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EDITORIAL

The quest for an HIV vaccine

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Despite the international community's best efforts the HIV pandemic countries unabated. In 2006, more than 39 million people were living with HIV worldwide. Over four million people became newly infected with HIV and an estimated 2.8 million lost their lives due to AIDS. On average, people require life-saving antiretroviral treatment (ARVs) 7-10 years after becoming infected. While there has been recent progress in increasing access to treatment and prevention programs, HIV continues to outplace the global response with at least 80% of those in clinical need of ARVs worldwide not receiving them. Further, while decline in national HIV prevalence has occurred in, for example, some sub-saharan African countries, these trends are not strong or widespread enough to have a major impact on the epidemics.

New technologies to prevent HIV transmission remain imperative. IAVI (International AIDS Vaccine Initiative) estimates the potential positive impact of AIDS vaccines would be enormous, especially in the developing world. Even in a relatively conservative scenario, an effective preventive HIV vaccine could prevent almost 30 million of the 150 million new infections projected in the coming decades. A highly effective vaccine could even prevent over 70 million infections in fifteen years. There is scientific progress underway in the search for an HIV vaccine. Presently, there are more than 30 clinical trials with vaccine candidates worldwide (1). Clinical trials for an candidate vaccine are divided into three distinct phases:

1. Phase I trials are the first human tests of a candidate vaccine, generally conducted on small numbers (10-30) of healthy adult volunteers who are not at risk for the disease in question. The main goal is evaluation of safety, and to a lesser extent, analysis of the immune responses evoked by the vaccine and of a different vaccine doses and immunization schedules. A phase I trial usually takes 8-12 months to complete.

2. Phase II testing involves a larger number of volunteers (50-500), usually a mixture of low-risk people and higher-risk individuals from the population where phaseIII (vaccine efficacy) trials will eventually be conducted. Phase II trials generate additional safety data as well as information for refining the dosage and immunization schedule. Although not set up to determine whether the vaccine actually works, Phase II trials are sometimes large enough to yield preliminary indications of efficacy. These trials generally take 18-24 months, with the increase over phase I due primarily to the additional time required for screening and enrolling larger numbers of trial participants.

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3. Phase III trials are the definitive test of whether a vaccine is effective in preventing disease. Using thousands of volunteers from high-risk populations in geographic regions where HIV is circulating, the incidence of HIV in vaccinated people is compared to that in people who receive a placebo. Successful demonstration of efficacy in a phase III trial can then lead to an application for licensure of the vaccine. Phase III trials of AIDS vaccines are generally expected to require a minimum of three years for enrollment, immunizations, and assessments of efficacy (1,2). In this section I will try to describe some experienced models of trials:

At least 60 phase I clinical trials of candidate vaccines against HIV/AIDS, three phase II trials & three phase III trials have been completed since 1990s, involving more than 35 different vaccine formulations, 14 different adjuvants and more than 15000 volunteers. Although several neutralization epitopes have been identified on the surface of the virus glycoprotein spikes, the design of an envelope-based HIV vaccine capable of eliciting broadly reactive neutralizing antibodies remains as an elusive goal. A gp 120-based vaccine, which was tested in phase III trials, one in the USA and the other in Thailand, was found to be devoid of protective efficacy in spite of repeated injections every 6 months. The observation that, in the monkey model, both viremia (virus load) and the clinical evolution of the disease are controlled by the CD8+ T cell response of the animals, has promoted the development of an array of vaccine candidates capable of inducing HIV-specific T cell responses. A series of HIV vaccines based on live virus vectors already are in clinical studies, including a live recombinant canary pox virus vaccine (ALVAC), which is in phase III in Thailand, a non replicative adenovirus type 5 (Ad 5) vaccine, which is entering phase II trial in the USA and the Caribbean's, and live recombinant vaccines based on the attenuated vaccine virus MVA vector, which already have been through several phase I studies either alone or in association with DNA vaccine priming. A whole array of other vaccines based on live vector vaccines, DNA, peptide and other designs, are being tested in nonhuman primates models. None of these vaccines has been able to prevent infection following challenge of the animals, but all were found to control viral loads and prevent CD4 loss. T cell stimulating vaccines illustrate the paradigm of vaccines which are unable to prevent infection, but are able to prevent the occurrence or slow down the evolution of disease through continuous control of virus replication, however, their efficacy in human volunteers remains to be proven (2,3).

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