ADHERENCE TO HIGHLY ACTIVE ANTI-RETROVIRAL TREATMENT (HAART) AND ITS ASSOCIATED FACTORS AMONG HIV-POSITIVE PATIENTS IN SUNGAI BULOH HOSPITAL, MALAYSIA

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Dedication

This work is dedicated in the memory of my parents - my father Yagoub Mohammed and my mother Nafisa Mohammed. To them I am indebted and I do not have words to express my gratitude. I say:

رَبِّ ارْحَمْهُمَا كَمَا رَبَّيَانِي صَغِيرًا

(O my Lord! Have mercy on them both, as they did care for me when I was young)

It is also dedicated to my beloved wife and two sons for their patience, care, love, encouragement and a whole unreserved support during my study.

ABSTRACT

HIV/AIDS is one of the most destructive health diseases of modern times, affecting approximately 45.5 million people worldwide. But the advent of the Highly Active Antiretroviral Therapy (HAART) in 1996 has significantly reduced HIV/AIDS-related mortality and morbidity and it has allowed many previously bed-ridden patients to live healthier and more productive lives. In order for the treatments to be successful, a very high level of adherence to HAART is required. It is estimated that at least 95% adherence to antiretroviral treatment is essential to reduce the replication of the virus and prevent the development of resistance to treatment. Generally, adherence is considered to be a complex clinical behaviour with a wide array of determinants. Thus, the aim of this study is to assess the level of adherence to HAART among HIV/AIDS-positive patients in a major hospital in Malaysia as well as its determinants.

Using prospective cohort study design, 925 participants who were on antiretroviral treatment were selected for the purpose of this study. Inclusion and exclusion criteria were also applied. The following three instruments for measuring the level of adherence to HAART were used in this study: self-reported adherence questionnaire, pharmacy refill records and Therapeutic Drug Monitoring (TDM) for testing drug in human plasma. Two blood samples were collected and tested for the presence or absence of three antiretroviral drugs, namely Efavirenz, Nevirapine and Lamivudine in human plasma using the LC-MS/MS machine. A test-retest reliability assessment was performed on a pilot test of 40 HIV/AIDS-positive patients. Three main data analysis techniques were used to analyze the collected data: descriptive analysis, comparative analysis of contingency tables, lastly logistic regression analysis. This is the first study in South East Asia and Malaysia to analyze three antiretroviral treatment using LC-MS/MS machine. It is also the first study in Malaysia to use three different methods for measuring the adherence level to Highly Active Antiretroviral Treatment (HART).

The overall adherence level as measured by the self-reported questionnaire was 81.7%. The adherence levels using TDM for Efavirenz, Nevirapine and Lamivudine were 71.2%, 69.6% and 60.3% respectively. Sensitivity was highest for Efavirenz (0.95; 95% CI 0.92, 0.96) and lowest for Lamivudine (0.89; 95% CI 0.85, 0.92). SRA specificity ranged between 0.56 and 0.63 and was highest for Nevirapine. Positive Predictive Value Positive (PPV) for Self-Reported Adherence (SRA) ranged between 0.76 (Lamivudine) to 0.84 (Efavirenz). Overall diagnostic accuracy ranged between 0.76 (Lamivudine) to 0.84 (Nevirapine) while Area Under the Curve (AUC) ranged between 0.76 (Lamivudine) to 0.83 (Efavirenz). In our findings of the logistic regression and cross tabulation analysis, we evaluated 48 variables which can be classified into four groups: reasons for missing medications, factors facilitating adherence, adverse effects of medications and alternative medications used for HIV treatment. Some of the factors associated with adherence include age, income, educational level, marital status, diarrhoea, vomiting, use of Alarm clock, acceptance of HIV status and use of herbal medicine.

In conclusion, according to the different methods of comparative analysis, it is evident that self-reported adherence is good enough for measuring adherence level in a poor resource setting and many factors have been found to be associated with adherence level to HAART.

