

**AFFECTIVE FACTORS TO MEDICATION ADHERENCE
AMONG PATIENTS RECEIVING HIGHLY ACTIVE
ANTIRETROVIRAL THERAPY (HAART)**



**A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF NURSING SCIENCE
(COMMUNITY HEALTH NURSING)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2004**

**ISBN 974-04-5546-8
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Thesis
Entitled

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was submitted to the Faculty of Graduate Studies, Mahidol University
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ACKNOWLEDGEMENT

I would like to express my grateful appreciation to Assistant Professor Dr. Wantana Maneesriwongul, my major adviser, whose kind assistance, encouragement and continuous guidance throughout this study have led me to the fulfillment of this study.

I am most grateful to Associate Professor Dr. Yupapin Sirapo-ngam, my co-adviser, Associate Professor Dr. Orasa Panpakdee and Dr. Krongkarn Sangkard for their enthusiastic support, invaluable feedback and advice.

I would also like to acknowledge the great contribution of several individuals at Bamrasnaradura Infectious disease Institute - the Director, the Administration Head and all staff at The Out Patient Department and the Ambulatory Care Unit, including the HIV-infected patients for their facilitation and indispensable cooperation.

I would like to thank Miss Yaowaret Deekong, Miss. Thitiporn Songkroh and my master degree program classmates for their help and fruitful ideas.

I would also like to thank the Director, the Administration Head, Mrs. Chantararat Tripak and all staff members at Sena Hospital. Their kind assistance has given me a good opportunity and freed me to concentrate on my study.

As this study is a part of my advisor's project "Medication adherence among people living with HIV" which was funded by the Delta Mu Chapter Sigma Theta Tau, Yale University School of Nursing, I would like to extend my deep gratitude to the Delta Mu Chapter as well.

Last but not least, I greatly value the opinions, encouragement and overall support of the Wongwikkarns and the Tulathongs that have made my study enjoyable and memorable.

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ABSTRACT

This study was conducted among patients receiving HAART who attended the Bamrasnaradura Infectious Disease Institute for a follow up visit. The research objectives were: 1) to examine relationships between medication adherence and personal background characteristics, knowledge about HIV/AIDS, and social support among patients receiving HAART, and 2) to examine factors that contribute to the prediction of medication adherence among patients receiving HAART. A sample of 406 subjects was recruited using purposive sampling. Data were collected using a questionnaire.

In this study, medication adherence ranged from 27.5% to 100% with a mean of 96.32% (SD = 8.39%). About 79.8% of the subjects had good medication adherence ($\geq 95\%$), whereas 20.2% had poor medication adherence ($< 95\%$). The results of bivariate analysis revealed that education ($p < .01$) and occupation ($p < .05$) inversely related to medication adherence, but social support was significantly and positively related to medication adherence ($p < .01$). Patients with lower education, household work/unemployment, and better social support had better medication adherence. However in multiple regression analysis, social support, income, and age were significant predictors of medication adherence (Overall $F_{(3, 395)} = 9.610$, $p < .001$).

The findings of this study are useful in planning intervention programs to monitor and increase medication adherence among patients receiving HAART. Social support in terms of emotional, appraisal, information and instrumental support among these patients should be enhanced.

**KEY WORDS: KNOWLEDGE / SOCIAL SUPPORT / MEDICATION
ADHERENCE / ANTIRETROVIRAL THERAPY / HIV**

147 P. ISBN 974-04-5546-8

ปัจจัยที่มีผลต่อการรับประทานยาอย่างสม่ำเสมอของผู้ป่วยที่รับประทานยาต้านไวรัสเอดส์
(AFFECTIVE FACTORS TO MEDICATION ADHERENCE AMONG PATIENTS
RECEIVING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART))

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บทคัดย่อ

การศึกษาครั้งนี้ มีวัตถุประสงค์ดังนี้ 1) เพื่อศึกษาความสัมพันธ์ระหว่างปัจจัยส่วนบุคคล ความรู้เกี่ยวกับเอชไอวี/โรคเอดส์ และแรงสนับสนุนทางสังคม กับการรับประทานยาอย่างสม่ำเสมอของผู้ป่วยที่รับประทานยาต้านไวรัสเอดส์ และ 2) เพื่อศึกษาอำนาจการทำนายการรับประทานยาอย่างสม่ำเสมอโดยปัจจัยส่วนบุคคล ความรู้เกี่ยวกับเอชไอวี/โรคเอดส์ และแรงสนับสนุนทางสังคม กลุ่มตัวอย่างคือผู้ป่วยที่รับประทานยาต้านไวรัสเอดส์ ที่มารับการรักษาในโรงพยาบาลบำราศนราดูร จำนวน 406 ราย ซึ่งถูกเลือกโดยอย่างเฉพาะเจาะจง ตามเกณฑ์ที่กำหนด การเก็บรวบรวมข้อมูลทำโดยใช้แบบสอบถาม

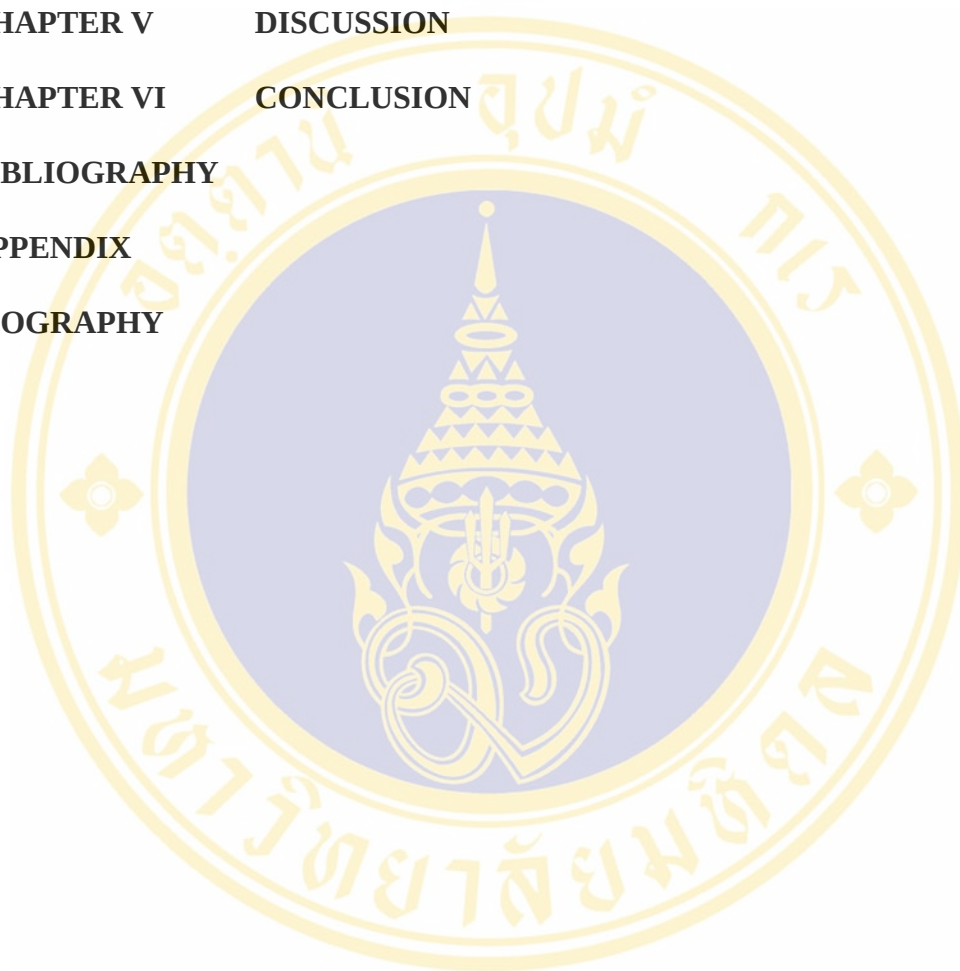
ผลการศึกษา พบว่า คะแนนการรับประทานยาต้านไวรัสอย่างสม่ำเสมออยู่ระหว่างร้อยละ 27.5 ถึง ร้อยละ 100 (ค่าเฉลี่ยเท่ากับ ร้อยละ 96.32 และส่วนเบี่ยงเบนมาตรฐานเท่ากับร้อยละ 8.39) โดยมีผู้ป่วยร้อยละ 79.8 รับประทานยาต้านไวรัสได้อย่างสม่ำเสมอ ($\geq 95\%$) และ ผู้ป่วยร้อยละ 20.2 ใช้น้ำต้านไวรัสได้อย่างไม่สม่ำเสมอ ผู้ป่วยที่มีระดับการศึกษาน้อยกว่า ($p < .01$) ทำงานบ้านหรือไม่ได้ประกอบอาชีพ ($p < .05$) และได้รับแรงสนับสนุนทางสังคมดีกว่า ($p < .01$) รับประทานยาต้านไวรัสอย่างสม่ำเสมอดีกว่าอย่างมีนัยสำคัญทางสถิติ และการวิเคราะห์สมการถดถอยพบว่า แรงสนับสนุนทางสังคม รายได้และอายุสามารถร่วมกันทำนายการรับประทานยาอย่างสม่ำเสมอของผู้ป่วยที่รับประทานยาต้านไวรัสเอดส์ได้อย่างมีนัยสำคัญทางสถิติ (Overall $F_{(3, 395)} = 9.610$, $p < .001$) ผลการศึกษานี้จะเป็นประโยชน์ในการวางแผนจัดโปรแกรมเพื่อติดตามและสนับสนุนให้ผู้ป่วยรับประทานยาต้านไวรัสได้อย่างสม่ำเสมอมากขึ้น โดยควรเพิ่มแรงสนับสนุนทางสังคมแก่ผู้ป่วยรับประทานยาต้านไวรัสเอดส์ให้มากขึ้น

147 หน้า ISBN 974-04-5546-8

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CHAPTER I

INTRODUCTION

Background and Rationale

AIDS is one of the serious global infectious diseases. It was first found in 1981 in the United States. In Thailand, since the first AIDS case was reported in 1984, there has been increasing in the number of AIDS cases. From three patients in 1984, the numbers of AIDS patients during 1991 - 1998 were increasing respectively as follows: 598; 1,834; 6,832; 13,866; 20,659; 24,872; 26,850 and 27,313 cases (http://epid.moph.go.th/epi32_aids.html). Although AIDS cases tended to decrease during 1999 – 2004 from 26,663; 25,412; 22,258; 23,384; 21,735 and 11,633 respectively, the cumulative symptomatic and AIDS cases are about 348,605 by the end of November 2004.

The spread of AIDS started from the homosexuals, injected-drug users and prostitutes. During 1984 -1990, transmission was among the group aged of 30 - 34 years old while, during 1991 - 1992, transmission spread to the younger and older age groups of 25 -29 and 30 -34 years old. However, it was found that transmission has spread out to all age groups during 1993 - 2002 and the most HIV infected cases are in the working age groups of 20 -39 years old. The highest number was in the age group of 25 -29 (26.98%), followed by the age group of 30 –34 (25.25%), 35 -39 (15.44%) and 20 -24 (10.31%). In addition, the number of patients in the age group of 15 - 19 also increased. Currently, AIDS patients are general workers (46.86%), farmers (20.70%), traders (4.3%), pre-school children (4.15%), housekeepers (3.59%) and prostitutes (0.22%) while the rest are categorized in unemployed group (5.31%). The top five highest rate of opportunistic infections are: 59,829 mycobacterium tuberculosis pulmonary or extrapulmonary patients (25.1%), 43,583 pneumocystis carinii (18.3%), 35,452 cryptococcosis (14.9%), 11,016 candidiasis of trachea, bronchi/lung (4.6%) and 7,592 pneumonia recurrent (bacteria) < 1 time/year (3.3%). This ranking has never changed (http://epid.moph.go.th/epi32_aids.html).

Due to successful national HIV prevention and control program, the number of AIDS patients has been decreased since 1999. However, vertical transmission has been increasing. Obviously, in spite of the decrease of AIDS cases, infection has spread into many age groups especially the working age group. As a result, AIDS epidemic has numerous impacts on the national economic and social development both directly and indirectly.

In the early stage when the antiretroviral drugs were not available, AIDS patients had to face with many opportunistic infection diseases resulted from low immunity and a lot of them died. In 1987 AZT, an antiretroviral drug was found to stop the virus's enzyme multiplying at the stage of Reverse Transcriptase (RT) and apparently decreased the amount of HIV in blood. This could help lengthen the patient's life (Larder, Kellam, & Kemp, 1989 cited by Suda Louisirirotchanakul, BE 2542: 191; Ungvarski, 2001: 27). However, the patients with a long period of AZT treatment were unable to stand the side effects of the drug and drug resistance could also result in failure of the treatment (Eric, & Balfour, 1994 cited by Suda Louisirirotchanakul, BE 2542: 191). Later, new antiretroviral drugs were discovered to act as RT inhibitor to stop enzyme multiplying or as protease inhibitor to stop the production of HIV-developing protein. Besides, highly active antiretroviral therapy (HAART) - combining drugs from three categories 1) Nucleoside Reverse Transcriptase inhibitors (NRTIs), 2) Non Nucleoside Reverse Transcriptase inhibitors (NNRTIs), and 3) Protease inhibitors (PIs) was employed to block HIV at several points in its replication, slowing its spread in the body. This combination of various antiretroviral drugs was used in order to lower an amount of the AIDS virus to the undetected level for a short and long period and delay HIV progression and drug resistance (Carpenter, 1998: 78-86). In addition, HAART helped improve survival rates dramatically. Instead of becoming sick and dying, many HIV-infected people became healthy and lived nearly normal lives (Jones, 2002: 25-30).

Many studies found that HAART could reduce viral load and decrease the risk of progression to AIDS and death (Belza, 2002: 285-291; Carrieri, 2003: 38-47; Navarro, 2003: 347-348). In a study of Palella and colleagues (1998), it was shown that HAART had decreased AIDS deaths by 46% in the U.S. and had greatly improved quality of patients' lives (Palella, et al., 1998 cited by Williams, 2001:38). From the

findings, it can be seen that HAART cannot completely eliminate HIV and it is likely the most effective way of employing HAART is that the patient has to strictly adhere to medication as prescribed. HAART had accomplished remarkable therapeutic success but at the expense of long-term adherence. Patients had to bear the burden of managing complex regimens, heavy pill burdens, and treatment-limiting toxicities (Currier, 2002: S1).

HAART was widely employed in 2000, but not in Thailand due to the high cost. However, in 2001, the Government Pharmaceutical Organization (GPO) could locally produce HAART and reduce the production cost (30 % - 50 % of the original cost) of HAART in Thailand. In response to this, the Ministry of Public Health had set the standard of HAART practice that HAART will be started when the CD4⁺ T-cell count is at 200 -250 cells/ μ l. In 2002, the GPO undertook research in combining the three-tablet dose to make one-tablet dose: GPO-VIR (30/40) (Nevirapine 200 mg + Lamivudine 150 mg + Stavudine 30/40 mg), which could help ease the intake of the drug, reduce the cost and increase the access to the HAART (Boonrawd Prasithiphol, 2002: 82, <http://epid.moph.go.th/epi32aids.html>, and <http://203.157.19.196/antiaids/antiaids.htm>).

Obviously, the goals of HIV infection treatment are to suppress viremia, improve immune function, and delay disease progression over the long term period (Gulick, 2000; Havlir, 1996 cited by Garcia, 2002: 105). In relation to this, medication adherence is believed to be an important determinant of both the degree and duration of virologic suppression. Excellent adherence has been shown to increase the likelihood of sustained virologic control, which is important for reducing HIV-related morbidity and mortality. A high degree of adherence is necessary for optimal virologic suppression with HAART. Several studies have shown that 90-95 % of doses must be taken for optimal suppression, and lesser degrees of adherence are more often associated with virologic failure (Arnsten, et al, 2000; Paterson, et al, 2000 cited by DHHS, 2002: 10).

Conversely, poor adherence has been shown to increase the likelihood of virologic failure and associated with increased morbidity and mortality (Carmona, et al., 2000; Paterson, et al., 2000 cited by DHHS, 2002: 10). The impact of poor adherence is heightened by the fact that variants resistant to one drug in a class are

frequently cross-resistance to others of the same class. Poor adherence leads to the development of drug resistance, limiting effectiveness of the therapy (Walsh, et al., 2000 cited by DHHS, 2002: 10). Drug resistance is one of the most significant threats to effective therapy. If patients develop resistance to a particular drug, their primary care provider should switch them to another drug in the same class. But this strategy may not work because the new strain may be resistant to every drug in the same class (Jones, 2002: 28).

Recent studies have found that antiviral-resistant HIV can be transmitted (Boden, et al., 1999: 1135-1141; Little, et al., 1999: 1142-1149). Numerous studies have found an association between poor adherence and virologic failure (Boden, et al., 1999: 1135-1141; Carmona, et al., 2000; Salomon, et al., 2000; Walsh, et al., 2000 cited by DHHS, 2002: 10). Nonadherence in patients on HAART appears to be the strongest predictor of failure in achieving viral suppression below the level of detection (Carmona, et al., 2000 & Walsh, et al., 2000 cited by DHHS, 2002: 10). Nonadherence also allows the virus to resume rapid replication and to potentially select for multidrug resistant strains of HIV. Indeed, high-level antiretroviral resistant virus has been identified among 15%-24% of newly infected person (Boden, et al., 1999: 1135-1141; Salomon, et al., 2000). Thus, imperiling the patient's health as well as the health of the public should be done to prevent HIV transmission.

Given the importance of maintaining very high adherence to HAART, it is very challenging for community nurses who closely work with their clients in the community to be able to enhance medication adherence among HIV-infected persons receiving HAART while most of them live at home. Although many studies in the U.S. explored factors associating with medication adherence (disease characteristics, treatment regimen, patient variables i.e. sociodemographics psychosocial factors, clinical setting, and patient – provider relationship) among HIV-infected persons who receive HAART, this kind of study has not been done in Thailand. Thus, a study exploring factors affecting with medication adherence among Thai HIV-infected persons receiving HAART is needed.

Research Framework

Health professionals first became concerned about uncooperative patients with

tuberculosis in the 1890s, and increased concerns about non adherence after the introduction of curative antibiotics for tuberculosis in 1945 (Lerner, 1996: 573 – 578). Later, the introduction of multiple new antibiotics in the 1950s led to studies of non adherence in patients with infections other than tuberculosis (Lerner, 1998: 573–578). Literature regarding non adherence found that 40% to 50% of patients do not adhere to either short-term antibiotic regimens or long-term therapies for asthma, diabetes, or hypertension (Eraker et al., 1984; Stephenson, et al., 1993: 2,779-2,781).

When access to HAART is assured, adherence emerges as a key to clinical management and public health, because the dynamic and chronic nature of HIV infection needs potent and continuous therapy for the duration of viral replicative capability. Patients who are not properly adherent to their HAART regimens or receive less than effective combinations of HAART may not reach therapeutic benefit (Wainberg & Friedland, 1998: 1,977–1,983). Thus, medication adherence has become a major issue in the treatment of HIV-infected individuals and the most important determinant of the outcome of HAART (Mannheimer, et al., 2002: 1,115 – 1,121). Adherence to antiretroviral medication is believed to be a crucial component in maintaining therapeutic drug levels, ensuring virologic suppression and reducing the risk of drug resistance (Altice & Friedland, 1998 cited by Mannheimer, et al., 2002: 1,115 – 1,121; Beer, et al., 2000 ; Gifford, et al., 2000: 386-395).

Poor adherence leads to the development of drug resistance, limiting the effectiveness of therapy (Walsh, et al., 2000 cited by DHHS, 2002: 10). The percentage of patients who fail to self-administer as prescribed is somewhere between 20% and 80% (Cramer, et al., 1989: 3,273-3,277; Wright, 1993 cited by Williams, 2001: 38). Similarly, among those taking HAART, 40%-60% are less than 90% adherent (Bangsberg, et al., 2000: 357-66; Bartlett, 2002: S2 – S10; Gordillo, 1999: 386-395). The level of adherence required for success, however, is thought to be a staggering 95% or greater (Bartlett, 2002: S2 – S10; Beer, et al., 2000). In HIV-infected patients who received HAART, suboptimal adherence was a strong predictor of treatment failure (Frank, 2002:S10). Obviously, HAART was the expense of long-term adherence, resulting in the burden of managing complex regimens and heavy pill, and treatment-limiting toxicities (Currier, 2002: S1).

In Thailand, the Ministry of Public Health (2001) conducted a cohort study to assess feasibility of HAART in district and provincial hospitals in the northern region where there was the highest HIV prevalence. This included 744 adults patients with HIV infection with CD4+ cell count < 200 cell/ml. It was found that after 24 weeks, average body weight of these patients increased from 48.6 kg to 53 kg and CD4+ cell count increased from 84 to 182 cell/ml. 68.6% were adherent while 31.4% discontinued due to adverse event 13.1%, failure or default 9.9%, death 5.3%, and other reasons 3.1% (Leusaree, et al., 2002).

Warangkana Munsakul and colleagues also (B.E. 2546) found that GPO-VIR was effective in the treatment of HIV-infected patients. The significant factors associated with good outcomes were body weight and CD+4 cell counts. The most common side effect was rash (13.79%) and occurrence of severe side effects was 14.94%. Somkid Ungkasrithongkul (B.E. 2540) had carried out a descriptive research on factors affecting on drugs administration in 70 AIDS patients in Bamrasnaradura Hospital and found that factors affecting drug usage included the adverse effects of any drug, the attention of patients to the directions of drugs administration, boredom with large dose and many items of drugs, the limitation of drugs administration due to other treatment, the severity of illness of the patients, and misunderstanding and misinformation about HIV and treatment. It was also found that most AIDS patients required support from family and friends which could lead to higher spirit and medication adherence. Medicines Sans Frontier (MSF) conducted a study to assess role of district hospitals in providing HAART and found that district hospitals could manage HAART effects. They suggested that educating about side effects and peer support could improve adherence among the patients (Naewbanij & Fredrix, 2002).

From review literature, many factors have been shown to influence medication adherence among patients receiving HAART for long-term success with any of the antiretroviral therapy. However, for the purposes of this study, only three significant concepts as suggested by a number of empirical studies will be explored: personal background characteristics, Knowledge about HIV/AIDS and social support as follows:

Personal background characteristics highlighted cover the following aspects

as they were found to have significant associations with medication adherence: (1) sociodemographic data which are: (a) age (Ammassari, et al., 2001: 445-449; Andreo, et al., 2001: 249-262; Fogarty, et al., 2002: 91-92; Gordillo, et al., 1999: 1,763-1,769; Hinkin, et al., 2002: 1,944-1,950; Howard, et al., 2002: 2,175 – 2,182 ; Mannheimer, et al., 2002: 1,115 – 1,121; Schectman, et al., 2002: 1,294 – 1,300; Spire, et al., 2002: 1,481-1,496; Tuldra, et al., 2000: 221-228), (b) gender (Patchara Rumakom. B.E. 2544; Vincke & Bolton, 2002: 487-495), (c) education (Gifford, et al., 2000: 386-395; Golin, et al., 2002: 812 – 813; Gordillo, et al., 1999: 1,763-1,769; Wagner, et al., 2002: 105 – 109), (d) occupation (Ammassari, et al., 2001: 445-449; Gordillo, et al., 1999: 1,763-1,769) and (e) income (Brigido, et al., 2001: 587 – 593; Kleeberger, et al., 2001; Spire, et al., 2002: 1,481-1,496), (2) side effects of HAART (Altice, et al.: 2001: 47-58; Ammassari, et al., 2001: 445-449; Bassetti, et al., 1999: 114-119; Catz, et al., 2000: 124-133; Roberts, 2000: 155-168; Simoni, et al., 2002: 431-439; Spire, et al., 2002: 1,481-1,496), (3) availability of a caregiver (s) (Frank, 2002: S3 - S9; Williams, 2001: 37-43), and (4) disclosure of HIV status (Chandra, et al., 2003; Murphy, et al., 2000: 47-58).

Knowledge about HIV/AIDS includes (1) disease and treatment (Eldred, et al., 1998: 117-125; Wagner, et al., 2002: 105 – 109; Roberts, 2000: 155-168; Mathews, et al., 2002: 157 –172), (2) antiretroviral medication use (Martinez, et al., 2000: 1266-1273; Mathews, et al., 2002: 157 –172), and (3) side effect of antiretroviral medications and management (Davis, et al., 1997: S122-S127; Murdaugh, 1998: 59-71; Wagner, et al., 2002: 105 – 109). A review of the scientific literature on medication adherence among patients populations relevant to HIV infection by Mehta and colleagues (1997) found that patients' non adherence has been reported to be significantly related with the patient not knowing the right dose of medications or that long-term medications have to be taken continuously. Decreased medication adherence has also been significantly associated with patients' lack of knowledge of their diagnosis and the expected course of their illness or treatment.

Social support, as an influence on adherence and self-management (Clark & Becker, 1998: 5-32) and significantly associated with medication adherence in patients receiving HAART (Catz, et al., 2000:124-133 ; Frank, 2002: S3 - S9; Gifford, et al., 2000: 386-395; Gordillo, et al., 1999: 1,763-1,769; Martinez, et al., 2000: 1266-1273;

Simoni, et al., 2002: 431-439; Singh, et al., 2000: 824-830; Spire, et al., 2002: 1,481-1,496), covers the following four different aspects: (1) emotional support i.e. esteem, affect, trust, concern, and listening, (2) appraisal support i.e. affirmation, feedback, and social comparison, (3) information support i.e. advice, suggestion, directives, and information, and (4) instrumental support i.e. aid in kind, money, labor, time, and modifying environment (House, 1981: 13-40). Sources of support include spouse or partner, other relatives, friends, neighbors, work supervisor, co-workers, service, caregivers, self-help groups, and health and welfare professionals (House & Kahn: 1985: 83-105). The definition and content of supportive acts described above by House and Kahn (1985) is used to develop the questionnaire in this study to measure social support of HIV-infected patients with HAART.

The research framework of affective factors to medication adherence among patient receiving HAART is shown in Figure 1.

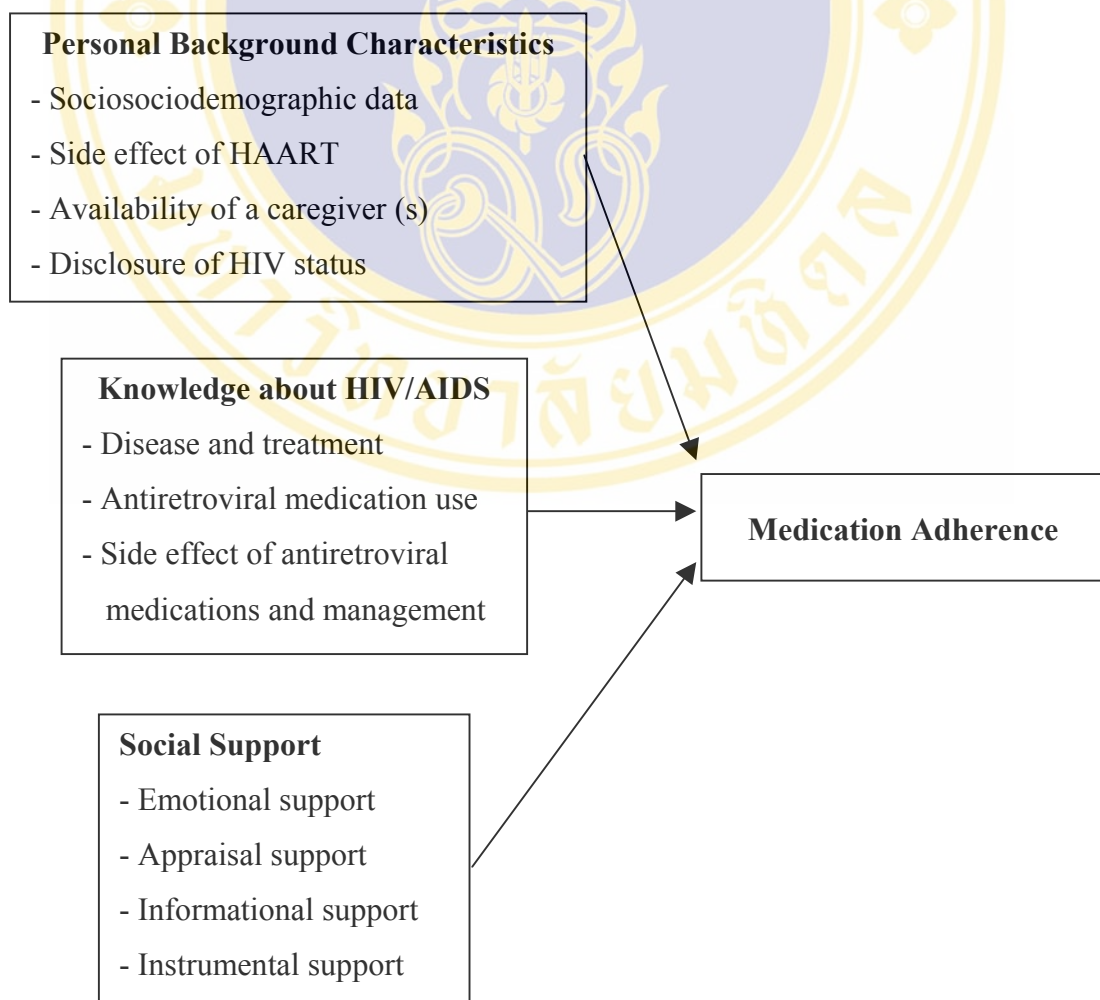


Figure 1. The research framework

Research Questions

1. Are personal background characteristics, knowledge about HIV/AIDS, and social supports related with medication adherent among patients receiving HAART?
2. What are the factors that contribute to the prediction of medication adherence among patients receiving HAART?

Objectives of Study

1. To examine relationship between medication adherence and personal background characteristics, knowledge about HIV/AIDS, and social support among patients receiving HAART
2. To examine factors that contribute to the prediction of medication adherence among patients receiving HAART.

Hypotheses

1. There are significant relationships between medication adherence and personal background characteristics (sociodemographic data, side effect of HAART, availability of a caregiver(s), and disclosure of HIV status), knowledge about HIV/AIDS, and social support among patients receiving HAART.
2. Background characteristics (sociodemographic data, side effect of HAART, availability of a caregiver(s), and disclosure of HIV status), knowledge about HIV/AIDS, and social support significantly contribute to the prediction of medication adherence among patients receiving HAART.

