CHAPTER II

LITERATURE REVIEW

Search Methods

The search methodology employed for this research included interrogating electronic databases, including MEDLINE (using PubMed or OVID search engines), the Cochrane Database of Systematic Reviews and WHOLIS, from July 2007 through August 2007, to identify relevant published articles. The search strategy used included the key words: antiretroviral therapy OR art OR haart AND pVL AND outcome OR durability AND time AND suppression AND failure AND hiv. This strategy resulted in 125 published articles. Manual review of abstracts resulted in significant culling. Reference lists from relevant articles and from Medline's "related articles" capability identified additional material. References were downloaded to EndNote X for Windows (The Thomson Corporation, 2007).

Rates of Virological Suppression

Two studies from Thailand by Kiertiburanakul et al. (2006) have examined time to virological suppression in treatment naïve patients commencing a NNRTI-based (either efavirenz or nevirapine) ART. The 2006 prospective cohort study compared virological and immunological responses of an efavirenz-based HAART regimen in patients with baseline CD4+ <100 (n=21) and CD4+ ≥100 cells/mm^3 (n=25). The primary outcome was time to a pVL <50 copies/mL.(Kiertiburanakul et al., 2006)

The Kiertiburanakul et al. (2007) retrospective cohort study examined the efficacy and tolerability of GPO-VIR, the fixed-dose combination of stavudine 30/40 mg, lamivudine 150 mg and nevirapine 200 mg manufactured by the Thai Government Pharmaceutical Organization. The primary study outcome was the time from initiation of this NNRTI-based HAART regimen to achieve the goal of therapy, either a pVL <50 copies/mL or a 50% increase from baseline CD4+ cell count. (Kiertiburanakul et al., 2007)

Porter et al. assessed virological response to HAART for antiretroviral-naive persons initiating therapy with low CD4+ counts (<50 cells/mm^3). The study also assessed the impact of the calendar year of starting HAART, gender, age, exposure category, ethnicity, baseline CD4+ count and pVL, and whether the regimen contained a PI, on achieving the endpoint by 48 weeks. (Porter et al., 2008)

Predictors of virological response were evaluated in a large multicenter cohort by the EuroSIDA Study Group (August 1996 to April 1999). (Paredes et al., 2000) The objective of the study was to assess the factors related to achieving and maintaining undetectable pVL levels in 1 469 treatment naïve patients commencing either a PI- or NNRTI-based regimen.

The Pediatric AIDS Clinical Trials Group (PACTG) 381 study examined the impact of initial HAART regimen and adherence on time to suppression. The study enrolled 121 adolescents between March 1999 and October 2001, to receive an efavirenz regimen (n=71) or a PI regimen (n=47).(Flynn et al., 2007)

Rates of Virological Failure

There are considerable published data on the importance of maintaining a high level of adherence to HAART, usually 95%, with virological outcomes improving in a linear dose-response manner as adherence to NNRTI-based regimens increases beyond 50%.(Nachega et al., 2007) Intriguingly, many studies report that patients are more likely to experience virological failure when they take ARV for longer periods.

Data from HIV-NAT studies on rates of virological failure have been published, for example HIV-NAT 005 and HIV-NAT 009, but these studies were conducted in individuals who were ARV-experienced (i.e., had taken any antiretroviral medication before enrolling into the study). (Boyd et al., 2005; Boyd et al., 2006; Burger et al., 2003) Rates of virological failure for the ARV-naive (never having taken any antiretroviral medication before) HIV-NAT cohort are not published.

The meta-analysis summarized below examined the efficacy of ART programs in resource poor settings (Table 3). (Ivers et al., 2005) The papers all were from Africa. The authors concluded that the rate of viral suppression observed was similar to that in developed countries. This analysis is interesting in the context of this research as it shows a trend to less virological suppression over time.

