CHAPTER I

INTRODUCTION

The Situation in Thailand

Since beginning more than 20 years ago, the epidemic of HIV infection and AIDS in Thailand has exploded. (Chariyalertsak et al., 2001) Thailand reported its first case of AIDS in September 1984. Since then, HIV has infected more than 1 million Thais, and of those, more than 400 000 have died. In 2005, an estimated 580 000 Thais were living with HIV/AIDS. In 2004, 49 500 would develop serious AIDS-related illnesses, and about the same number would die of AIDS-related complications. In addition, there were estimates of 19 500 new infections. This was considerably less than the 143 000 new infections that occurred in 1990 and less than the 23 000 new infections from 2002, indicating a declining trend (Table1). It is interesting that by the end of 2006, 88% of HIV-infected Thais were receiving antiretroviral therapy.

Table 1: Estimated cumulative numbers with HIV/AIDS in Thailand, 2004 - 2006

	Cumulative number
Total HIV infections (adults and children)	1 074 155 (2004) (Revenga 2006)
Total deaths (adults and children)	501 600 (2004) (Revenga 2006)
People living with HIV	580 000 [330 000 – 920 000]* (2005) (UNAIDS 2007a)
Projected new HIV infections in 2004	19 471 (Revenga 2006)
Projected new AIDS cases in 2004	49 542 (Revenga 2006)
Adults aged 15 to 49 HIV prevalence rate	1.4 [0.7 – 2.1]* % end 2005 (UNAIDS 2007a)
Adults aged 15 and up living with HIV	560 000 [320 000 – 900 000]* (UNAIDS 2007a)
% HIV-infected people receiving therapy	88% (end 2006) (USAID 2008)

* The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information

The following table shows relevant figures for a global summary of HIV/AIDS as published by UNAIDS in 2007 (Table 2).

Table 2: Global summary of the AIDS epidemic, December 2007 (Joint United Nations Programme on HIV/AIDS [UNAIDS] & World Health Organization [WHO], 2007)

Number of people living with HIV in 2007
Total 33.2 million [30.6–36.1 million]
Adults 30.8 million [28.2–33.6 million]
Women 15.4 million [13.9–16.6 million]
Children under 15 years 2.5 million [2.2–2.6 million]
People newly infected with HIV in 2007
Total 2.5 million [1.8–4.1 million]
Adults 2.1 million [1.4–3.6 million]
Children under 15 years 420 000 [350 000–540 000]
AIDS deaths in 2007
Total 2.1 million [1.9–2.4 million]
Adults 1.7 million [1.6–2.1 million]
Children under 15 years 330 000 [310 000–380 000]

* The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information

The Response in Thailand

In 1989, to monitor the progress of the epidemic, the Thai Ministry of Public Health (MOPH) established sentinel surveillance of HIV infection in several groups of persons with high-risk behaviour. Included in this surveillance were female commercial sex workers, patients at sexually transmitted disease clinics, injection drug users, blood donors and patients attending antenatal clinics. Subsequently, the MOPH established an HIV/AIDS prevention program, frequently called the "100% condom program". Its objectives were twofold; to decrease the likelihood of transmission of HIV during commercial or casual sex through the promotion of condom use, and to encourage safe sex practices generally through public education about the risk of HIV infection.

The Royal Thai government and Thai society have demonstrated a strong commitment to providing comprehensive care and support to persons living with HIV/AIDS. However, it is only recently that they have been able to provide ART to large numbers of people with symptomatic HIV infection. (Kleinman et al., 1978)

Thailand has a generalised epidemic of HIV infection. (Anderson, 1990; Cohen, 1994; Hill et al., 2007; UNAIDS & WHO, 2006; Nelson, 1994; Ruxrungtham & Phanuphak, 2001; Sittitrai & Brown, 1994; Wangroongsarb et al., 1985; Weniger et al., 1991) An epidemic is considered 'generalized' when HIV prevalence is consistently greater than 1% in pregnant women. In Thailand, initial efforts to stem the rate of new infections were effective. (Rojanapithayakorn & Hanenberg, 1996) However, by 1999, there was evidence of further growth in the rate of HIV-infection. (Kilmarx et al., 1999).

HAART

Highly active antiretroviral therapy (HAART) for the treatment of HIV infection was introduced in the United States when saquinavir (SQV), the first protease inhibitor (and sixth antiretroviral approved for the treatment of HIV infection) was approved by the Food and Drug Administration (FDA). It was approved on December 6, 1995, as Invirase®.(AIDS.ORG 1995) Clinical trials in Thailand have used SQV since 1998. SQV became available commercially in Thailand as Fortovase® in 2000.