Scope of the Study

This research is a study of factors affecting medication adherence among patients aged 15 years old and older who receive HAART at the out patient department or ambulatory care unit at Bamrasnaradura Infectious Disease Institute from September, 2003 to June, 2004.

Expected research outcome

The potential benefit of this study is that the findings of this study can be used to plan for intervention programs to enhance medication adherence among patients receiving HAART and especially among those with poor adherence.

Definition of Terms

Personal Background Characteristics include sociodemographic data (age, gender, education, occupation, income), side effect of HAART, availability of a caregiver (s), and disclosure of HIV status.

Sociodemographic data include in this study are age, gender, education, occupation, and income.

- **Age** is defined as the period in years between the date of birth reported and the date of data collection. Less than six months will be not counted, but six months or more over that will be counted as one year.

- **Gender** is defined as male or female.

- **Education** is defined as the number of years of education that the respondents have received. It was calculated from reported education which includes uneducated, elementary education, junior high school and senior high school, certificate in vocational education, higher certificate in vocational education, diploma, bachelor's degree, master degree and doctorate degree. Assuming that they were educated in regular program with no repeated year, for example, the respondent took 6 years to finish elementary school.

- **Occupation** is defined as a way that people earn their income or get employment. Occupation here includes civil service/state enterprise, company employee, merchant, agriculturist, employee, household worker, student, monk, and others.

- **Income** is defined as an amount of money that the respondent receives per month. It was also categorized to interval scale from highest to lowest of his/her income.

Side effect of HAART is defined as adverse effects of HAART reported by individual HIV-infected patient.

Availability of a caregiver (s) is defined as availability of a person who takes care of HIV-infected patients without any payment.

Disclosure of HIV status is defined as informing the other people about their own HIV-infection.

Knowledge about HIV/AIDS is defined as the information gained about disease and treatment, antiretroviral medication use, side effect and management. Operationally, knowledge about HIV/AIDS is defined as the composite score on the 38 items of knowledge about HIV/AIDS. Score on this scale range from a low of 0 to high of 38. Higher score means better knowledge about HIV/AIDS.

Social Support is defined as interaction among people, which brings about positive health behaviors, maintenance good behaviors and enhancement of quality in personal social transaction across individual lifestyles. Social support is comprised of four components: (1) emotional support, (2) appraisal support, (3) informational support, and (4) instrumental support. Operationally, social support is defined as the composite score on the 55 items of social support scale. Score on this scale range from a low of 55 to high of 275. Higher score means better social support.

Medication Adherence is defined as an average of medication adherence score, measured by visual analog scale and self-report of a percent of antiretroviral medication taken in the past month among patients receiving HAART.

CHAPTER II

LITERATURE REVIEW

The AIDS-related literature from various sources has been reviewed and analyzed. Presentation of this includes four parts as follows: Acquired Immunodeficiency Syndrome (AIDS), antiretroviral drugs and management of the adverse effects, medication adherence, and factors affecting medication adherence as follows:

Part 1. Acquired Immunodeficiency Syndrome (AIDS)

AIDS is the most severe disease as a continuum of illnesses related to infection by human immunodeficiency virus (HIV). The virus was known in the past as human T-cell lymphotropic virus type III or lymphadenopathy-associated virus. HIV infection and AIDS are not synonymous terms. HIV infection ranges from asymptomatic infection to the full-blown clinical disease AIDS. The clinical presentations of HIV infection vary. In the past, published classification schemes for HIV infection stratified various HIV-related illnesses into separate syndromes such as AIDS-related complex and lymphadenopathy syndrome. These different presentations of HIV disease are now considered a continuum of host response to HIV infection and not separate syndromes (Flaskerud, 1992: 1).

1.1 Mechanism of Disease

1. HIV and the immune system (WHO, 1994: 6).

The body cells that are the main targets of HIV are T-helper lymphocytes and the scavenger cells known as monocytes, which turn into macrophages when they leave the bloodstream to enter a body organ. In a healthy immune system, the monocytes/macrophages defend the body by seeking out and eliminating foreign particles and dead or infected cells. The body also defends itself by manufacturing special proteins called antibodies to render foreign bodies (known collectively as antigens) harmless. HIV infection interference with both of these processes gradually weakens the immune system.

The cells that produce antibodies are a type of lymphocyte (white blood cell) known as B cells. These cells manufacture antibodies specific to the antigen they seek to destroy and some retain a memory of the antigen they have encountered. This enables the immune system to react swiftly if the antigen should reappear even years later.

Other important lymphocytes in the immune system are the T cells, which circulate in the bloodstream and concentrate at sites of invasion by a foreign body. Apart from serving as specialized killers and helping B cell to make antibodies, the T cells coordinate the immune system's response to an antigen and switch the system off when danger is past. Some T cells, too, retain a memory of antigens they have encountered.

The T cell that regulates and coordinates the other cells is called a T-helper cell whose full name is the CD4 + T lymphocyte commonly known as a CD4 + cell. It is the main target of HIV. The virus breaks into the cell and throws the whole immune system into chaos by sidelining all the other cells dependent on the T-helper cell. HIV further outwits the immune system by changing constantly and becoming unrecognizable to antibodies produced against it.

Once inside the CD4 + cell, HIV uses the host cell's machinery to reproduce rapidly and massively. The new viruses form buds on the surface of the host cell before bursting into the bloodstream to invade other cells. A very low number of CD4 + cells in the blood indicates an impaired immune system that means a person is unable to fight off diseases or infections that would normally pose little threat.

HIV is also attracted to monocytes/macrophages but it does not destroy them in the same way as it does to the CD4 + cells. Instead, it hides in them and is carried to the brain, lungs and other parts of the body, particularly the lymph nodes.

2. Pathogenesis

The hallmark of symptomatic HIV infection is immunodeficiency caused by continuing viral replication. The virus can infect all cells expressing the T4 (CD4) antigen, which HIV uses to attach to the cell. Chemokine receptors (CCR5 and CXCR4) are important for virus import, and individuals with CCR5 deletions are less likely to become infected, and once infected, the disease is more likely to progress slowly. Once it enters a cell, HIV can replicate and cause cell fusion or death by

unknown mechanisms. In many cases, a latent state is established, with integration of the HIV genome into the cell's genome. The cell principally infected is the CD4 (helper-inducer) lymphocyte, which directs many other cells in the immune network. With increasing duration of infection, the number of CD4 lymphocytes falls. Some of the immunologic defects, however, are explained not by quantitative abnormalities of lymphocyte subsets but by qualitative defects in CD4 responsiveness induced by HIV.

Other cells in the immune network that are infected by HIV include B lymphocytes and macrophages. The defect in B cells is mainly due to disordered CD4 lymphocyte function. These direct and indirect effects can lead to generalized hypergammaglobulinemia and can also depress B cell responses to new antigen challenges. Because of these defects, the immunodeficiency of HIV is mixed. Elements of humoral and cellular immunodeficiency are present, especially in children. Macrophages act as a reservoir for HIV and serve to disseminate it to other organ systems (e.g. the central nervous system).

Apart from the immunologic effects of HIV, the virus can also directly cause a variety of neurologic effects. Rare glial cell and oligodendrocytes express CD4 antigen and thus may be permissive of infection by HIV. However, these cells are rarely infected, whereas multinucleated giant cells of macrophage origin are more commonly seen in brain specimens of infected individuals. Neuropathology largely results from the release of cytokines and other neurotoxins by infected macrophages. Other factors such as coexistent CMV infection may also be important. Perturbations of excitatory neurotransmitters and calcium flux may contribute to neurologic dysfunction.

1.2 Transmission of HIV/AIDS.

The transmission of HIV/AIDS are sexual contract, exposure to infected blood or blood components, and from an infected mother to her neonate, in utero, peripartum, and probably, by breast feeding (United Nations, 1995: 5, Patt, 1994: 28). Pratt (1995: 28) stated that "Now, well into the second decade of our experience with this disease, the know means of viral transmission are generally understood. HIV is a blood borne virus and has been isolated from blood, semen, saliva, tears, breast milk, and cerebrospinal fluid."

1.3 Disease progression

Disease progressions are classified into six categories as follow:
(<http://www.tthivclinic.com/overview.html>)

1. Acute primary HIV infection is the first stage of HIV disease, when the virus first establishes itself in the body. The period of time between when a person is first infected with HIV and when antibodies against the virus are produced by the body usually between 6- 12 weeks. Up to 70% of people newly infected with HIV will experience some "flu-like" symptoms. These symptoms, which usually last no more than a few days, might include fevers, chills, night sweats and rashes (not cold-like symptoms) (http://www.sfaf.org/aids101/hiv_disease.html).

2. Asymptomatic HIV disease is usually with no clinical sign and symptoms. CD4 cells generally decline at a rate of 40-80 cells/ μ L per year in untreated individuals. However the stage is labeled "asymptomatic", HIV viral replication is continuing constantly and the immune system is slowly weakening (http://www.tthivclinic.com/overview_asympt.htm).

3. Early Symptomatic HIV disease Those who have a CD count > 500 cells/ μ L have less than a 5% chance of developing AIDS within the next 18-24 months. Constitutional complaints of variable severity may be seen and include: fevers, night sweats, headache, malaise, fatigue, diarrhea, weight loss (greater or equal to 10 lb over 6-8 weeks), etc (http://www.tthivclinic.com/overview_early.htm).

4. Middle Symptomatic HIV disease At this stage, the CD4 count is between 200-500 cells/ μ L. Monthst individuals are still without symptoms. Other symptoms that may occur during this stage include: herpes zoster, recurrent herpes simplex lesions, candidiasis (oral and/or vaginal), oral hairy leukoplakia, various constitutional symptoms previously described (http://www.tthivclinic.com/overview_middle.htm).

5. Late Symptomatic HIV disease At this stage, the CD4 count is between 50 - 200 cells/ μ L. The patients at the late symptomatic stage of HIV infection are now at an increased risk of opportunistic infections (http://www.tthivclinic.com/overview_late.htm). The five monthst commonly reported opportunistic infections in Thailand are mycobacterium tuberculosis pulmonary or extrapulmonary, pneumocystis carinii, cryptococcal meningitis, candidiasis of trachea,

bronchi/lung and pneumonia recurrent (bacteria) < 1 time/year (http://epid.moph.go.th/epi32_aids.html). Constitutional symptoms usually worsen. Wasting and AIDS Dementia Complex may be other serious problems encountered. Human papilloma virus associated malignancies (cervical and anal) may occur (http://www.tthivclinic.com/overview_late.htm).

6. Advanced HIV disease In addition to all the previous conditions, several new opportunistic infections may occur. Cytomegalovirus disease, disseminated mycobacterium avium complex (MAC), cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), and several other conditions are associated with this severe degree of immunosuppression. Several opportunistic infections occur concomitantly. At this stage, treatment is usually suppressive rather than curative.

Patients may also suffer from many medication-induced side effects which may be challenging to sort out and modify. The psychosocial ramifications of this degree of illness and debilitation are great and require intensive counseling and support (http://www.tthivclinic.com/overview_adv.htm).

CDC has introduced the revised HIV classification system for adolescents and adults (CDC, 1993), categorizing persons on the basis of clinical conditions associated with HIV infection and CD4+ T-lymphocyte counts. The system is based on three ranges of CD4+ T-lymphocyte counts and three clinical categories and is represented by a matrix of nine mutually exclusive categories as shown in Table 1. This system replaces the classification system published in 1986, which included only clinical disease criteria and which was developed before the widespread use of CD4+ T-cell testing.

CD4+ T-lymphocyte categories

The three CD4+ T-lymphocyte categories are defined as follows:

- Category 1: ≥ 500 cells/ μ L
- Category 2: 200 - 499 cells/ μ L
- Category 3: < 200 cells/ μ L

Table 1. 1993 revised classification system for HIV infection and expanded AIDS surveillance case definition for adolescents and adults

CD4+ T-cell categories	Clinical categories		
	(A) Asymptomatic, acute (primary) HIV or PGL	(B) Symptomatic, not (A) or (C) conditions	(C) AIDS-indicator Conditions
(1) > 500/ μ L	A1	B1	C1
(2) 200-499/ μ L	A2	B2	C2
(3) < 200/ μ L	A3	B3	C3
AIDS-indicator T-cell count			

PGL = persistent generalized lymphadenopathy.

1.4 Opportunistic infection

Opportunistic infection (OI) is an infection with a microorganism that does not ordinarily cause disease, but that becomes pathogenic in a person whose immune system is impaired, as by HIV infection (WHO, 1991: 49)

The top five highest rates of opportunistic infections are following:
(http://epid.moph.go.th/epi32_aids.html).

1. Mycobacterium tuberculosis pulmonary or extrapulmonary

Tuberculosis is a chronic bacterial infection caused by *Mycobacterium tuberculosis*, which starts as a pulmonary infection and is characterized pathologically by the formation of granulomas. Clinical status is based mainly on the presence or absence of tubercle bacilli in the sputum and chest radiographs. Fatigue, fever, night sweats and weight loss may occur early, while localizing symptoms of cough, chest pain, hemoptysis and hoarseness become prominent in advanced stages. From infection to demonstrable primary lesion or significant tuberculin reaction, about 2-10 weeks. While the subsequent risk of progressive pulmonary or extrapulmonary TB is greatest within the first year or two after infection, latent infection may persist for a lifetime. HIV infection appears to increase the risk greatly and shorten the interval for the development of TB disease. TB disease may affect any organ or tissue such as the lymph nodes, pleura, pericardium, kidneys, bones and joints, larynx, middle ear, skin, intestines, peritoneum and eyes. If untreated, about half the patients will die within 5

years, a majority of these within 18 months (http://www.state.nj.us/health/cd/cd_tuberculosis.htm).

2. Pneumocystis carinii

Pneumocystis carinii pneumonia (PCP or pneumocystis) is the monthst common opportunistic infection in people with HIV. Without treatment, over 85% of people with HIV would eventually develop PCP. It has been the major killer of people with HIV. PCP is a kind of pneumonia caused by the Pneumocystis carinii bacteria. The PCP bacteria is common all over the world. Monthst people infected with this bacteria do not get pneumonia because their immune systems are healthy and strong. People whose immune systems are weak because of HIV infection can get PCP (<http://www.thebody.com/nmai/pcp.html>). Monthst cases are mild, but people with severe PCP may die if the infection is not treated quickly.

However, PCP is now almonthst entirely preventable and treatable. A good medicine for preventing PCP is trimethoprim-sulfamethoxazole or TMP-SMZ, for short. TMP-SMZ is a combination of 2 medicines. It has different brand names, such as Bactrim, Septra and Cotrim. It comes in pill and liquid forms (<http://familydoctor.org/handouts/475.html>).

3. Cryptococcosis (Cryptococcal Meningitis)

Cryptococcus is a fungus. It is very common in the soil. It can get into your body when you breathe in dust. It does not seem to spread from person to person. Meningitis is the monthst common illness caused by Cryptococcus. Meningitis is an infection of the lining of the spinal cord and brain. It can cause coma and death. Cryptococcus can also infect the skin, lungs, or other parts of the body. The risk of cryptococcal infection is highest when your T-cell (CD4+) counts are below 100.

The first signs of meningitis include fever, fatigue, a stiff neck, headache, nausea and vomiting, confusion and vision problems. The symptoms may come on slowly. HIV disease or medications can also cause these symptoms. Therefore, laboratory tests are used to confirm that you have meningitis. Meningitis is treated with antifungal drugs. Some physicians use fluconazole. It is available in pill form or as an intravenous drug. Fluconazole is fairly effective, and is generally easy to tolerate. Other doctors prefer to use a combination of amphotericin B and flucytosine capsules. Amphotericin B is a very strong drug. It is given as an injection or a slow

intravenous infusion. It can have serious side effects. Cryptococcal meningitis usually comes back after the first time. Repeat cases are reduced if people keep taking antifungal drugs (<http://www.thebody.com/nmai/meningitis.html>).

4. Candidiasis of trachea, bronchi/lung

Candidiasis is a fungal infection and among the most common conditions seen in people with HIV. The fungus called *Candida* causes candidiasis. This fungus is normally found in small amounts in the mouth, vagina, digestive tract and skin. In a healthy person, other bacteria and the immune system keep it from becoming a problem. However, a weak immune system makes it easier for *Candida* to grow and cause infection. In HIV disease, the most serious *Candida* outbreaks occur when CD4⁺ cell counts are very low (below 100). In people with weak immune systems, candidiasis can recur and be difficult to treat.

While candidiasis is a rather common condition in general, it's often the first illness and sign that HIV disease is progressing to a more severe stage. Candidiasis of the mouth (thrush) is the most common opportunistic infection in people with HIV. Infection of the esophagus with *Candida* is the most common AIDS-defining condition and is more common in women than men (<http://www.thebody.com/step/equine> 050603/candida.html; <http://www.thebody.com/pinf/candidiasis.html>).

5. Pneumonia recurrent (bacteria) < 1 time/year

Two or more episodes of acute pneumonia occurring within twelve months. Both episodes must have infection with a pathogen that typically causes pneumonia (other than *P. carinii* or *M. tuberculosis*) proven by culture or some other organism-specific diagnostic method and new (not present earlier) radiological evidence of pneumonia (http://www.stdservices.on.net/management/appendices/hiv_case_defn.htm).

1.5 Therapy of HIV/AIDS

Treatment for HIV infection can be divided into four categories: therapy for opportunistic infections and malignancies, antiretroviral treatment, hematopoietic stimulating factors, and prophylaxis of opportunistic infections (Katz & Hollander, 2002: 1340-1351). This study will focus on antiretroviral treatment.

1. Therapy for opportunistic infections and malignancies.

OIs are important part of the HIV disease process. It is common to find AIDS patients with multiple OIs. These OIs result in more rapid decline in CD4 T-cell count than the decline resulting from HIV disease itself. Thus effective therapy is required to treat and prevent these infections. The incidence and type of OIs in HIV patients is directly related to the CD4 count in that individual.

Common OIs are tuberculosis both pulmonary and extra-pulmonary, oropharyngeal candidiasis, herpes zoster, herpes simplex, toxoplasmosis, cryptococcal meningitis, pneumocystis carini pneumonia, cytomegalovirus retinitis, cryptosporidial diarrhea (<http://www.manbir-online.com/std/hiv.5.htm>).

Kaposi's sarcoma (KS) is a malignant, multifocal systemic disease that originates from the vascular endothelium and has a very variable clinical course. In HIV-infected patients, KS is an AIDS-defining illness. Particularly aggressive courses of disease, that ended lethally, have been observed mainly in HIV patients with severe and untreated immunodeficiency. Since the introduction of HAART in 1996, the frequency of KS in HIV-infected patients has decreased sharply, and the clinical course of disease has improved significantly. In many cases, stabilization or complete remission of tumors is possible with immune reconstitution and reduction of the HIV viral load. Of all possible therapies, efficient HAART is therefore the first choice for treatment. It can be combined with local treatments (cryotherapy, retinoids, radiation, etc.). Additional treatment with interferon alpha, paclitaxel or chemotherapy with liposomal anthracyclines is only necessary if there is progression of the disease under HAART with visceral involvement.

If KS is diagnosed in HIV-infected patients who have not yet been treated, or who are no longer being treated with antiretroviral drugs, it is essential to start HAART. If the HIV viral load can be reduced (ideally below the level of detection) and immune reconstitution is achieved with an increase in the CD4+ T cell count, KS stabilizes or even resolves completely in many patients (<http://hivmedicine.com/textbook/ks.htm>).

2. Antiretroviral therapy.

Antiretroviral drugs attack the virus at different stages of life cycle. The goal of antiviral therapy is to disable HIV replication. For instance, AZT, ddI and ddC all

interfere with production of reverse transcriptase, a protein the virus must use in order to reproduce. Protease inhibitors, such as Crixivan, interfere with HIV's use of the protease enzyme, another essential component to its reproduction (http://www.sfaf.org/aids101/hiv_disease.html), thus triple drug therapy offers the best chance of reducing the multiplication of the virus and allowing the immune system to stay healthy (<http://www.manbir-online.com/std/hiv.3.htm>).

Thouree classes of antiretroviral agents are currently available for the treatment of HIV infection: nucleoside and nucleotide analogs (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Some 20 drug products have been licensed, including formulations of both individual and combined antiretroviral agents. The fusion inhibitor T-20 has been launched in 2003 as the prototype of a fourth drug class. A number of other drugs and new classes of drug are in the pipeline and expected to be licensed in the next years. Research is also focusing on immunomodulatory approaches with vaccines or cytokines (interferons, interleukins) (<http://hivmedicine.com/textbook/haart/classes.htm>).

The side effects of the antiviral drugs can be severe and may significantly contribute to the patient's symptoms. The monthst frequent dose limiting side effects are painful neuropathy, gastrointestinal disturbances and myelosuppression (Woodruff, 1996: 386).

3. Hematopoietic stimulating factors.

Epoetin alfa (erythouropoietin) is approved for use in HIV- infected patients with anemia, including those with anemia secondary to zidovudine use. It has been shown to decrease the need for blood transfusions. Hypertension is the monthst common side effect (Katz & Hollander, 2002: 1350-1351).

4. Prophylaxis of opportunistic infections.

In general, decisions about prophylaxis of opportunistic infections are based on the CD4 count, other evidence of severe immune suppression (eg, oral candidiasis), and a history of having had the infection in the past. In the era prior to HAART, patients started on prophylactic regimens were maintained on them indefinitely (Katz & Hollander, 2002: 1351).

Part 2. Antiretroviral Drugs and Management of the Adverse Effects

2.1 Current Antiretroviral Drugs in Clinical Use. (Kirton, 2001: 605-613, Jones, 2002:28; <http://www.hivmedicine.com/textbook/drugs.htm>). Antiretroviral drugs work inside infected CD4+ cells by inhibiting the action of enzymes necessary for HIV replication:

1. Nucleoside Reverse Transcriptase inhibitors (NRTIs)

become part of HIV's DNA and derail its building process. Damaged viral DNA cannot take control of the cell's DNA. That is

1.1 Zidovudine (AZT, ZDV) FDA approval: 3/87. The oldest and most thoroughly investigated HIV drug. Due to gastrointestinal and myelotoxic side effects, the drug was out of fashion for a while. However, it remains an important component of many HAART regimens even today, particularly as it has good CNS penetration and relatively low mitochondrial toxicity (good long-term tolerability.), AZT can be used as monotherapy in cases to prevent vertical transmission.

Trade name: Retrovir[®], Combivir[®], Trizivir[®]

Usual Regimen: 600 mg daily-200 mg q8h or 300 mg q12h. Prevention of vertical transmission- Start treatment at 14 weeks gestation: 100 mg five times daily until labor. Intrapartum-Load with 2 mg/kg over first hour, followed by a maintenance dose of 1 mg/kg/hour until umbilical cord is clamped. Neonates-Syearup 2 mg/kg PO q6h x 6 weeks. Start 8-12 hours after birth. If unable to use oral route, deliver IV dose of 1.5 mg/kg q6h. Pediatric dosing, for ages 3 months-2 years-90-180 mg/m² q6-8h. Usual pediatric dose is approximately 160 mg/m² q8h. Continuous IV infusion-20 mg/m²/hour. Intermittent IV infusion-120 mg/m²/q6h.

Side effects: Nausea, vomiting, abdominal discomfort, fever, rash, weakness, headache, myalgia, dizziness. Macrocytic anemia (MCV almost always elevated); rarely, neutropenia. Elevations in LDH, CPK and transaminases may occur. Episodes of lactic acidosis are rare.

Drug-food interactions: Food and milk do not appear to affect GI absorption substantially.

Adverse effects:

- Anemia may be seen in clients taking AZT, usually occurring after 2-12 weeks of

therapy.

- Other cytopenias may occur, such as leukopenia or thrombocytopenia.
- Prolonged use (i.e., >1 year) may result in myopathies.

Comments/Warnings: Do not combine with stavudine. There is increased myelotoxicity when concurrently used with other myelosuppressive drugs, especially ganciclovir, but also cotrimoxazole, dapsone, etoposide, pyrimethamine, interferon, daunorubicin, vinblastine, vincristine, sulfadiazine, amphotericin B and ribavirin. Ribavirin antagonizes the antiviral activity of zidovudine in vitro. Concurrent use of zidovudine and ribavirin should therefore be avoided. Initially monthly monitoring of blood count, transaminases, CPK and bilirubin is required. The gastrointestinal complaints can be treated symptomatically and usually subside after a few weeks. Anemia can develop late, even after months on treatment. Zidovudine should always be a component of transmission prophylaxis.

Dosage adjustments:

- AZT is metabolized by the liver. Dosage may need alteration in severe liver disease.
- AZT is eliminated by the kidneys. For clients with renal failure receiving dialysis, the recommended dosage is 100 mg q6-8h. The IV dose is 1 mg/kg.

1.2 Didanosine (ddI) FDA approval: 10/91. An important, well investigated and frequently used NRTI. Combination with stavudine can be problematic as there are cumulative toxicities. Even though once-daily dosing is possible, the drug must be taken on an empty stomach, and many antiretroviral drugs must be taken at intervals before or after didanosine.

Trade name: Videx[®]

Usual Regimen: 400 mg b.i.d.-200 mg q12h or 400 mg o.d. Buffered tablets: for <60 kg-125 mg q12h, for >60 kg-200 mg q12h. Buffered powder (25% less bioavailable than buffered tablets): for <60 kg-167 mg PO q12h, for >60 kg-250 mg PO q12h. Neonatal (infants aged >90 days) dosage-50 mg/m² q12h. Pediatric dosage-90-150 mg/m² q12h. The usual dosage in combination with other antiretrovirals is 90 mg/m² q12h. Didanosine must be taken on an empty stomach, at least 2 hours after or 1 hour before a meal.

Side effects: Diarrhea, nausea, headache, rash. Pancreatitis, even after longer periods on treatment. Peripheral polyneuropathy. Rarely lactic acidosis, especially in combination with stavudine.

Drug-food interactions:

- Must be taken on empty stomach $\frac{1}{2}$ hour before meals or 2 hours after meals. Tablets are chewable.
- Acid rapidly degrades drug. Contains a buffering agent to prevent degradation. When ddI dosage requires more than one pill, the pills must be taken together to achieve benefit from buffers. Doses are ineffective if done otherwise.
- Powder must not be placed in acidic liquids, such as orange juice.
- Alcohol should be taken with caution.

Adverse effects:

- Neuropathy with pain can occur 2-6 months after drug administration.
- Pancreatitis has been reported and in some cases has been fatal. This finding increases in those who drink alcohol or take other medications that can cause pancreatitis.

Comments/Warnings: Acute and chronic pancreatitis are contraindications - caution in patients with alcoholism. If possible, concurrent treatment with drugs that can cause pancreatitis (e.g. intravenous pentamidine) should be avoided. The following drugs should be used with caution: ethambutol, cisplatin, disulfiram, ethionamide, INH, vincristine, etc. (peripheral neuropathy). Indinavir, zalcitabine, dapsone, ketoconazole, itraconazole, or tetracyclines, when given concurrently, should be administered 2 hours before or after didanosine. Dose reduction is necessary for concurrent treatment with tenofovir. Initially, monthly monitoring of amylase, blood count, transaminases, and bilirubin is required. Patients should be informed about the risk of pancreatitis. If pancreatitis is clinically suspected, didanosine should be discontinued without subsequent rechallenging.

Dosage adjustments:

- ddI is eliminated by the kidney. In clients with renal failure receiving dialysis, it is recommended that $\frac{1}{4}$ of the total daily dose be administered once daily.
- No specific dose has been listed, but it is recommended that the dose be reduced for severe hepatic impairment.

1.3 Zalcitabine (ddC) FDA approval: 6/92. One of the first antiretroviral drugs. It is now used very rarely due to complicated dosing regimen, the risk of polyneuropathy and cross-resistance with didanosine. It is possibly less potent than didanosine and stavudine. This drug should always be used in combination with other medications to treat HIV infection.

Trade name: Hivid[®]

Usual Regimen: 2.25 mg daily-0.75 mg q8h. Dose adjustment in renal failure: if creatinine clearance is 10 to 40 ml/min: 0.75 mg bid, CrCl < 10 ml/min: 0.75 mg qd. Pediatric dosage-Range: 0.005-0.01 mg/kg q8h. Usual pediatric dose-0.01 mg/kg q8h.

Side effects: Peripheral neuropathy (in up to 30 %), stomatitis with oral ulcers (in up to 4 %), pancreatitis (in <1 %). Rarely: rash, lactic acidosis, hepatic steatosis.

Drug-food interactions: Food dose not significantly interfere with absorption of medication but dose delay absorption time.

Adverse effects:

- Peripheral neuropathy is common and can occur 2-6 months after therapy begins.
- Stomatitis and aphthous esophageal ulcers can occur.
- Pancreatitis can occur.
- Hepatitis can occur.

Comments/Warnings: Zalcitabine is contraindicated in patients with pre-existing polyneuropathy. Use with caution where there is a history of pancreatitis. Zalcitabine should not be administered with neurotoxic drugs, e.g. ethambutol, cisplatin, disulfiram, ethionamide, INH, vincristine. Combination with didanosine and stavudine is not recommended, as there is little available data and a risk of cross-resistance. Combination with zidovudine is preferable.

Dosage adjustments: ddC is eliminated by the kidneys. In clients with impaired renal function, the dosage should be reduced to 0.75 mg q12h; severe renal impairment requires a dosage reduction to 0.75 mg q24h.

1.4 Stavudine (d4T) FDA approval: 6/94. This drug should always be used in combination with other medications to treat HIV infection. Stavudine is a thymidine analog like zidovudine. Subjective tolerability is good; the drug was long considered at least equivalent to zidovudine. Newer guidelines are more cautious, due

to neuropathy and data on mitochondrial toxicity (lipoatrophy, lactic acidosis), particularly in combination with didanosine. New 75 mg and 100 mg capsules will be available shortly, allowing once-daily dosing.

Trade name: Zerit[®]

Usual Regimen: 80 mg daily-40 mg q12h, for <60 mg-30 mg q12h. Pediatric dosage-for <30 mg: 1mg/kg/day q12h (in two divided doses).

