

Update on VRC Clinical Trials of Multi-Clade DNA and rAd5 Vaccines

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The Vaccine Research Center (VRC) in the National Institute of Allergy and Infectious Diseases (vrc.nih.gov) is devoted to developing a vaccine for HIV. The program is mission-oriented and can develop vaccine candidates from basic research through analysis of Phase I clinical trials. Expanded clinical evaluation is done in collaboration with extramural clinical trial networks. The VRC development plan for the initial HIV candidate is based on gene delivery of vaccine antigens using a combination of plasmid DNA for priming and replication incompetent adenoviral vector (rAd5) for boosting. This combination induces high levels of HIV-specific CD8+ CTL responses in mice and macaques. The initial goal is to ask whether this level of HIV-specific CD4+ or CD8+ T cell induction is sufficient to impact the HIV epidemic by preventing infection, controlling replication, or reducing transmission to others. The vaccine is designed to induce T cell responses against multiple HIV proteins to diminish immune escape, and includes sequences from multiple clades to be relevant for a large portion of the global epidemic.

Four Phase I studies have been fully enrolled evaluating a series of three plasmid candidates (expressing constructs encoding clade B gag, pol, and nef, and clades A, B, and C envelope) and one combination of four rAd5 vectors encoding clade B gag/pol and envelope from clades A, B, and C. The studies have evaluated 1-, 4-, and 6-plasmid combinations with dose-ranging from 2 to 4 to 8 mg, delivered by a needleless injection device. CD4+ and CD8+ T cell responses have been detected primarily against envelope epitopes in the majority of vaccines using peptide pools to stimulate PBMCs followed by IFN- γ ELISpot and flow cytometric detection of intracellular IL-2 or IFN- γ production. HIV-specific antibody responses have also been detected in a significant number of subjects receiving the DNA or rAd5. T cell responses were detected after two DNA injections, but there is a dose effect with responses improving at higher dose levels, and after 3 DNA injections. There is also a dose effect for the rAd5 candidate vaccine in both systemic reactogenicity and immunogenicity. The clinical development plan and early data from trials evaluating the combination of the DNA and rAd5 products will also be presented.