However, reports of this trend are not consistent. Boyd, et al. show a similar result, with initial suppression reported as approximately 75%, falling to 68% by week 96. Dragsted and colleagues from the EuroSIDA group saw a slight increase in virological suppression over a period of 36 weeks while Boyd and the HIVNAT 005 group saw virtually no change over a period of 112 weeks, a long period of follow-up. (Boyd et al., 2005; Boyd et al., 2006; Dragsted et al., 2004)

Table 3: Meta analysis, studies of efficacy of ART programs in resource poor settings Showing percentage with undetectable pVL at various months (Mocroft et al., 2003)

Months 3-4	6	12	18	24	n
88.1	89.2	84.2	75.0	69.7	287
54.5	59.2	54.3			276
	71.2	51.2	59.3		58
75.0	80.0				60
	89.8				743
45.0	48.0	37.0			399
50.0	55.0	51.0	68.0	46.0	101
	59.2	47.3	48.8	32.3	217

The 2NN study was an open-label, randomized, comparative trial of nevirapine versus efavirenz-based HAART regimens. The 2NN study randomized over 1 200 individuals, and 84% of the participants completed the anticipated 48 weeks of follow-up. (van Leth et al., 2004) After 48 weeks, rates of virological failure were below 50% and in some geographical regions below 25%.

These inconsistencies reported in various studies from differing geographical regions indicate that there may be regional differences in the ability to maintain virological suppression. Van Leth and colleagues in their 2004 report of the 2NN study found a considerably lower proportion of patients with virological failure in the Asian/Australian regional group compared with the other three regional groups (Figure 2).

The current analysis should provide data on this question representative of a significant Southeast Asian cohort of HIV-infected, ARV-naive, HAART-treated individuals.

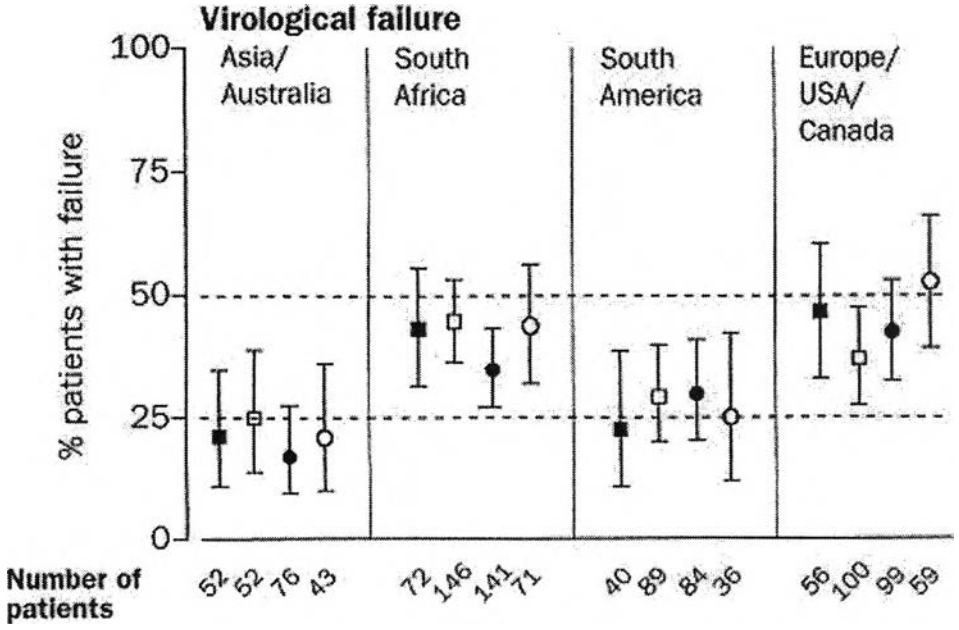

Figure 2: Proportion of patients with virological failure by region (Leth et al., 2004) following 48 weeks of HAART - error bars = 95% Confidence Intervals.

Why is the Length of Time Taking Antiretroviral Treatment Important?

