Abstract: Despite more than three decades of intense efforts, a safe and efficacious vaccine against HIV/AIDS remains elusive. To-date, the only clinical trial that has yielded any indication of protective efficacy against HIV acquisition is the RV144 study reported by Rerks-Ngarm et al. (NEJM, 2009). The vaccine is based on recombinant canarypox virus for priming and recombinant HIV envelope proteins for boosting. Although the efficacy of this vaccine was modest (~30%) and the protective mechanisms not completely understood, results from this trial raised a glimmer of hope for vaccines against HIV/AIDS and established a baseline for further improvements. Our lab developed the poxvirus prime - protein boost immunization strategy and demonstrated its potential efficacy against a pathogenic simian immunodeficiency virus infection in a non-human primate (NHP) model in the early 1990s (Hu et al., Science 1992). Using NHP and other preclinical models, we have explored a number of parameters that may impact the protective efficacy of the prime boost immunization approach. These include the role of glycans in modulating the immunogenicity of HIV envelope proteins and alternative immunization modalities for priming. Results from these studies may inform the design and clinical development of more effective vaccines against HIV/AIDS.