ABSTRAK

HIV/AIDS adalah salah satu penyakit zaman moden yang paling banyak memusnahkan nyawa, di mana seramai lebih 45.5 juta orang di seluruh dunia telah dijangkiti. Walau bagaimanapun, penemuan Terapi Retroviral Sangat Aktif (HAART) pada tahun 1996 telah mengurangkan jumlah kematian dan morbiditi disebabkan oleh HIV/AIDS dengan kadar yang signifikan. Terapi ini telah membolehkan ramai pesakit yang sebelumnya hanya terlantar kembali sihat dan mampu hidup dengan produktif. Untuk membolehkan rawatan ini berjaya, tahap pematuhan yang sangat tinggi kepada rawatan adalah diperlukan. Sekurang-kurangya 95% tahap pematuhan terhadap rawatan antiretroviral diperlukan untuk mengurangkan replikasi virus dan mengelakkan perkembangan daya ketahanan terhadap rawatan. Secara umumnya, pematuhan dianggap sebagai tingkahlaku klinikal yang kompleks dan mempunyai pelbagai penentu. Oleh sebab itu, tujuan kajian ini ialah untuk menilai tahap pematuhan terhadap HAART serta penentu-penentunya dalam kalangan para pembawa HIV positif dan pesakit AIDS di salah sebuah hospital utama di Malaysia.

Dengan menggunakan rekabentuk kohort prospektif serta teknik pensampelan mudah**,** 925 orang peserta yang ketika itu sedang menjalani rawatan antiretroviral telah dipilih dalam kajian ini. Kriteria serta dan kriteria singkir turut digunakan. Dalam kajian ini, ketiga-tiga instrumen berikut telah digunakan untuk mengukur tahap pematuhan terhadap HAART: soal selidik laporan kendiri, pengisian semula rekod farmasi dan Pemantauan Terapeutik Ubat (TDM) untuk menguji ubat-ubatan dalam plasma manusia. Dua sampel darah telah dikumpulkan dan diuji dengan menggunakan mesin LC-MS/MS bagi menentukan kewujudan atau ketidakhadiran tiga jenis ubat antiretroviral, iaitu Efavirenz, Nevirapine dan Lamivudine dalam plasma manusia. Penilaian kebolehpercayaan uji-uji semula telah dilaksanakan dalam ujian rintis terhadap 40 orang pembawa HIV positif dan pesakit AIDS. Empat teknik analisis data utama telah digunakan bagi menganalisa data yang telah dikumpulkan, iaitu analisis deskriptif, analisis perbandingan jadual kontingensi, tahap 3 jenis ubat daripada kaedah TDM dengan soal selidik laporan kendiri, dan analisis regresi logistik.

Tahap keseluruhan pematuhan seperti yang diukur oleh soal selidik laporan kendiri adalah 81.7%. Tahap pematuhan yang menggunakan TDM untuk Efavirenz, Nevirapine dan lamivudine adalah 71.2%, 69.6% dan 60,3%. Sensitiviti adalah tertinggi untuk Efavirenz (0,95; 95% CI 0,92, 0,96) dan terendah untuk lamivudine (0,89; 95% CI 0,85, 0,92). Spesifisiti SRA adalah antara 0,56 dan 0,63 dan tertinggi adalah untuk Nevirapine. PPV untuk SRA adalah antara 0,76 (lamivudine), dan 0.84 (Efavirenz). Ketepatan diagnostik keseluruhan adalah antara 0,76 (lamivudine), dan 0.84 (Nevirapine) manakala AUC adalah antara 0,76 (lamivudine), dan 0,83 (Efavirenz)Berdasarkan hasil dapatan bagi analisa regresi logistik serta penjadualan silang, kami telah menilai 48 pembolehubah yang boleh diklasifikasikan mengikut 4 kumpulan, iaitu: sebab tidak mengambil ubat, faktor yang memudahkan pematuhan, kesan buruk ubat-ubatan dan penggunaan perubatan alternatif untuk merawat HIV. Beberapa faktor yang dikaitkan dengan kepatuhan termasuk umur, pendapatan, tahap pendidikan, status perkahwinan, cirit-birit, muntah-muntah, penggunaan jam Alam, penerimaan status HIV dan penggunaan perubatan herba
Kesimpulannya, berdasarkan kepada kaedah analisis perbandingan yang berbeza, ia adalah jelas bahawa kepatuhan yang dilaporkan sendiri adalah cukup baik untuk mengukur tahap kepatuhan dalam suasana sumber yang miskin dan banyak faktor yang telah didapati akan dikaitkan dengan tahap kepatuhan kepada HAART.