A key goal of HAART is durable suppression of pVL to below the limits of detection. This goal should be achieved as quickly as possible and at least by 16–24 weeks for the most effective and durable outcomes. (DHHS, 2008) Some patients will take longer than others to suppress pVL levels and the timing and slope of pVL decrease may predict long term virological response. (DHHS, 2008; Weverling et al., 1998)

Following infection with HIV, a diverse viral population is rapidly established due to high rates of viral replication and frequent mutations. (Collins et al., 2002)

Everyday, the estimated average total HIV production is 10.3 X 10^9 virions. Mutations to all available antiretroviral (ARV) drugs are generated as a result of poor control of the replicative capacity of the virus. HIV pVL decays rapidly upon initiation of HAART, with 99% clearance within the first two weeks of therapy. (Perelson et al., 1997). A slower, second phase of viral decay follows. (Wei et al., 1995).

The time to pVL suppression after commencing HAART impacts long term treatment outcomes. Mutations in the key enzymes involved in HIV replication (reverse transcriptase, integrase and protease) occur during viral decay under ARV drug pressure. The mutations which confer ARV resistance are selected out by the presence of drug. The longer viral replication continues in the presence of ARV, the greater the chance of developing resistant virus.

Adherence to an effective antiretroviral regimen is the most important determinant of patient survival with HIV infection or AIDS. (Le Moing et al., 2002; Nachega et al., 2007) As stated previously, it is well established that the viral suppressing effects of HAART require strict adherence to prescribed dosing schedules. (Kozal et al., 2002) It is essential to reach and maintain therapeutic levels of these drugs, and strict adherence is crucial for preventing the development of drug-resistant viral strains. (Katz et al., 2002)

Many patients surviving now and many more in the future will be required to take ARV for a long time. It is worth investigating whether or not these very long time periods in themselves may eventually lead to virological failure.

Predictors of virological failure

Various authors have examined the question of predictors of virological failure with many different predictors of failure identified.

Table 4: Predictors of virological failure

Some predictors of virological failure	Author
Lower pre-treatment CD4+ count	Dragsted 2004
Ongoing viral replication (low-level viremia)	
History of intravenous drug use	
Older age at time of initiating HAART	Gutierrez 2006
Previous ART without a PI	Le Moing 2002
Younger age at time of initiating HAART	
Baseline CD4+ <500	
Higher baseline pVL	
Poor adherence	
Choice of PI or NNRTI	Manegold 2004
Any pre ART (i.e., changing therapy)	
Amount of viral replication	
Haemoglobin level	
Number of previously used NRTIs	

Table 4 shows a summary of reasons for virological failure from some recent publications. The literature supports the examination of several covariates, especially age, gender, baseline CD4+ count and pVL, the degree of HIV disease, indicated by the CDC stage, and the regimen at commencement of antiretroviral treatment. Smith et al. has reported the importance of time to virological suppression as predictive of virological failure. (Smith et al., 2004) All of these possible covariates were modelled in the current study.

In developing countries, researchers have not studied time as a predictor of virological failure. This is a very important issue as many patients now have the opportunity to take ART for a very long time, as a consequence of the implementation of mechanisms in the developing world since 2000 when HAART became more readily available. By the end of 2006, WHO, UNAIDS and UNICEF estimated that 88% of HIV-infected Thais who needed antiretroviral therapy were receiving antiretroviral therapy. Thailand was one of only three low- and middle-income countries who had surpasses a treatment coverage rate of 80%. (USAID, 2008)

Summary

There are many potential reasons that determine when patients achieve virological suppression after commencing HAART and why patients experience virological rebound after suppression. Additionally, the burden of taking medication that requires high adherence and a rigid schedule can introduce treatment fatigue. It is important to identify if time is contributing to this effect in these patients. Despite the high burden of HIV in developing countries compared with developed countries, considerably more information is available in developed countries compared with developing countries regarding virological suppression and virological failure. Data regarding the length of time taking antiretroviral treatment to predict virological failure, and more especially in an Asian, ARV-naive cohort starting HAART, are not published. There are indications of possible regional differences in the ability to maintain virological suppression even when using HAART. There needs to be further research to determine if the element of time is relevant. This examination of the HIV-NAT cohort may provide valuable insight into this important and interesting question.