Side effects: Peripheral neuropathy, especially in combination with didanosine (up to 24 %). In many studies, stavudine has been linked to lipoatrophy more frequently than other NRTIs. However, the following occur less frequently than with zidovudine: diarrhea, nausea, vomiting, headache. Very rare, but potentially fatal: lactic acidosis which occurs monthly in combination with didanosine (especially in pregnancy.). Further side effects: hepatic steatosis, pancreatitis.

Drug-food interactions: Stavudine should be taken on an empty stomach.

Adverse effects: Peripheral neuropathy is common and can occur 2-6 months after therapy begins.

Comments/Warnings: Stavudine should not be combined with zidovudine due to the antagonistic effects. If possible, no concurrent treatment with other neurotoxic drugs (zalcitabine, ethambutol, cisplatin, INH, vincristine, etc.). Stavudine can be taken on an empty stomach or with a light meal. If symptoms of peripheral neuropathy occur, treatment with stavudine should be discontinued.

Dosage adjustments: d4T is partially eliminated by the kidney. Dosage adjustment varies by severity of renal function impairment and body weight. With severe renal impairment (creatinine clearance between 10-25 ml/min) dosage may be adjusted to 20 mg q24h. For those with severe renal impairment weighing <60 kg, the dosage should be reduced to 15 mg q24h.

1.5 Lamivudine (3TC) FDA approval: 11/95. A well tolerated drug, but with rapid development of resistance. This drug should always be used in combination with other medications to treat HIV infection.

Trade name: Epivir[®], Combivir[®], Trizivir[®]

Usual Regimen: 300 mg daily for >50 kg-150 mg bid, for <50 kg-2 mg/kg PO bid. Neonatal (infants aged <30 days) dosage-2 mg/kg bid. Pediatric dosage, for ages 3 months-12 years-4 mg/kg (not to exceed 150 mg) bid

Side effects: Fatigue, nausea, vomiting, diarrhea, headache, insomnia, myalgia and arthralgia may occur, but are usually due to the other drugs in the combined preparations (see sections on zidovudine and abacavir). Peripheral polyneuropathy, pancreatitis and lactic acidosis are rare.

Drug-food interactions: Epivir tablets and solution may be taken with or without food.

Comments/Warnings: Doses of lamivudine require adjustment according to renal function.

Dosage adjustments: 3TC is eliminated by the kidneys. Dosage adjustment varies with the severity of renal function. In severe renal function, the dosage should be reduced to 25 mg daily.

1.6 Abacavir (ABC) FDA approval: 12/98. The hypersensitivity reaction, though rare, complicates the use of abacavir. Abacavir should therefore be prescribed by HIV clinicians. Abacavir is otherwise well tolerated, possibly causing less mitochondrial toxicity, and therefore quite likely to have a better future than other NRTIs. Unfortunately, there is cross-resistance with many other NRTIs. This drug should always be used in combination with other medications to treat HIV infection.

Trade name: Ziagen[®], Trizivir[®]

Usual Regimen: 600 mg daily-300 mg q12h. Pediatric dosage, for ages 3 months-16 years-8 mg/kg (not to exceed 300) mg q12h.

Side effects: Abacavir causes a hypersensitivity syndrome (HSR) in approximately 2 to 6 % of patients. This usually occurs within the first six weeks following the initiation of treatment. Pruritus and rash are common, but do not always occur. The HSR may present with just fever and a slowly developing malaise. Gastrointestinal complaints (nausea, vomiting, diarrhea, abdominal pain) and fatigue are also possible, but are not necessarily linked to the HSR. Elevated liver function tests, insomnia and dizziness are rare. There is probably a genetic predisposition towards development of the HSR.

Drug-food interactions: There are no known dietary restrictions for this drug. Abacavir can be taken with or without food. **Interactions:** 0.7 g/kg ethanol (e.g. 0.5 l wine) increases the AUC of abacavir by 41 % and increases the half-life by 26 %.

Adverse effects: May cause hypersensitivity reaction consisting of fever, nausea, vomiting, malaise, and rash, in which case the medication should be stopped permanently. Rechallenging can be life-threatening. Hypersensitivity reaction should be reported to the ABC Hypersensitivity Registry (1-800-270-0425).

Comments/Warnings: Abacavir is contraindicated in cases with a previously diagnosed abacavir hypersensitivity reaction and after interruption of therapy, if a prior HSR cannot be ruled out retrospectively. Patients should be well advised about the HSR, but not frightened. When only mild symptoms occur (see below), abacavir should not be stopped too quickly, as an intercurrent infection may "simulate" the HSR. Therapy may be continued for one or two days under close observation. Rechallenge after suspected HSR is contraindicated, as a repeated allergic reaction can rapidly become fatal. Patients should be told to consult a doctor immediately if at least two of the following symptoms occur:

- fever
- shortness of breath, sore throat or cough
- rash (erythema and/or pruritus)
- nausea or vomiting or diarrhea or abdominal pain
- extreme fatigue or diffuse pain or general malaise

Dosage adjustments: No renal or hepatic dosage adjustment necessary.

1.7 Emtricitabine (FTC) US application for approval in September 2002. Emtricitabine is a well tolerated NRTI, with a resistance profile comparable to that of lamivudine. It can be taken once a day.

Trade name: Coviracil[®]

Oral dose: 200 mg qd.

Side effects: Rare. Most commonly headache, nausea, and gastrointestinal complaints.

1.8 Tenofovir (TDF) is approval for initial therapy is expected in

2003. Tenofovir DF is the prodrug of the acyclic nucleotide analog tenofovir, and has good oral bioavailability. It also has efficacy against hepatitis B virus. Tenofovir, at least according to current data, has good tolerability.

Trade name: Viread®

Indication: Previously treated HIV infection **Oral dose:** 300 mg qd, to be taken with a meal.

Side effects: Generally well tolerated. In several studies, side effects were comparable to those reported in placebos. Rarely: elevation of liver enzymes; possibly leucopenia. It is not currently known, whether long-term treatment with tenofovir can lead to bone density changes. Animal studies showed changes in bone density at doses 30 times higher than the therapeutic dose. In contrast to its predecessor, adefovir, there has been no indication of nephrotoxicity – however, there is no long-term data available yet.

Comments/Warnings: Tenofovir should not be prescribed to patients with a creatinine clearance of less than 60 ml/min. In cases of mild renal dysfunction, retention parameters should be monitored monthly. Concurrent treatment of tenofovir and other drugs that are eliminated via active tubular secretion can lead to increased serum concentrations of both drugs: cidofovir, aciclovir, valaciclovir, ganciclovir, valganciclovir. Use with caution in combination with didanosine: co-medication with tenofovir increases the C_{max} and AUC of didanosine by 28 % and 44 %, respectively. Even though the data published so far does not show an increased incidence in the side effects typical of didanosine, the dose of didanosine should be reduced to 250 mg. Tenofovir should be taken two hours before or one hour after didanosine. Controlled studies on the use of tenofovir in pregnancy are yet to come. In monkey studies, tenofovir was effective in the prophylaxis of SIV transmission, but also resulted in growth disorders (<http://hiv.net/link.php?id=134>).

2. Non Nucleoside Reverse Transcriptase inhibitors (NNRTIs)

attach to the reverse transcriptase enzyme, preventing the enzyme from converting HIV RNA into DNA.

2.1 Nevirapine (NVP) FDA approval: 6/96. Nevirapine is a frequently prescribed NNRTI. As with all NNRTIs, a single point mutation is sufficient to develop a high-level resistance. Nevirapine is very useful for simplification of successful HAART regimens. It has a good long-term tolerability with a favorable lipid profile. The main problem, besides development of resistance, is hepatotoxicity in the first months of treatment (see below). Nevirapine is effective for prophylaxis of mother-to-child transmission.

Trade name: Viramune®

Usual Regimen: 400 mg daily-200 mg qd x 14 days, then 200 mg bid.

Oral dose: 1 tablet bid. Always start with lead-in dosing. The initial lead-in dose (1 tablet/day over two weeks) reduces the frequency of rash. For resumption of treatment after treatment interruption, lead-in dosing is generally not necessary if the drug was well tolerated before. Due to its long half-life, nevirapine should be discontinued three days before other backbone drugs are administered, in order to prevent the development of resistance. Nevirapine may be taken on an empty stomach or with meals.

Side effects: Mainly hepatotoxicity, rash. Less frequently: fever, nausea, drowsiness, headache, myalgia. These side effects may occur with or without hepatotoxicity and/or rash. γ GT is frequently elevated. To detect hepatotoxicity (occurring in 15 %; defined as an increase in transaminases to at least three times the upper limit of normal), liver function tests should be monitored biweekly for the first two months. Thereafter, monthly tests are necessary, as more than half of the hepatotoxic episodes occur after the first quarter of treatment. In cases of hepatotoxicity, treatment must be interrupted until liver function tests have returned to initial levels. Treatment is restarted with 200 mg qd. The dose may be increased to 200 mg bid only after a prolonged period of observation. If liver enzymes increase again, nevirapine should be permanently discontinued. The website of the EMEA provides detailed guidelines: <http://hiv.net/link.php?id=120>. A rash, often pruritic and usually occurring within the first six weeks of treatment, can be treated with antihistamines if mucous membranes are not involved and if transaminases are normal. Topical formulations are effective against pruritus. Nevirapine must be discontinued if a severe rash occurs; in these cases, steroids may be used (eg. prednisolone 1 mg/kg for 3-5

days). Nevirapine should also be discontinued if other systemic symptoms occur (fever, conjunctivitis, myalgia, arthralgia, malaise). If the rash occurs during the first two weeks of treatment, the dose should not be increased until the rash has resolved completely. Prophylactic treatment with steroids is not advised.

Drug-food interactions:

- The drug may be administered with food, antacids, or ddI.
- Has good oral bioavailability with or without food.

Adverse effects:

- Drug is metabolized in the liver by the cytochrome P450 system. There are many drug-drug interactions.
- Rash is common early in treatment. If severe rash occurs, especially if accompanied by fever, blistering, lesion, swelling, or general malaise, discontinue medication.
- Stevens-Johnson syndrome can occur.
- Clinical hepatitis can occur.

Comments/Warnings: Cautious use in hepatic dysfunction (measure plasma levels). Contraindicated for co-medication with rifampicin, ketoconazole, St. John's wort and the pill. Azole derivatives: Fluconazole should be used for antimycotic treatment.

Dose adjustment in combination with

- Indinavir: increase indinavir dose to 1000 mg tid.
- Methadone: if withdrawal symptoms occur, dose may need to be increased.
- Lopinavir: possibly increase Kaletra[®] dose to 4 capsules bid (measure plasma levels.)

Nevirapine has a favorable long-term profile. In particular, lipid levels are usually favorably influenced. γ GT is almost always increased during long-term treatment. Values of up to 150 U/l can be tolerated. Nevirapine should not be given for post-exposure prophylaxis.

Dosage adjustments: The drug is partially eliminated by the kidney. Dosage adjustments for clients with renal failure have not been studied.

2.2 Delavirdine (DLV) FDA approval: 4/97. Delavirdine is rarely used, because of impractical dosing regimens and drug interactions, and it

has been completely marginalized by the other two NNRTIs nevirapine and efavirenz. However, the drug has some theoretical potential: it is fairly well tolerated (no hepatotoxicity, no CNS problems), and increases levels of indinavir and saquinavir. If more data were available, delavirdine could be an alternative to ritonavir for boosting. It has the usual NNRTI cross-resistance.

Trade name: Rescriptor[®].

Usual Regimen: 1200 mg daily-400 mg tid or 600 mg bid. Dosage is for clients 16 years and older.

Side effects: Rash, usually occurring within the first six weeks of treatment. In uncomplicated cases, treat symptomatically with antihistamines. If systemic effects such as fever, conjunctivitis, myalgia and arthralgia occur, delavirdine should be discontinued. In addition: nausea, and elevated transaminases.

Drug-food interactions:

- The drug can be taken with or without food but should not be taken with a fatty meal.
- Clients taking antacids and ddI should take these at least 1 hour apart from delavirdine (Rescriptor).
- The drug can be dispersed in water for consumption. A dispersion consists of four tablets placed or mixed in at least 3 ounces of water, allowed to stand for a few minutes, and then stirred. The dispersion should be consumed promptly.

Adverse effects:

- Rash is a common side effect. The drug can be continued or restarted in monthst cases.
- The drug is metabolized in the liver by the cytochourome P450 system, which may alter the activity of other drugs.

Comments/Warnings: Delavirdine is contraindicated for concurrent treatment with rifabutin, rifampin, carbamazepine, phenytoin, alprazolam, astemizole, phenobarbital, cisapride, midazolam, terfenadine and triazolam.

There is little data available on combined therapy with nelfinavir, lopinavir and ritonavir. Amprenavir levels seem to be reduced by delavirdine.

Delavirdine interacts with numerous drugs via reduction of CYP3A-activity. It increases the AUC of sildenafil, dapson, clarithromycin, quinidine and warfarin. Delavirdine levels are lowered by didanosine, H₂ blockers, carbamazepine, phenytoin and antacids.

Patients should know that they may also dissolve delavirdine in water: stir tablets in a glass for a few minutes and drink. Rinse the glass with a small amount of water and drink the rest.

Dosage adjustments:

- The drug is partially eliminated by the kidneys. Dosage adjustments for clients with renal failure have not been studied.
- Severe hepatic insufficiency may warrant decreased dosage.

2.3 Efavirenz (EFV) FDA approval: 12/98. Efavirenz is a frequently used NNRTI, with uncontested antiretroviral potency. It has multiple CNS side effects, for which the pathogenesis is not sufficiently understood. Drug interactions have been documented for a variety of drugs commonly prescribed to HIV patients. This drug should always be used in combination with other medications to treat HIV infection.

Trade name: Sustiva[®], Stocrin[®]

Usual Regimen: 600 mg daily-600 mg qd hs. Tablets can be placed in water to form slurry.

Side effects: Nightmares, confusion, dizziness, somnolence, abnormal thinking, impaired concentration, insomnia, depersonalization. These CNS symptoms usually resolve substantially after a few weeks. A rash (in 15 %) may also occur in the first few weeks, but severe cases of blistering, desquamation and ulceration are rare. Elevation of liver function tests and biliary enzymes, especially γ GT; hypercholesterinemia, hypertriglyceridemia.

Drug-food interactions:

- The drug can be taken with or without food. A high fat meal should be avoided. Foods high in fat may increase the bioavailability of efavirenz by 50%.
- Capsules may be opened and added to liquids or foods but efavirenz has a peppery taste; grape jelly has been used to disguise the taste.

Adverse effects: The most common type of rash seen in studies of this drug was a diffuse maculopapular type. The rash often appeared within the first 2 weeks of initiating therapy and resolved within 1 mo when therapy was continued.

Comments/Warnings: Contraindicated in pregnancy.

Contraindicated for concurrent treatment with ergotamines, astemizole, cisapride, midazolam, terfenadine and triazolam. Should not be combined with contraceptive pills. Should not be given in combination with saquinavir or amprenavir without a ritonavir boost (insufficient plasma levels of saquinavir and amprenavir).

Dose adjustments in combination with

- Lopinavir: Increase lopinavir dose to 4 capsules bid.
- Indinavir: Increase indinavir dose to 1000 mg tid.
- Rifabutin: Increase rifabutin dose to 450 to 600 mg/day.
- Methadone: Possibly increase methadone dose by 20 to 40 %.

When switching therapy from a PI to efavirenz, overlapping therapy is recommended for one week. Efavirenz should not be taken with fatty meals, as this reduces the absorption.

Dosage adjustments: No renal or hepatic dosage adjustment necessary.

3. Protease inhibitors (PIs) work at a later stage in the replication process, preventing the protease enzyme from cutting HIV viral proteins into the virions that infect new CD4⁺ cells. New copies of HIV will be defective and unable to infect other CD4⁺ cells.

3.1 Saquinavir (SQV) FDA approval: 12/95. One of the first PIs, and the only one with two available formulations. Relatively "benign" (well tolerated except for gastrointestinal problems, no serious short-term problems). Intolerable pill burden if unboosted. Due to low bioavailability, the formulation was improved from Invirase[®] to Fortovase[®], which is unfortunately less well tolerated. According to recent data, Invirase[®], which had almost been abandoned, is just as effective when boosted with ritonavir. Strangely enough, Invirase[®] is significantly more expensive. Cross-resistance with other PIs is frequent. This drug should always be used in combination with other medications to treat HIV infection.

Trade name: Fortovase[®], Invirase[®]

Oral dose: Treatment without boosting (only in exceptions): 1200 mg tid (6 capsules tid). Combination with ritonavir is generally preferred: Fortovase® or Invirase®: 1000 mg bid plus 100 mg ritonavir bid is optimal. An alternative is 400 mg ritonavir bid plus 400 mg Fortovase® or Invirase®.

Side effects: Mainly gastrointestinal: diarrhea, nausea, vomiting, abdominal discomfort, meteorism. Rarely elevation of transaminases or γ GT, headache. As with other PIs, lipodystrophy, dyslipidemia and reduced glucose tolerance may occur with long-term treatment.

Drug-food interactions:

- The drug should be taken with a meal that is high in fat.
- Saquinavir absorption may be enhanced with ingestion of grapefruit juice.

Comments/Warnings: Contraindicated for concurrent treatment with rifampicin, astemizole, terfenadine, cisapride, triazolam, ergotamine, simvastatin, lovastatin, and St. John's wort. If saquinavir is not combined with other protease inhibitors it must be taken with meals.

Dosage adjustments: No dosage adjustment for renal impairment necessary. Severe hepatitis insufficiency may warrant decreased dosage.

3.2 Saquinavir (Fortovase, "soft gel capsule") FDA approval: 11/97. This drug should always be used in combination with other medications to treat HIV infection.

Usual Regimen: 3600 mg daily-1200 mg q8h.

Common Side Effects: Nausea.

Drug-food interactions:

- The drug should be taken with a meal that is high in fat.
- The drug can be kept out of the refrigerator but not for longer than 3 months.

Adverse effects:

- There are many drug interactions.

Dosage adjustments:

- No dosage adjustment for renal impairment necessary. Severe hepatitis insufficiency may warrant decreased dosage.

3.3 Ritonavir (RTV) FDA approval: 3/96. Due to its gastrointestinal side effects, the therapeutic dose of ritonavir is hardly acceptable and rarely prescribed. However, ritonavir has become an important drug for boosting other protease inhibitors. In these combinations, when lower doses are used, side effects of ritonavir are tolerable. Numerous drug interactions must be considered.

Trade name: Norvir[®]

Usual Regimen: 1200 mg daily-600 mg PO bid. To minimize side effects Ritonavir can be administered in escalating doses: Day 1-300 mg q12h; day 2-3-400 mg q12h; then 600 mg q12h; day 4-13-500 mg q12h; then 600 mg q12h.

Oral dose: In rare cases, in which ritonavir is used as a single PI, the dose is 600 mg bid (increase dose over two weeks: 300 mg bid on day 1-2, 400 mg bid on day 3-5, 500 mg bid on day 6-13). The optimal use of ritonavir, however, is for boosting of other PIs. Daily doses in combination with

- Saquinavir (Fortovase[®] or Invirase[®]): 100 mg ritonavir bid + 1000 mg saquinavir bid or 400 mg ritonavir bid + 400 mg saquinavir bid
- Indinavir (Crixivan[®]): 100 mg ritonavir bid + 800 mg indinavir bid or 400 mg ritonavir bid + 400 mg indinavir bid
- Amprenavir (Agenerase[®]): 100 mg ritonavir bid + 600 mg amprenavir bid or 200 mg ritonavir qd + 1200 mg amprenavir qd
- Lopinavir (Kaletra[®]): Fixed combination, see lopinavir.

Side effects: Very frequent with therapeutic doses: nausea, vomiting, diarrhea, headache, perioral paresthesia and electric sensations on arms and legs. Elevated transaminases and γ GT, often significant dyslipidemia, reduced glucose tolerance and, rarely, diabetes mellitus. Lipodystrophy with long-term treatment.

Drug-food interactions:

- Soft-gel capsule refrigeration is recommended but not required if the drug is used within 30 days and stored below 77° F.
- Drug must be taken with meals. There may be a bitter aftertaste. To decrease the aftertaste, the drug can be mixed in chocolate milk or Ensure or another nutritional supplement.

Adverse effects:

- The client may report circumoral paresthesias (i.e., numbness around the mouth).

This diminishes after several weeks of therapy.

- This drug is metabolized thorough the cytochrome P450 system.

Comments/Warnings: Even the low boosting doses used in combination with other PIs have multiple drug interactions. The following are contraindicated: rifampicin, amiodarone, astemizole, bepridil, terfenadine, encainide, flecainide, cisapride, triazolam, ergotamine, simvastatin, lovastatin, quinidine, and St. John's wort. Sildenafil should be avoided. Caution should be taken and plasma levels measured for both ritonavir and (if possible) the following co-medications: Methadone, immunosuppressants (cyclosporine, tacrolimus), macrolide antibiotics (erythromycin, clarithromycin), steroids, calcium antagonists, tricyclic antidepressants, other antidepressants (fluoxetine, paroxetine, sertraline), neuroleptics (haloperidol, risperidone, thioridazine), antimycotic drugs (ketoconazole, itraconazole), carbamazepine, tolbutamide, rifabutin, theophylline, and warfarin.

Dosage adjustments:

- There are no adjustments for renal insufficiency. Ritonavir has not been studied in hepatic insufficiency.

3.4 Indinavir (Crixivan) FDA approval: 3/96. This drug should always be used in combination with other medications to treat HIV infection. Effective and well-investigated PI, the use of which is slightly limited due to skin, kidney and intestinal problems. There is multiple cross-resistance to other PIs, but the drug has good CNS penetration. Today, indinavir is generally used with ritonavir boosting, which simplifies dosing.

Trade name: Crixivan®

Usual Regimen: 2400 mg daily-800 mg q8h.

Oral dose: In combination with ritonavir: 800 mg bid (two 400 mg capsules bid) plus 100 mg ritonavir bid (one 100 mg capsule bid) or 400 mg bid (one 400 mg capsule bid) plus 400 mg ritonavir bid (four 100 mg capsules bid). Without ritonavir boosting: 800 mg tid (two 400 mg capsules tid) one hour before or two hours after meals. Impaired liver function: 600 mg tid (three 200 mg capsules tid).

Side effects: Nephrolithiasis (in up to 25 %): flank pain, hematuria (suggests a kidney stone). Less frequently: nephrotoxicity with elevated serum creatinine.

Diarrhea, nausea, vomiting. A sicca syndrome occurs relatively frequently (dry skin, mouth, eyes); ingrown toenails and paronychia; rarely alopecia. Asymptomatic hyperbilirubinemia. Lipodystrophy ("Crixbelly"), dyslipidemia, disorders of glucose metabolism.

Drug-food interactions:

- Drug must be taken on an empty stomach or with a light meal-with skin milk, juice, or coffee.
- Clients must drink at least six 8-ounce glasses of water daily to prevent the formation of kidney stones.

Adverse effects:

- Nephrourolithiasis can occur.
- Hemolytic anemia has been reported.
- Hepatitis, although rare, can occur.
- Thrombocytopenia, although rare, can occur.

Comments/Warnings: The concurrent use of rifampicin, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, or St. John's wort is contraindicated.

The following dose adjustments are necessary:

- Rifabutin: 1000 mg indinavir tid + 150 mg rifampicin.
- Lopinavir: 600 mg indinavir bid.
- Ketoconazole and itraconazole: 600 mg indinavir tid.
- Sildenafil: maximum 25 mg sildenafil/48h.

Unboosted, indinavir must be taken on an empty stomach. At least 1.5 liters of fluid should be consumed daily to prevent nephrourolithiasis. Symptoms must be explained (hematuria, flank pain). The occurrence of nephrourolithiasis and skin problems correlates with plasma levels. Didanosine decreases indinavir absorption. Combination of the two drugs is therefore generally avoided. In combination with ritonavir, indinavir can be taken twice daily and with meals. Sufficient fluid intake is still necessary.

3.5 Nelfinavir (NFV) FDA approval: 3/97. A relatively well tolerated and well investigated PI, but is slightly less potent than boosted PIs. A

Nelfinavir-based PI regimen is less potent than NNRTI regimens. Main problems include high pill burden and frequent diarrhea. Due to its favorable resistance profile (after failure of nelfinavir treatment, other PIs may still have good efficacy), it is well suited as a first-line PI. This drug should always be used in combination with other medications to treat HIV infection.

Trade name: Viracept®

Usual Regimen: 2250-2500 mg daily-1250 mg bid or 750 mg tid. with meals.

Side effects: Mild to moderate diarrhea, meteorism, and nausea also occur. Lipodystrophy, dyslipidemia, reduced glucose tolerance.

Drug-food interactions: The drug must be taken with food.

Adverse effects: This drug is metabolized thorough the cytochourome P450 system; several medications are contraindicated for concurrent use.

Comments/Warnings: Contraindicated for co-medication with rifampicin, the pill, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, and St. John's wort. In combination with rifabutin: 150 mg rifabutin qd and increase nelfinavir dose to 1000 mg tid. Methadone: If withdrawal symptoms occur, dose may be increased. Sildenafil: maximum 25 mg/48 h. Nelfinavir should be taken with meals. Diarrhea can usually be controlled with loperamide (2 mg with each fluid bowel movement, up to a maximum of 16 mg/day). Boosting with ritonavir is not advisable, as levels are not significantly changed.

Dosage adjustments: No adjustment for hepatic or renal insufficiency are necessary.

3.6 Amprenavir (APV) FDA approval: 4/99. Due to the high quantities of pills required, unboosted dosing with amprenavir is hardly acceptable today. When boosted with ritonavir, amprenavir is well suited for salvage therapy because of its interesting resistance profile. The availability of the pro-drug fos-amprenavir will presumably make this drug more attractive in the future. This drug should always be used in combination with other medications to treat HIV infection.

Trade name: Agenerase®

Indication: HIV infection with previous PI-treatment

Oral dose: 8 capsules of 150 mg amprenavir bid (1200 mg bid) or 4 capsules of 150 mg amprenavir bid (600 mg bid) plus 100 mg ritonavir bid or 8 capsules of 150 mg amprenavir qd (1200 mg qd) plus 200 mg ritonavir qd

Dose of amprenavir solution: 1.5 ml/kg bid. Important note: The bioavailability of amprenavir in the oral solution is 14 % lower than the in the encapsulated formulation; as a result Agenerase[®] capsules are not interchangeable with the oral solution on a milligram-per-milligram basis. Amprenavir solution is dosed higher: 17 mg/kg tid (=1.1 ml/kg tid), with a maximum total dose of 2800 mg daily.

Usual Regimen: 2400 mg daily-1200 mg bid.

Side effects: Monthstly gastrointestinal, including nausea, vomiting, diarrhea, flatulence, tenesmus, and perioral paresthesia. Occasionally: headache, fatigue, and, in 5-10 % of patients, a rash occurs usually in the second week of treatment. Stevens-Johnson syndrome is rare (<1 %). In combination with ritonavir: levels of cholesterol, triglycerides and transaminases are more frequently elevated; lowered glucose tolerance; rarely diabetes mellitus; and lipodystrophy.

Drug-food interactions:

- The drug may be taken with or without food; however, a high fat meal decreases absorption of amprenavir.
- Vitamin E supplements should not be taken with amprenavir, which already contains vitamin E.
- Clients taking ddi or antacids should take these at least 1 hour before or after Agenerase.

Adverse effects:

- This drug is a sulfonamide. It should be used with caution in clients with allergies to sulfonamides.
- This drug is metabolized thorough the cytochourome P450 system; several medications are contraindicated for concurrent use.
- Stevens-Johnson syndrome has been reported. Clients should notify provider if skin changes occur.
- Acute hemolytic anemia may occur.

- Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, Agenerase oral solution is contraindicated in infants and children below the age of 4 years, pregnant women, clients with hepatic or renal failure, and clients treated with disulfiram or metronidazole.

Comments/Warnings: Amprenavir is contraindicated in pregnancy and in children under 4 years; and as a concurrent treatment with rifampin, ergotamines, cisapride, bepridil, pimozone, midazolam and triazolam. Concurrent treatment with amiodarone, warfarin, lidocaine, tricyclic anti-depressants, quinidine, cyclosporine and tacrolimus should be avoided. Amprenavir is not recommended for concurrent treatment with lovastatin, simvastatin, carbamazepine, phenobarbital, phenytoin or sildenafil (Viagra[®]: increased incidence of hypotension, priapism.). Use with caution in patients with a history of sulfonamide allergy. Concurrent treatment with rifabutin: reduce rifabutin dose by 50%. Amprenavir should be taken at least one hour before or after antacids or didanosine. Dose adjustment (measure plasma levels.) should be considered when given in combination with lopinavir. Amprenavir solution contains 50 % propylene glycol. It is therefore contraindicated for use in children under 4 years of age, pregnant women, patients with renal or liver failure, and for concurrent administration with disulfiram or metronidazole.

Dose adjustment in hepatic impairment: Decrease dosage for liver impairment. Child-Pugh score 5-8: 450 mg bid; 9-12: 300 mg bid.

3.7 Atazanavir (AZV) First approval is expected in mid-2003. Atazanavir is the first once-daily PI, and has an antiviral potency that should be comparable to nelfinavir. In comparison to boosted PIs, atazanavir is slightly weaker, but has a more favorable lipid profile. Whether this will have an effect on lipodystrophy still remains to be shown.

Formulations: 200 mg capsules

Oral dose: 400 mg qd, with a meal if possible.

Side effects: Relatively frequently increases bilirubin, but so far this has not limited treatment. Diarrhea occurs in approximately 30 %. In addition: nausea, vomiting, headache, and abdominal pain. These complaints usually resolve within the

first weeks of treatment. In contrast to other PIs: no dyslipidemia. The effect on lipodystrophy remains unknown.

Comments/Warnings: Concurrent treatment with efavirenz reduces plasma levels of atazanavir. In one study (O'Mara et al. 2002) this was compensated by additional administration of 200 mg ritonavir. Rifabutin has no effect on the pharmacokinetics of atazanavir.

3.8 Lopinavir (LPV) is a very effective and relatively well tolerated PI. Kaletra[®] is an ideal drug for salvage therapy, as it has astonishing potency in PI-experienced patients with multiple resistance mutations. It remains to be proven whether or not Kaletra[®] is superior to other boosted PIs in the initial therapy. Disadvantages include high lipid levels and drug interactions.

