ENHANCED SENSITIVITY OF DETECTION OF CYTOTOXIC T LYMPHOCYTE RESPONSES TO HIV TYPE 1 PROTEINS USING AN EXTENDED *IN VITRO* STIMULATION PERIOD FOR MEASURING EFFECTOR FUNCTION IN VOLUNTEERS ENROLLED IN AN ALVAC-HIV PHASE I/II PRIME BOOST VACCINE TRIAL IN THAILAND

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A phase I/II prime-boost vaccine trial in HIV-1-seronegative adults was conducted in Thailand using ALVAC-HIV (vCP1521) as a prime, boosting with either oligomeric gp160 TH023/LAI or Chiron HIV Thai subtype E (CM235) plus U.S. subtype B (SF2) gp120. Cytotoxic T lymphocyte (CTL) assays were conducted at one of the vaccine trial sites (Siriraj Hospital) at a single time point following the completion of immunization demonstrated that 8 of 50 (16%) vaccine recipients showed HIV-specific CTL by standard chromium release assay (CRA) after *in vitro* stimulation (IVS) for 2 weeks. Five additional vaccinees (13/50 = 26%) showed CTL responses after IVS for up to 4 weeks. Moreover, one volunteer with a positive CTL response to a single HIV antigen at Day 14 demonstrated a response to an additional HIV-1 antigen(s)after the longer IVS period. CTL activity was $CD8^+$ restricted. Despite extension of the IVS up to 4 weeks, no CTL responses were detected in placebo recipients. These results imply that extension of the IVS period may increase the sensitivity of the CRA when measuring HIV-specific CTL in ALVAC-HIV prime-boost recipients without compromising specificity.

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EVOLUTION OF ENVELOPE SEQUENCES IN HIV-1 SUBTYPE CRF01_AE INFECTED THAI PATIENTS WITH DIFFERENT RATES OF DISEASE PROGRESSION

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Background: To understand the relationship between disease progression and amino acid variations of envelope region of HIV-1 subtype CRF01_AE and to determine whether sequence changes on env due to selective immune pressure.

Methods: We obtained and analyzed sequences of the V1-V5 region of the HIV-1 env gene from nine HIV-1 subtype CRF01_AE (E) infected Thais. Five are progressors (PRs; follow-up CD4+ cells<200/mm? and progression to AIDS) and four are slower progressors (SPs; asymptomatic and/or follow-up CD4+cells>350/mm? at the end of follow-up). HIV-1 DNA from two time points per individual were directly sequenced. They were followed at least 16 months. Selective pressure at the amino acid level was measured by using the synonymous/ nonsynonymous base substitutsions (ds/dn) ratio and ds/dn ratio of PRs and SPs were compared between early and late time points.

Results: Phylogenetic trees showed that there was no specific clustering between PR's env gene versus those in SPs. In V3 region, GPGQ motifs were found in all SPs and predicted phenotype of SPs were all NSI, while V3 region of PRs evolved more rapidly. There was deglycosylation of env V3 sequence of HIV-1 subtype CRF01_AE infected PRs, whereas it was conserved in SPs. Positive selective pressure operated only on env V3 region in PRs and this reflected nonsynonymous substitution accumulation on env V3 region in PRs.

Conclusions: These findings showed that the host immune responses may be one selective pressure driving sequence changes in V3 region in PRs.

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FOUNDATIONS FOR A PHASE III HUMAN IMMUNODEFICIENCY VIRUS VACCINE TRIAL: A DECADE OF THAI-U.S. ARMY COLLABORATIVE RESEARCH

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As part of the response of the Royal Thai Army to the outbreak of human immunodeficiency virus (HIV)in Thailand, a collaboration was established with the U.S. Army to jointly work toward the development of vaccines for the prevention of HIV infection. During the first decade of this collaboration, studies have been carried out in the diverse disciplines that are crucial to providing the foundations for efficacy trials of candidate HIV vaccines. Studies of host, pathogen, and vaccine interventions included studies of viral diversity, epidemiology, disease course, potential vaccine cohorts, and Phase I/II clinical trials. Collaborations were expanded to other Thai institutions and to overseas partners, resulting in the Thai AIDS Vaccine Evaluation Group. The efforts of these collaborations resulted in the development of candidate vaccines specifically designed for use in Thailand, and sequential evaluations that have lead to the threshold of the world's next and largest efficacy trial of HIV vaccines.

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HLA CLASS I SEROTYPES AND CYTOTOXIC T-LYMPHOCYTE RESPONSES AMONG HUMAN IMMUNODEFICIENCY VIRUS-1-UNINFECTED THAI VOLUNTEERS IMMUNIZED WITH ALVAC-HIV IN COMBINATION WITH MONOMERIC GP120 OR OLIGOMERIC GP160 PROTEIN BOOSTING

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Antigen-induced cellular immunogenicity may vary between populations due to differences in human leukocyte antigen (HLA) diversity and, hence, may play a critical role in the protection