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Editorial

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Current Status of Human Immunodeficiency Virus Vaccines

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Highly Active Antiretroviral Therapies (HAARTs) have been developed to treat HIV+ individuals, increasing the quality and quantity of life of many HIV+ patients. Despite these effective strategies, human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) epidemic continues to uphold globally with 39 million infected individuals.[1] However, the HIV retrovirus integrates into the (cluster of differentiation 4) CD4+ cells' genomes where it can persist for years in a latent stage forming HIV reservoirs throughout the body.[2] Due to these reservoirs, infected individuals need to be under treatment for the rest of their lives, as HAARTs cannot fully cure HIV.[3,4] As a result, preventive strategies have now been introduced in the plan to completely eradicate the HIV/AIDs endemic.[5] Effective preventative strategies that decrease bodily fluids transmissions like the usage of condoms, sterile needles, abstinence, monogamy between uninfected individuals, and voluntary testing have been developed. The development of vaccines as preventative and treatment strategies against HIV has been proposed to aid in the eradication of this disease.[5,6] Typically, vaccines have been successful in the disappearance of past endemics such as polio and small pox. Vaccine development for HIV began in the 1980's.[1] Two types of vaccines have been proposed: those as protection against acquisition of HIV-1 and those as treatment to cure HIV in conjunction with HAART.[1,5]

Vaccines with the purpose of reducing HIV acquisition are controversial due to its necessity to compete with the broad genetic diversity of HIV and overcome multiple transmission modalities.[7] Nonetheless, a few have gone through phase 3 and phase 2b clinical trials. Examples of these case trials include VAX 004, VAX 003, Step, Phambili, RV144, and HVTN 505. While efficacy in VAX 004, VAX 003, Step, and Phambili clinical studies were not achieved in regards to finding significant differences in HIV acquisition for both the vaccinated and placebo groups, another type of vaccine has had a more successful outcome.[8,9] The RV144 study showed the potential for an HIV/AIDS vaccine to prevent infectivity of HIV.[10] This study used a vaccine combining the bivalent (B/E) gp120 vaccine used in VAX 003 with an ALVAC vector prime. The results showed a 60.5% vaccine efficacy at 1 year and 31.2% vaccine efficacy at 3.5 years with ALVAC-HIV (vCP1521) (0, 1, 3, 6 months) followed by protein boosts with alum adjuvant, AIDS-VAX1 clades B/E gp120 (3, 6 months). Further studies using these vaccines have suggested that the V2 region of HIV-1 is a target site of protective antibodies associated with vaccine efficacy of the RV144 regimen.[11] Due to a reduced efficacy over time, there is a potential for waning immunity in respect to HIV acquisition over a period time after vaccination needs to be resolved. Currently, studies are being conducted to improve efficacy of this vaccine through the use of different adjuvants, MF591 and ASO1B, and improvement of B- and T-cell priming by the introduction of immunogenic vector platforms. Studies using vaccines with a replication-incompetent Ad26 vector in combination with MVA/trimeric gp140/ASO1B adjuvant have shown protection from mucosal challenge. In a non-human primate study, a correlation among envelope-specific non-neutralizing binding antibodies with protection against acquisition have been demonstrated.[11]

Vaccines as therapeutic treatment for HIV are being developed to eradicate HIV res-

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ervoirs, HARTs major obstacle.[12] Reservoirs persist due to the invisibility of latent provirus provided by: (1) dormant CD4+ T-cells against the body's immune system, (2) HARTS inefficient targeting of activated CD4+ T-cells, and/or (3) non-induction of immune response due to low levels of residual virus production. In order to combat these obstacles, a "shock and kill" strategy has been developed. This strategy consists of therapeutic vaccines introducing HIV-specific T-cells capable of killing the reactivated infected cells producing HIV antigens. A phase I/II, open-label, single-arm clinical trial has been conducted to evaluate a dendritic cell (DC) based HIV-1 vaccine loaded with autologous HIV-1-infected apoptotic cells.[13,14] Results showed the vaccine was safe and induced T-cell activation. However, it did not prevent viral rebound during treatment interruption. Four of 10 participants had an increase in the HIV-1 ribonucleic acid (RNA) load in plasma following vaccination, despite continuous antiretroviral therapy (ART). Evidence of cytolysis in HIV-1-infected cells was also present.[14] Other studies evaluating TAT therapeutic vaccines have shown TAT vaccination is safe and immunogenic. A non-blinded with no placebo controls phase 2 study gave evidence for restoration of CD4+ and CD8+ T-cell numbers and functional central memory T-cell subsets of B and natural killer (NK) cell number, and a reduction of immune activation in HAART-treated participants. Furthermore, TAT immunization induced a statistically significant reduction of blood HIV-1 deoxyribonucleic acid (DNA) load that persisted for up to three years post-vaccination.[11]

To conclude, antibody-mediated preventative HIV vaccines will in the future provide a great strategy in the eradication of the HIV epidemic pending further developments of neutralizing antibodies. VRCO1, a human monoclonal antibody targeting the HIV-1 CD4 binding site, has demonstrated protection in animal studies, and has acceptable human safety. HVTN 703 will investigate the effectiveness of VRC01 and the level of neutralizing activity required in reducing HIV acquisition. As for therapeutic vaccines, further studies need to be conducted using TAT based vaccines in order to evaluate its efficacy in reducing HIV-1 DNA.

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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