CHAPTER I

INTRODUCTION

The acquired immunedeficiency syndrome (AIDS) emerged during the 1980s as a major and burgeoning global health problem. It results from infection of certain components of the human immune system by the human immunedeficiency virus (HIV). Its victims died of a variety of rare infections and malignancies, among them a pneumonia caused by Pneumocystic carinii and Kaposi's sacoma were reported in preiously healthy homosexual men.[1,2,3,4] From the initial pathogenic event of the binding of HIV to functionally important receptor (CD4 molecule) on a subset of T cells and monocyte, macrophages. [5,6,7,8,9] The result of the infection is destruction of the CD4+ subclass of T lymphocytes, which play a central role in the capacity of the host to mount effective and protective immunologic response to a wide range of infections. [10,11,12,13]

Since the first description of this disease in 1981 and the discovery of the aetiological agent in 1983, an enormous amount of knowledge has accumulated concerning the epidemiology, pathogenesis, and molecular biology of HIV. Knowledge that the etiologic agent was a human retrovirus naturally led to an attempt to develop agent that would inhibit the enzyme of this virus, the reverse trancriptase (RT).[14] The RNA-dependent DNA polymerase activity of the reverse transcriptase is a major target of anti-HIV therapies. Azidothymidine (3'-azido-3'-deoxythymidine; AZT, ZDV) is nucleoside analogue reverse transcriptase inhibitor, has been approved for treatment of AIDS patients and those with HIV-infection since 1985. It suppresses multiplication of the virus in a certain efficacy (up to 0.7 $\log_{10}$ reduction of plasma HIV-RNA) and prolong life.[15,16] The antiviral effect of AZT is confered by competitive inhibition and 3'-azido group which prevents the formation of 3',5'-phosphodiester bonds and makes AZT as a terminator of DNA chain elongation. [17,18,19] Following this initial advance, studies were quickly organized to examine

[17,18,19] Following this initial advance, studies were quickly organized to examine AZT efficacy at lower doses and in earlier infected populations (ACTG trails 002, 016, and 019). These major trials led to official recommendations in 1990 that established AZT monotherapy as the standard of care in the United States for patients with CD4 cell counts lower than 500/mm^3, irrespective of symptoms.[14,20]

Infection with HIV virus is a chronic process with persistant, high rate of viral replication. The virus has been shown to exhibit high rate of mutation over time within the same individual.[17] This variability is normally caused by the transcription error of reverse transcriptase.[5,21]

Soon after AZT was introduced into the clinic, it was found that virus isolated from AIDS patients after 6 months of AZT-therapy have shown reduced sensitivity to this drug (*in vitro*).[22,23,24] The reducction in sensitivity to AZT was accompanied by the appearance of specific mutations in the gene encoding the reverse transcriptase (*pol* gene), with sensitive strain having five amino acid substitutions at specific residues in reverse transcriptase: at position 41, 67, 70, 215 and 219.[24 ,25] HIV isolated from individuals during long-term treatment with AZT frequently shows reduced susceptibility, as determined by cell culture assay of virus isolates. The phenotypic changes in AZT-resistant viruses are associated with a set of mutation at five codon in the reverse transcriptase (RT) of HIV (Met^{41} --> Leu, Asp^{67} --> As , Lys^{70} --> Arg, Thr^{215} --> Phe or Tyr, Lys^{219} --> Glu).[22,25,26,27] The mutation at codon 215 was associated with the greatest decline in sensitivity to AZT.[15,22,28]

To investigate the clinical significance of resistance, rapid and large-scale susceptibility assessment of all individuals is required, preferably without the need to isolate HIV by coculture of peripheral blood mononuclear cells (PBMCs). The proven association between the degree of AZT resistance and the number of specific mutations in RT has provided a rational basis for using genetic assays to assess AZT sensitivity. The approach to detect those point mutation is a modification of a "selective" PCR procedure.[15,24,27,29,30,32]

The technique of DNA amplification by polymerase chain reaction (PCR) has been extended to include RNA as the starting template by first converting RNA to cDNA by a retroviral reverse transcriptase. The process of RT-PCR has proved invaluable for detecting gene expression, generating cDNA for cloning, and diagnosing infectious agents or genetic disease.[27,33]

In Thailand, most of the individuals infected with Human Immunodeficiency Virus type 1 (HIV-1) are heterosexuals and majority carries HIV-1 subtype E. Much has been reported of azidothymidine (AZT) resistance of HIV-1 in North America and Europe where HIV-1 subtype B predominates. However little is known about the HIV-1 AZT-resistance in other part of world, particulary in regards to other subtypes. Therefore, this study is to determine the prevalence of HIV-1 AZT resistance genotype in Thai patients with HIV-1 infection. The prevalence of AZT genotypic resistance among AZT-naive patients, the time to the occurrence of resistance after initiation AZT monotherapy, and the correlation of CD4 cell count and the risk of developing AZT resistance, are important informations in formulating an appropriate guideline for antiretroviral therapy in Thailand.