

What are the scientific approaches and indications and target/age/geographic groups being pursued? What public health needs will these vaccines meet if successfully developed? Where there are several different possible indications/target groups, how much consensus is there as to prioritization between these for vaccine development in LMIC.

Multiple HIV vaccine candidates have been developed and tested clinically since 1986, yet only four vaccines have completed efficacy trials, with only one providing evidence for prevention of acquisition of HIV [7]. An Env subunit vaccine (gp120, VaxGen) formulated in alum failed to elicit antibodies that neutralized most isolates and to prevent or control HIV infection. An adenovirus type 5 vector (Ad5-gag-pol-nef; Merck) not only failed to control HIV infection, but surprisingly led to acquisition of more HIV infections in the vaccine versus placebo group, for reasons that remain unclear. Similarly, a DNA prime + Ad5 vector boost delivering gag-pol-nef and multiple Env genes (DNA + Ad5 HIV Vaccine, NIAID Vaccine Research Center), failed to prevent or control HIV infection. More promisingly, a prime-boost regimen of a Canarypox vector + gp120 boost (ALVAC- Sanofi; gp120-Vaxgen), designed to combine cellular and humoral immunity, demonstrated for the first time that a vaccine could prevent acquisition of HIV infection. This trial, termed RV-144, demonstrated 31.2% efficacy.

Once an HIV vaccine is found, target populations for vaccination include high risk groups exposed through sex or injected drug use in countries with concentrated epidemics and adolescents or young adults in countries with generalized epidemics. Vaccination of infants has also been proposed, however ancillary treatment with drugs or passive antibodies would be needed to prevent infection initially, until an immune response could develop.

III. Technical and Regulatory Assessment

Highlight perceived positive/negative aspects in clinical/regulatory pathways e.g. well established product development and regulatory pathway to licensure, accepted immune correlates and/or functional assays, accepted surrogate efficacy endpoints, existence of well accepted animal or challenge models, agreed trial designs and endpoints. Possibilities to develop case for correlates/surrogates should be included.

The choice of vaccine candidates for advancement is based on safety and immunogenicity from Phase 1 trials and on data from animal models. Over 210 HIV vaccine Phase 1 trials have been conducted in more than 30 countries, and regulators have been generally supportive of these small trials. Immune responses to HIV include neutralizing antibody, antibody that mediates other antiviral functions such as cell-mediated killing, and (primarily CD8) T cells that suppress virus growth or kill virus-infected cells. CD8+ T cells, particularly those directed at Gag, are correlated with control of virus replication in HIV-infected humans [3]. Antibodies to the V1V2 region of Env inversely correlated with HIV infection in the RV144 trial, but may have been blocked by IgA antibodies of similar specificity [8]. Activated CD4+ T cells are particularly vulnerable to HIV infection and infections with other agents may increase susceptibility to HIV.

The general consensus is that vaccine candidates should induce classical CD8 T effector or effector memory cells (restricted by Class I MHC) and/or neutralizing antibody. Some data, however, are not entirely consistent with this notion, including the presence of unconventional T effector cells in some macaques vaccinated with CMV vectors expressing multiple SIV antigens, which were almost completely
protected from SIV challenge, and the correlation of IgG Env V1V2 binding antibodies with protection in RV144, even though these antibodies do not neutralize HIV [4, 8].

The primary animal models of HIV infection include infection of the Rhesus macaque with SIV or a chimeric virus constructed of SIV with HIV Env (SHIV). The most common SIV strain used, mac239, is very difficult to neutralize. CD8+ T cells provide limited protection against this virus. SHIV constructs are generally less virulent and can be relatively easily neutralized by antibodies to HIV Env. Potent bnAbs can prevent infection by SHIV.

HIV vaccine efficacy trials have enrolled different populations, including men who have sex with men, injection drug users, heterosexual men and women at high risk and general population, respectively, in the Americas, South Africa and Thailand. As non-vaccine prevention methods, such as antiretroviral drug treatment of infected people to reduce their risk of transmission or of HIV negative vulnerable people before or just after exposure to HIV, become more effective and HIV prevalence drops, it will be more difficult to find appropriate at-risk individuals for such trials, and questions may be raised about the standard of preventive interventions that is required in these trials.

IV. Status of vaccine R&D activities

Summarize status of vaccine design, pre-clinical and clinical trial activity, including platforms, vectors, and adjuvants. Note academic, government, biotech and industry entities engaged. Summarize antigenic targets (if subunit approaches). Section on major advances in last 3-5 years, including key opportunities highlighted by recent science developments in the area.