Trade name: Kaletra[®]

Formulations: Capsules with 133.3 mg lopinavir (LPV) + 33.3 mg ritonavir (RTV); bottles of 180 capsules. Solutions with 80 mg lopinavir + 20 mg ritonavir per ml; bottles of 160 ml. Keep refrigerated.

Oral dose: 3 capsules bid or 5 ml solution bid with meals

In combination with efavirenz or nevirapine, the dose should be increased to 4 capsules bid or 6.5 ml solution bid. Measure plasma levels.

Side effects: Mainly diarrhea, nausea, and dyslipidemia. Also: headaches, and elevated transaminases.

Comments/Warnings: Drug interactions are numerous. All drugs metabolized by the CYP3A or CYP2D6 enzyme systems are contraindicated: flecainide, propafenone, astemizole, terfenadine, ergotamines, cisapride, pimozide, midazolam, triazolam. Rifampicin and St. John's wort reduce the efficacy of lopinavir.

Caution with: lovastatin, simvastatin (myopathy, rhabdomyolysis), carbamazepine, phenobarbital, phenytoin or sildenafil (hypotension), amiodarone, warfarin, lidocaine, tricyclic antidepressants, quinidine, cyclosporine, tacrolimus. Measure plasma levels in patients with reduced liver function tests, especially in cases with concurrent hepatitis B or C or significantly elevated transaminases. If lopinavir is being combined with didanosine, didanosine must be taken one hour before or two hours after lopinavir. Lopinavir solution contains alcohol, therefore no co-medication with

disulfiram or metronidazole. Caution with the pill (contraception not safe). When used with rifabutin, the rifabutin dose should be reduced by 75 %, i.e. 150 mg qd every two days. Increasing the methadone dose may be necessary.

In Thailand, the GPO could locally produce HAART and reduce the production cost by combine 3 ARV drugs in each tablet for HIV-infected patients take the medicine easy.

GPO-VIR (Nevirapine, Lamivudine and Stavudine combination tablets)

Compositions:

GPO-VIR S30: each tablet contains: Nevirapine 200 mg, Lamivudine 150 mg and Stavudine 30 mg.

GPO-VIR S40: each tablet contains: Nevirapine 200 mg, Lamivudine 150 mg and Stavudine 40 mg.

Pharmacological actions: Lamivudine and stavudine are cytidine and thymidine nucleoside analogs reverse transcriptase inhibitors, respectively. The drugs are intracellularly phosphorylated to their respective active metabolites, lamivudine triphosphate and stavudine triphosphate. Lamivudine triphosphate and stavudine triphosphate inhibit HIV replication by competing with the natural substrates for reverse transcriptase and thus inhibit viral DNA synthesis by acting as terminator of chain elongation. Nevirapine is a nonnucleoside reverse transcriptase inhibitor. The drug binds directly to HIV-1 reverse transcriptase and blocks viral RNA-and DNA-dependent DNA polymerase activities by disrupting the catalytic site of enzyme.

Indications: GPO-VIR is indicated for the treatment of patients with human immunodeficiency virus (HIV) infection.

Dosage: Adult and adolescents 60 kg of body weight and over: - Oral, GPO-VIR S40 1 tablet two times a day.

Adult and adolescents less than 60 kg of body weight : - Oral, GPO-VIR S30 1 tablet two times a day.

Children up to 12 years of age: - Use under physician's prescription.

Instruction for use: Special precaution for patients receiving nevirapine is the occurrence of skin rash, the major toxicity that usually occurs within the first 28 days of therapy. Therefore, patients should be instructed to start the 3-drugs combination regimen with separated drug dosage. The recommended dose is,

nevirapine tablet 200 mg, orally once a day for the first 14 days, followed by 200 mg twice a day for 14 days; in combination with lamivudine tablet 150 mg and stavudine tablet 30 or 40 mg, orally twice a day. Patients experiencing rash during the first 14 days of therapy should not have their nevirapine dosage increased until the rash has resolved. Patients, who do not experience rash within 28 days of therapy, can then have their combination regimen changed to GPO-VIR.

Contraindications and precautions:

1. It is contraindicated in patients with known hypersensitivity to nevirapine, lamivudine or stavudine.
2. Use with extreme caution in patients with hepatic and/or renal function impairment, bone marrow depression, pancreatitis or a history of pancreatitis, peripheral neuropathy or a history of peripheral neuropathy.
3. Should be used in pregnancy only if clearly needed. Nursing women who treated with GPO-VIR should be instructed to discontinue nursing.
4. Patients who interrupt GPO-VIR therapy for more than 7 days, should restart the combination dosing with recommended separated drug dosage for 28 days before changing to GPO-VIR.

Drug interactions: Concurrent use of GPO-VIR with the following medications should be avoided, or if necessary, use with caution:

- Drugs associated with pancreatitis (e.g. alcohol, sulfonamides)
- Drugs associated with peripheral neuropathy (e.g. dapsone, isoniazid, ethambutol)
- Drugs that metabolized by cytochrome P450 isoenzyme CYP3A4 (e.g. calcium channel blockers, clindamycin)
- Drugs that induce cytochrome P450 isoenzyme CYP3A4 (e.g. rifabutin, rifampicin, phenytoin, carbamazepine)
- Drugs that inhibit cytochrome P450 isoenzyme CYP3A4 (e.g. cimetidine, macrolides)

Adverse effects: The major effects include peripheral neuropathy (tingling, burning, numbness or pain in the hands or feet); pancreatitis (nausea, vomiting, severe abdominal or stomach pain); skin rash, mild to moderate (consists of maculopapular

erythematous eruption, with or without itching); severe and life-threatening skin reactions (e.g. Stevens-Johnson syndrome).

Other effects include diarrhea, insomnia, headache, fever, bone marrow depression, anemia, arthralgia, myalgia, abnormal liver function test results, hepatitis.

All the above mentioned antiretroviral are efficacious therapies. However, patient adherence is the necessary interface between efficacious therapies and treatment effectiveness.

2.2 Managing the Adverse Effects of Antiretroviral Therapy

A patient's understanding of the possible side effects of medications and the management of them also has a significant effect on adherence (Williams, 2001: 37). Managing the adverse effects of antiretroviral therapy includes gastrointestinal effects of antiretroviral therapy, pancreatitis, hematologic effects of therapy, renal effects, peripheral nervous system effects, central nervous system effects, metabolic and endocrine effects, lipid disorders and altered glucose metabolism.

Gastrointestinal effects of antiretroviral therapy

Most antiretroviral agents produce GI disturbances. Nausea is particularly notable with zidovudine (46%), nevirapine (20%), amprenavir (38%-73%), ritonavir (26%), saquinavir soft-gel capsules (10%-18%), and indinavir (12%) (Fortovase, 1997; Agenerase, 1999; Norvir, 1999). The most common side effect of ZDV induction is nausea (Groopman, 1990: 500-506; Richman et al., 1987: 192-197). This nausea is usually transient, subsiding within the first four weeks of treatment. Administration of ZDV with food can help alleviate this adverse effect. Eating smaller but more frequent meals also helps to reduce nausea.

Watery diarrhea is associated with the use of saquinavir-SGC (20%), indinavir (25%), ritonavir (45%), amprenavir (33%-56%), and nelfinavir (26%-32%). Severe diarrhea is most commonly associated with nelfinavir, but in general this adverse reaction does not result in weight loss (Jarvis & Faulds, 1998: 147-167; Viracept, 1998).

Diarrhea can also occur with didanosine, because of the magnesium-

hydroxide buffer added to the tablet formulation. It is anticipated that patients taking this drug will experience less diarrhea on two of the 200-mg tablets than on four 100-mg doses, because there is an equal amount of diarrhea-inducing buffer in the 200-mg and 100-mg tablets. Reducing the pill count should reduce GI irritation.

Pancreatitis

Pancreatitis has been associated with ddI therapy, occurring in 2.3% of patients (Jarvis & Faulds, 1998: 147-167). This reaction is dose-related. Several factors can increase the risk that individuals taking ddI will develop pancreatitis. These include alcohol ingestion, a prior history of pancreatitis, advanced HIV disease, and CD4 counts below 50 cells/ μ L (Whitefield, Bechtel & Starich, 1997: 122-127; Dassopoulos & Ehourenpreis, 1999: 78-84).

This adverse event generally occurs after one to six months of ddI therapy, and it usually resolves within one to three weeks after drug discontinuation. Didanosine-induced pancreatitis can be fatal (Dassopoulos & Ehourenpreis, 1999: 78-84). Protease inhibitors can cause a significant increase in serum triglycerides, and hypertriglyceridemia—specifically, triglyceride levels greater than 1,000 mg/dL—may be associated with pancreatitis (Churchill et al., 1998: 518-519).

Hematologic effects of therapy

Anemia and neutropenia are the major toxicities associated with zidovudine therapy (Groopman, 1990: S500-S506; Richman et al.; 1987: 192-197; Gelmon et al., 1989: 555-561). They are directly related to dosage and duration of therapy and are more likely to occur in patients with lower baseline CD4 lymphocyte count, hemoglobin concentration, and granulocyte count. Anemia most commonly develops after four to six weeks of treatment and appears to be related to impaired erythrocyte maturation, as evidenced by increasing macrocytosis in patients taking ZDV.

Because these hematologic toxicities are seen in a significant number of patients taking ZDV, especially during the induction phase, all individuals assigned to a ZDV-containing regimen—including those on Combivir—should be monitored very closely during the first eight weeks of treatment. Protease-inhibitor-containing regimens have also been associated with increased bleeding and hematomas in patients with hemophilia (Stanworth, Bolton & Hay, 1998: 109-114; Ginsburg et al., 1997:

338-339). Care providers should counsel patients with hemophilia and HIV infection who are taking protease inhibitors that a larger amount of factor products may be required to control bleeding. However, patients rarely need to switch to a protease-sparing regimen when episodes of bleeding do occur (Pai & Nahatat, 1999: 325-328).

Renal effects

The most common preventable adverse effect of indinavir sulfate therapy is nephrolithiasis. Although the liver does metabolize indinavir sulfate, 19% of the drug is excreted in urine, and once excreted, indinavir is highly insoluble—which is why it tends to form crystals or stones.

Physicians should warn patients of the potential risk of kidney stones with indinavir therapy, and all individuals assigned to an indinavir-containing regimen should be reminded at every clinic visit to drink at least 1.5 liters (48 ounces) of liquid every day (Crixivan, 1998). Patients should be counseled to strain their urine to determine if a stone has passed, and regular evaluations of renal function should be performed. With severe or recurrent symptoms, another protease inhibitor should be substituted for indinavir (Rich et al., 1997: 2228).

Peripheral nervous system effects

Peripheral neuropathy has been noted with ddI (14%-34%), ddC (17%-31%), and d4T (15-21%). When neuropathies do develop, they appear to be dose-related (Lambert et al., 1990: 1333-1340; Merigan & Skowron, 1990: S11-S15). These neuropathies generally have a “stocking-glove” distribution, primarily in the feet. Paresthesias and peripheral neuropathy are also reported with 3TC.

These drugs should be withheld in individuals who develop severe neuropathic pain, because nerve damage can be irreversible if the drugs are not discontinued. It can take up to 18 weeks for peripheral-neuropathy-associated pain to subside after patients are taken off of the offending drug or drugs (Lambert et al., 1990: 1333-1340).

When patients are assigned an antiretroviral regimen that includes one or more of the nucleoside analogs that can cause peripheral neuropathy, they should be told to be on the watch for signs of nerve damage, and they should be instructed to report any symptoms to their primary care provider.

Central nervous system effects

Efavirenz is the antiretroviral agent most likely to produce CNS symptoms, which occur in 52% of treated patients. These symptoms generally manifest within one to two days of the initiation of therapy, and tend to resolve over the next two to four weeks (Ziagen, 1998). Symptoms include drowsiness, dizziness, impaired concentration, insomnia, and vivid dreams or nightmares.

To reduce the severity of CNS effects, the drug should be administered at bedtime. Efavirenz may produce a hangover effect the following day, so patients should be counseled not to operate heavy machinery or drive until the effect of the drug subsides. Patients who experience significant anxiety, depression, or suicidal ideation should be taken off efavirenz (Colebunders & Verdonck, 1999: 869).

Metabolic and endocrine effects

A number of significant metabolic disorders are associated with antiretroviral therapy. These include mitochondrial dysfunction, lactic acidosis, hyperlipidemia, abnormal glucose utilization, and body-fat redistribution. Mitochondrial dysfunction and lactic acidosis occur in patients taking nucleoside reverse-transcriptase inhibitors; the other reactions are most frequently reported in individuals taking protease inhibitors. If a patient receiving one or more of the nucleoside analogs develops tachypnea, dyspnea, or a fall in serum bicarbonate concentrations, lactic acidosis should be suspected and the drug or drugs should be discontinued (Churchill, 1998: 518-519; Mirete, 1998: 810-811; Retrovir, 1998).

Lipid disorders

Protease inhibitors produce large increases in total cholesterol and triglyceride concentrations in many individuals (Sullivan & Nelson, 1997: 938-939; Echevarria, Hardin & Smith, 1999: 859-863). In particular, the use of ritonavir has been associated with 30% to 40% increases in cholesterol and 200% to 300% increases in serum triglyceride concentrations (Danner, 1995: 1528-1533). When starting any patient on any multidrug antiretroviral combination that includes a protease inhibitor, providers should obtain baseline lipid panels and liver-function tests, and they should repeat these tests after four weeks of therapy.

Fat redistribution

Protease inhibitors are also associated with disfiguring changes in fat

distribution in some individuals. Fat redistribution may be a result of the direct action of the protease inhibitors on lipid production or it may be an indirect result of the partial immune reconstitution that occurs with reduced viral replication (Aboulafia & Bundow, 1999: 970). These fat depositions usually occur during the first 2 to 12 months of therapy, and they generally produce little or no weight gain—suggesting a rough equivalency between fat loss in some areas and fat accumulation in others (Wurtz, 1998: 1735-1736). Although the fat redistribution bears a superficial resemblance to Cushing syndrome, no elevations in serum cortisol concentrations have been observed in patients taking protease inhibitors (Stephenson, 1998: 641-642; Yanovski et al., 1999: 1925-1931).

Altered glucose metabolism

A syndrome of insulin resistance, hyperlipidemia, and lipodystrophy has been identified in patients taking protease inhibitors (Carr, 1998: F51-F58; Flexner, 1998: 1281-1292). These disorders may appear individually or in combination. All patients starting antiretroviral therapy with a drug combination that includes a protease inhibitor should have baseline and follow-up blood glucose concentrations measured, to help assess if insulin resistance or hyperglycemia is likely to develop.

Part 3. Medication adherence

Medication adherence is the necessary interface between efficacious therapies and treatment effectiveness. Nonadherence is a problem in many clinical settings (Markowitz, et al.; 2000: 250-251; Mehta, et al.; 1997: 1665-1670) and anecdotal information suggests that it is a prevalent problem. Nonadherence among persons with chronic illnesses is widespread, occurring in 20% - 82% of cases (Cramer, et al., 1989: 3273-3277). It is common across all populations and diseases and is a familiar challenge in nursing practice.

There is still no gold standard measurement of medication adherence. Several methods have been utilized with different success (Melkinow et al., 1994 cited in Mannheimer et al., 2002: 1115 – 1121). Although more objective methods such as direct observation and therapeutic drug monitoring yield more reliable compared to indirect methods, such as self-report, electronic monitoring and pill counting (Bond &

Hussar, 1991 cited in Mannheimer et al., 2002: 1115 – 1121), the direct methods are practical in only some situations, and not generally practical.

Direct observed technique is highly labor intensive and impractical outside an institutional or residential settings. Therapeutic drug monitoring using plasma drug testing can be costly, is useful only if the pharmacokinetic profile is well defined and cannot discern whether patient is taking medication only right before blood specimen is obtained and omitting other doses (Friedland & Williams, 1999: S61-S72; Williams, 1999: 113 – 129).

Indirect methods, such as self-report, pharmaceutical records, pill counting and electronic monitoring are less objective; however, less labor intensive and less expensive, except electronic monitoring. All adherence measures and all research regarding adherence are subject to limitations. Most of these measures tend to give overestimation of adherence, and define non adherence as missing doses, not including taking doses at the wrong times (Bartlett et al., 2002: S2 – S10). Thus, measurement of medication adherence has been an unsolved challenge due to the wide range of reported rates and success.

Bangsberg and colleagues (2000) reported the median rate of medication adherence of 89% by self-report, 73% by pill counts, and 67% by MEMs. However, Arnsten and colleagues (2001) reported that medication adherence estimates measured by both self-report and MEMs were significantly correlated with current HIV load ($r=.43$ – $r=.60$). Interestingly, self-report, which is widely utilized in community settings (Eldred et al., 1998: 117-125; Gordillo et al., 1999: 1763-1769; Holzemer et al., 1999: 185-197; Monforte et al., 1998: 1631-1637) and clinical trials (Haubrich et al., 1999: 1099-1107; Montaner et al., 1998: 930-937), has been presented with higher medication adherence estimates than MEMs (Golin et al., 1999: 812 – 813; Melbourne et al., 1999: 329-338). Walsh and colleagues (2002) found that medication adherence measured by the VAS was strongly associated with pill counts ($p< .001$) and MEMs ($p< .001$).

In accordance with recent HIV literature (Mehta et al., 1997: 1665-1670), good adherence is defined as taking more than 90% of the pills prescribed in any regimen. However, according to the International AIDS Society-USA Panel Guidelines, 'less than excellent adherence may result in virus breakthrough and the emergence of

drug-resistant strains' (Carpenter et al., 1997: 78-86). The level of adherence required for success, however, is thought to be a staggering 95% or greater (Bartlett, 2002: S2 – S10; Beer, et al., 2000). According to a study by Paterson and colleagues (2000) that used Medication Event Monitoring System (MEMS) caps (Aprex) to electronically measure medication adherence among initially antiretroviral-naïve and antiretroviral-experienced patients found that very high level of adherence (>95%) to protease inhibitors were needed to achieve virologic suppression, and small differences in levels of adherence (e.g. >95% adherence versus 90%-95% adherence) were associated with substantial differences in virologic outcome (78% virologic suppression at >95% adherence versus 45% at 90%-95% adherence). This study will use a cut point of 95% to classify good adherence.

The literature review of medication adherence involving chronic illness and HIV/AIDS is presented as follows:

3.1 Chronic illnesses

Adherence (compliance) is believed to be affected by chronic disease itself (Kyngas, 2000: 550). The following discussion will touch upon adherence and nonadherence concerning chronic illnesses: hypertension, tuberculosis, and diabetes.

Hypertension

The disease in which adherence and persistence have been best studied is hypertension, and it can serve as a model. Obviously, the aim of the management of hypertensive patients is to improve the quality of life and to prevent complications, thus decreasing mortality and morbidity (Kyngas, 1999: 833), while the goals of antihypertensive therapy are to achieve and maintain blood pressure control by the least intrusive means possible to prevent future cardiovascular and renal events. One way to achieve these goals is to increase patient adherence to treatment regimens (Coyne, et al., 2002: 142-169). One among other reasons for inadequate blood pressure control is poor adherence to therapy (Anonymous, 2000: S211-S221) and adherence to the medical regimen continues to rank as a major clinical problem in the management of patients with essential hypertension, as in other conditions treated with drugs and life-style modification (Morisky, 1986).

Perceptions of effects of a medical regimen may affect patients' adherence to therapy (Kiellgren, et al., 1998). However, the lack of symptoms, which is common in hypertension, has been found to decrease adherence (compliance). If a patient does not have any symptoms, they do not necessarily feel ill and do not see any reason to treat themselves (Kyngas, 2000: 827). In spite of a modifiable risk factor associated with long-term target-organ damage by uncontrolled hypertension, many that are unaware they have hypertension, as many as 50% are not receiving treatment, and an estimated 70% of those being treated do not achieve adequate blood pressure control (Anonymous, 2000: S211-S221). About half the people with hypertension receive drug treatment; in about half of them is blood pressure controlled, and half stop taking their drugs during the initial year of treatment. The median time to discontinuing drugs is 90 days (Benson, et al., 2000; Klein, 1988; and Bloom, 1998 cited by Bloom, 2001). Physicians reported a 66% of hypertension patients rate of discontinuation of treatment or switching to another drug (Ambrosioni, et al., 2000: 1691-1699). Lijutipoom (2001) found that risk factors of essential hypertensive patients with blood pressure control were significantly associated adherence (compliance). Chutima Autthakornkovit (BE2534) found that adherence to hypertensive medications and sleeping not less than 6 hours per day were significantly related to control ability of blood pressure level. Good adherence (compliance) with medication is shown by 50 – 80 % of the hypertensive patients (Sackett & Snow, 1979; Kiein, 1988 cited in Kyngas, 1999: 833). Wiwatkunooopakarn (2001) found that 72 % of hypertensive patients were defined as good drug adherence (compliance) at the rate of 83.1 %.

Poor adherence (compliance) with antihypertensive therapy is a major cause of unsatisfactory blood pressure control (Waeber, et al., 1999: 973-985). Despite the clear evidence for the benefits of antihypertensive therapy, blood pressure is often not adequately controlled in clinical practice. Population surveys indicate that the proportion of patients achieving even conservative blood pressure targets may be only 20% or lower. A number of factors contribute to poor control of hypertension, including an emphasis by the physician on diastolic blood pressure, rather than the more prognostically important systolic pressure, and poor adherence to therapy by patients. Poor adherence may be largely attributable to adverse events (Lindholm, 2002: S3-S8). Punyawantanee (1998) found that nonadherence (noncompliance)

problems of hypertensive patients receiving antihypertensive drug were added up to 67.6 %.

Persistence varies with individual drugs, and adverse side effects are the prime culprit (Bloom, 1998 cited in Bloom, 2001: 647). This is a reasonable conclusion, given that hypertension usually causes no symptoms and monthst antihypertensive drugs have uncomfortable side effects (Bloom, 2001: 647).

There are many factors affecting adherence (compliance) with medical regimen among hypertensive patients. Age and sex, for example, can lead to different results. Brannon and Feist (1997) reported that hypertensive patient's medication adherence (compliance with medical regimen) tends to increase as they get older and women seem to have better adherence with healthy diets and taking some types of medication. Kyngas and Lahdenpera (1999) found that non-smoking, absence of symptoms, high level of education, and female sex were related to good adherence with dietary restrictions. Oparil and Calhoun (1998) reported that cost of medication and related care, inadequate patient education, complex drug regimen, patient's level of literacy and education, the adverse side effects of the medications related hypertensive patients' poor adherence.

Kyngas and Lahdenpera (1999) showed that compliance with the dietary restrictions among patients with hypertension was the poorest, while adherence (compliance) with medication was the best. Similarly, good adherence (compliance) with medication was confirmed by Sakett & Snow (1979) and Klein (1988). Srisuda Watcharaarpapibul (BE 2538) found that self-care factors, perception of less barrier, and knowledge of hypertension were related to regularity of attendance to treatment among essential hypertensive patients. However there are also many problems with adherence (compliance), especially with dietary regimens (JNC V, 1993).

In summary, the factors affecting adherence (compliance) with medical regimen among hypertensive patients may include the following: age, gender, absence of symptoms, education, family support, inadequate patient education, complex drug regimen, disruption of life-style, and self-efficacy. Many studies on the adherence (compliance) with particularly medication were conducted and good adherence (compliance) with medication was reflected.

Diabetes

Diabetes mellitus is a chronic metabolic disorder that can lead to multiple organ system complications (Foote, 1997 cited in Navuluri 2000:191). Several well-controlled studies have shown convincingly that reducing elevated blood sugar levels can reduce the risk of developing diabetes-related macrovascular complications, and microvascular complications such as nephropathy, retinopathy, and neuropathy (Diabetes Control and Complications Trial Research Group, 1993; Klein, 1995; Ohkubo, et al., 1995; Reichard, et al., 1993; United Kingdom Prospective Diabetes Study Group, 1998 cited by Navuluri 2000:191).

Patient adherence to diabetic regimens is an important factor in diabetic treatment. Nonadherence to controlling blood sugar to the baseline level leads to diabetic complications as well as economic and social problems.

Rittichu (2002) found that the proportion of overall good adherence to diabetic regimens was 25 %. Only 33.3 % were patients who could control the blood sugar level. Univariate analysis showed that good adherence to diabetic regimens was overall adherence to diabetic regimens, physical health care, diet, exercise and taking medication.

With regard to adherence to drug treatment, it has been demonstrated that even the most effective interventions achieve little improvement (Haynes et al, 1996 cited in Pijls et al., 1996: 347). The full benefits of any regimen will, obviously, not be achieved until efforts are directed towards increasing adherence. The improvement of adherence is expected to pay larger dividends than the development of any new medication or diet regimen (Pijls et al., 1996: 347).

A lack of knowledge about the disease (diabetes) and limited finances were primary reasons for nonadherence to guidelines for diabetic eye care (Julie et al, 1994). Donnan and colleagues (2002) found that 2,920 subjects identified, adequate adherence. There were significant linear trends of poorer adherence with each increase in the daily number of tablets taken and increase in co-medication for sulphonylureas alone after adjustment for other factors. Knowledge of the predictors of diet adherence is essential in order to improve strategies to promote adherence

(Coyne, et al., 2002: 142-169; Dolecek, et al., 1986; Gillis, et al., 1995; Milas et al, 1995 cited by Pijls et al, 2000: 347).

Tuberculosis

Tuberculosis (TB) has long been recognized as a major public health problem. The rate of TB is high in immigrants, and the frequency of drug resistance is increasing. A major reason for the development of resistant infections as well as relapse is poor adherence to TB treatment (Mac et al., 1999: 426: 426-431).

Although effective drugs exist for treating TB, it is difficult to ensure completion of treatment. Cultural factors such as misconceptions about appropriate treatment methods in combination with other barriers may adversely affect adherence and lead to improper uses of TB medication (Sumatojo, 1993 cited in Mac et al., 1999: 427).

A major contributor to the re-emergence of TB was a lack of adherence to anti-TB medication regimens. Nonadherence has been a persistent problem throughout the history of TB treatment (Addington, 1997 cited in McDonnell, 2001: 392). Poor adherence to treatment may contribute to the emergence of drug-resistant bacilli. Some patients may not fully understand their condition, comprehend its significance, or be aware of appropriate treatment (Van-Si, 1992 cited in Mac et al., 1999: 427). Difference between patients' and providers' understandings of illnesses can interfere with adherence to treatment (Cohen, 1994 cited in Mac et al., 1999: 427).

Based on the California TB Control Report 1992, an estimated 11% of the total TB patients reported in 1991 did not complete appropriate treatment and had an increased risk of developing drug resistance and transmitting drug-resistant strain to others (Santa Clara County Health Department, 1992 cited in Mac et al., 1999: 427).

McDonnell (2001) found that the mean self-reported adherence to antituberculosis therapy score was 92.6%. Higher levels of self-reported adherence were associated with an annual income of \$11,000 or more, education beyond high school, no current alcohol use, perceived support and absence of barriers to medication taking, strong intentions to adhere, and a high capacity for self-care. Additionally, belief in the usefulness and benefit of the medications was strongly correlated with intentions to adhere, and interpersonal aspects of care was significantly correlated with

perceptions of medication utility, supports/barriers, intentions, and self-care. Persons who were diagnosed with both TB and HIV reported significantly lower adherence.

Somsong (2002) found that the adherence of patients who had a good attitude on appropriate number of medicine for treatment were 93.8 %. The adherence of patients who had a good attitude on appropriate size of medicine for treatment was 89.6 %. The factor significantly associated with the adherence to tuberculosis treatment was number of medicine and size of medicine.

Hong (2000) found that 87 % of tuberculosis patients adhered to Direct Observed Therapy Strategy (DOTS). More than 13 % were irregular in taking the prescribed medication, mainly in the continuation phase. There was a highly significant association between the time treated and the adherence. Similar significantly associations were demonstrated concerning patients' knowledge of treatment, overall knowledge, overall perception of illness and treatment, and traveling time.

Poor medication adherence has been associated with dissatisfaction with the interpersonal aspects and financial aspects of care (Shebourne, et al., 1992 cited by McDonnell: 2001: 393) and emotional distress about one's health (Dimatteo & Sherbourne, et al., 1993 cited by McDonnell: 2001: 393).

3.2 HIV/AIDS

Current guidelines for the treatment of HIV-infected individuals recommend lifelong use of antiretroviral therapy (CDC, 2002: 1-19; DHHS, 2002: 1-74). Adherence to medication has become a major issue in the treatment of HIV-infected individuals and an important determinant of the outcome of HAART (Mannheimer, et al.; 2002: 1115 – 1121). Adherence to antiretroviral medication is believed to be a crucial component in maintaining therapeutic drug levels, ensuring virologic suppression and reducing the risk of drug resistance (Altice & Friedland, 1998 cited in Mannheimer, et al.; 2002: 1115 – 1121; Gifford, et al.; 2000: 386-395). Poor adherence leads to the development of drug resistance, and limitation of the effectiveness of therapy (Walsh, et al., 2000 cited in DHHS, 2002: 10). The percentage of patients who fail to self-administer as prescribed is somewhere between 20% and 80% (Cramer, et al., 1989: 3273-3277; Wright, 1993 cited in Williams, 2001: 38). Similarly, among those taking HAART, 40%-60% are less than 90% adherent

(Bangsberg, et al., 2000: 357-366; Bartlett, 2002: S2 – S10; Gordillo, 1999: 1763-1769). The level of adherence required for success, however, is thought to be a staggering 95% or greater (Bartlett, 2002: S2 – S10; Beer, et. al., 2000).

Several studies have demonstrated a significant correlation between medication adherence and virologic suppression (Bangsberg, et al., 2000: 357-366; Gifford, et al., 2000: 386-395; Haubrich, et al., 1999: 1099-1107; Mannheimer, et al, 2002: 1115 – 1121; Montaner, et. al., 1998: 930-937). In HIV-infected patients who received HAART, suboptimal adherence was a strong predictor of treatment failure (Frank, 2002: S10). HAART was the expense of long-term adherence, resulting in the burden of managing complex regimens and heavy pill, and treatment-limiting toxicities (Currier, 2002: S1).

