CHAPTER 1

Introduction

After thirty-two years since the Human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome (AIDS) was first discovered, AIDS still remains a global health problem. Although antiretroviral therapy (ARV) currently cannot extinguish the virus entirely, HIV vaccination studies are still being conducted in voluntary trials. The major impediment to achieving successful control of the HIV pandemic and develop a harmless and globally effective HIV vaccine, is due to the extensive genetic diversity and its error-prone reverse transcriptase (RT). RT transcribes RNA to DNA but lacks 3'exonuclease activity or the ability to confirm an accurate copy of the RNA code. RT can introduce 5.4×10^{-5} mutations per 1 base pair during one infection cycle, or average 1 mutation for each viral genome transcribed. Moreover, HIV has high viral turnover rates that replicate new generations 10^9 virions per day [1; 2], including genetic recombination overtime [3] for the possibility of HIV to mutate and evade the host's immunity, both cellular and humeral immune responses, and antiretroviral therapy that leads to diversification of the HIV-1 population giving sudden resistance to ARV, which is the greatest barrier to HIV vaccine development.

The World AIDS Day 2014 Report of the UNAIDS showed at the end of 2013, about 35 million people worldwide were living with HIV, and 2.1 million people were infected with HIV [4]. The pandemic HIV-1 group M (main) consists of nine subtypes (A to D, F to H, J, and K), circulating recombinant forms (CRFs), and unique recombinant forms (URFs). Currently, 72 CRFs were reported in the HIV Database at Los Alamos National Laboratory (www.hiv.lanl.gov).

The first study on genetic epidemiology of HIV in Thailand was the study performed by Ou C.Y., *et.al*, 1992. The phylogenetic analysis of C2-V3 *env* regions showed subtype E (later called CRF01_AE) and was the predominant subtype in sexual infection, while subtype B was most common in intravenous drug users, IDUs. Several

years later in 1993-1995, there were studies to confirm that both HIV-1 subtypes were of high prevalence in different groups; CRF01_AE was more common in sexual risk infection, while subtype B was frequently found in IDUs [5-7]. Subbarao and team reported in 1995-2000 [8], CRF01_AE was the most predominate by more than 80% in Thailand, including sexual risk infection and IDUs group. CRF01_AE was more frequently in IDUs. Moreover, CRF01_AE was found in more than 80% in newly infected people in Bangkok, and up to 90% in newly infected people in Northern of Thailand.

Not only do HIV mutations affect the huge genetic diversity, but the genetic recombinant also lead to the emergence of various novel CRFs and URFs overtime. Dual infection with two or more HIV subtypes in the same host cell occurs when mosaic strains with segments from two or more subtypes alternating across the genome that form URFs and CRFs. In Thailand and Southeast Asia, there is a broad co-circulation and intersubtype recombinant between CRF01_AE and subtype B or B' (Thai variant of subtype B). For example, CRF15_01B was found in Thailand in 2001 [9], CRF33_01B has been found in Malaysia since 2003-2005 [10], CRF34_01B was discovered in Thailand in 2007 [11], and CRF48_01B was met in Malaysia in 2007 [12]. Since 2011 to present, many CRFs that were recovered and reported in HIV-Database, were the intersubtype recombinants between CRF01_AE and subtype B in Southeast Asia, compose of CRF51_01B [13], CRF52_01B [14], CRF53_01B [15], CRF54_01B [16], CRF55_01B [17], CRF58_01B [18], CRF59_01B [19], CRF67_01B and CRF68_01B [20]. In addition, recent studies showed that many URFs and intersubtype recombinants CRF01_AE, B and C have been found in Myanmar and Thailand. In Myanmar, the highest proportion of intersubtype recombinants, CRF01_AE/B'/C recombinants (42.6%), formed new 64 URFs in 2012 [21]. There was also a report of CRF01_AE/B'/C recombinants from this area that developed from South China and Myanmar strains. The study has suggested that in Chinese HIV infected patients, CRF01_AE was associated with faster disease progression when compared with other subtypes [22].

Although the epidemiology of HIV in Southeast Asia is co-circulation between CRF01_AE and subtype B, these intersubtype recombinants have extensive genetic

diversity, and with subtype C circulating more in this region. The monitoring of HIV-1 subtypes and emergence of new recombinant strains in the population are important for HIV surveillance programs to track the HIV evolutionary epidemic, and lead to the understanding of the mechanisms which the virus evolves before Thailand's participation in the Asean Economic Community (AEC) in 2016 and ASEAN Free Trade Area (AFTA). Since Thailand is the trade and travel epicenter of this region, the independent moving of new workers and tourists may affect to the public health in Thailand, especially concerning the spread of HIV. This study investigates the HIV-1 subtype distribution and intersubtype recombinants circulating in Northern Thailand.

The objectives of this study are to examine the HIV epidemiology study in Thailand and, the it is impact on HIV prognosis, diagnosis, response to antiretroviral therapy, the prevention of circulating and implication of vaccine development.