Current efforts in HIV vaccine development include building from the RV-144 efficacy trial results, and developing candidate vaccines designed to elicit broader protection against HIV. Plans are underway to test the prime-boost regimen ALVAC + gp120 in South Africa, with additional booster immunizations aimed at extending durability of protection, and more potent adjuvants. If vaccine efficacy of >50% is demonstrated, a licensure application in South Africa is possible as early as 2021. In addition, test of concept efficacy trials are now under consideration for prime-boost regimens utilizing next generation pox vectors (NYVAC; Sanofi), gp120 boosters, and DNA in adaptive clinical trials. The Pox-Protein Public Private Partnership, consisting of Sanofi, Novartis, NIAID, Bill & Melinda Gates Foundation, MHRP, and the HIV Vaccine Clinical Trials Network are coordinating the planning of this next set of efficacy trials, potentially to include a trial of the RV144 vaccine regimen in a high-risk population of men who have sex with men in Thailand, and in heterosexual populations in Africa [9].

In parallel, vaccine development is ongoing with candidates aimed at addressing the hyper-variability of HIV, which is one of the major challenges impeding the development of a safe and effective HIV vaccine. Different hypotheses are addressing T cell and antibodies, respectively. Vaccines based on two different hypotheses to elicit broad cellular immune responses aimed at controlling HIV infection are in development. One utilizes conserved regions across the HIV genome, with the goal of focusing immune responses to those regions of HIV that are highly conserved and therefore may be required for viral replicative fitness (Oxford University, IAVI, EDCTP) [10]. The other, termed “mosaic antigens” used in silico methods (Los Alamos National Laboratories) to design immunogens representing diverse sequences from as many HIV strains as possible in a vaccine, for broad coverage of circulating viruses (Johnson and Johnson/Crucell, Beth Israel Deaconess Medical Center, NIAID, Ragon Institute) [11].

Work is progressing to design strategies to elicit bnAbs against HIV Env that can prevent HIV infection. Recent technological advances in B cell immunology, next generation sequencing and bioinformatics have now yielded several bnAbs, their binding sites on HIV Env, the structural characteristics of these binding sites with atomic precision, the structure of the HIV Env trimer which is the target for bnAbs, and insights on the evolution of bnAbs in HIV+ subjects [12]. Designing immunogens to elicit bnAbs
remains a major challenge, so in parallel, recent clinical trials are exploring passive antibody (NIH Vaccine Research Center, Rockefeller University) and delivery of bnAbs by gene transfer using aden-associated virus vector (Children’s Hospital of Philadelphia, IAVI) [13].

Finally, since the RV-144 trial showed that HIV acquisition could be prevented without bnAbs or robust CD8+ cellular immune responses, studies are ongoing to develop vaccines that elicit antibodies that work through other effector mechanisms, such as Fc mediated antibody-dependent cellular cytotoxicity [14].

Since the HIV vaccine field will not likely see data emerging from the next planned set of efficacy trials until 2019-2020, current promising leads, strategies and technologies are focused on advancing leading candidates through clinical development and improving the next generation of candidates entering clinical development. These include:

- HIV Env Trimers: Recent generation of the structure of a stabilized HIV Env trimer will lead to clinical evaluation of immunogens more closely mimicking the native Env spike.
- HIV Antibody Epitope Based Vaccines: Recent elucidation of at least five major epitopes on HIV Env that are the binding sites for bnAbs will lead to the generation of clinical candidates targeting each of these epitopes, including glycopeptides, computationally derived scaffolds and novel immunogens designed to bind to putative germline ancestors of the bnAbs.
- Sequential Immunization with Different Immunogens: Increased understanding of how bnAbs evolve along with virus evolution in the human host will lead to the testing of the hypothesis that sequential immunization with different immunogens may be required to drive antibody affinity maturation leading to bnAbs.
- Conserved/Mosaic Hybrids: Next generation immunogens to elicit broad cellular immune responses will take advantage of the attributes of both conserved and mosaic antigens, to drive breadth, depth and enhanced coverage of cellular immune responses by immunization.
- Replication Competent Viral Vectors: Replicating adenovirus, poxvirus and Sendai virus vectors are in preclinical and early clinical development, including vectors providing persistent infection, mucosal delivery, and targeting of the gut-associated lymphoid tissues, designed to mimic the efficacy of live attenuated vaccines.
- Antigen Presentation Systems and Novel Adjuvants: Several virus-like particle and nanoparticle antigen presentation systems are in development, along with novel adjuvants, based on advances in understanding innate and adaptive immune linkages to optimize vaccine-induced immunity.
- Synthetic Biology Technologies: Novel DNA and RNA vaccines are being explored in efforts to achieve the efficacy of viral vectors, while mitigating concerns for anti-vector immunity. Delivery of such genetic vaccines by electroporation has shown promise in clinical trials.
- Glycobiology: Advances in glycobiology are yielding important insights for HIV vaccine research, both in characterization and synthesis of targets recognized by bnAbs, and in strategies to manipulate vaccine-induced Fc-mediated immune responses such as ADCVI and ADCC.