In a study of Mannerheimer and colleagues (2000) found that adherence tended to decline over time based on information from two multicenter, randomized trials in which patients completed 7-day recall adherence reports at 1 month, 4 months, and 8 months of the follow-up. About 70% of patients reported 100% adherence at 1 month, but this proportion declined to 63% at 4 months and to 58% at 8 months. Elevations in HIV RNA and decreases in CD4⁺ T-cell counts correlated with the decline in adherence at each time point, indicating that treatment fatigue could have a marked effect on long-term efficacy (Mannerheimer, et al; 2000 cited in Frank 2002: S11). In addition, the causes of nonadherence in monthst AIDS patients were often dealing with multiple health problems, their medications which often included antidepressants, anxiolytics and drugs to prevent opportunistic infections, and their need to manage the side effects of antiretroviral (Williams, 2001: 42).

Paterson and colleagues (2000) compared the proportions of subjects achieving an undetectable viral load based upon the proportion of doses taken and found that antiretroviral adherence was significantly associated with successful virologic suppression and immune reconstitution i.e. higher CD4⁺ T-cell counts (Paterson et. al., 2000 cited in Ian Frank, 2002: S10).

Adherence rates among HIV-infected patients are not different from those among patients who suffer from other chronic diseases. In contrast, with patients with diabetes or hypertension, patients with HIV who take only half of their prescribed doses monthst likely compromise the future effectiveness of those and related

medications, forfeiting the opportunity to benefit from potentially life-saving therapies. Even if these patients later attain perfect adherence, the virus will have developed resistance to the prescribed medications and possibly to other drugs in the same class (Williams, 2001:38).

A study of Singh and colleagues (1999) found that HIV-infected patients with <90% adherent to antiretroviral therapy had a mean decrease in CD4⁺ cell counts of 5/ μ L. However, mean CD4⁺ cell counts increased by 78/ μ L for patients whose adherence rates were $\geq$ 90% (Singh, et al; 1999 cited in Bartlett 2002: S3).

Haubrich and colleagues (1999) found that the adherence portion of the study provided the first quantitative assessment of the relationship between adherence and HIV suppression. The immunologic response to antiretroviral therapy was correlated with greater adherence reported at months 2 and 6. Patients with the poorest adherence (<80%) at month 6 lost an average of $19 (\pm 37) \times 10^6$ CD4 cells/l, while those with 80-95% adherence gained $54 (\pm 81) \times 10^6$ cells/l, those with 95-99% gained $87 (\pm 77) \times 10^6$ cells/l, and patients with 100% gained $72 (\pm 81) \times 10^6$ cells/l ($p=0.01$). Moreover, patients with greater than 80% adherence had the monthst sustained HIV RNA reductions, 4.6-4.8 (± 4.1 -5.2) log₁₀ copies/ml-months, compared with patients with less than 80% adherence, who had small overall HIV RNA increases ($p=.04$). Patients with increased adherence at month 6 also had better CD4 cell outcomes, ranging from an average reduction of 8×10^6 cells/l over 6 months for <80% adherence to an average gain of 59×10^6 cells/l over 6 months for 95-99% adherence ($p = .009$).

It is apparent that adherence medication among patients with chronic illness and HIV/AIDS involves various factors and attempts should be exerted to encourage the existence of these factors so that medication adherence among these patients can be ensured.

Part 4. Factors associated to medication adherence

Many factors have been shown to influence medication adherence among patients receiving HAART for long-term success with any of the antiretroviral therapy. These factors can be conceptualized as (a) patient characteristics, (b) treatment regimens, (c) patient-provider relationship, (d) clinical setting, and features

of the disease (Ickovics & Meade, 2002: S98-S102; Ickovics & Meisler, 1997: 385-391). A multifactorial framework for medication adherence in AIDS clinical trials proposed by Ickovics and Meade (2002) illustrates linkages of these concepts as presented in Figure 2.

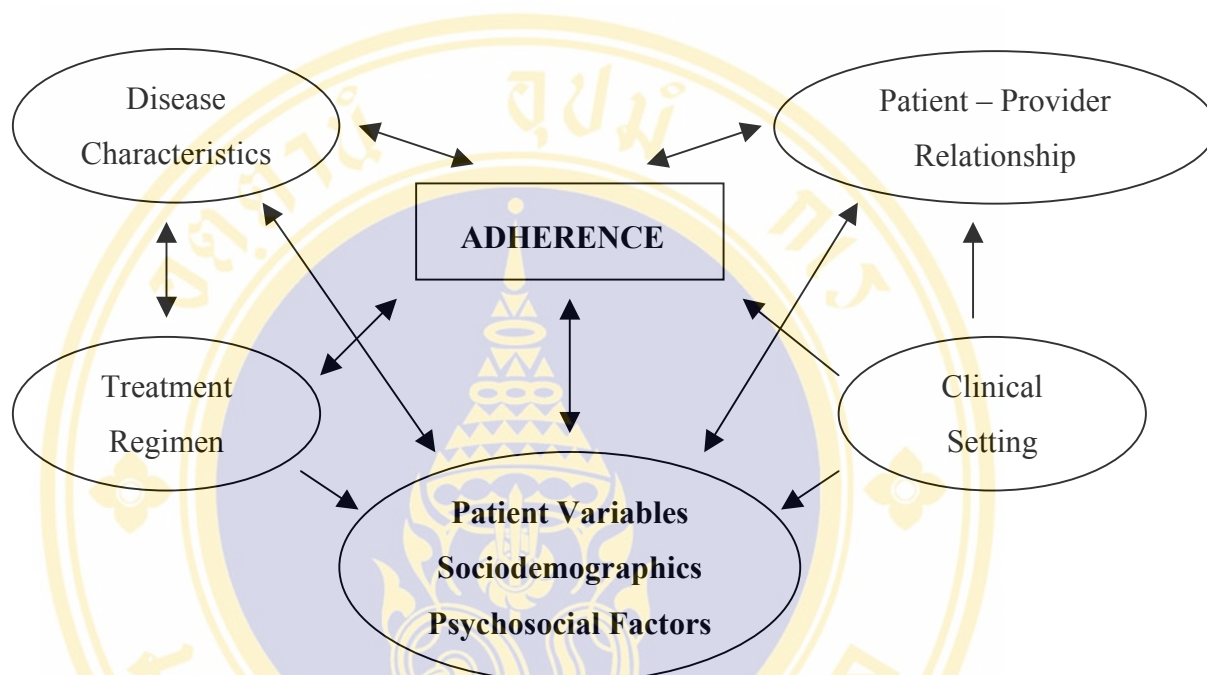


Figure 2. A Conceptual Framework for Medication Adherence in Clinical Trials

At a theoretical level, the nature and determinants of nonadherent behavior are more complex and not well understood. Low adherence is a problem with self-administered treatments for all disorders. Long waiting times at clinics and long times between appointments lead to patients' missing appointments and dropping out of care. The more complex or costly the regimen, and the longer it must be taken, the less the adherence (Stephenson, et al.: 1993: 2779-2781). Concerning HIV-infected patients, predictors of good adherence may include confidence in the effectiveness of HAART medication, understanding of the importance of adherence and the consequences of the lack of it (Farnk, 2002: S11).

In this study, relationships between only medication adherence and patients' factors were explored. These factors were described in three categories: personal background characteristics, knowledge about HIV/AIDS and social support as follows:

4.1 Personal Background Characteristics. These include sociodemographic data, side effects of HAART, availability of a caregiver(s), and disclosure of HIV status.

4.1.1 Sociodemographic data Sociodemographic data include age, gender, education, occupation, and income. These had been associated with medication adherence in a variety of disorder, including chronic illness, mental illness, and amongst the elderly. Many studies showed that factors related to medication adherence were as follows:

Age Age is a basic factor to define the difference in terms of physical and mental development. According to Orem (1991: 238-246), age normally is closely related to the characteristics of a person's behavior, and it has meaning in relationship to the self-care behavior. As one among the other factors, it has influence on the therapeutic self-care demands and the self-care agency of patients and it also has an impact in limiting the capacity of self-care, which increased to the peak in adult and declined in old age. Orem (2001: 245) stated that age was one of ten factors that affected individuals' abilities to engage in self-care or the kind and amount of self-care required i.e. "basic conditioning factors". Pender (1990: 55) stated that age explained health-promoting lifestyle.

In HIV-infected patients, several studies have shown that older age is significantly associated with better adherence to antiretroviral therapy/or HAART (Hinkin, et al., 2002: 1944-1950; Mannheimer, et al., 2002: 1115 – 1121; Schectman, et al., 2002: 1294 – 1300; Tuldra, et al., 2000: 221-228) while younger age is a significant predictor of lower adherence to antiretroviral therapy/or HAART (Ammassari, et al., 2001: 445-449; Andreo, et al., 2001: 249-262; Fogarty, et al., 2002: 91-92; Gordillo, et al, 1999: 1763-1769; Howard, et al., 2002: 2178-2182; Spire, et al., 2002: 1481-1496). Similarly, Stone and colleagues (2001) found that younger-age HIV-infected patients was associated with a reduced likelihood of skipping doses antiretroviral medication.

Gender Gender is assigned for the social differential individual. Orem (1991: 136) stated that gender was a individual characteristic that identified the difference of body change and need of self-care. It determined universal and health deviation, self-care requisites, performance power, or ability and methods or choice of

self-care requisites. Pender (1996) found that gender was personal biologic factors which could explain or predict a person's behavioral outcome. Consistently with the report of Muhlenkamp and Broerman (1988), different gender was related to different life style. Females showed more positive health promoting behaviors than males. Similarly, Jariyawat Kompayak and colleagues (BE 2537) found that sex appeared to have a major impact on health practices. Female patients had better health practices than male.

Concerning HIV-infected patients, the following thourree researches reported significant association between gender and medication adherence and female showed more adherence than male (Patchara Rumakom (B. E. 2544); Vincke & Bolton, 2002: 487-495), while one reported that gender was not significantly associated with medication adherence (Fogarty, et al., 2002: 91-92).

Many studies found that female patients receiving HAART also presented somewhat more significant adherence than male (Patchara Rumakom (B. E. 2544); Vincke & Bolton, 2002: 487-495). However, Fogarty and colleagues (2002) conducted a literature search to review published articles reporting associations of HIV medication adherence and interventions designed to increase HIV medication adherence, found that gender was not consistently related to adherence.

Education Education is essential for learning, thinking and decision-making, including health-promoting behaviors. Obviously, level of education is one of the factors, which influence personal behaviors. Pender (1987: 161-162) stated that education allowed human being to achieve their full potential of intelligence and knowledge. Education is one of the factors, which influences personal behavior, allows to better perceive of information about health and illness, and allows people to decide to carry out health behaviors appropriately. Pender (1987: 241) claimed that people who have the high education could learn, understand and make decision for the proper practice, while people with low-level of education have difficulty in understanding about the etiology, the treatment planning and the benefits of health promoting behaviors. Orem (1985:175) stated that education level was an important factor in developing the knowledge, skills and positive attitude that were essential for self-care. Winoker and colleagues (1973: 29) stated that years of education was a key to help individual intellectual development and intellectual was

important for adaptation. Higher educated person would improve acknowledge, experience, reasonable ability, positive attitude, and give a chance to seek for information and benefit sources which would help in advance role adaptation.

In HIV-infected patients, several studies have shown that education is significantly associated with adherence to antiretroviral therapy/or HAART. One study showed that subjects with low level of education had the worst adherence, whereas individuals with a university degree had the best (Gifford, et al.; 2000: 386-395; Gordillo, et al.; 1999: 1763-1769). Similarly, lower education was independently associated with worse adherence (Golin, et al.; 2002: 812 – 813) and higher adherence was associated with more years of education (Wagner, et al.; 2002: 105 – 109).

Occupation Pattana Phokaew (BE 2537) found that the adherence on tuberculosis treatment of the unemployed patients with HIV infection was significantly better than the employed patients ($p = 0.05$). In contrast, Gordillo and colleagues (1999) found that HIV-infected patients who had a job were associated with better adherence (OR, 2.24; 95% CI, 1.27-2.73). Similarly, Ammassari and colleagues (2001) found that unemployed HIV-infected patients were significantly associated with antiretroviral medication nonadherence (OR, 2.92; CI, 1.55-5.49; $p < .001$).

Income Economic status is one of the potential components influencing self-care. High income will enable patients to take appropriate action to promote self-care (Pender, 1996: 161-162). Income is a factor influenced basic life support of person (Orem, 1985: 186). Herman (1972) found that higher income families showed a much better rate of protection than poorer families (Herman, 1972 cited by Rosenstock, 1974: 29). Pattana Phokaew (BE 2537) found that income per month had a significant positive relationship with patient's adherence to tuberculosis treatment of patients with HIV infection ($p = 0.05$). In HIV-infected patients, several studies have shown that income is significantly associated with adherence to antiretroviral therapy/or HAART. Lower income is a significant predictor of lower adherence (Kleeberger, et al.; 2001:). Similarly, Spire and colleagues (2002) found that patients living in poor socio-economic environment (living on welfare, poor housing conditions) were more likely to be nonadherent in univariate analysis. Brigido and colleagues (2001) found that HIV-infected patients who were receiving

antiretroviral therapy but lacked the money for transportation to obtain medication were significantly associated with nonadherence.

4.1.2 Side effect of HAART

The current antiretroviral treatment standard for HIV-infected patients is to use combination therapies / HAART to reduce and maintain HIV-RNA plasma concentration below detectable levels (Carpenter, et al., 2000: 381-390; MMWR, 2002: 1-55; DHHS, 2002: 1-74). However, HAART regimens are associated with a significant incidence of side effects (especially abdominal discomfort, nausea, vomiting, diarrhea, headache, unpleasant taste), some of which alter the quality of daily life (Ammassari, et al., 2001: 445-449; Bartlett, et al., 2001: S2-S10; Chesney, et al., 2000: 255 – 266; Cramer, et al., 1989: 3273-3277; Eldred, et al., 1998: 117-125; Stone, et al., 2001: 124-131).

Powderly (2002) stated that the monthst significant concern regarding early initiation of antiretroviral therapy was the impact of short-and long-term toxicities. Aside from quality of life implication, significant metabolic effects are of concern. These long-term effects need to be included in the treatment initiation decision. Because toxicities and adverse effects from HAART can jeopardize adherence and contribute to the development of viral resistance.

For the majority of HIV-infected patients who received HAART (80.8%), these events were associated with only mild or moderate toxicity (Spire, et. al., 2002). Moderate/severe symptom or medication side effects were significantly associated with nonadherence (Ammassari, et al., 2001:445-449; Simoni, et al., 2002: 431-439). Roberts (2000) found that medication side effects were one of the five main barriers in HIV-positive patients' adherence to antiretroviral regimens. Several studies found that side effect of HAART significantly associated with nonadherence. Simoni and colleagues (2002) found that side effect intensity was correlated with medication adherence ($p = 0.007$). Catz and colleagues (2000) found that side-effect severity distinguished patients with good and poor adherence among persons prescribed HIV new treatment. Bad experience of side-effects has already been shown to be associated with poor adherence to HIV/AIDS antiretroviral treatments including HAART (Bassetti, et al., 1999: 114-119; Spire, et al., 2002: 1481-1496). Bassetti and colleagues (1999) found that the monthst common reasons for discontinuing HAART

were side effects (61.1%), the patient's fear of side effects (25.4%), and the perception by the patient that the treatment was too complicated (23%). Similarly, Altice and colleagues (2001) stated that the strongest correlates of medication adherence had to do with whether the patient experienced side effects (92% vs 72%, $p = 0.004$), and what their response would be if they experienced symptoms that might be side effects resulting from their medication. Those who would stop their medication immediately if side effects were perceived had much lower adherence than those who would keep taking their medication until they could speak to a friend or doctor about the symptoms (91% vs 74%, $p = 0.004$).

4.1.3 Availability of a caregiver (s)

In early stage of HIV infection, an infected person may have no symptoms. A spectrum of clinical expression of disease can occur after HIV infection. Although about 5% to 10% of HIV infected persons can remain clinically asymptomatic after 8 to 15 years, about 10% of HIV-infected persons will progress to AIDS within the first 2 to 3 years of HIV infection (rapid progressors), and monthst will progress to AIDS within 12-13 years after infection. It has been estimated that about 50% HIV-infected persons will progress to AIDS within 8 years after infection (Stine, 2000: 198-199). The suppression of the immune system ($CD4^+$ cells count < 500 cells/ μ L) presents an opportunity for the harmless to become harmful agents leaving HIV-infected persons open to an endless series of opportunistic infections which would not occur in persons with healthy immune responses such as the five monthst frequently - reported opportunistic infections are *Mycobacterium tuberculosis*, *Pneumocystis Carinii* Pneumonia, Cryptococcal meningitis, recurrent bacteria pneumonia, and Cerebral Toxcplasmonthsis etc.

The symptoms and opportunistic infections (OIs) associated with AIDS are varied with $CD4^+$ cells counts. Decreasing of $CD4^+$ cells counts can lead to increasing OIs and debilitating (CDC, 1992: 1-19; DeVita, 1992: 126; Woodruff, 1996: 385). Some of OIs cause cognitive impairment, for example, cryptococcal meningitis. As a result, HIV-infected persons require intensive and long-term care during an endless series of illnesses and rigorous treatments. As medical breakthouroughs have prolonged the lives of the infected person, the complicated regimens of the treatments and the physical effects of both treatments and disease

continue to make them require support and care by family members (Bunting, 2001: 131-148).

Support from parents and other family members and friends is also considered crucial for compliance (O'Brien, 1980; Carlberg, 1993; Kyngas, 1995 cited by Kyngas & Lahdenpera, 1999: 834). Family members and significant others can provide great support in the patient's adherence to the medication regimen by incorporating it into the routines of shared domesticity; those without such support often struggle alone (Williams, 2001: 42). Frank and colleagues (2002: S11) stated that trust in caregiver was predictor of good adherence in patients receiving HART. While persisting stigma associated with AIDS can be barriers for many patients to conceal the diagnosis to friends and family, making it impossible for them to seek support.

4.1.4 Disclosure of HIV status

Disclosure of HIV status is one topic of discussion whether the patient makes it voluntarily, to whom the disease is revealed, what the reasons are, and how much this can affect medication adherence. In a study, voluntary disclosure was noted in 44 subjects (65%), while in other 24 (35%) subjects disclosure occurred without consent. Of those who disclosed, 78% of the subjects reported self-disclosure to family members, 7% to friends and 15% exclusively to health professionals. Expectations of emotional and material support from the family members were one of the commonly reasons given for voluntary disclosure. Only half of the subjects disclosed complete and truthful information while in the rest, disclosure was partial or disguised as a less stigmatizing illness. Stigma, fear of discrimination, disgrace to family and self and futility were reported as the main reasons for non-disclosure. The majority of the subjects (73%) reported anticipation of negative societal reaction as the main concern following disclosure. In India, where HIV-related counseling services are still not freely available, there continue to be non-uniform practices related to confidentiality and disclosure. The findings of this study are important in identifying cultural factors related to disclosure in HIV infection and highlight the need to examine the varying patterns and concerns related to disclosure among HIV-infected individuals (Chandra, Deepthivarma & Manjula, 2003: <http://gateway2.ovid.com/ovidweb.cgi>).

Women were less likely to disclose their HIV status to others (e.g., family, friends, or neighbors) than to their partners (34% versus 84%; $p < 0.001$). The main

reason for nondisclosure was fear of the outcome. Of all the women, monthst (77%) believed that HIV was a disease of which their families would be ashamed. Overt HIV stigmatization was rarely reported, but women generally kept their HIV status secret from everyone except their partners. Monthst women reported that they had disclosed their HIV status to their partner (84%) or that their partner had found out indirectly (3%). Among women who knew their partner's HIV result (85%), women with HIV-positive partners were more likely than women with HIV-negative partners to disclose their HIV status (94% versus 77%; $p = 0.02$) (Manopaiboon, et al., 1998: 54-63).

Parents of HIV-positive children are known to delay disclosure of diagnosis. Findings showed that parents generally partially disclose information about the illness without naming it and delay full disclosure. The monthst frequently given reason for delay in talking to their child about HIV was fear that the child may accidentally reveal their diagnosis, thereby simultaneously revealing maternal HIV status and exposing the family to potential stigmatization, discrimination and prejudice (Waugh, 2003: <http://gateway2.ovid.com/ovidweb.cgi>). The importance of disclosure of HIV disease in perinatally infected patients is found to be related directly to medication adherence. (Lee & Johann-Liang, 1999: <http://gateway2.ovid.com/ovidweb.cgi>).

Chandra and colleagues (2003) found that certain disclosure-related variables appear to relate significantly with quality of life among HIV-infected persons. A positive outcome related to disclosure and extent to which a subject felt the need to disclose were significantly associated with higher scores on the total quality of life measure and in the social and environmental domains. Murphy and colleagues (2000) found that 16% of HIV-infected patients with HAART who found disclosing HIV status to family / friends / co-workers – no need for privacy was helped in taking their medications.

4.2 Knowledge about HIV/AIDS

Knowledge about HIV/AIDS this study includes disease and treatment, antiretroviral medication use, side effect of antiretroviral medications and management. The patient must understand specifically what is being prescribed, the rationale of the regimen, and specifically, how it is to be followed (Rosenstock, 1975: 402-403). Several studies have found that knowledge about HIV disease and therapy

significantly associated with nonadherence. Knowledge about HIV disease and HAART regimens may influence adherence (Eldred, et al.: 1998: 117-125; Wagner, et al.: 2002: 105 – 109). Knowledge of HAART is effective and that poor adherence may promote viral resistance and treatment failure have been shown to affect patients' ability to adhere to their medication (Wagner, et al.: 2002: 105 – 109). Less adherent patients in HIV clinical trials were less sure of the link between nonadherence and the development of resistance than other patients (Chesney, et al.: 2002: 255 – 266). Roberts (2000) found that patient's inadequate knowledge was a main barrier to adhere to medication.

A study medication adherence in HIV-infected patients who received antiretroviral therapy by Mathews and colleagues (2002), measured medication adherence by (1) Medication Event Monitoring System (MEMS) therapeutic coverage, (2) MEMS adherence, and (3) self-reported adherence. All results indicated that high knowledge of antiretroviral therapy drug classes, knowledge of tests of antiretroviral therapy effectiveness, belief that HIV medications were significantly independent predictors of better adherence. Similarly, Williams (2001: 40) stated that patients who understood how their medications helped them were more likely to adhere to their regimens.

Patient's understanding of the possible side effects of medications and the management of them also had significant effect on adherence. In the study of Davis and colleagues (1997) concerning successful ritonavir induction and intensive patient management, it was found that patients who had been told how to manage GI distress and diarrhea were successful in beginning and maintaining their regimen. Without this information, patient might either stop following them or reduce the doses without consulting their providers.

Pattana Phokaew (BE2537) found that knowledge was significantly positive related to patients compliance on treatment of tuberculosis in the patients with HIV/AIDS. Similarly, Roberts (2000) found that inadequate knowledge was one of the five main barriers to adhere to antiretroviral regimens of medications in HIV-positive patients.

Martinez and colleagues (2000) found that knowledge of medication schedule was significantly associated with adherence to antiretroviral drugs and that of their

side effects was found to be a major factor in adherence (Murdaugh, 1998: 361). Wagner and colleagues (2002) found that higher adherence was associated with greater knowledge of HIV treatment and consequences of poor adherence. Knowledge about medications' impact on each patient's clinical markers can also be a powerful motivating tool for medication adherence (Williams, 2001: 40).

4.3 Social support

House and Kahn (1985: 83-105) refer to it as a number of different aspects of social relationship like the terms social network and social integration. Social support is sometimes defined conceptually or operationally in terms of the existence or quantity of social relationships in general, or of a particular type such as marriage, friendship, or organization membership. Social support is also sometimes defined and measured in terms of the structure of a person's social relationships. In addition, such as the degree to which the relationships involve flows of effect or emotional concern, instrumental or tangible aid, information, and the like. In addition to this, the four potential forms of social support mentioned earlier: emotional, appraisal, informational, and instrumental (House, 1981: 83-108) are later described in more detail as follows:

Content of supportive acts composes of four aspects as follows:

1. Emotional support: esteem, affect, trust, concern, and listening.
2. Appraisal support: affirmation, feedback, and social comparison.
3. Informational support: advice, suggestion, directives, and information.
4. Instrumental support: aid in kind, money, labor, time, and modifying environment.

Among all, the definition and content of supportive acts described above by House (1981) were used to develop the questionnaire in this study to measure social support of HIV-infected patients with HAART.

Social support has been defined as an exchange of resources between at least two individuals perceived by the provider or recipient to be intended to enhance the well being of the recipient (Shumaker & Brownell, 1984 cited in Callaghan & Morrissey, 1993: 20). It is in another way defined as the factors, which make people want to do positive healthy behaviors and to develop health status. Support may be received in several ways from other persons, groups of people, or organizations such

as giving information, listening to her/him, encouraging to her/him to do something, assisting with some money, equipment or some other things. This support can help preserve individuals' continuity of positive health behavior. An individual will also feel better after receiving it when he/she fell in difficulty (Birch, 1998: 159-161; Isael & Schurman, 1990: 187-215). Obviously social support is beneficial to health and that social isolation leads to ill health. Social support has a positive effect on many different aspects of both physical and mental health. However, the exact nature of the positive influence of social support on health remains elusive (Stansfeld, 1999: 155). While social support has been linked to positive health practices, indirect health risk behaviors such as seat belt use, exercise, nutrition, medical and dental care, and other screening examinations were influenced by social environment and individual characteristics (Langlie, 1977 cited in Muhlenkamp & Sayles, 1986: 335). In two separate studies of Hubbard, Muhlenkamp, and Brown (1984) it was found that perceived levels of social support had strong positive association with participation in positive health practices.

Points in common include the ideal of social support as a multifaceted construct comprised of the communication of positive affect, a sense of belonging or social integration, and elements of reciprocity. In addition, the construct may or may not encompass instrumental behavior (Dimond & Jones, 1983 cited in Hubbard et al., 1984: 266). Several possible explanations for the positive relationship between social support and good health were hypothesized. According to one explanation, the socially isolated person may be more likely to adopt self-destructive health practices. Another explanation is the possibility that social isolation may lead to depression, which, in turn, may predispose toward accidents or suicide (Berkman & Syme, 1979 cited in Hubbard, et al., 1984: 267). Gibson and colleagues (1998) found that in persons with multiple-chemical sensitivity, level of fatigue correlated significantly negative with perceived social support. Perceived social support was higher in persons who reported an improved course of illness compared to those whose conditions had reportedly worsened ($p = 0.001$).

In assessing the impact of support on health, it is also important also to acknowledge the source of the support, as the impact of emotional support from different sources may have a different meaning, depending on closeness of that source

to the respondent (Stansfeld, 1999: 155). A relationship between social support and recovery from physical illness may be mediated by the effects of support on health behavior and/or the mobilization of the immune system. In the case of health behaviors, information from others about proper health care and about coping with illness may influence perceived and actual ability to affect health status instrumental aid, such as nonprofessional patient care, and may also have a direct impact on the patient's well being. Besides, information about the esteem in which a person is held by others may influence motivation to get well and consequently increase adherence with medical regimens and performance of health care behaviors (Cohen & Syme, 1985: 8).

Pender (2002: 248 - 249) stated that lower levels of support were consistently linked to higher rates of morbidity and mortality and social support systems influenced health behavior such as, making decisions to seek professional care for health promotion, illness prevention, or care in illness. In addition, social support has been correlated with adoption of other health behaviors or cessation of negative behaviors. Support-induced elevations in self-esteem, ability to cope, and motivation to get well may similarly aid in recovery from mental health problems by directly influencing emotional and cognitive states associated with the disorder or by increasing adherence (compliance) with medical regimens (Cohen & Syme, 1985: 8-9).

Social support may play a key role for medication's success or failure. Supportive contact and relationships may positively affect health thought, earlier recognition of symptoms and a greater likelihood of seeking medical care, which decreases the need for hospitalization or nursing home admissions, and provision of assistance to sustain treatment regimens. Social isolation, the lack of social and community relationships, has been associated with poor health (Berkman, 1983; Dean, Kalody, & Wood, 1989 cited in Murdaugh, 1998: 364). The study of the role of social support and infectious disease has also led to important evidence regarding potential bio-physiological pathways thorough which social support may operate (Berkman & Glass, 2000: 137 – 173). Empirical literature review of Clark & Becker (1998:24) stated that evidence that suggested social support (particularly support provided by the patient's family) as a influence on adherence and self-management. The family can enhance supervision of the patient, as well as provide assistance and encouragement.

Social support is important, especially in long-term treatment plans that require continuous action on the part of the patient. A family's own health beliefs and its evaluation of the patient's illness and treatment plan may influence adherence. Success is greatest when the family's normal roles and patterns are compatible with the illness of the patient or when the family members are willing to make accommodating changes in their lives and in the family environment.

Social support is not only useful in preventing or decreasing the risks of illnesses, but also useful in coping with a chronic illness (Stanfeld, 1999: 164). It can protect individual from stressful situations (Friedmen & King, 1994: 433). These were confirmed by the research of Marmot & Wilkinson (1999: 163). One important of study in relation to any chronic health problem is that of social support. The link between low levels of social support and a high incidence of morbidity and mortality in the chronically ill is well established (House, Landis & Umberson, 1988; Shumaker & Hill, 1991 cited in Gibson, et al., 1998: 105). Singhakhumfu (1989) found that social support was positively related to quality of life of hypertensive patients in Out Patient Department of Medical Therapy and Occupational Therapy Unit of Siriraj Hospital and Prasat Neurological Hospital. Chevacomnuen (1992) found that social support was significantly positive correlated to health status, but negative correlated to fasting plasma glucose in type 2 diabetic patients at Endocrine Clinic of Udonthani Hospital. At the point of self-care, behavior of diabetic patients was significantly positive associated with social support (Kaewpralome, 1995; Promprakarn, 1998; Skulpan, 1992). Teichman and colleagues (2000) showed that family support was significantly correlated with self-reported compliance in patients who had had lung transplants.

