CHAPTER I
INTRODUCTION

Human immunodeficiency virus (HIV) is the etiologic agent of acquired immune deficiency syndrome (AIDS) [1]. Infection by HIV is characterized by a progressive deterioration of the immune system. In 2005, the number of people living with HIV/AIDS worldwide was estimated to be 40.3 million, including 2.3 million of children less than 15 years old. In South and South-East Asia, 7.4 million adults and children were estimated to be living with HIV and 990,000 newly infected with HIV [2] (Figure 1). Currently, HIV/AIDS is the sixth leading cause of death in children under 5 years of age worldwide [3].

Although, the introduction of highly active antiretroviral treatment (HAART) in 1997 has remarkly decreased the risk of disease progression or death [4]. However, many researchers are still attempting to identify cofactors implicated in HIV disease progression. These may help designing strategies to delay the progression of HIV disease. Cofactors in HIV disease, in particular other viral infections such as human cytomegalovirus (HCMV) infection, have been reported to accelerate progression to AIDS.

Figure 1. Estimated number of adults and children living with HIV in 2005 [2].

HCMV causes opportunistic infections in patients infected with HIV-1. Before the widespread availability of HAART, HCMV was isolated in up to 40% of patients with advanced AIDS [5]. Regarding a widespread of HCMV in general Thai population, most of HIV infected patients are infected with HCMV prior to the acquisition of HIV, thus CMV disease is usually caused by reactivation of latent virus rather than primary infection. The development of CMV disease in HIV infected persons is clearly correlated with the severity of immunodeficiency, occurring predominantly in patients with CD4+T cells less than 50 cells/μL [6]. The most common manifestation of CMV disease in these adult patients is retinitis, which is manifested by a painless loss of visual acuity and ultimately results in blindness. HCMV has been responsible for retinitis in up to 25% of patients in developed countries [7], whereas neurological disease is common in children [8].

HIV progressively causes immune deficiency which allows HCMV to reactivate, in people with a low CD4+T cells count, as a result of loss of cytomegalovirus specific CD4+ T cell responses [9]. Increasing HCMV replication then leads to a high HCMV viral load sufficient to cause opportunistic disease, usually HCMV retinitis in AIDS patients. Reciprocally, HCMV infection could potentially activate HIV replication. Thus, active HCMV infection can drive HIV replication to higher levels which could in turn drive HCMV replication setting up a vicious cycle toward accelerated progression to AIDS (Figure 2). Moreover, HIV itself may directly accelerate HCMV replication.

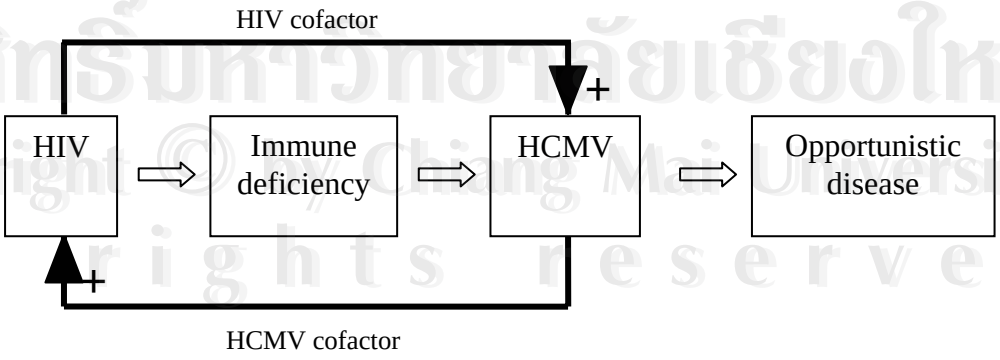

Figure 2. Pathways leading to opportunistic versus cofactor relationships between HCMV and HIV [10].

However, several studies [11-15] showed HCMV co-infection may be acting as a cofactor in the progression of HIV-1 disease in adults. Whether co-infection with HCMV promote progression of HIV-1 infection, or the occurrence of HCMV infection and disease are simply markers for immune dysfunction remains unclear.

The direct causal relation between HCMV and HIV disease progression in adults is difficult to clearly established as adult patients are usually infected with HCMV before contacting HIV-1 infection. However, perinatal period is a unique situation where the time of acquiring HCMV and HIV infections can be investigated from birth thus allowing the study of natural history of both infections, along with immunological and clinical outcomes. Therefore, the aims of this study are emphasized to examine the association between HCMV infection and the progression of HIV disease in HIV-1 perinatally infected infants.

Thus, we hypothesize that HCMV co-infection is a risk factor for HIV-1 rapid disease progression in HIV-1 infected children in Thailand.

Objectives of this study:

1. To assess and compare the rate of HCMV infection in perinatally HIV-1 infected and matched non-infected infants.
2. To evaluate the predictive risk factors associated with HCMV perinatal transmission in children born to HIV-1 infected mothers
3. To assess the acquisition time of HCMV infection in HIV-1 infected children.
4. To assess the impact of HCMV infection in the progression of HIV-1 disease in infected children.

Education/Application advantages of this study

Relationships between HCMV/HIV and progression to HIV disease in infants born to HIV infected mothers are not fully understood. Investigations of these relations are needed to provide further insight into mechanisms of HIV disease progression in infants. Therefore, the study may provide additional knowledge and understanding of HIV disease progression in HIV infected infants. Consequently, it may help physician in improving the strategy to prevent vertical and horizontal HCMV infection in HIV-1-infected infants and children. It could be applied to decrease and delayed disease progression and prevent CNS disease. Such preventive measures may include the use of anti-CMV drugs (e.g. the nucleotide analog cidofovir, the pyrophosphate analog forcarnet) applicable in early infancy, active immunization by vaccination [16], or by passive immunization with HCMV specific immunoglobulin [17].