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Dr. Umar Yagoub Mohammed

ABBREVIATIONS

AACTG	Adult Aids Clinical Trials Group
AIDS	Acquired Immune Deficiency Syndrome
CAPS	Centre for Aids Prevention Studies
DOT	Direct Observed Therapy
ELISA	Enzyme- Linked Immune-Sorbent Assay
EMEA	European Agency for Evaluation of Medicinal Products
ART	Anti retroviral Therapy
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immune deficiency Virus
HPLC	High-performance liquid chromatography
MTCT	Mother To Child Transmission
MOH	Ministry of Health
MRM	Multiple Reaction Monitoring
LC-MS/MS	Liquid Chromatography-Mass -Spectrometry
LLOQ	Lower Limit Of Quantification
PCP	Pneumocystis Pneumonia
UNAIDS	Joint United Nations Program on HIV/AIDS
MEMS	Medication Events Monitoring System
VAS	Visual Analog Scale
WHO	World Health Organization
TDM	Therapeutic Drug Monitoring
NGOS	None Governmental Organizations
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NNRTIs	Non-nucleoside Reverse Transcriptase Inhibitors
PI	Protease Inhibitors
TB	Tuberculosis
ULOQ	Upper Limit Of Quantification
RT	Reverse Transcriptase
QC	Quality Control
RT-PCR	Reverse –Transcription Polymerase Assay
ROC	Receiver Operating Characteristics

SRA Self Reported Adherence

AUC Area Under the Curve

PPV Positive Predictive Value

CHAPTER 1

In Malaysia, Human Immunodeficiency Virus (HIV) infection was first detected in 1986(Jing & Ismail, 2001). It has continued to be one of the health problems affecting the country due to the increase in incidence rate especially among the high-risk groups. Through the past 25 years, the rate of new infections has always been on an upward trend and it only started to decrease in the past three years(Zhou, 2007). Currently, the rate of new infections has declined from its peak of 7000 cases in 2002 to 3080 cases in 2009. In this chapter, we examine the background information of the epidemic, the problem statement and rationale for this study. We also list and describe the research question, objectives of this study and the contributions made by this study.

1.1 Background

HIV is a virus which infects humans, causing a disease known as the Acquired Immune Deficiency Syndrome (AIDS). In 2009, approximately 45.5 million people around the world were affected by the disease(Muangchan & Nilganuwong, 2009). AIDS continues to be a global health problem with the most number of infections in Africa and Southeast Asia(Garrett, 2007). In Southeast Asia, there were about 4 million people living with the disease by the end of December 2009 (prevalence of 5%) and an estimated 27,000 reported deaths. In Malaysia, the disease was mainly acquired through injecting drugs of abuse, but now the infection through heterosexual route has increased(Hamouda, 2011). Malaysia - with a population of over 28 million people and a multi-ethnic society - has an estimated 106,000 people living with HIV as of December 2009 (Kamarulzaman, 2009). Since the first case was detected in 1986, the disease has caused approximately 14,000 reported deaths and the prevalence rate[1] is

[1] Estimated adult (aged 15-49 years) HIV prevalence

about 0.5% (87,710 cases) but may reach up to 20% in populations with high risk behaviours such as sex workers drug users (MOH, 2010) (W. Y. Low, 2009).

The annual number of new HIV reported cases in the country has declined from a total number of 7,000 in 2002 to 3, 931 cases in 2009 (Kamarulzaman, 2009). Currently, there are about 9 new cases of HIV infections daily and the most common route of infection is through injecting drug use (70%) followed by the heterosexual route (19.6%) and the homosexual route which is about 2% (Choi et al.). Malaysia is a country with many different ethnic groups such as Malays, Chinese and Indians, with HIV most prevalent in the Chinese ethnic group.

Most Malays become infected through injecting drug use and they are usually men aged between 20-29 years while the Chinese on the other hand usually acquire the infection through the sexual route via both heterosexual and homosexual route of infection (Kamarulzaman, 2009). The spread of the disease to both the Indian and *Orang Asli* populations (*Orang Asli* is the general Malaysian term used for any indigenous group found in Peninsular Malaysia which means "original people") who used to be free from this infection need urgent attention from the Ministry of Health authorities.

The benefit of new treatments which could be used these affected areas will go ahead in reducing the burden of the disease and help patients in improving and building their immune system.

