CHAPTER 1

INTRODUCTION

1.1. Introduction

Acquired Immunodeficiency Syndrome (AIDS) is a pandemic disease affecting several millions of adults and children in the developed and developing countries. Although this disease still remains a major social problem in several countries and a definitive cure is not currently available, in the last ten years impressive progress has been made in the treatment of AIDS infected patients [Gazzard *et al*., 1998; US/DHHS, 2006]. The causative agent of AIDS is the human immunodeficiency virus (HIV), a retrovirus of the lentivirus family that produces a progressive immunosuppression by destruction of CD_4^+ T lymphocytes and macrophages, resulting in opportunistic infections, neurological and neoplastic diseases, and death. According to the AIDS Epidemic Update 2005 by UNAIDS/WHO, released on December 2005, 40.3 million people were living with the Human Immunodeficiency Virus (HIV) and 3.1 million have died from HIV/AIDS (UNAIDS/WHO, 2005). An estimated number of 1,054,684 were infected in Thailand at the end of 2003 and 450,742 have died from the infection (Phanuphak *et al*., 2004).

During the past few years, significant advances have been made in the pharmacological treatment of HIV infections using highly active antiretroviral strategy. Considered a very effective therapy, HAART (highly active antiretroviral therapy) decreased HIV viral load and leads to the increased of CD_4^+ lymphocytes counts, causing on improvement of immunity and a decrease in the incidence of opportunistic infection (Powderly *et al*., 1998; Sepkowitz, 1998).

To date, most clinical use of combination therapy in treatment-naïve individuals has been based on three different types of combination regimens, namely: NNRTI-based (1 NNRTI + 2 NRTI), PI (protease inhibitors)-based (1-2 PI+2NRTI), and triple NRTI-based regimens. NNRTI-based regimens are commonly prescribed as initial

therapy for treatment-naïve patients. In general, these regimens have the advantage of lower pill burden as compared to most of the PI-based regimens. Use of NNRTI-based regimens can preserve the PIs for later use, reducing or delaying patient exposure to some of the adverse effects which are more commonly associated with PIs. The major disadvantage of currently available NNRTIs is their low genetic barrier for development of resistance (DHHS, 2006).

There are two main categories of NNRTI-based antiretroviral drugs (ARV) currently under recommendation. The first type, NRTI, inhibits reverse transcriptase (RTase) by binding the enzyme's active site and adding to the growing DNA chain. The second category are the NNRTIs (namely, delavirdine, efavirenz and nevirapine) , bind RTase at a site that is distal from the active site, inducing a detrimental conformational change within the enzyme. These drugs show high antiviral activity and low toxicity *in vitro*, but are very specific. Single mutations have been shown to reduce or eliminate efficiency. For this reason, drugs of this type are usually coadministered with other drugs (Lythgo, 2004; Weller *et al*., 2001).

To date, recommendations are designated as the initial regimen in treatment naïve patients, who have CD_4^+ falls below 350 cells/mm^3 in all asymptomatic individuals. The preferred regimen of NNRTI-based has been based on a combination of efavirenz plus 2NRTIs as shown in Appendix B (DHHS, 2006; WHO, 2005). The government of Thailand launched the programme aims to provide GPO-Vir, a generic fixed dose combination of stavudine, lamivudine and nevirapine, as a firstline HAART regimen to an additional 10,000 patients in 2003 (Phanuphak, 2004). Due to severe side effects, e.g. hepatotoxicity (Sanne *et al*., 2005) and severe rash (Leth *et al*., 2005) of nevirapine , and the results from several large cohort-studies have suggested that efavirenz is more effective and safer than nevirapine (Cozzi-Lepri *et al*., 2002; Keiser *et al*., 2002; Matthews *et al*., 2002). In addition, the favorable side effect profile and diminished pill burden on patients due to once-a-day dosing have contributed to efavirenz's extensive use (Savini *et al*., 2001). These factors make efavirenz an important component of NNRTI-based instead of nevirapine.

Several clinical studies have reported a reduction in the plasma levels of other cytochrome P450 (CYP)3A4 substrates when they are coadministered with efavirenz (Aarnoutse *et al*., 2002; Clarke *et al*., 2001, Falloon *et al*., 2000). Efavirenz caused a concentration-dependent CYP3A4 induction and activation of the human pragnane X receptor (hPXR), a key transcriptional regulator of CYP3A4, *in vitro* (Hariparsad *et al*., 2004). However, efavirenz did not appear to induce intestinal CYP3A4 or intestinal P-glycoprotein (Berruet *et al*., 2005; Mouly *et al*., 2002).

Opportunistic infections (OIs) continue to cause morbidity and mortality in patients with human immunodeficiency virus (HIV)-1 infection throughout the world. Potent combination antiretroviral therapy has reduced the incidence of OIs for certain patients with access to care. However, certain patients in the developed and developing world do not have access to care and have OIs. Other patients do not have a sustained response to antiretroviral agents for multiple reasons, including poor adherence, drug toxicities, drug interactions, or initial acquisition of a drug-resistant strain of HIV-1. Therefore, OIs will continue to cause substantial morbidity and mortality in patients with HIV-1 infection. Fungal infection is one of the opportunistic diseases in HIV-infected patients. Oropharyngeal and esophageal candidiasis are common (Klein, 1988). On the other hand, infections with *Penicillium marneffei*, penicillosis, have been reported in patients infected with HIV, especially in Southeast Asia and South China (Clyti *et al*., 2006; Supparatpinyo *et al*., 1992; Tsang *et al*., 1991; Tsui *et al*., 1992). Penicillosis has been reported as the third most frequent opportunistic infection in Thailand. According to the Ministry of Public Health of Thailand, the cumulative number of AIDS patients during 1984—2004 with penicilliosis was 6,323 cases (Mootsikapun *et al*., 2006).

Ketoconazole, an imidazole piperazine antifungal agent, is also used for the threatment of penicillosis, which rapidly spreads among AIDS patients in Thailand (Hospenthal, 2000). The drug is also used for the treatment of candida infection, where oropharyngeal and esophageal candidiasis are the two most common fungal infection in HIV-infected patients (Glick *et al*., 1994; Greenspan, 1990; Teanpaisan *et al*., 1998).

Ketoconazole is extensively metabolized by hepatic microsomal enzymes (Rodriguez *et al*., 1997). The major metabolic reactions in human are hydroxylation of imidazole ring and oxidative N-deacetylation of piperazine ring by CYP3A (Shannon *et al*., 2005; Brown, 2001; Cupp *et al*., 1998; Daneshmend *et al*., 1988). The N-deacetyl ketoconazole (DAK) is a potent cytotoxicant than its parent compound. It is directly toxic to liver cells in a distinct time- and dose-response relationship (Rodriguez *et al*., 1997a).

Thus, the possibility of ketoconazole and efavirenz co-administration tends to have a chance to occur in clinical practice and may lead to failure of treatment with ketoconazole.

1.2. Objective of the Study

This study was conducted to elucidate the effect of efavirenz on ketoconazole pharmacokinetics in HIV-infected patients.