



CHAPTER I

INTRODUCTION

The human immunodeficiency virus (HIV), which is the cause of the acquired immunodeficiency syndrome (AIDS)⁽¹⁾ is in family *Retroviridae*, subfamily *Lentivirinae* and genus *Lentivirus*⁽²⁾. There are two HIV types, 1 and 2. The first, HIV-1 contains 3 broad groups M, O and N. The spread of distinct clades in different parts of the world can be used to monitor the routes of spread of HIV. In Thailand, HIV-1 clade B and clade A/E have been identified. Clade B is found mainly in homosexual and intravenous drug users (IVDU) and clade A/E in heterosexuals and IVDU^(4,5).

After infection, HIV as free viral particles or within infected CD4+ T cells, can stimulate the cellular and humoral immune responses necessary to combat viral infection. During the early period after infection, free virus and viral proteins such as p24 can be detected at high levels in the blood and the level of HIV infection of CD4+ T cells is high. Within 2 to 4 weeks, an increasing number of HIV-specific CD8+ cytotoxic T lymphocytes (CTL) can be detected. The recovery of CD4+ T cells to the pre-infected level is observed. HIV-specific antibodies are usually present from around the second and third week of infection^(6,7).

Several research groups have found high levels of specific cytotoxic T cell activity directed to most HIV proteins in patients during or even before seroconversion. These findings suggest that the decline of cell-free and cell-associated virus is due to the specific lysis of HIV-infected cells by CTL.

CTLs are the major cell-mediated immune response to virus infection⁽¹⁾. CTL is capable of killing target cells expressing specific antigens. CTL uses the T cell receptor (TCR) to interact with peptide antigens derived from internally processed protein presented in the groove of human leukocyte antigen (HLA) class I on HIV-infected cells^(1,8,9). HLA is highly polymorphic in humans. HLA allele frequencies vary greatly among different ethnic groups. For the common HLA class I molecules around the world, a 17% prevalence of HLA-A2 and 11% of HLA-A28 are found in North America, 30% HLA-A35 is found in South America, 17% HLA-A2 is found in Africa and 33% HLA-A11, 25% HLA-A2 and 14% HLA-A24 and HLA-A33 are found in Southeast Asia and Thailand⁽¹⁰⁾. Phenotypic and genotypic diversity of HIV-1 have also been widely observed.

At least 4 techniques use into detecting CTL activities have been described, i.e. the classical chromium-51 release assay, enzyme-linked immunospot (ELISPOT) assay, intracellular IFN- γ assay and HLA-peptide tetrameric complex (Tetramer) assay⁽¹¹⁾.

Several studies have demonstrated that cross-clade CTL activity can be detected among clade B-infected Caucasians and in African and Thai patients infected with subtypes A, C, D, E and G⁽¹²⁻¹⁶⁾. Cross-clade specific CTL responses were identified in a cohort of infants infected with either HIV-1 clade B or non-clade B at a rate of 88% for *pol*, 83% for *nef*, 67% for *gag* and 55% for *env*⁽¹⁷⁾. CTL responses in highly exposed but persistently seronegative (HEPS)^(18,19) and in uninfected children born to HIV-1 infected mothers⁽²⁰⁾ have also been reported.

Cross-clade CTL activity can be elicited depending upon 2 important factors: viral sequence diversity of the different clades and the HLA class I molecule in the infected host or vaccine recipient⁽¹⁶⁾. This is of critical importance in planning future vaccine trials. Vaccine development has focused mainly on clade B since it was the first clade described in the epidemic and has mainly spread in developed countries. It is of concern that such vaccines may not effective in the areas of the world where they mostly needed. It is now believed that an effective vaccine should be able to generate broad cross-clade CTL responses⁽¹⁵⁾.

As mentioned above, HIV-1 A/E is the most common subtype epidemic in Thailand and in some other parts of the world. The identification of HIV-1 *gag*, *pol* cross-clade specific CTL responses among clade B and clade A/E will be important for the development of HIV-1 vaccines in Thailand.