With the increase in the number of cases, the Government responded in 2008 by providing the first line of Highly Active Antiretroviral Treatment (HAART) for free and subsidizing the second line of treatment. Today, not less than 10,000 infected patients are on HAART in different parts of the country. This is considered as a significant achievement. However, the biggest challenge is the level of adherence to treatment in Malaysia, which is not known as there are no published studies on adherence or non-adherence to treatment. This could lead to the development of viral resistance resulting in treatment failure when the adherence level is less than 95%.

1.2 Problem statement

There are three classes of anti-retroviral drugs commonely used for treating HIV in Malaysia(Altice, Kamarulzaman, Soriano, Schechter, & Friedland, 2010). These include the Protease Inhibitors (PI) which is used mainly for the second line of treatment; and the Nucleoside Reverse Transcriptase Inhibitors (NRTI) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI), both used in the first line of therapy (Alexander et al., 2003; Byakika-Tusiime, Orrell, & Bangsberg, 2008). Other new antiretroviral therapy such as Maraviroc, which belongs to the group of Entry Inhibitors or Fusion Inhibitors which has been recently produced with different mechanisms of action where the quality, reduced dose frequency and safety have been improved as compared to HAART [78, 79]. Is also available in the country but not commonly prescribed. WHO recommends first-line antiretroviral treatment that consists of two NRTIs and one NNRTI(Akileswaran, Lurie, Flanigan, & Mayer, 2005).

The effect of HAART in HIV-positive patients is assessed and evaluated by monitoring the viral load and measuring CD4+ cell count (Cambiano et al., ; Gutierrez et al., 2004). These two parameters do not provide information about optimal prevention of development of resistance and cross resistance to antiretroviral treatment, since viral resistance has usually developed by the time an increase in viral load is observed (D. Murphy, K. J. Roberts, D. Hoffman, A. Molina, & M. Lu, 2003; PROCTOR, TESFA, & TOMPKINS, 1999). Non-adherence to treatment results in development of drug resistance and then treatment failure (Bangsberg et al., 2006; Bangsberg et al., 2000).

Adherence of HIV/AIDS-positive patients to antiretroviral treatment is one of the most challenging issues affecting them in Malaysia. It is estimated that 95% adherence or more to antiretroviral treatment is essential for reducing replication of the virus thus, preventing the development of resistance to treatment (Bennett, Bertagnolio, Sutherland, & Gilks, 2008; de Olalla et al., 2002; Tuboi, Harrison, Sprinz, Albernaz, & Schechter, 2005). Adherence is considered to be a complex clinical behaviour with a wide array of determinants. A useful framework is to identify the factors which can lead to non-adherence to antiretroviral treatment. These factors can be classified into treatment factors such as side effects of treatment(vomiting and itching) and cost of treatment, service factors such patients waiting time for collection of medication and patient healthcare provider relationships , patient factors such forgetfulness to swallow tablets at prescribed time and depression, socioeconomic factors such as cost of paying for transportation to hospital for follow up and collection of medication, cultural factors such as use of tradional medicine as alternative treatment, clinical setting and the disease itself (Berg & Arnsten, 2006; M. A. Chesney, 2000; I. Escobar, M. Campo, J. Martin et al., 2003).

In addition, the development of resistance in patients with poor adherence to treatment can accelerate the progression of disease to AIDS status (Hirsch et al., 1998). More information on factors and circumstances, which affect HIV-positive patients' adherence to treatment, is required. With the introduction of Antiretroviral Therapy (ART) and the possibility of patients developing resistance and infecting other individuals with the resistant virus, it is necessary to explore the factors and/or circumstances affecting adherence to ART (Attia, Egger, Müller, Zwahlen, & Low, 2009).

Adherence counselling has emerged as an important component in HIV/AIDS counselling. However, little knowledge and information is available regarding this topic in most treatment centres in Malaysia (Ghailan et al., 2010). More knowledge with regards to the factors influencing HIV/AIDS patients' adherence to ART will clarify circumstances or specific factors that should be considered in assessing patients for ART. This new knowledge could improve service delivery by means of relevant assessment and screening procedures that are responsive to the needs of patients in order to enhance adherence.

