CHAPTER I

INTRODUCTION

Human immunodeficiency virus (HIV) has been clearly identified as the primary cause of the acquired immunodeficiency syndrome(AIDS). This disease was first recognized in the United states in 1981 when severe infections by normally avirulent microorganisms and a rare Kaposi's sarcoma were reported with high frequency in previously healthy male homosexuals.[1,2,3] The observation that T-lymphocytes bearing the CD4 marker were depleted in these patients reinforced the conclusion that the disease is a result of immune system failure caused by HIV. After more detailed studies of the virus, it can be further classified into HIV-1 and HIV-2. There are evidence that HIV-2 is 50-60% different from HIV-1, in terms of genetics informations.

An important characteristic of HIV-1 is its antigenic variability. This variability is mainly caused by the inaccurate readings of the reverse transcriptase enzyme (RT). Misincorporations, made by RT, are not repaired by a 'proofreading' mechanism (exonuclease activity). The error rate of HIV-1 RT lies between 1 in 1700 and 1 in 7400 base pairs.[4,5,6,] For the HIV-1 genome which is approximately 10,000 bases in length, this would mean 2.5 to 10 errors per each replication cycle of a diploid genome. Additional variations may be the results of deletions and recombination events.[8] Due to this high replication error rate, HIV-1 infection, although initiated by a single virus, will often lead to a viral population with a range of genotypes. This closely related but diverse population of virus has been termed a 'quasispecies'.[9,10] The variation of the viral genotype affects the biological properties of the virus.

An important property in which HIV variants have been reported to differ is cellular tropism. Although all variants appear to be able to infect primary T-cells, some replicate well in immortalized T-cell lines while others are tropic for macrophages and monocytes.[11,12,13,14,15,16] HIV-1 variants also differ in the rate of replication[11,15] and in the ability to induce the formation of syncytia. Syncytia are multinucleated giant cells resulting from the fusion of infected cells with uninfected cells.[17,18] Growth capacity as well as cytopathicity in immortalized T-cell lines such as MT-2 is correlated with the syncytium inducing (SI) phenotype. Furthermore, it is clear that the differences in the amino acid sequence of viral proteins leads to differences in antigenic properties.[19,20] As a consequences, host antibodies to viral proteins may or may not be effective due to varying antigenic properties proteins are recognized by host antibodies and, as a consequence, whether or not such antibodies are biologically effective. The principal neutralizing epitope on HIV-1 is located in the third variable region (V_3) of the exterior envelope glycoprotein (gp 120).[21,22,23] Based on the principal neutralizing domain, HIV-1 can be divided in to different subtypes such as those found in North America with GPGR motif at the tip of the V3 loop and those found in Africa with GPGQ motif.[24]

Thailand like most countries in Asia, experienced a small number of HIV-seropositive individuals and AIDS cases during the early 1980s.[25,26,26] However, a sudden rise to an epidemic proportion occured noted during the year 1988.[28,29] This increase was initially observed among the IVDUs in Bangkok. The subsequent spread of HIV-1 into other high-risk groups was also found to be associated with IVDUs and heterosexuals. Currently, HIV-1 infection is spreading rapidly in the general population.

HIV-1 strains in different geographic regions are highly diverse and have been classified into several distinct genetic subtypes, A to O.[30,31,32,33,34,35] For the HIV-1 strains isolated from HIV-1 infected Thais, two distinct genetic variants of HIV-1 have been found by genetic analysis, which are designated genotype Thai A (corresponding to subtype E) and genotype Thai B (corresponding to subtype B). [36,37] These two subtypes were found to segregate by mode of transmission. Greater than 80% of sexually infected Thai patients had subtype E. In contrast, up to 80% of parenterally infected patients (IVDU) had subtype B.[37] Different HIV-1 subtypes might have different cytopathicity, infectivity and natural history.

Several methods can be used to differentiate HIV-1 subtypes, for example, genotyping[37,38,39,40] and heteroduplex mobility assay.[41] Among all methods, serotyping,[42,43,44,45] is the most convenient method, in defining HIV-1 subtypes. Therefore with facilitate the larger scale studies to research into the roles of HIV-1 subtypes in the pattern of epidemiology, the mode of transmission the disease progression. In addition, the assay may also play an important role in vaccine development as well as in drugs efficacy evaluation.

It is therefore the objective of this study to investigate the HIV-1 subtypes and the natural courses in the Thai HIV-1 infected individuals. The information obtained may also be useful in future therapeutic or vaccine development.

OBJECTIVES

1. To develop peptide serotyping using indirect enzyme immunosorbent assay (indirect ELISA) for HIV-1 subtype analysis.
2. To develop PCR-based genotyping for peptide serotyping validation
3. To study the natural history of HIV-1 subtypes in HIV-1 infected individuals at Chulalongkorn Hospital.