One of the goals of HAART is to reduce the HIV pVL to below the limit of detection. Measurement of pVL is part of the monitoring process of chronic viral infections in immunocompromised patients. In HIV medicine, HIV pVL (pVL) is a measure of the number of viral particles in a sample of blood plasma and is a measure of the rate of viral replication. HIV pVL is a surrogate marker for treatment response and may be useful in predicting clinical progression. (Department of Health and Human Services [DHHS], 2007) pVL is measured by polymerase chain reaction (PCR) and branched DNA (bDNA) tests and the result is expressed as the number of HIV copies per millilitre of blood plasma. Higher pVLs are associated with more severe HIV disease in that they result in a more rapid rate of decline in CD4+ count (immunological suppression) and subsequent disease progression.

Adherence to HAART is a powerful predictor of survival for individuals living with HIV and AIDS. (Dragsted et al., 2004; Gutierrez et al., 2006; Maneesriwongul et al., 2006; Manegold et al., 2004; Nachega et al., 2007; Oette et al., 2006; Robbins et al., 2007) The introduction of HAART has made possible newer and less complicated ARV regimens that usually involves taking fewer pills and taking them less often.

These newer ARV regimens are less complicated than earlier regimens, with once daily options of as few as one pill per day now available, even if very expensive. (Gilead/BMS, 2007) These new and uncomplicated regimens target the problem of poor adherence in a very positive way. However, as effective treatment of HIV currently requires a life-long commitment to daily therapy, the question of the length of time on treatment and its possible effect on viral suppression needs to be investigated.

One of the most threatening risks to the effectiveness of ART is non-adherence to HAART.

HIV-NAT

HIV-NAT is a collaboration between the International Antiviral Therapy Evaluation Center, the Netherlands (IATEC), the Australian National Centre in HIV Epidemiology and Clinical Research (NCHECR), University of New South Wales, Sydney, Australia, and the Thai Red Cross AIDS Research Centre (TRCARC), Bangkok, Thailand. (HIV Netherlands Australia Thailand Research Collaboration (HIVNAT), 2007) HIV-NAT was established in 1996 with the aim of advancing ARV research in Thailand that would lead to effective and affordable ARV treatments for the Thai HIV-infected population.(Safreed-Harmon et at., 2004)

The clinical trials conducted at HIV-NAT in Bangkok, often in collaboration with other centres in Bangkok and provincial Thailand, allow access to increasingly potent ARV therapies for a growing number of Thai HIV-infected individuals. The first clinical trial at HIV-NAT using a HAART regimen was HIVNAT 001.1 [begun 1998 using two nucleoside reverse transcriptase inhibitors (NRTIs) plus SQV]. (HIV Netherlands Australia Thailand Research Collaboration [HIV-NAT], 1998) In 2000,

the Thai Government's treatment guidelines, and more recent recommendations for scaling-up access to ARVs from the World Bank and other agencies, mean that more and more individuals will have access to these medications for longer periods of time. (DHHS, 2006; World Bank, 2006).

Why is this study needed?

There are limited data on the rates of virological suppression and virological failure related to the duration of time on HAART in a Southeast Asian cohort. The re-emergence of virological failure following successful suppression means that the virus has succeeded in replicating and that the drug treatment has failed. The pVL returns to a detectible level (>50 copies/mL) after having been below the limit of detection (<50 copies/mL).

This study will examine the incidence of virological suppression and subsequent virological failure for the ARV-naive HIV-NAT 006 cohort, to determine whether virological suppression or risk of virological failure is related to time on HAART, and to investigate the influences of other factors on risk of virological suppression or failure.

Inadequate antiviral therapy that allows viral replication has important treatment implications for the individual and implications for increased rates of transmission. Evidence suggests that the use of HAART decreases sexual transmission of HIV to uninfected persons and leads to a rapid decline in HIV genital shedding. (Graham et al., 2007) Results from this study may provide further evidence regarding the achievement of sustainable virological suppression that would prevent virological rebound and thus reduce the risk of further transmission as outlined above.

Research questions

1. What proportion of patients initially virologically suppressed and subsequently failed after commencing HAART in the HIVNAT 006 cohort?
2. Do differences in the length of time taking HAART predict virological suppression or failure?
3. What is the incidence and what are the associated determinants of virological suppression and virological failure?

