CHAPTER I

INTRODUCTION

Recent evidences suggested that cytotoxic T lymphocyte (CTL) play an important role in protection against viral infections. In animal model, CTL were important in the clearance of several viruses relevant to human diseases, such as influenza and respiratory syncytial virus (1, 2). Recent studies in human suggested that transfer of CMV-specific CTL clones after allogenic bone marrow transplant could effectively reconstitute cellular immunity to CMV (3). Likewise, CTL specific for HIV-1 have been shown to contribute the control of HIV infection. The emerging HIV-specific CTL responses observed during primary infection followed a close temporal association with acute viral load reduction (4, 5). In addition, CTL were commonly found in high numbers during the asymptomatic phase of infection showing an inverse correlation between the number of circulating HIV-specific CTL and the plasma viral load (6, 7). Moreover, HIV-specific CTL responses were a major component of the host immune response in long-term nonprogressors (8-13) and the demonstration of HIV-1-specific CTL activity in exposed uninfected individuals further supported a protective role for CTL (14). Insights into HIV-specific CTL responses would therefore be essential for HIV vaccine development. However, most previous HIV-specific CTL studies were performed in the West where the prevalent strain of HIV is subtype B, and moreover the CTL responses were analysed in the context of Caucasian HLA alleles. In order to develop HIV vaccine for Thailand, the HIV-specific CTL study in Thai HIV-infected donors is necessary.

HIV-1 can be classified into three broad group such as group M, N and O. HIV-1 group M comprises the great majority of HIV-1 isolated and can be assigned to a subtype designated A through K, excluding I and 16 circulating recombinant forms (CRFs). In Southeast Asia including Thailand, CRF01_AE (subtype A/E) is most common subtype (15)

For HLA molecule, HLA-A11 is one of the most common class I allele in worldwide population. This HLA molecule has been divided to 20 alleles (www.ebi.ac.uk/imgt/hla/allele.html) which HLA-A*1101 is of highest frequency (16). Especially, HLA-A11 molecule is the most frequent allele in Thailand (http://hiv-

web.lanl.gov). Although HLA-A11-restricted CTL epitopes have been study in the other country, HIV-1 has difference between the other country and Thailand. We therefore used HLA-A*1101-restricted CTL epitope from other country to identify CTL epitopes for HIV-1 subtype A/E in Thailand.

In present study, we analysed HLA-A*1101-restricted HIV-specific CD8+ T cell responses in Thai patients with subtype A/E infection. We found that Nef (QVPLRPMTYK and GAFDLSFFLK peptides) was the most immunodominant epitopes followed by Pol, Gag, and Env. In addition, we demonstrated that there were no correlation between viral load and immunodominant Nef epitopes in most patients. Moreover, we found that the patients who were lacked Nef-specific T cell responses had the amino acid mutation either within epitope or in the flanking region. This information supported that Nef may be appropriate protein that used for epitope-based vaccine.