Simoni and colleagues (1999) found that mediation analyses provided partial support for their proposed model of social support and adherence. Specifically, regression analyses controlling for social desirability indicated that need for social support was positively correlated with acknowledged nonadherence and that this relationship was mediated by self-efficacy and depressive symptomatology. Concerning HIV-infected patients, many researchers have been studying the effects between social support and AIDS. WHO (1990:34) stated that for many HIV-infected people, including those with HIV-related disease, families were the main source of

care and support. The type of care required would depend on the stage of infection: as the patient's condition deteriorated, the demands on the family increased. The time and energy required and the emotional involvement would increase and draw the family away from other activities and responsibilities. Currently, the role of social support in enhancing adherence was highlighted in a working model although relatively little research has specifically addressed the role of social support in adherence (DiMatteo & Mays, 1981 and Truk, et al., 1981 cited in Simoni, et al., 2002: 431-439). Social support was believed to be predictor of good adherence (positive effect) to antiretroviral therapy in the cases of HIV (Frank, 2002:S11). Taweethong Hongwiwat (BE 2536) found that AIDS cases who received social support (family and relatives) significantly were happier than those without social support. Martinez and colleagues (2000) found that social support was significantly associated with adherence to antiretroviral drugs. Catz and colleagues (2000) found that social support distinguished patients with good and poor adherence to new prescribed treatment for HIV disease.

A study of adherence to antiretroviral therapy among HIV-infected patients conducted by Singh and colleagues (2000) found that satisfaction with social support, problem-focused coping, and active-behavioral coping were correlated significantly with adherence, whereas loss of motivation, hopelessness, and avoidant coping were correlated with nonadherence. Some researches have demonstrated that support can be a significant factor in enhancing medication adherence (Becker: 1980, Earp: 1979, Kirscht: 1981 cited in Simoni, 2002: 431-439) and thourree groups of factors: self-efficacy, negative affective states, and knowledge of the medication regimen were thought to mediate the association between social support and adherence. Obviously, having social support was associated with better adherence - OR, 2.03; 95% CI, 1.26-3.27 (Gordillo, et al, 1999: 1763-1769). Gifford and colleagues (2000) also found that better social support was associated with better adherence. On the contrary, Simoni and colleagues (2002) found that HIV-infected patients who received HAART and felt the need for social support was significantly associated with nonadherence. It was also found that HIV-infected patients receiving HAART who declared a lack of social support from partner, family and friend, were more likely to be nonadherence (Spire, et al., 2002: 1481-1496).

Marayat Wongsabutr (BE 2539) found that there was a positively significant relationship between social support and hope as well as self-care behavior of persons with AIDS at Phourabatnumpu Temple Lob-Buri Province. Chaicharoen (2000) found that social support was associated with health perception and health promoting behavior among clients with HIV-seropositive at Camillian Social Center, Rayong Province. Similarly, a study of Kabinlapat (1998) found that social support was significant predictability 32.59 % of the variation in problem-focused coping behavior and 22.15 % of the variation in emotional-focused coping behavior in HIV-seropositive mothers at Well Baby Clinic at Chulalongkorn Hospital, Bumrasnaradura Hospital, Jareankrungpracharuk Hospital and Wachira Hospital.

In conclusion, social support has been regarded as not only useful in preventing or decreasing the risks of illnesses, but also useful in studying of chronic illnesses. As social support may be received in several ways from other persons, groups of people, or organizations such as giving information, listening to her/him, encouraging to her/him to do something, assisting with some money, equipment or some other things, social support can help preserve individuals' continuity of positive health behaviors. Social support can be beneficial to health and that social isolation can lead to ill health. Social support has been regarded as one of the significant factors associated with medication adherence among chronically- ill persons, including patients receiving HAART. Family members and significant others can provide great support in the patient's adherence to the medication regimen by incorporating it into the routines of shared domesticity, reminding them to take medication. Those without such support often struggle alone, as poor or lack of social support has been found to associate with poor or nonadherence to antiretroviral medications.

CHAPTER III

MATERIALS & METHODS

This is a cross-sectional study, exploring the relationship between personal background characteristics, Knowledge about HIV/AIDS, social support, and medication adherence among patients receiving HAART at the out patient departments and ambulatory care unit at Bamrasnaradura Infectious Disease Institute. The purposes of this study were: 1) to examine relationships between medication adherence and personal background characteristics, knowledge about HIV/AIDS, and social support among patients receiving HAART, 2) to examine factors that contribute to the prediction of medication adherence among patients receiving HAART. Materials and methods used in this study are as follows:

Setting of the Study

This study was conducted at the out patient departments (OPD) and ambulatory care unit (AB Care) of Bamrasnaradura Infectious Disease Institute. There were about 1,200 patients receiving HAART. About 100 – 150 patients attended the OPD clinics each weekday and the majority came on Wednesday during 08.00 – 12.00 a.m. In addition, about 10 – 15 patients attended Ambulatory Care (AB Care) every weekday.

Population and Samples

The population of this study are all patients receiving HAART at the OPD and AB Care of Bamrasnaradura Infectious Disease Institute. A sample was recruited using a purposive sampling based on the following inclusion criteria:

1. 15 years old and older.
2. Has been treated with any regimen of HAART for at least 1 month.
3. Ability to read and understand Thai language.
4. Has good mental status: patients who are 60 years old and older were screened for cognitive impairment using Chula Mental Test.
5. Willingness to participate.

Sample size

According to Tabachnick and Fidell (1989), a ratio of 40 subjects should be used for each independent variable when using a stepwise regression analysis (Tabachnick and Fidell, 1989 cited in Polit, 1996: 284). The sample size was calculated as follows:

$$\begin{aligned} n &= 10 \times 40 \\ &= 400 \end{aligned}$$

Measurements

The instruments used in this study consist of four parts: (1) personal background characteristics, (2) medication adherence, (3) knowledge about HIV/AIDS, and (4) social support. In addition to these, the Chula Mental Test was used to screen for cognitive impairment if the subjects were 60 years old and older. Details about the questionnaires are as follows:

1. Personal Background Characteristics (See Appendix A).

This is to collect demographic data (age, gender, education, occupational, and income), side effects of HAART, availability of a caregiver (s) and disclosure of HIV status.

2. Medication adherence (See Appendix B).

An average of the following adherence measured by patient self report and a visual analog scale was calculated and used to indicate medication adherence among patient receiving HAART in this study. A reason for using both measurements was that some patients with visual loss due to CMV retinitis can be included in this study.

1. Patient self-report: Patient self-report is the most commonly used assessment of medication adherence although it has been found to have less inaccuracy as a result of imprecise or inconsistent questioning, forgetfulness or intention to provide socially reliable answers (Lay 1988 cited by Mannheimer et al., 2002: 1115-1121). In this study the patients were asked to give an estimation about how many percent of medication that they took in the past month from 0% to 100%. It can be interpreted as 0% means no medication taken, 50% means half of medication, and 100% means every single dose taken.

2. The visual analog scale (VAS) The visual analog scale of proportion of doses taken in the preceding month was used to measure medication adherence by Walsh and colleagues (2002: 269-277). Patients were asked to put a cross on the line below at the point showing your best guess about how many percent of medication you have taken in the last month. It can be interpreted as 0% means no medication taken, 50% means half of medication, and 100% means every single dose taken. It was also inversely associated with plasma HIV RNA ($p = .01$). According to Williams (1999: 113-129), assessment of medication adherence should be very concrete, be very specific, give permission for lapses in adherence, identify unique problem areas, and assess for unexpected side effects. Visual analog scale could also be used to reveal patient self-report (Walsh et al., 2002: 269-277). The VAS was also used by Maneesriwongul and Williams (2004) to measure medication adherence among patients receiving HAART in Thailand, and significantly validated with viral load ($p < .05$).

3. Knowledge about HIV/AIDS (See Appendix C).

An instrument measuring knowledge about HIV/AIDS to be used in this study was developed based on literature reviews by Maneesriwongul and colleagues (2003). Knowledge about HIV/AIDS includes (1) disease and treatment (Eldred, et al., 1998; Roberts, 2000; Mathews, et al., 2002; Wagner, et al., 2002), (2) antiretroviral medication use (Martinez, et al., 2000; Mathews, et al., 2002), (3) side effects of antiretroviral medications and management of these side effects (Davis, et al., 1997; Murdaugh, 1998; Wagner, et al., 2002).

This instrument is a self-administered questionnaire that composed of 38 items to measure knowledge about AIDS in terms of: the disease and progression (13 items), usage of antiretroviral medications (12 items), and side effects of antiretroviral medications and its management (13 items) using tree point scales: “yes”, “no” or “don’t know” (see Appendix A). Each item was scored for correct/incorrect responses. A correct response was scored as one while an incorrect response (and “don’t know”) was scored as zero. Eighteen items were negatively worded.

This questionnaire was validated for its content validity by 6 experts (2 physicians, 2 nursing faculty members, and 2 nurses specializing in AIDS care). Subsequently, it was piloted among 48 patients receiving HAART and 19 caregivers

(caregivers of some of these patients) at the Out Patient Department, Bamrasnaradura Infectious Disease Institute. Internal consistency coefficient alphas of the three subscales are .73, .71 and .79 respectively with an overall coefficient alpha of .86 which indicates adequate reliability for a newly-developed instrument. Possible scores on this scale range from a low of 0 to a high of 38. A higher score means higher knowledge about AIDS.

4. Social Support (See Appendix D).

An instrument measuring social support to be used in this study was developed based on literature reviews by Maneesriwongul and colleagues (2003). Social support covers the following four different aspects (House, 1981): (1) emotional support i.e. esteem, affect, trust, concern, and listening, (2) appraisal support i.e. affirmation, feedback, and social comparison, (3) information support i.e. advice, suggestion, directives, and information, and (4) instrumental support i.e. aid in kind, money, labor, time, and modifying environment. Sources of support include spouse or partner, other relatives, friends, neighbors, co-workers, service, caregivers, and health and welfare professionals. The definition and content of supportive acts described by House (1981) and House and Kahn (1985) was used to guide a development of this questionnaire to measure social support among HIV-infected patients with HAART.

This instrument is a self-administered questionnaire that composed of 55 items to measure social support among HIV-positive patients receiving HAART in terms of: emotional support (14 items), appraisal support (14 items), informational support (14 items), and instrumental support (13 items) using five-point Likert's scales ranging from "strongly agree", "agree", "not sure", "disagree" to "strongly disagree" (see Appendix D). Responses were scored for 5, 4, 3, 2, and 1, respectively. Eight items were negatively worded.

Validity and reliability testing

This questionnaire was validated for its content validity by 6 experts (2 physicians, 2 nursing faculty members, and 2 nurses specializing in AIDS care). Subsequently, it was piloted among 48 patients receiving HAART who attended the Out Patient Department, Bhumrasnaradura Infectious Institute. Internal consistency coefficient alphas of the four subscales are .71, .88, .81, and .82 respectively with an

overall coefficient alpha of .88 which indicates adequate reliability for a newly-developed instrument. Possible scores on this scale range from a low of 55 to a high of 275. A higher score means higher social support.

5. Cognitive Impairment (See Appendix E)

Screening test for cognitive impairment patients who are 60 years old and older used Chula Mental Test. Cognition was assessed by the Chula Mental Test (CMT). Jitapunkul and colleagues developed this tool in 1996. The CMT, whose criterion validity has been proved, was used for cognitive function assessment. The CMT has also shown that it is better than the Mini-Mental Status Examination (Thai-version MMSE) and the Abbreviated Mental Test (AMT) in term of superior discrimination for dementia screening with less educational effect. It consisted of 13 questions included age, time, registration of three thing, month, person, rice, do follow, proverb, speak follow, judgement, count 10 to 20, naming objects, and subtraction. Registration of three things and subtraction have 3 scores. Remember of persons and naming objects have 2 scores and the others have 1 scores. The total scores from 0 to 19 (See Appendix E). Total scores less than 15 are considered to have cognitive impairment. Sensitivity for screening dementia was 83% - 100% and specificity was 90% - 94% (Jittapunkul, et al., 1996: 715 – 719).

Protection of Human Subjects (See Appendix F)

This study is a part of the project entitled "Medication adherence among people living with HIV" (Protocol No. ID 06-46-31) which was approved by the Ethical Clearance Committee on Human Rights Related to Researches, Faculty of Medicine Ramathibodi Hospital, Mahidol University on June 18, 2003, and received a permission by the Ethical Committee at the Bamrasnaradura Infectious Disease Institute in July 2003.

Data collection

Prior to data collection, a permission for collecting data is obtained from the Ethical Clearance Committee on Human Rights Related to Researches, Faculty of Medicine Ramathibodi Hospital, Mahidol University and the Director of

Bamrasnaradura Infectious Disease Institute. The Director of Nursing and the Head-Nurse, and staff of the OPD and AB Care were notified and informed about the nature and data collecting procedure of the study.

Data collection procedures were conducted in the following sequences:

1. Identify the patients receiving HAART from medical records based on the inclusion criteria.
2. The researcher informed the patients about the nature and data collecting procedures of the study. The patients were asked to indicate their willingness to participate in this study, and sign a consent form (See Appendix G).
3. Explanation about the questionnaires is given to the patients. The researcher clarified any patients' query. The patients were told that participation can be terminated upon the subjects' consent and this would not affect the treatment that they received.
4. Data were collected from Part 1: personal background characteristics, Part 2: medication adherence, Part 3: knowledge about HIV/AIDS, and Part 4: social support. The whole process took about 30 – 40 minutes.
5. The obtained data were then edited and analyzed.

Data Analysis

Data were analyzed by using the Statistical Package for Social Science for Window Program 10.0 (SPSS/FW) as follows.

1. Descriptive statistics: personal background characteristics, Knowledge about HIV/AIDS, social support, and medication adherence were described by means of descriptive statistics: frequency distribution and appropriate statistics for central tendency and variability.

2. Inferential statistics:

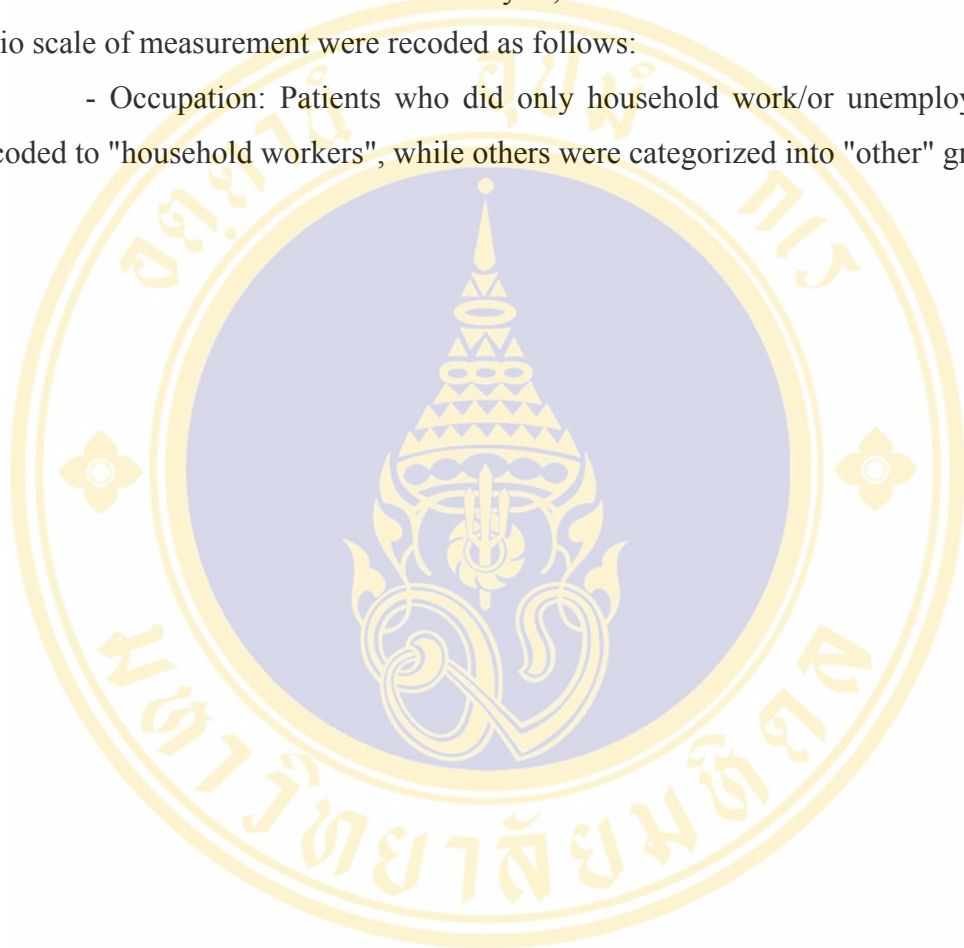
- 2.1 Pearson's product moment correlation coefficient were performed to explore the relationship between each variable as follows: personal background characteristics, knowledge about HIV/AIDS, social support, and medication adherence.

- 2.2 Multiple regressions was performed to examine predictability of medication adherence by using personal background characteristics, knowledge about

HIV/AIDS, and social support. However, prior to regression analysis, Pearson's product moment correlation coefficients were used to explore correlations among pairs of predictors of medication adherence. The assumptions for appropriate use of multiple regression analysis were tested.

For both inferential statistic analysis, variables which are not in interval or ratio scale of measurement were recoded as follows:

- Occupation: Patients who did only household work/or unemployed were recoded to "household workers", while others were categorized into "other" group.



CHAPTER IV

RESULTS

This cross-sectional study was conducted to explore the relationship between personal background characteristic, knowledge about HIV/AIDS, social support, and medication adherence among patients receiving HAART. A sample composed of 406 patients receiving HAART who came for a follow up visit at out patient department or ambulatory care unit at Bamrasnaradura Infectious Disease Institute. Objectives of this study were: 1) to examine relationship between medication adherence and personal background characteristics, knowledge about HIV/AIDS, and social support among patients receiving HAART, and 2) to examine factors that contribute to the prediction of medication adherence among patients receiving HAART. Data were analyzed, and presented in this chapter as follows:

Part I: Personal Background Characteristics of the Sample

Subjects' Personal Background Characteristics

About 434 patients receiving HAART were approached. However, only 406 patients agreed to participate in this study. Three patients who are older than 60 years old were screened for cognitive impairment. All 406 patients met the inclusion criteria for this study. There were 240 male (59.1%) and 166 female (40.9%). Their ages ranged from 20 to 68 years old with a mean of 35.9 (SD = 7.5). More than a half of the subjects were young adults: 20-29 years old (20.7%) and 30-39 years old (49.5%). Subjects were with different education – elementary (25.9%), junior high school (20%) and senior high school (16.5%) and bachelor' s degree (16.5%). Concerning occupation, 107 of the subjects were household workers (26.4%); 95 employees (23.4%) and 73 merchants (18%). Their income ranged from 0 to 66,000 Bahts per month with a mean of 7,453 Bahts (SD = 8,551.12). The three most frequently-reported side effects of HAART were peripheral neuropathy (117 = 28.8%), muscle ache (91=22.4%) and insomnia (64 = 15.8%). The majority of the subjects reported that they had a caregiver (s) availability to remind them about their medication

(85.7%) and disclosed their HIV status to someone in their family, relatives, or friends (94.1%), as shown in Table 2.

Table 2 The Frequency and Percentage of Personal Background Characteristics of HIV-Infected Patients Receiving HAART (n = 406).

Personal Background Characteristics	Number	Percentage
Sociodemographic data		
Age groups (years)		
20 - 29	84	20.7
30 – 39	201	49.5
40 – 49	104	25.6
50 – 59	14	3.4
60 or over	3	0.7
(Range 20 – 68, Mean = 35.9, SD = 7.5)		
Gender		
Male	240	59.1
Female	166	40.9
Education (years)		
Uneducated	3	0.7
Elementary Education	105	25.9
Junior High School	81	20
Senior High School	67	16.5
Certificate in Vocational Education	39	9.6
Higher Certificate in Vocational Education	30	7.4
Diploma	10	2.5
Bachelor's Degree	67	16.5
Master Degree	1	0.2
(Range 0 – 18, Mean = 10.7, SD = 3.7)		

Table 2 The Frequency and Percentage of Personal Background Characteristics of HIV-Infected Patients Receiving HAART (n = 406) (continued).

Personal Background Characteristics	Number	Percentage
Occupation		
Civil Service/State Enterprise	46	11.3
Company Employee	40	9.9
Merchant	73	18
Agriculturist	14	3.4
Employee	95	23.4
Household worker	107	26.4
Student	5	1.2
Monk	2	0.5
Others	24	5.9
Income/Month (Bahts)		
None	73	18
3,000 or less	62	15.3
3,001 – 6,000	101	24.9
6,001 – 10,000	94	23.2
> 10,000	76	18.7
(Range 0-66,000, Mean = 7,453.4, SD = 8,551.1)		
Side effects of HAART		
None	163	40.1
Had at least one side effects	243	59.9
Characteristics of side effects		
Rash	61	15
Nausea/Vomiting	62	15.3
Headache/Dizziness	62	15.3
Diarrhea/Stomachache	29	7.1
Peripheral Neuropathy	117	28.8

Table 2 The Frequency and Percentage of Personal Background Characteristics of HIV-Infected Patients Receiving HAART (n = 406) (continued).

Personal Background Characteristics	Number	Percentage
Characteristics of side effects (continued)		
Muscle ache	91	22.4
Jaundice	8	2
Insomnia	64	15.8
Anemia	12	3
Fat redistribution	12	3
Availability of a caregiver (s)		
Yes	348	85.7
No	56	13.8
Disclosure of HIV status		
Yes	382	94.1
No	24	5.9

Knowledge about HIV/AIDS

Knowledge about HIV/AIDS in this study composed of 3 aspects; 1) disease and treatment, 2) antiretroviral medication use, and 3) side effects of antiretroviral medications and management. As shown in Table 3, scores of knowledge of disease and treatment reported by the subjects ranged from 3 to 13 with a mean of 10.4 (79.8%), SD = 1.8, scores of knowledge of antiretroviral medication use ranged from 1 to 12 with a mean of 8.5 (70.5%), SD = 2.1, and scores of side effects of antiretroviral medications and management ranged from 2 to 13 with a mean of 9.6 (70.4%), SD = 2.5. The overall knowledge scores ranged from 11 to 38 with a mean of 28.5 (74.9 %), SD = 4.9 indicating that the subjects in this study had moderate knowledge about HIV/AIDS. Although the subjects demonstrated to have fairly good knowledge about AIDS and treatment, they appeared to have poorer knowledge regarding antiretroviral medication as well as side effects of antiretroviral medications and management.

Table 3 Range, Mean, and Standard Deviation of Knowledge about HIV/AIDS
(n =406)

Variables	Possible Range	Actual Range	M	S.D.
Knowledge about HIV/AIDS				
- Disease and treatment	0 – 13	3 - 13	10.4	1.8
- Antiretroviral medication use	0 – 12	1 - 12	8.5	2.1
- Side effects of antiretroviral medications and management	0 – 13	2 - 13	9.6	2.5
Overall Knowledge	0 - 38	11 - 38	28.5	4.9

Social support

In this study, social support composed of 4 subscales: 1) emotional support, 2) appraisal support, 3) informational support, and 4) instrumental support. As displayed in Table 4, scores of emotional support ranged from 31 to 70 with a mean of 55.5 (79.3%), SD = 8.1; appraisal support ranged from 14 to 70 with a mean of 57.3 (81.9%), SD = 10.2; informational support ranged from 26 to 70 with a mean of 54.1 (77.3%), SD = 9.3 and instrumental support ranged from 20 to 65 with a mean of 46.3 (71.2%), SD = 9.9. The overall scores of social support ranged from 122 to 270 with a mean of 213.4 (77.6%), SD = 26.3. Apparently, the percentages of the mean scores of appraisal support (81.9%), emotional support (79.3%), and informational support (77.3%) were moderately good, while instrumental support was poorer (71.2%). This implied that subjects in this study had moderate social support (77.6 % overall social support).

Table 4 Range, Mean, and Standard Deviation of Social support (n = 406)

Variables	Possible Range	Actual Range	M	S.D.
Social support				
-Emotional support	14 - 70	31 – 70	55.5	8.1
-Appraisal support	14 - 70	14 – 70	57.3	10.2
-Informational support	14 - 70	26 – 70	54.1	9.3
-Instrumental support	13 - 65	20 – 65	46.3	9.9
Overall Social support	55 - 275	122 - 270	213.4	26.3

Medication adherence

Medication adherence scores among patients receiving HAART ranged from 27.5 to 100 with a mean of 96.3 (SD = 8.4). About 79.8 % of the subjects adhered to their medication at 95% or better, while the rest adhered to their medication poorer as shown in Table 5.

Table 5 Medication Adherence (n = 406)

Variable	Number	Percentage
Medication adherence		
Good Adherence ($\geq 95\%$)	324	79.8
Poor Adherence ($< 95\%$)	82	20.2

(Range 27.5-100, Mean = 96.3, SD = 8.4)

Part II: The results of hypothesis testing**The Relationships between Personal Background Characteristics, Knowledge about HIV/AIDS, Social Support, and Medication Adherence**

In response to the hypothesis 1 “There were significant relationships between medication adherence and personal background characteristics (sociodemographic data, side effects of HAART, availability of a caregiver(s), and disclosure of HIV

status), knowledge about HIV/AIDS, and social support among patients receiving HAART", it was found that having education ($r = -.136$, $p < .01$) and occupation ($r = -.116$, $p < .05$) were inversely related with medication adherence, and social support was positively related with medication adherence in terms of emotional support ($r = .136$, $p < .01$), appraisal support ($r = .153$, $p < .01$), informational support ($r = .140$, $p < .01$), and instrumental support ($r = .137$, $p < .01$). In bivariate analysis, knowledge about HIV/AIDS and other personal background characteristics did not have a significant relationship with medication adherence as illustrated in Table 6.

Table 6 Relationships between Medication Adherence and Personal Background Characteristics, Knowledge about AIDS, and Social support (n = 406)

Variables	r
Age	.087
Gender	.014
Education (years)	-.136**
Occupation	-.116*
Income	-.096
Side effects of HAART	-.081
Availability of a caregiver (s)	.019
Disclosure of HIV status	-.065
Overall Knowledge about HIV/AIDS	.011
- Disease and treatment	-.033
- Antiretroviral medication use	-.024
- Side effects of ARV medications and management	.072
Overall Social support	.202**
- Emotional support	.136**
- Appraisal support	.153**

Table 6 Relationships between Medication Adherence and Personal Background Characteristics, Knowledge about AIDS, and Social support (n = 406) (continued).

Variables	r
	.140**
- Informational support	.137**
- Instrumental support	

* P< .05; ** P< .01; Gender 0 = female, 1 = male; Occupation 0 = household workers, 1 = others; side effects 0 = none, 1 = had at least one side effects; Availability of a caregiver (s) 0 = no, 1 = yes; Disclosure of HIV status 0 = no, 1 = yes

In response to the hypothesis 2 “Background characteristics (sociodemographic data, side effects of HAART, availability of a caregiver(s), and disclosure of HIV status), knowledge about HIV/AIDS, and social support significantly contribute to the prediction of medication adherence among patients receiving HAART”, correlations among all independent variables were tested prior to multiple regression analysis. It was revealed that these correlations were mild to moderate (from - .003 to - .203, and from .005 to .479) as shown in Table 7. Therefore, all of these independent variables were included in multiple regression analysis by using a stepwise method.

Table 7 Correlation among variables (n = 406)

Measure	1	2	3	4	5	6	7	8	9	10
1. Age	1.000									
2. Gender	.075	1.000								
3. Education (years)	-.040	.092	1.000							
4. Occupation	.005	.196**	.163**	1.000						
5. Income	.058	.145**	.277**	.370**	1.000					
6. Side effects of HAART	-.021	.055	-.020	-.022	-.053	1.000				
7. Availability of a caregiver	.009	.068	.073	-.203**	-.060	.037	1.000			
8. Disclosure of HIV status	-.034	-.039	-.010	.088	-.013	-.014	-.003	1.000		
9. Knowledge about HIV/AIDS	.014	-.035	.242**	.053	.093	.058	-.032	-.007	1.000	
10. Social support	-.053	.070	.012	.079	.134**	-.004	.479**	.103*	.011	1.000

* $P < .05$; ** $P < .01$; Gender 0 = female, 1 = male; Occupation 0 = household workers, 1 = others; side effects 0 = none, 1 = had at least one side effects; Availability of a caregiver (s) 0 = no, 1 = yes; Disclosure of HIV status 0 = no, 1 = yes

Table 8. Factors Predicting Medication Adherence among Patients Receiving HAART From a Stepwise Multiple Regression Analysis (n = 399*).

Variables	R Square	R Square change	B	t	p
1. Social support	.041	.041	.072	4.591	.000
2. Income	.057	.016	.000	-2.745	.006
3. Age	.069	.012	.121	2.205	.028
Constant 77.749, Overall $F_{(3, 395)} = 9.610$, $p < .001$					

Gender 0 = female, 1 = male; Occupation 0 = household workers, 1 = others; side effects 0 = none, 1 = had at least one side effects; Availability of a caregiver (s) 0 = no, 1 = yes; Disclosure of HIV status 0 = no, 1 = yes, * There are 7 patients had missing data in some of independent variables.

In order to test autocorrelations, Durbin-Watson test was performed. This regression model revealed Dubin-Watson test statistics of 2.061 which indicated none autocorrelations. To test multicollinearity among dependent variables, collinearity

statistics was calculated. It was shown that tolerance values of social support, income, and age were .978, .977, and .992 respectively. When tolerance values closed to one, multicollinearity was not a problem in this multiple regression analysis although some dependent variables had mild to moderate correlations as shown in Table 8.

From a stepwise multiple regression analysis, only 3 variables – social support, income, and age were able to contribute to the prediction of medication adherence. Social support, the first variable entered the model, explained 4.1 percent of variance in the total medication adherence. Income, the second variable entered the model additionally explained 1.6 percent. The last variable entered the model was age which helped to explain additional 1.2 percent. The final model could explain 6.9 percent of variance in the total medication adherence ($F_{(3, 395)} = 9.610, p < .001$), as presented in Table 8.