Conceptual framework

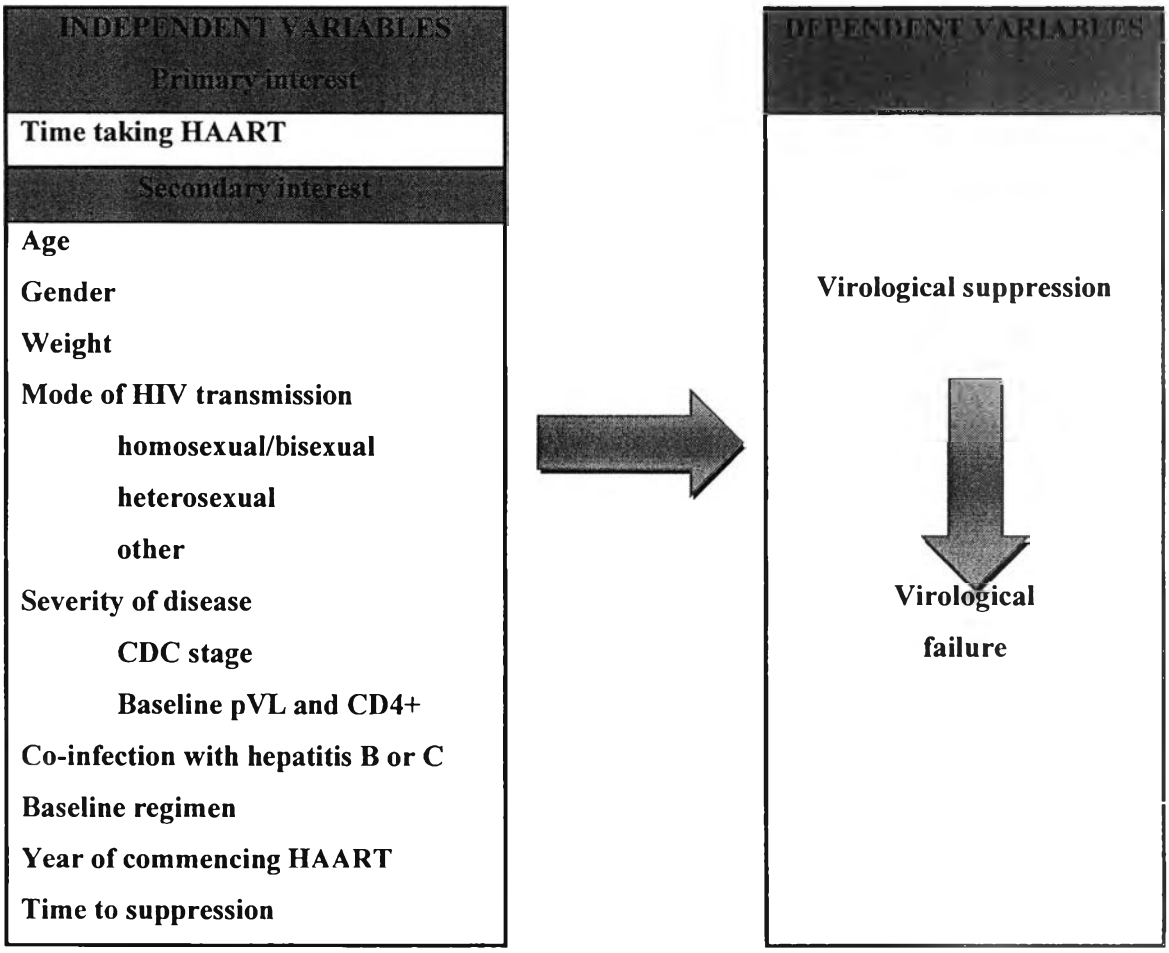

Figure 1: Conceptual framework

Objectives

The objectives of the current study are to assess if time to virological suppression and subsequent virological failure following initial suppression is related to the duration of time taking HAART, and to examine the determinants and incidence of virological suppression and failure, among a cohort of adult, mainly Thai patients from HIV-NAT treated with HAART since 2000. In this study, virological suppression means a sustained pVL<50 copies/mL. Virological failure means a rebound of pVL to >50 copies/mL on two occasions at least four weeks apart in patients who previously were virologically suppressed. Virological suppression usually is achieved quickly (by four weeks) after the commencement of HAART. (Fournier et al., 2005) It has been reported that those who achieve virological suppression quickly are less likely to experience virological rebound. (Mocroft et al., 2003)

Expected outcomes

This study should elucidate whether or not time since the commencement of ART as part of a HAART regimen is a determinant of virological suppression and virological failure in this Southeast Asian cohort of HIV-positive, ART-naive individuals.