CHAPTER V

DISCUSSION

This cross-sectional study was conducted to explore the relationship between personal background characteristic, knowledge about HIV/AIDS, social support, and medication adherence among patients receiving HAART. A sample composed of 406 patients receiving HAART who came for a follow up visit at out patient department or ambulatory care unit at Bamrasnaradura Infectious Disease Institute. There were two hypotheses: (1) to examine relationships between medication adherence and personal background characteristics (demographic data, side effect of antiretroviral medications, caregiver, and disclosure of HIV status), knowledge about HIV/AIDS, and social support among patients receiving HAART; (2) to examine factors that contribute to the prediction of medication adherence among patients receiving HAART. Descriptive and inferential statistics were used to analyze the data. In bivariate analysis, it was demonstrated that education, occupation, social support were significantly related to medication adherence. Additionally, in multiple regression analysis, it was found that social support, income, and age are incorporated predictors of medication adherence among patients receiving HAART. This chapter presents a discussion of personal background characteristics and the results in responding to each hypothesis.

Personal Background Characteristics

In this study, the 406 subjects consisted of 240 male (59.1%) and 166 female (40.9%), with the average age of 35.9 (SD = 7.5) years old and a range between 20 to 68 years old. More than a half of the subjects (70.2%) were young adults: 20 – 29 years old (20.7%) and 30 – 39 years old (49.5%). Subjects were with different education – elementary (25.9%), junior high school (20%), senior high school (16.5%) and bachelor's degree (16.5%). Concerning occupation, 107 of the subjects were household workers wives (26.4%), 95 general employees (23.4%) and 73 merchants

(18%). Their income ranged from 0 to 66,000 Bahts per month with a means of 7,453 Bahts (SD = 8,551.1).

For gender, the subjects in this study consisted of 240 male (59.1%) and 166 female (40.9%). This finding was slightly different from the data reported by the Ministry of Public Health that most AIDS/HIV patients during 1985 - 2004 were male 71.79% and female 28.21% (<http://epid.moph.go.th>). Considering the age characteristic, more than a half of the subjects (70.2%) were young adults: 20 – 29 years old (20.7%) and 30 – 39 years old (49.5%). This finding was in correspondence with the report given by the Ministry of Public Health that most AIDS/HIV patients during 1985 - 2004 were in the working-age group of 20 – 39 years old: 20 – 29 years old (34.95%), and 30 – 39 years old (42.13 %) (<http://epid.moph.go.th>). It was, therefore, likely that most of the HIV/AIDS patients in this study were similar to those in the national report. In terms of occupation, most of the subjects in this study were household workers (Unemployed) (26.4%), 95 employee (23.4%) and 73 merchant (18%). This was different from the report by the Ministry of Public Health during 1985 - 2004 that AIDS/HIV patients were mostly general employees (44.19%), agriculturalists (20.72%), unemployed (9.17%), and merchants (4.38%) (<http://epid.moph.go.th>). There is no statistical report on education and income level of the patients with AIDS/HIV by the Ministry of Public Health during. No comparison can be made on these aspects. However, it was noticed that about a quarter of the subjects finished elementary school (25.9%). This information will be useful in planning intervention for patients receiving HAART in Thailand.

In regard to side effects, the three most frequently - reported side effects of HAART found in this study were peripheral neuropathy (117 = 28.8%), muscle ache (91=22.4%) and isomnia (64 = 15.8%). These side effects are commonly caused by antiretroviral medications that are availability in Thailand. Ammassari and colleagues (2001) found that the following side effects at different degrees were reported: highest frequencies for anxiety (30%), fatigue (24%), abnormal fat accumulation (19%), diarrhea (17%), nausea (16%), anorexia (11%), and insomnia (10%). Spire and colleagues (2002) reported that during the last 4 weeks, the most often quoted symptoms were fatigue (56.5%), diarrhea (45.6%) and abdominal pain (37.3%). Fumaz and colleagues (2002) found that the patients who used efavirenz reported the

following side effects at week 4: dizziness (66%), abnormal dreaming (48%), light-headedness (37%), and difficulty sleeping (35%). The others who used protease inhibitors reported the following at week 4: light-headedness (8%), dizziness (5%), difficulty sleeping (4%), nervousness (4%), and headaches (3%). They also found that the side effects at weeks 24 were decreased in these patients: dizziness (13%; $p < .001$), abnormal dreaming (18%; $p < .002$), light-headedness (13%; $p < .01$), difficulty sleeping (7%; $p < .001$), and nervousness (13%; $p < .01$), while irritability, abnormal dreaming, and nervousness persisted at weeks 48 (13%, 10%, and 8%, respectively). Therefore, side effects among these patients should be assessed and monitored. Additionally, knowledge about side effects of HAART should be provided to these patients.

In this study, the majority of the subjects disclosed their HIV status to someone in their family, relatives, or friends (94.1%). The patients who disclosed HIV status to their family or some significant others i.e. their relatives, or friends had benefit of having a caregiver (s) at some degree. Murphy and colleagues (2000) found that 16% of HIV-infected patients with HAART who found disclosing HIV status to family / friends / co-workers – no need for privacy was helpful in taking their medications. In a study of Chandra and colleagues (2003) found that, voluntary disclosure was noted in 65% of the subjects. Of those who disclosed, 78% of the subjects reported self-disclosure to family members, 7% to friends and 15% exclusively to health professionals. Expectations of emotional and material support from the family members were one of the common reasons given for voluntary disclosure. Stigma, fear of discrimination, disgrace to family and self and futility were reported as the main reasons for non-disclosure. The majority of the subjects (73%) reported anticipation of negative societal reaction as the main concern following disclosure.

The majority of the subjects in this study reported availability of a caregiver (s) (85.7%). Fukfon (2001) found that caregivers served as an integral part of continuity of care for HIV/AIDS patients at home. They were very important in helping or providing care for HIV/AIDS patients (Daud, 1983; Nuttachaipun, 1996; Stewart, et al., 1995; Theis, et al., 1997). Bunrung (1999) found that caregiver were necessary to provide continuous biological, psychological and social care for HIV/AIDS patients. According to Williams (2001), family members and significant others can provide

great support in the patient's adherence to the medication regimen by incorporating it into the routines of shared domesticity; those without such support often struggle alone.

The possible scores of knowledge about HIV/ AIDS ranged from 0 to 38. This study found that the scores of overall knowledge about HIV/AIDS reported by the subjects was moderate ranging from 11 to 38 with a mean score of 28.5 (S.D. = 4.9). Knowledge about HIV/AIDS includes: 1) knowledge about disease and Treatment reported by the subjects ranged from 3 to 13 with a mean score of 10.4 (SD = 1.8), 2) knowledge about antiretroviral medication use reported by the subjects ranged from 1 to 12 with a mean score of 8.5 (SD = 2.1), 3) knowledge about side effect of antiretroviral medications and management reported by the subjects ranged from 2 to 13 with a mean score of 9.6 (SD = 2.5). This study found that the patients had fairly good knowledge about HIV/AIDS in term of disease and treatment, but poorer in terms of antiretroviral medication, side effects and management of these side effects.

Several studies have found that knowledge about HIV disease and therapy significantly associated with nonadherence. Knowledge about HIV disease and HAART regimens may influence adherence (Eldred, et al.: 1998; Wagner, et al.: 2002). Poor adherence may promote viral resistance and treatment failures have been shown to affect patients' ability to adhere to their medication (Wagner, et al.: 2002). Roberts (2000) found that patient's inadequate knowledge was a main barrier to adhere to medication.

In this study, the possible scores of social support ranged from 55 to 275. The mean of overall social support scores was moderate ranging from 122 to 270 with a mean of 213.4 (SD = 26.3). Social support composed of 4 subscales: 1) emotional support (mean = 55.5; SD = 8.1), 2) appraisal support (mean = 57.3; SD = 10.2), 3) informational support (mean = 54.1; SD = 9.2), and 4) instrumental support (mean = 46.3; SD = 9.9). Apparently, the percentages of the mean scores of appraisal support (81.9%), emotional support (79.3%), and informational support (77.3%) were moderately good, while instrumental support was poorer (71.2%). This implied that subjects in this study had moderate social support (77.6 % overall social support).

Medication adherence scores among patients receiving HAART ranged from 27.5 to 100 with a mean of 96.3 (SD = 8.4). These subjects apparently had good medication adherence. However, about 79.8 % of the subjects adhered to their medication at 95% or higher, while the rest adhered to their medication at lower than 95%. That means there were about 20% of the subjects still had suboptimal adherence which may promote viral resistance and treatment failure. In other studies, a mean of medication adherence obtained from self-report using a 30-day recall by a visual analog scale was 70.6% (Liechty, et al., 2004), 93.3% (Walsh et al., 2002), and 93.5% (Oyugi, et al., 2004). Median medication adherence by a pill-count was 65%. One-third (31%) had low adherence ($\leq 50\%$); half (49%) had moderate adherence (51–90%); and 20% had high adherence ($> 90\%$) (Bangsberg et al., 2001).

Furthermore, Mannerheimer and colleagues (2002) used a 7-day recall of medication adherence and found that 74% of the cohort reported 100% medication adherence at 1 month, 68% at 4 months, 65% at 8 months, and 67% at 12 months. A similar pattern was seen among the cohort of participants who completed 12 months of follow-up, with 100% adherence being reported by 76% of the cohort at 1 month, 66% at 4 months, 66% at 8 months, and 67% at 12 months. There was a significant difference ($p < .001$) in adherence scores noted between follow-up at 1 and 4 months. Mean adherence scores were 89% at 1 month of follow-up, 86% at 4 months, 85% at 8 months, and 85% at 12 months. Similar to the study of Howard and colleagues (2002) found that the mean monthly adherence rate was 64%, 55%, 52%, 49%, 47%, and 45% during the first, second, third, fourth, fifth, and sixth month of observation, respectively.

Results in Responding to Each Hypothesis

Hypothesis I: There were significant relationships between medication adherence and personal background characteristics (sociodemographic data, side effect of HAART, availability of a caregiver(s), and disclosure of HIV status), knowledge about HIV/AIDS, and social support among patients receiving HAART.

In bivariate analysis, this study found that age and medication adherence was not significantly related ($r = .087$; $p > .05$). In contrast, Stone and colleagues (2001) found that younger-age HIV-infected patients were associated with a reduced

likelihood of skipping doses antiretroviral medication while others found that age was significantly associated with adherence, increased age predicted better adherence (Ammassari, et al., 2001; Andreo, et al., 2001; Fogarty, et al., 2002; Gordillo, et al., 1999; Hinkin, et al., 2002; Howard, et al., 2002; Klosinski & Brooks, 1998 cited in Chesney, et al., 1999; Mannerheimer, et al., 2000; Mannheimer, et al., 2002; Schectman, et al., 2002; Spire, et al., 2002; Tuldra, et al., 2000).

For gender, a non significant relationship between gender and medication adherence was found in this study ($r = .014$; $p > .05$). This was similar to several studies which found that gender was not consistently related to adherence (Fogarty, et al., 2002; Klosinski & Brooks, 1998; Hirschhorn, et al., 1998; Weidle, et al. cited in Chesney, et al., 1999). However, many studies found that female patients receiving HAART also presented somewhat more significant adherence than male (Ohmit, et al., 1998 cited in Chesney, et al., 1999; Rumakom, 2001; Vincke & Bolton, 2002).

This study showed a significant relationship between education and medication adherence ($r = -.136$; $p < .01$). This was similar to several studies which found that subjects with low level of education had the worst adherence, whereas individuals with a university degree had the best medication adherence (Gifford, et al., 2000; Golin, et al., 2002; Gordillo, et al., 1999; Wagner, et al.: 2002).

This study revealed that having an occupation was inversely related with medication adherence ($r = -.116$, $p < .05$) which was similar to Pattana Phokaew's finding (BE 2537) which found that the adherence to tuberculosis treatment among the unemployed patients with HIV infection was significantly better ($p = 0.05$). In other words, the medication adherence of the patients who household workers or unemployed was significantly better than that of the employed patients. For this study, there are several reasons that unemployment has led to better medication adherence. First, unemployed patients may have more time to stay home, so they might have more time taking care of themselves. Secondly, unemployed patients may stay home, so family can take closer care of them. In this case, they would be better able to follow their medication regimens. For the employed patients, they may have more work responsibilities that might prevent or disturb them from strictly following the regimens. Whenever they take their medication, they may be afraid that other people

or the co-workers might know about their HIV status, so they sometimes have to delay or skip their medication.

In contrast, other studies reflected different findings that the patients who had a job were associated with better adherence (Gordillo, et al. 1999), and unemployment among HIV – infected patients had a positive significant association with medication non-adherence (Ammassari, et al., 2001). These may be explained that the patients who were employed had money to buy medication.

Concerning income, a non-significant relationship between income and medication adherence was detected in this study ($r = -.096$; $p > .05$). Contrary to this, Pattana Phokaew (BE 2537) found that income per month had a significant positive relationship with patient's adherence to tuberculosis treatment of patients with HIV infection ($p = 0.05$) while Brigido and colleagues (2001) found that HIV-infected patients who were receiving antiretroviral therapy but lacked the money for transportation to obtain medication were significantly associated with non-adherence. Similarly, Golin and colleagues (2002) found that lower income was independently associated with worse adherence in ARV of 140 HIV-infected patients.

Another important characteristic, side effects of medication usage, was found to have a non-significant relationship with medication adherence ($r = -.081$; $p > .05$). However, other studies reflected different finding that moderate/severe symptom or medication side effects were significantly associated with non-adherence (Altice, et al., 2001; Ammassari, et al., 2001; Bassetti, et al., 1999; Catz, et al., 2000; Simoni, et al., 2002; Spire, et al., 2002).

In this study, availability of a caregiver (s) revealed a non significant relationship with medication adherence ($r = .019$; $p > .05$). Family members and significant others can provide great support to help with the patient's medication adherence by incorporating it into the routines of shared domesticity; those without such support often struggle alone (Williams, 2001).

In terms of disclosure of HIV status, a non significant relationship between disclosure of HIV status and medication adherence was found in this study ($r = -.065$; $p > .05$). On the contrary, the importance of disclosure of HIV disease in perinatally infected patients was found to be related directly to medication adherence. (Lee & Johann-Liang, 1999: <http://gateway2.ovid.com/ovidweb.cgi>). About 16% of patients

with HAART found disclosing HIV status to family / friends / co-workers – no need for privacy was helpful in taking their medications (Murphy et al., 2000). While, 4.1% of the patients reported not “disclosed their treatment to anyone one” as one of the main reasons for non-adherence (Mukabutera et al., 2004).

In the review of the medication adherence studies by Chesney and colleagues (1999), it was also suggested that demographic characteristic was not consistently related to medication adherence (Davis, et al., 1997; Eldred, et al., 1997 cited in Chesney, et al., 1999). The following would be additional discussion on individual characteristics other than personal background characteristics.

Concerning knowledge, a non-significant relationship between knowledge about HIV/AIDS and medication adherence was found in this study ($r = .011$, $p > .05$). This was on contrary to other findings that knowledge about HIV and HAART regimens might influence medication adherence (Eldred, et al., 1998; Martinez, et. al, 2000; Murdaugh, 1998; Pattana Phokaew, BE 2537; Robert, 2000; Wagner, et al., 2002; Williams, 2001). Approximately 30% of patients on combination therapy reported that the complexity of the regimen and a lack of knowledge about the reason for the drug are associated with non-adherence (Eldred et al., 1997 cited in Chesney et al., 1999).

A study medication adherence in HIV-infected patients who received antiretroviral therapy by Mathews and colleagues (2002), measured medication adherence by (1) MEMS therapeutic coverage, (2) MEMS adherence, and (3) self-reported adherence. All results indicated that high knowledge of antiretroviral therapy drug classes, knowledge of tests of antiretroviral therapy effectiveness, belief that HIV medications were significantly independent predictors of better adherence. Similarly, Williams (2001: 40) stated that patients who understood how their medications helped them were more likely to adhere to their regimens. Mathew and colleagues (2002) found that knowledge of tests of antiretroviral therapy effectiveness independently predicted better adherence from self-reported adherence. For MEMS adherence and MEMS therapeutic coverage found that high knowledge of antiretroviral therapy drugs class independently predicted better adherence. Eldred and colleagues (1998) found that knowledge of antiretroviral therapy action was associated with antiretroviral therapy adherence.

Pattana Phokaew (BE2537) found that knowledge was significantly positive related to patients compliance on treatment of tuberculosis in the patients with HIV/AIDS. Similarly, Roberts (2000) found that inadequate knowledge was one of the five main barriers to adhere to antiretroviral regimens of medications in HIV-positive patients.

Martinez and colleagues (2000) found that knowledge of medication schedule was significantly associated with adherence to antiretroviral drugs and that of their side effects was found to be a major factor in adherence (Murdaugh, 1998: 361). Wagner and colleagues (2002) found that higher adherence was associated with greater knowledge of HIV treatment and consequences of poor adherence. Knowledge about medications' impact on each patient's clinical markers can also be a powerful motivating tool for medication adherence (Williams, 2001: 40).

Although a significant relationship between knowledge about HIV/AIDS and medication adherence was not detected, informational support ($r = .140$; $p < .01$) was found to have a significant relationship to medication adherence as well as emotional support ($r = .136$; $p < .01$), appraisal support ($r = .153$; $p < .01$), and instrumental support ($r = .137$; $p < .01$). Overall social support was also significantly related with medication adherence ($r = .202$, $p < .01$). This finding was in agreement with others that social support significantly associated with medication adherence in patients receiving HARRT (Catz, et al., 2000; Clark & Becker, 1998; Frank, 2002; Gifford, et al., 2000; Gordillo, et al., 1999; Martinez, et al., 2000; Simoni, et al., 1999; Simoni, et al., 2002; Singh, et al., 2000; Spire, et al., 2002). As Mannheimer and colleagues (2002) and Maneesriwongul and colleagues (2003) revealed that the most frequently-reported reason for missing doses was "I forget to take a pills", appraisal support which found to have the strongest relationship to medication adherence in this study should have been a very important factor in enhancing medication adherence among patients receiving HAART.

In contrast with this, one research result stated that there were no significant relationships between measures of social support and measures of adherence (Ncama, et al. 2004). However, emotional support and a trusting social environment in which to discuss HIV/AIDS were unmet needs. The perception of social support was more important than the actual number of people available in the social support system. The

majority of participants stated that family members provided more support than friends. However, participants actively using drugs suggested that friends provided more support than family. Of major concern to participants was family ability to carry on if they became sicker and family having the availability of the needed resources to continue being supportive. Of all, perceived social support appeared to be particularly important to women (Edwards, 2004).

Hypothesis II: Background characteristics (sociodemographic data, side effect of HAART, availability of a caregiver (s), and disclosure of HIV status), knowledge about HIV/AIDS, and social support significantly contribute to the prediction of medication adherence among patients receiving HAART.

In response to the second hypothesis, the result revealed that 3 of 10 variables: social, income, and age were significant incorporated predictors of medication adherence. Among these, social support was the most dominant predictor (4.1%, $p < .000$) firstly entered the model, followed by income (1.6%; $p < .006$), and age (1.2%, $p < .028$). This equation model explained approximately 6.9 percent of the total variances ($p < .001$) in medication adherence.

Stone and colleagues (2001) found that younger-age HIV-infected patients were associated with a reduced likelihood of skipping doses antiretroviral medication while others found that age was significantly associated with adherence, increased age predicted better adherence (Ammassari, et al., 2001; Andreo, et al., 2001; Fogarty, et al., 2002; Gordillo, et al., 1999; Hinkin, et al., 2002; Howard, et al., 2002; Klosinski & Brooks, 1998 cited in Chesney, et al., 1999; Mannerheimer, et al., 2000; Mannheimer, et al., 2002; Schectman, et al., 2002; Spire, et al., 2002; Tuldra, et al., 2000). A reason for the patients with lower income in this study to be able to have better medication adherence may due to two free medication programs: Access to Care (ATC) and National Access to Antiretroviral Program for persons with HIV/AIDS (NAPHA). Through these programs, patients can receive free antiretroviral medication with low expense for CD4 + count and viral load investigation. It was obvious that social support played a significant role in enhancing medication adherence, possibly in a way that the patients felt safe to talk about the effects of medication and gained positive feedback/encouragement that helped to keep them strict to the medication

regimens. Moreover, some other forms of support like information on how to, equipment / facilities, and attentive listeners helped raise their spirit/will in fighting against the suffering disease. On the contrary, patients without any kind of or fewer social supports might feel like having the 'death sentence' and tend to give up to follow the treatment regimens more easily.

According to Frank (2004), categories of factors investigated as predictors of adherence included treatment regimen, medication side-effects, institutional resources, socio-demographic factors, psychosocial factors, as well as personal attributes and beliefs of HIV positive individuals. Substance abuse problems, younger age, minority group status, and complexity of the treatment regimen were identified as statistically significant factors associated with poorer adherence.

It was suggested that high knowledge of antiretroviral therapy drug classes were significant independent predictors of better adherence. Predictors of adherence, which is varied by adherence measures, also included: gender, race, prior antiretroviral therapy experience, substance abuse, prior adherence behavior, health beliefs, and pharmacist prediction of adherence (Mathew et al., 2002). Other suggestions were that complex associations of health, psychosocial and lifestyle variables predicting adherence and sexual risk were found; drug use, anxiety, social support, self-efficacy and health status were differentially associated with HAART adherence/safer sex status (Remien et al., 2004 //aids2004); social predictors of adherence included: spirituality, young children, and supportive family (Edwards, 2004).

Limitation of the Study

A cross-sectional design was conducted for this study to explore relationships between personal background characteristic, knowledge about HIV/AIDS, social support, and medication adherence among patients receiving HAART. Using this design, a conclusion about causal relationship cannot be drawn. This design also has a limitation in making an assessment of changes of medication adherence over-times.

CHAPTER VI

CONCLUSION

Research Conclusion

This cross-sectional study was conducted to explore the relationships between personal background characteristics, knowledge about HIV/AIDS, social support, and medication adherence among 406 patients receiving HAART who came for a follow-up visit at the out patient department and ambulatory care unit at Bamrasnaradura Infectious Disease Institute. Data were collected using questionnaire of four parts – personal background characteristics, medication adherence, knowledge about HIV/AIDS and social support. Descriptive statistics, correlation and stepwise multiple regression were used in data analysis.

In this study found that 434 patients receiving HAART were approached. However, only 406 patients agreed to participate in this study. Three patients who are older than 60 years old were screened for cognitive impairment. All 406 patients met the inclusion criteria for this study. There were 240 male (59.1%) and 166 female (40.9%). Their ages ranged from 20 to 68 years old with a mean of 35.9 (SD = 7.5). More than a half of the subjects were young adults: 20-29 years old (20.7%) and 30-39 years old (49.5%). Subjects were with different education – elementary (25.9%), junior high school (20%) and senior high school (16.5%) and bachelor' s degree (16.5%). Concerning occupation, 107 of the subjects were household workers (26.4%); 95 employees (23.4%) and 73 merchants (18%). Their income ranged from 0 to 66,000 Bahts per month with a mean of 7,453 Bahts (SD = 8,551.12). The three most frequently-reported side effects of HAART were peripheral neuropathy (117 = 28.8%), muscle ache (91=22.4%) and insomnia (64 = 15.8%). The majority of the subjects reported that they had a caregiver (s) availability to remind them about their medication (85.7%) and disclosed their HIV status to someone in their family, relatives, or friends (94.1%).

Knowledge about HIV/AIDS in this study composed of 3 aspects; 1) disease and treatment, 2) antiretroviral medication use, and 3) side effects of antiretroviral

medications and management, scores of knowledge of disease and treatment reported by the subjects ranged from 3 to 13 with a mean of 10.4 (79.8%), SD = 1.8, scores of knowledge of antiretroviral medication use ranged from 1 to 12 with a mean of 8.5 (70.5%), SD = 2.1, and scores of side effects of antiretroviral medications and management ranged from 2 to 13 with a mean of 9.6 (70.4%), SD = 2.5. The overall knowledge scores ranged from 11 to 38 with a mean of 28.5 (74.9 %), SD = 4.9 indicating that the subjects in this study had moderate knowledge about HIV/AIDS. Although the subjects demonstrated to have fairly good knowledge about AIDS and treatment, they appeared to have poorer knowledge regarding antiretroviral medication as well as side effects of antiretroviral medications and management.

Social support composed of 4 subscales: 1) emotional support, 2) appraisal support, 3) informational support, and 4) instrumental support, scores of emotional support ranged from 31 to 70 with a mean of 55.5 (79.3%), SD = 8.1; appraisal support ranged from 14 to 70 with a mean of 57.3 (81.9%), SD = 10.2; informational support ranged from 26 to 70 with a mean of 54.1 (77.3%), SD = 9.3 and instrumental support ranged from 20 to 65 with a mean of 46.3 (71.2%), SD = 9.9. The overall scores of social support ranged from 122 to 270 with a mean of 213.4 (77.6%), SD = 26.3. Apparently, the percentages of the mean scores of appraisal support (81.9%), emotional support (79.3%), and informational support (77.3%) were moderately good, while instrumental support was poorer (71.2%). This implied that subjects in this study had moderate social support (77.6 % overall social support).

From this study, it was found that education and occupation were the only two of all personal background characteristics that had significant relationships to medication adherence, $r = -.136$, $p < .01$; and $r = -.116$, $p < .05$ respectively. While other personal background characteristics did not demonstrate significant relationship. In other words, the patients with lower education had significantly better medication adherence compared to those with higher education. The unemployed patients' medication adherence on HAART was significantly better than that of the employed patients.

There was no significant relationship between knowledge about HIV/AIDS and medication adherence was found, but social support was significantly related to medication adherence ($r = .202$, $p < .01$)

The result also revealed that 3 of 10 variables were significant incorporated predictors of medication adherence. This model explained approximately 6.9 percent of variances ($p < .001$) in medication adherence.

Recommendations for Nursing Action

According to the findings of bivariate analysis, the four aspects of social support – emotional support, appraisal support, informational support and instrumental support were found to have significant relationships with medication adherence. In the prediction equation model, four variables which were appraisal support, occupation, informational support and age were significant predictors of medication adherence.

Therefore, services enhancing the four social support aspects should be adopted as the mainstream in any hospital or primary care unit and a follow-up scheme should be seriously taken into account in monitoring medication adherence among patients receiving HAART. It was found that although the subjects demonstrated to have fairly good knowledge about AIDS and treatment, they appeared to have poorer knowledge regarding antiretroviral medication as well as side effects of antiretroviral medications and management, information about antiretroviral medication, side effects and management of these side effects including the current development of advanced treatment should be provided to well understood level for both the patients and family caregivers involved so that informational and appraisal support can be met and this can hopefully lead to increasing medication adherence.

Recommendations for Future Study

1. Since the subjects for this research were patients from only one institute, Bamrasnaradura Infectious Disease Institute, which is located in Bangkok and specializes in HIV/AIDS, the results may not represent patients in other hospitals of different nature or be generalized to patients receiving HAART in other settings in Thailand. Therefore, this study should be replicated in other types of hospitals or primary care units which are of different natures and locations – both up country and metropolitan so that the result can reflect the over-all nature of HIV/AIDS patients all over the country and be applicable in linking into the national policy to plan for

effective implementations in downscaling the serious effects of HIV/AIDS to treat this disease as a chronic illness.

2. Subjects for this research were patients who came for a follow up visit during official-hour service from 8:00 – 16:00, not including patients during an evening service (16:00 – 20:00). It was more likely that it recruited unemployed patients and those who tended to disclose themselves. Therefore, the sample might under-represent the patients who preferred to come to the evening clinic because of their work responsibility or less willingness to disclose themselves. Therefore, future research should include patients during overtime service period (16:00 – 20:00) in order to involve medication adherence of a wider range of patients receiving HAART, both employed and unemployed.

3. In addition, future research should focus other affective factors to medication adherence, such as disease characteristics, treatment regimen, clinical setting and patient-provider relationship.

4. It should also be important to explore the caregivers' factors affecting medication adherence of patients receiving HAART.

5. Longitudinal study should be also carried out to follow the change over time of medication adherence.

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APPENDIX A

INSTRUMENTS FOR DATA COLLECTION:

Personal Background Characteristics

ส่วนที่ 1. ข้อมูลทั่วไป

คำชี้แจง โปรดเติมข้อความลงในช่อง.... หรือทำเครื่องหมาย ✓ ลงใน () ที่ตรงกับความจริงเกี่ยวกับท่าน

HN.....

1. อายุ.....ปี

2. เพศ

(1) ชาย

(2) หญิง

3. สถานภาพสมรส

(1) โสด

(2) สมรส

(3) หม้าย

(4) หย่า

(5) แยก

4. ระดับการศึกษาที่สำเร็จ

(1) ไม่ได้รับการศึกษา

(2) ประถมศึกษา

(3) มัธยมศึกษาตอนต้น

(4) มัธยมศึกษาตอนปลาย

(5) ปวช.

(6) ปวส.

(7) อนุปริญญา

(8) ปริญญาตรี

(9) ปริญญาโท

(10) ปริญญาเอก

5. อาชีพ

(1) รับราชการ/รัฐวิสาหกิจ

(2) พนักงานบริษัท

(3) ค้าขาย

(4) เกษตรกรรม

(5) รับจ้างทั่วไป

(6) แม่บ้าน/พ่อบ้าน/อยู่บ้านเฉยๆ

(7) นักเรียน/นักศึกษา

(8) อื่นๆ ระบุ.....

6. วิธีชำระค่ารักษา

(1) เบิกได้

----- ชำระการ

----- รัฐวิสาหกิจ

----- ประกันสังคม

----- 30 บาท

(2) เบิกไม่ได้

----- จ่ายเองทั้งหมด

----- จ่ายเองบางส่วน

----- สังคมสงเคราะห์/ช่วยเหลือจาก.....

7. รายได้ต่อเดือนโดยประมาณ.....บาท

8. รายได้ที่ท่าน ได้รับ (1) พอใช้และมีเงินเหลือเก็บ (2) พอใช้แต่ไม่มีเงินเหลือเก็บ
(3) ไม่พอใช้แต่ไม่มีภาระหนี้สิน ระบุวิธีแก้ปัญหา.....
(4) ไม่พอใช้ และมีหนี้สิน
9. บทบาทในครอบครัว (ตอบได้มากกว่า 1 ข้อ)
(1) บิดา (2) มารดา (3) สามี
(4) ภรรยา (5) บุตร (6) อื่นๆ ระบุ.....
10. ทราบว่าติดเชื้อมาเป็นระยะเวลา.....ปี.....เดือน
11. มีโรคฉวยโอกาสอื่นหรือไม่
(1) ไม่มี (2) มี ระบุ.....
12. ใช้จ่ายด้านไวรัสครั้งแรกเมื่อ.....
13. รับประทานยาอื่นด้วยหรือไม่
(1) ไม่ใช่ (2) ใช่ ระบุ.....
14. ใช้จ่ายด้านไวรัสตลอดต่อเนื่องมาเป็นเวลา.....ปี.....เดือน
15. เคยหยุดใช้จ่ายด้านไวรัสเคยสักเป็นระยะหนึ่งหรือไม่ (ถ้าเคย เพราะอะไร).....
(1) เคย (2) ไม่เคย
16. บุคคลที่ท่านบอกให้ทราบว่าติดเชื้อ (ตอบได้มากกว่า 1 ข้อ)
(1) บิดา (2) มารดา (3) สามี
(4) ภรรยา (5) บุตร (6) เพื่อน
(7) อื่นๆ ระบุ.....
17. ท่านเคยใช้ยาเสพติดหรือไม่
(1) ไม่เคยใช้ (2) เคยใช้ปัจจุบันเลิกแล้ว
(3) ปัจจุบันยังใช้อยู่ ระบุชนิด.....
18. ท่านดื่มเครื่องดื่มที่ผสมแอลกอฮอล์หรือไม่ (ถ้าไม่ดื่มไม่ต้องตอบข้อ 19 และ 20)
(1) ไม่เคยดื่ม (2) เคยดื่มปัจจุบันเลิกแล้ว
(3) ปัจจุบันยังดื่มอยู่ ระบุชนิด.....
19. ปริมาณที่ดื่ม.....แก้ว/วัน
20. ความถี่ในการดื่ม (1) ทุกวัน (2) วันเว้นวัน (3) 2-3 วัน/สัปดาห์
(4) 1 วัน/สัปดาห์ (5) อื่นๆ ระบุ.....

21. ยาด้านไวรัสสูตรที่ใช้ในปัจจุบัน

- (1) GPO-VIR (30) 1 Tab q 12 hr. (2) GPO-VIR (40) 1 Tab q 12 hr.
 (3) (4)

22. ผลข้างเคียงที่เกิดจากยาด้านไวรัสเอดส์ ที่เกิดกับท่านในปัจจุบัน (0 = no, 1 = yes)

- (1) ผื่นแดงตามร่างกาย (2) คลื่นไส้ อาเจียน
 (3) ปวดศีรษะ/เวียนศีรษะ (4) ปวดท้อง/ท้องเสีย
 (5) ชาปลายมือปลายเท้า (6) ปวดเมื่อยตามตัว
 (7) ตาตัวเหลือง/ตับอักเสบ (8) นอนไม่หลับ
 (9) ชีด/เลือดน้อย (10) อื่นๆ.....



APPENDIX B
INSTRUMENTS FOR DATA COLLECTION:
Medication Adherence

1. ใน 30 วันที่ผ่านมา ท่านรับประทานยาต้านไวรัสครบทุกเม็ด ทุกมื้อตามเวลาที่กำหนด คิดเป็นกี่เปอร์เซ็นต์ (เช่น จำนวนมื้อทั้งหมด 60 มื้อ ถ้าท่านรับประทานยาครบทุกมื้อภายใน 30 วัน จะคิดเป็น 100 เปอร์เซ็นต์)

2. ใน 30 วันที่ผ่านมา ท่านรับประทานยาต้านไวรัส ครบทุกเม็ด ทุกมื้อตามเวลาที่กำหนด คิดเป็นกี่เปอร์เซ็นต์

0

100

ไม่สม่ำเสมอเลย
(ไม่รับประทานยาเลย)

สม่ำเสมอมากที่สุด
(ไม่เคยขาดแม้แต่เม็ดเดียว)

APPENDIX C
INSTRUMENTS FOR DATA COLLECTION:
Knowledge about HIV/AIDS

ส่วนที่3. ความรู้เกี่ยวกับโรคเอดส์

คำชี้แจง โปรดทำเครื่องหมาย ✓ ลงในช่องว่าตามระดับความเป็นจริง

ข้อ	คำถาม	ระดับความคิดเห็น		
		ใช่	ไม่ใช่	ไม่รู้
1.	ความรู้เกี่ยวกับโรคเอดส์ โรคเอดส์เป็นโรคที่สามารถรักษาให้หายขาดได้ในปัจจุบัน			
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.				
.				
12.	ยาต้านไวรัสเอดส์สามารถรักษาโรคติดเชื้อฉวยโอกาสให้หายได้			
13.	เมื่อได้รับยาต้านไวรัสเอดส์ ไม่จำเป็นต้องป้องกัน/รักษาโรคติดเชื้อฉวยโอกาส อื่นอีก			

ข้อ	คำถาม	ระดับความคิดเห็น		
		ใช่	ไม่ใช่	ไม่รู้
1.	ความรู้เกี่ยวกับการใช้ยาต้านไวรัสเอดส์ ในขณะที่รับประทานยาป้องกัน/รักษาโรคติดเชื้อฉวยโอกาส ผู้ติดเชื้อไม่ควร รับประทานยาต้านไวรัสเอดส์			
.				
.				
11.	การหยุดรับประทานยาต้านไวรัสบางตัว ไม่ทำให้เชื้อไวรัสเอดส์คือยา			
12.	การหยุดรับประทานยาต้านไวรัสเอดส์ในช่วงสั้นๆ ไม่ทำให้เชื้อไวรัสเอดส์คือยา			

ข้อ	คำถาม	ระดับความคิดเห็น		
		ใช่	ไม่ใช่	ไม่รู้
1.	ความรู้เกี่ยวกับผลข้างเคียงของยาและการจัดการต่ออาการข้างเคียงของยา			
.	ผู้ติดเชื้อบางรายที่รับประทานยาต้านไวรัสเอดส์อาจมีอาการข้างเคียงต่างๆ ได้			
.				
.				
12.	ผู้ติดเชื้อสามารถนำตัวอย่างยาต้านไวรัสเอดส์ไปซื้อได้เองจากร้านขายยา โดยไม่จำเป็นต้องมาพบแพทย์			
13.	เมื่อผู้ติดเชื้อที่สามารถดูแลตนเองได้เมื่อมีอาการข้างเคียงซึ่งไม่รุนแรงจากการรับประทานยาต้านไวรัสเอดส์ เช่น คลื่นไส้ อาเจียน อ่อนเพลีย สามารถรับประทานยาต่อไปได้			

APPENDIX D
INSTRUMENTS FOR DATA COLLECTION:
Social Support

ส่วนที่4. แบบวัดการสนับสนุนทางสังคม

คำชี้แจง โปรดทำเครื่องหมาย ✓ ลงในช่องว่างที่ตรงกับความคิดเห็นของท่าน

ข้อ	คำถาม	ระดับความคิดเห็น				
		มั่นใจ ว่าใช่	คิดว่า ใช่	ไม่ แน่ใจ	คิดว่า ไม่ใช่	มั่นใจว่า ไม่ใช่
1.	1.การสนับสนุนทางสังคม ด้านอารมณ์ ท่านรู้สึกว่าคุณค่าของท่านมีคุณค่า					
2.	ท่านรู้สึกว่าตนเองมีความสำคัญในครอบครัว					
.	.					
14.	ญาติพี่น้อง/เพื่อนฝูงที่คอยดูแลไม่เข้าใจท่านหาว่าแก่งหรือ เรียกร้องความสนใจ เมื่อท่านมีอาการไม่สบายหลังกินยาต้าน ไวรัสเอดส์					

ข้อ	คำถาม	ระดับความคิดเห็น				
		มั่นใจ ว่าใช่	คิดว่า ใช่	ไม่ แน่ใจ	คิดว่า ไม่ใช่	มั่นใจว่า ไม่ใช่
1.	2.การสนับสนุนทางสังคมด้านการประเมินเปรียบเทียบ พฤติกรรม ญาติพี่น้อง/เพื่อนที่คอยดูแลเตือนให้ท่านรับประทานยา ต้านไวรัสเอดส์อย่างต่อเนื่อง					
.	.					
.	.					
14.	กลุ่มผู้ติดเชื้อด้วยกันเตือนให้ท่านรับประทานยาต้านไวรัส อย่างสม่ำเสมอ					

ข้อ	คำถาม	ระดับความคิดเห็น				
		มั่นใจ ว่าใช่	คิดว่า ใช่	ไม่ แน่ใจ	คิดว่า ไม่ใช่	มั่นใจว่า ไม่ใช่
1.	3. การสนับสนุนทางสังคมด้านข้อมูลข่าวสาร ท่านได้รับคำแนะนำเกี่ยวกับโรคเอดส์และการปฏิบัติตน จากแพทย์					
2.	ท่านได้รับคำแนะนำเกี่ยวกับโรคเอดส์และการปฏิบัติตน จากพยาบาล					
.						
.						
13.	ท่านได้รับคำแนะนำเกี่ยวกับวิธีบรรเทาอาการข้างเคียงของ ยาต้านไวรัสเอดส์จากพยาบาล					
14.	ท่านได้รับความรู้เกี่ยวกับผลเสียที่เกิดจากการรับประทาน ยาต้านไวรัสเอดส์ไม่สม่ำเสมอ					

ข้อ	คำถาม	ระดับความคิดเห็น				
		มั่นใจ ว่าใช่	คิดว่า ใช่	ไม่ แน่ใจ	คิดว่า ไม่ใช่	มั่นใจว่า ไม่ใช่
1.	4. การสนับสนุนทางสังคมด้านวัสดุสิ่งของ สมาชิกในครอบครัวของท่านให้การช่วยเหลือด้านการเงิน แก่ท่านเสมอ					
.						
.						
.						
12.	ท่านมีที่อยู่อาศัยเป็นหลักแหล่ง					
13.	เมื่อญาติพี่น้อง/เพื่อนที่คอยดูแลต้องไปทำงาน ท่านใช้ บริการดูแลช่วงกลางวันจากสถานบริการของรัฐ					

APPENDIX E

Chula Mental Test (CMT)

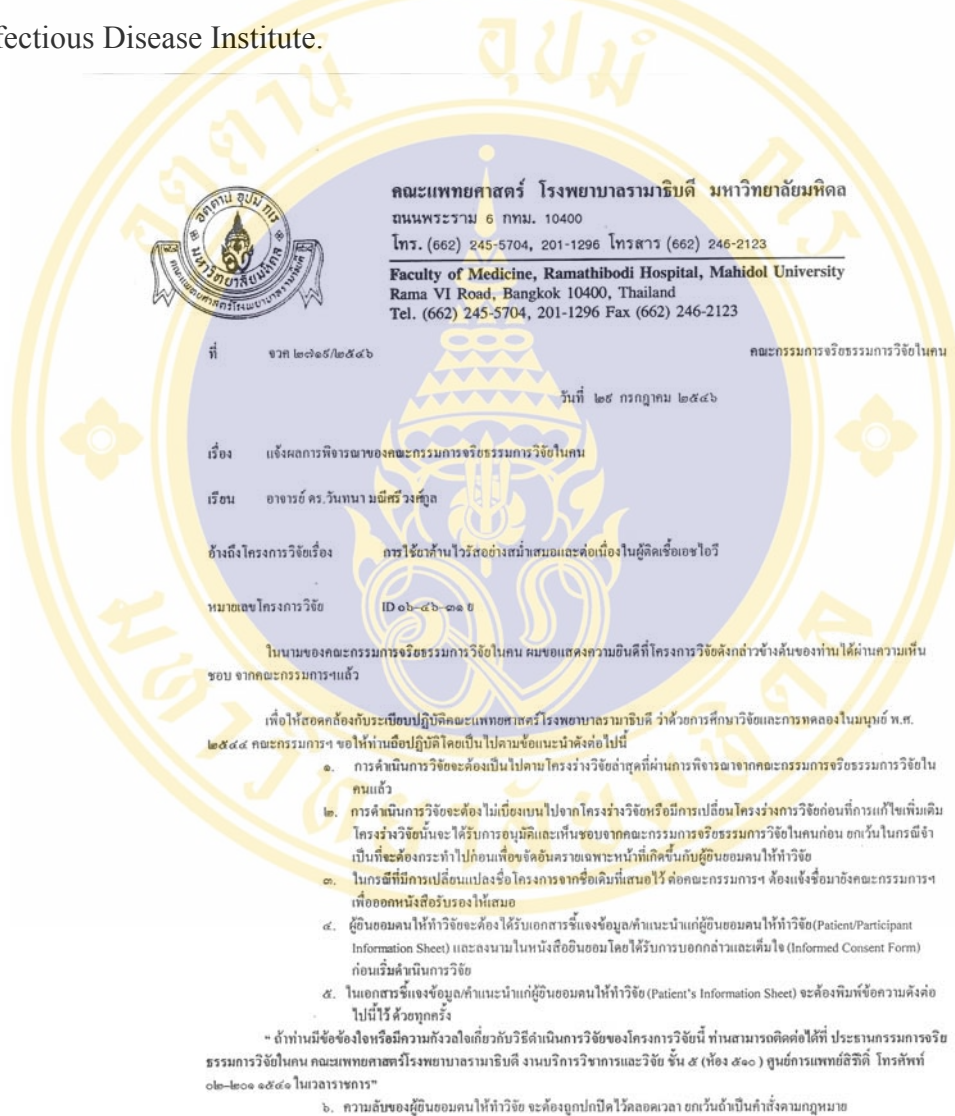
Total score.....

Screening test for cognitive impairment patients who are 60 years old and older used Chula Mental Test. If total score was less than 15, the subject was considered to have cognitive impairment.

No.	Question	Answer	Score
1.	How old are you ?		1/0
2.	What time is it ? (Can error 1 hour)		1/0
3.	Registration of "umbrella, pan and door"	Umbrella Pan Door	1/0 1/0 1/0
4.	What is this month ?		1/0
5.	Who is he/she ? (e.g. doctor, nurse)	Person 1 Person 2	1/0 1/0
6.	How many kilograms are there in one tang of rice ? (Thai measure)	20 litres/15kgs	1/0
7.	Follow command "clap your hands 3 times and then cross your arms"		1/0
8.	Proverb "Nee suea pa cho-ra-ke" (Escape from a tiger and meet a crocodile)		1/0
9.	Repeat "Chan chob dok-mai seang-pleang tae mai chob ma" (I like flowers, music, but not dogs)		1/0
10.	What would you do if you forgot a key to your locked house?		1/0
11.	Count 10 to 20		1/0
12.	What is it ? (watch and pen)	Watch Pen	1/0
13.	Subtract 3 from 20 for 3 times 20-3 = a 17-3 = b 14-3 = c	a = 17 b = 14 c = 11	1/0 1/0 1/0

APPENDIX F

Documentary proof of ethical clearance committee on human right of Faculty of Medicine, Ramathibodi Hospital, Mahidol University and Bamrasnaradura Infectious Disease Institute.



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ที่ จวก ๒๐๖๕/๒๕๕๖ คณะกรรมการจริยธรรมการวิจัยในคน

วันที่ ๒๕ กรกฎาคม ๒๕๕๖

เรื่อง แจ้งผลการพิจารณาของคณะกรรมการจริยธรรมการวิจัยในคน

เรียน อาจารย์ ดร. วันทนาวดี ศรีวงศกุล

อ้างถึงโครงการวิจัยเรื่อง การใช้ผ้ากันไวรัสอย่างสม่ำเสมอและต่อเนื่องในผู้ติดเชื้อเอชไอวี

หมายเลขโครงการวิจัย ID๐๖-๔๖-๓๑๒

ในนามของคณะกรรมการจริยธรรมการวิจัยในคน ผมขอแสดงความยินดีที่โครงการวิจัยดังกล่าวข้างต้นของท่านได้รับความเห็นชอบ จากคณะกรรมการฯ แล้ว

เพื่อให้สอดคล้องกับระเบียบปฏิบัติ คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี ว่าด้วยการศึกษาวิจัยและการทดลองในมนุษย์ พ.ศ. ๒๕๔๔ คณะกรรมการฯ ขอให้ท่านยึดปฏิบัติโดยเป็นไปตามข้อแนะนำดังต่อไปนี้

๑. การดำเนินการวิจัยจะต้องเป็นไปตามโครงการวิจัยสุดท้ายผ่านการพิจารณาจากคณะกรรมการจริยธรรมการวิจัยในคนแล้ว
๒. การดำเนินการวิจัยจะต้องไม่เบี่ยงเบนไปจากโครงการวิจัยหรือมีการเปลี่ยนแปลงโครงการวิจัยก่อนการแก้ไขเพิ่มเติมโครงการวิจัยนั้น จะได้รับการอนุมัติและเห็นชอบจากคณะกรรมการจริยธรรมการวิจัยในคนก่อน ยกเว้นในกรณีจำเป็นที่จะต้องกระทำไปก่อนเพื่อขอจัดสรรงบประมาณหรือเพื่อซื้อวัสดุอุปกรณ์ก่อนดำเนินการวิจัย
๓. ในกรณีที่มีการเปลี่ยนแปลงชื่อโครงการจากชื่อเดิมที่เสนอไว้ ต่อคณะกรรมการฯ ต้องแจ้งชื่อคณะกรรมการฯ เพื่อออกหนังสือรับรองให้เสมอ
๔. ผู้ยินยอมคนให้ทำวิจัยจะต้องได้รับเอกสารชี้แจงข้อมูลคำแนะนำแก่ผู้ยินยอมคนให้ทำวิจัย (Patient/Participant Information Sheet) และลงนามในหนังสือยินยอมโดยได้รับการบอกกล่าวและเต็มใจ (Informed Consent Form) ก่อนเริ่มดำเนินการวิจัย
๕. ในเอกสารชี้แจงข้อมูลคำแนะนำแก่ผู้ยินยอมคนให้ทำวิจัย (Patient's Information Sheet) จะต้องพิมพ์ข้อความดังต่อไปนี้ไว้ด้วยทุกครั้ง

"ถ้าท่านมีข้อสงสัยหรือมีความกังวลเกี่ยวกับวิธีดำเนินการวิจัยของโครงการวิจัยนี้ ท่านสามารถติดต่อได้ที่ ประธานกรรมการจริยธรรมการวิจัยในคน คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี งานบริการวิชาการและวิจัย ชั้น ๕ (ห้อง ๕๑๐) ศูนย์การแพทย์วิถีชีวิต โทรศัทพ์ ๐๒-๒๐๑ ๕๕๕๐ ในเวลาราชการ"

๖. ความลับของผู้ยินยอมคนให้ทำวิจัย จะต้องถูกปกปิดไว้ตลอดเวลา ยกเว้นอันเป็นคำสั่งตามกฎหมาย

สุดท้ายนี้ ขอให้โครงการวิจัยของท่านประสบผลสำเร็จตามความมุ่งหมายอันจะนำมาซึ่งความเจริญก้าวหน้าทางวิชาการ และเพื่อประโยชน์ของมนุษยชาติสืบต่อไป

ขอแสดงความนับถือ



(ศาสตราจารย์ ดร. วุฒนา ศรีวงศกุล)
ประธานกรรมการจริยธรรมการวิจัยในคน



คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล
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Tel. (662) 245-5704, 201-1296 Fax (662) 246-2123

เอกสารรับรองโดยคณะกรรมการจริยธรรมการวิจัยในคน

คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี

มหาวิทยาลัยมหิดล

๐๓๓๓/๒๕๔๖ (I)

ชื่อโครงการ	การใช้อาณัติบัตรอย่างสม่ำเสมอและต่อเนื่องในผู้ติดเชื้อเอชไอวี
เลขที่โครงการ/รหัส	ID ๐๖-๔๖-๓๑ ข
ชื่อหัวหน้าโครงการ	อาจารย์ ดร.วันทนา นิลศรีวงศ์กุล
ที่ทำงาน	ภาควิชาพยาบาลศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

ขอรับรองว่าโครงการดังกล่าวข้างต้นได้ผ่านการพิจารณาเห็นชอบโดยสอดคล้องกับแนวปฏิบัติ
เชิงจริยธรรมจากคณะกรรมการจริยธรรมการวิจัยในคน คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี

ลงนาม

ประธานกรรมการจริยธรรมการวิจัยในคน

(ศาสตราจารย์นายแพทย์กฤษฏา รัตนโอฬาร)

ลงนาม

คณบดีคณะแพทยศาสตร์โรงพยาบาลรามาธิบดี

(ศาสตราจารย์นายแพทย์ประกิจ วาทีสาธกิจ)

วันที่รับรอง

๑๘ มิถุนายน ๒๕๔๖



คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล
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**Documentary Proof of Ethical Clearance Committee on Human Rights
Related to Researches Involving Human Subjects
Faculty of Medicine, Ramathibodi Hospital, Mahidol University**

0377/2003 (I)

Title of Project	Medication Adherence among People Living with HIV
Protocol Number	ID 06-46-31
Principal Investigator	Mrs. Wantana Maneesriwongul
Official Address	Department of Nursing Faculty of Medicine, Ramathibodi Hospital Mahidol University

The aforementioned project has been reviewed and approved by Committee on Human Rights Related to Researches Involving Human Subjects, based on the Declaration of Helsinki.

Signature of Chairman Committee on Human Rights Related to Researches Involving Human Subjects	 Prof. Krisada Ratana-olarn, M.D., FRCST, FICS.
Signature of Dean	 Prof. Prakrit Vathesatogkit, M.D., ABIM., FRCP.
Date of Approval	June 18, 2003

แบบสรุปผลการพิจารณาโครงการวิจัยโรงพยาบาลบาราศณราดูร

1905 FM - REC - 06 - 01

วันที่ 4 ก.ค. 46

เวลา 13.00 น.



แบบสรุปผลการพิจารณาโครงการวิจัยโรงพยาบาลบาราศณราดูร

เลขที่งานวิจัย ว. 19 / 2546 วันที่ 30 มี.ค. 46

เรื่อง การสรุปการพิจารณาโครงการวิจัย

เรียน ผู้อำนวยการ โรงพยาบาลบาราศณราดูร

จากการพิจารณาโครงการวิจัยเรื่อง การศึกษานโยบาย 5 ปี ของ สภ. สบ. และ กอ. สบ.

ในเขตจังหวัดร้อยเอ็ด

ผู้วิจัย ดร. สันติภาพ มณีธรรมวงศ์

มีผลการพิจารณาของคณะกรรมการดังนี้

☒ คณะกรรมการพิจารณาโครงการวิจัย	☒ ผ่านการพิจารณา	☐ ไม่ผ่านการพิจารณา
☐ คณะกรรมการพิจารณาผลประโยชน์งานวิจัย	☐ ผ่านการพิจารณา	☐ ไม่ผ่านการพิจารณา
☒ กลุ่มงานที่เกี่ยวข้อง	☒ ผ่านการพิจารณา	☐ ไม่ผ่านการพิจารณา
☐ สรุปความคิดเห็นอื่นๆ <u>ให้ ผอ. สบ. และ 7 น. ประชุม คณะที่ 1 และ 2</u>		
<u>1. ขอ ให้ ผ. พง. สบ. เป็นประธานในที่ประชุม</u>		

จึงเรียนมาเพื่อโปรดพิจารณา


 (แพทย์หญิงรุจิณี สุนทรขจิต)
 ประธานคณะกรรมการพิจารณาโครงการวิจัย

☒ อนุมัติ ☐ ไม่อนุมัติ
☐ ขอแต่งตั้งอาจารย์ที่ปรึกษา/ผู้ร่วมวิจัย คือ ผอ. สบ. และ 7 น. ประชุม คณะที่ 1 และ 2
☒ อื่นๆ ตามข้อ 1

๑๒๖
 (แพทย์หญิงอรรดา เชาวฉวี)
 ผู้อำนวยการ โรงพยาบาลบาราศณราดูร
 9 ก.ค. 2546

APPENDIX G

Consent of Samples in Research Study

การพิทักษ์สิทธิของกลุ่มตัวอย่าง

ข้าพเจ้านางสาวสมจิตร์ ตูลาทอง นักศึกษาพยาบาลหลักสูตรพยาบาลศาสตรมหาบัณฑิต สาขาการพยาบาลอนามัยชุมชน ภาควิชาพยาบาลศาสตร์ คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล กำลังศึกษาวิจัยเรื่อง “การใช้ยาต้านไวรัสอย่างสม่ำเสมอและต่อเนื่องในผู้ติดเชื้อเอชไอวี” ซึ่งการรับประทานยาต้านไวรัสนั้นจำเป็นจะต้องรับประทานให้ตรงเวลา และต่อเนื่องสม่ำเสมอเพื่อให้ได้ประสิทธิภาพสูงสุดและถ้ารับประทานยาไม่ต่อเนื่องจะทำให้เชื้อมีชีวิต เมื่อเชื้อมีชีวิตจะทำให้การรักษาด้วยยาต้านไวรัสไม่ได้ผล ข้าพเจ้าขอเชิญท่านเป็นผู้ให้ข้อมูลในการศึกษาครั้งนี้ ผลการศึกษายกเว้นให้พยาบาลและบุคลากรทีมสุขภาพเข้าใจเกี่ยวกับสถานการณ์การใช้ยาต้านของผู้ติดเชื้อเอชไอวี/เอดส์ เพื่อเป็นประโยชน์ในการให้ความช่วยเหลือและดูแลในการรับประทานยาต้านไวรัสของผู้ติดเชื้อเอชไอวี/เอดส์ต่อไป

เมื่อท่านเข้าร่วมในการศึกษา ท่านจะได้รับการสัมภาษณ์ 1 ครั้ง ใช้เวลาประมาณ 30 นาที ในการสัมภาษณ์จะทำที่โรงพยาบาลในห้องที่มีประตูปิดมิดชิด การเข้าร่วมงานวิจัยนี้ ท่านมีสิทธิตอบรับหรือปฏิเสธโดยไม่มีผลกระทบต่อการรักษาของท่านแต่อย่างใด หากท่านยินดีจะให้ความร่วมมือขอให้ท่านลงนามเพื่อแสดงถึงการให้ความร่วมมือในการวิจัย และท่านยังมีสิทธิที่จะยกเลิกการเข้าร่วมหรือยุติการสนทนาเมื่อใดก็ได้ตามที่ท่านต้องการ ข้อมูลจากการสัมภาษณ์จะถูกเก็บเป็นความลับ ไม่มีการเปิดเผยชื่อจริงของท่าน และจะนำเสนอผลการวิจัยแบบภาพรวมเท่านั้น ข้อมูลทั้งหมดจะถูกทำลายเมื่อการศึกษาวิจัยแล้วเสร็จ

ยินดีให้ความร่วมมือในการวิจัย

ขอขอบคุณในความยินดีเป็นผู้ให้ข้อมูลของท่าน

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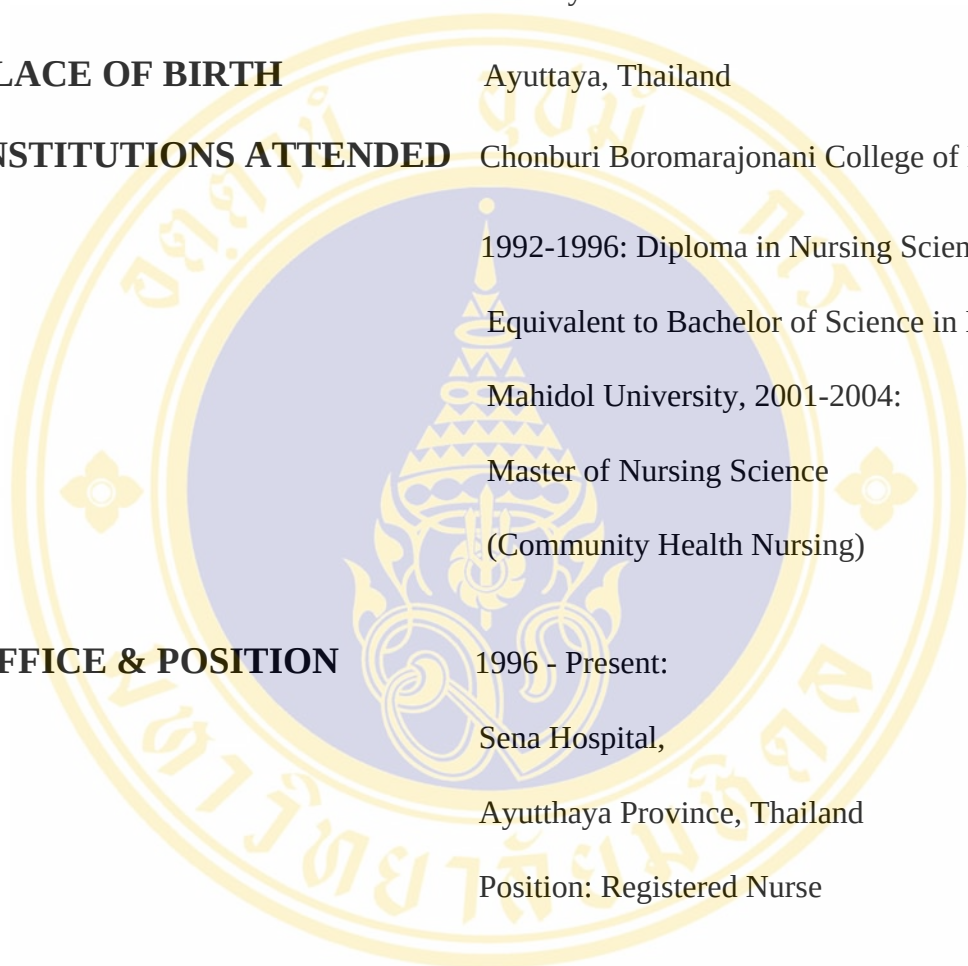
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ผู้ให้ข้อมูล

สมจิตร์ ตูลาทอง

วันที่.....

ผู้วิจัย

BIOGRAPHY

NAME	Miss Somchit Tulathong
DATE OF BIRTH	3 May 1973
PLACE OF BIRTH	Ayuttaya, Thailand
INSTITUTIONS ATTENDED	Chonburi Boromarajonani College of Nursing, 1992-1996: Diploma in Nursing Science Equivalent to Bachelor of Science in Nursing Mahidol University, 2001-2004: Master of Nursing Science (Community Health Nursing)
OFFICE & POSITION	1996 - Present: Sena Hospital, Ayutthaya Province, Thailand Position: Registered Nurse