The following research problem has been formulated: Factors affecting or associated with adherence to antiretroviral treatment in HIV/ AIDS-positive patients are unknown. There are insufficient guidelines for assessing the factors affecting adherence to antiretroviral therapy in HIV/AIDS-positive patients in Malaysia. Sufficient guidelines for assessment and screening could lead to enhanced adherence and thus minimize the development of resistance to antiretroviral drugs. Also, the adherence level to HAART is not known yet and there is no valid method for measuring adherence to antiretroviral therapy in Malaysia. Thus, it is necessary to identify the factors that should be assessed

when screening patients for ART. This is a study on adherence to antiretroviral drugs and it focuses on investigating factors related to HIV/AIDS, specifically those that influence adherence to antiretroviral therapy. It also focuses on measuring the adherence level by different methods and eventually identifies which methods are most valid and suitable for measuring adherence to HAART in Malaysia.

1.3 Rationale for the study

First line treatment has been provided for free by the Ministry of Health for all HIV/AIDS-positive patients since most of them cannot pay for antiretroviral treatment (Mazlan et al., 2006). However, the biggest challenge is the adherence level and factors affecting it are not known in Malaysia. Determining the adherence level and its determinants is very important since adherence level of less than 95% is associated with developing drug resistance which leads to unsuccessful treatment (Muñoz-Moreno et al., 2007). If treatment failure is confirmed, the patient has to be shifted from first line treatment - which is relatively cheap - to second line treatment which is very costly the cost will be doubled due to the high cost of second line treatment and patients may not be able to purchase such drugs even though the Ministry of Health in Malaysia subsidizes such treatment(Komatsu et al., 2010).

When patients are prescribed second line antiretroviral therapy, their medication cost will be doubled due to the high cost of second line treatment(Komatsu et al., 2010). This will have serious economic implications on both the patient and the country due to the increase in the total number of patients testing positive for the virus on a daily basis (i.e. new cases). This will be the first study of its kind on measuring adherence level to HAART in HIV positive patients using three different methods namely self-reported

adherence questionnaire, use of pharmacy refill method and use of Therapeuitic Drug Monitoring (TDM) in Malaysia.

Since there have not been any published studies on measuring adherence level or factors associated with it in this country, this study will be the first in measuring the adherence level by a self-reported method. It will also be the first study in Malaysia and Southeast Asia that aims at validating the accuracy of self-reported adherence to three antiretroviral therapy (efavirenz, nevirapine and lamivudine) with therapeutic drug monitoring using high-performance liquid chromatographic-mass spectrometry (which combines the physical separation of liquid chromatography with the mass analysis of mass spectrometry) in Malaysia. More importantly, the factors associated with adherence level will be identified and taken into consideration in the treatment and follow-up of HIV-positive patients in this country.

1.4 Research questions

1. What are the adherence levels as measured by self-report, pharmacy records and therapeutic drug monitoring in HIV-positive patients on HAART in Sungai Buloh Hospital?
2. What are the factors affecting adherence to highly active antiretroviral treatment in HIV/AIDS-positive patients in Sungai Buloh Hospital?
3. How well does self-reported adherence compare to therapeutic drug monitoring in Malaysian patients?

1.5 Study objectives

1.5.1 General objective

To determine the adherence level to highly active antiretroviral treatments in HIV/AIDS-positive patients in a major hospital in Malaysia and its determinants

1.5.2 Specific objectives

1. To determine the level of adherence to antiretroviral treatment in HIV-positive patients in Sungai Buloh Hospital.
2. To develop a method for determination of antiretroviral drug level in human plasma by high-performance liquid chromatographic-mass spectrometric (LC-MS-MS) method.
3. To validate self-reported adherence to therapeutic drug monitoring method in HIV-positive patients.
4. To determine the factors affecting adherence to highly active antiretroviral treatments among HIV/AIDS-positive patients.
5. To recommend policy measures that will be usefull for both physicians and pharmacists in the treatment of HIV positive patients.
6. To recommend policy measures that will improve adherence and hence reduce transmission of HIV.

1.6 Contribution of the study

This is the first study of its type to be carried out in Malaysia on measuring the adherence level to Highly Active Antiretroviral Therapy in HIV-positive patients and it is also the first to describe and predict the factors affecting the adherence level to treatment. Regionally it is the first study in Southeast Asia to measure the adherence level objectively by detecting the drug levels for three highly active antiretroviral therapies (efavirenz, niverapine and lamivudine) in human plasma using therapeutic

drug monitoring via Liquid Chromatography Mass Spectrophotometry (LC-MS/SM) machine.

We also developed and validated a self-reported study instrument (i.e. questionnaire) which can be used by other researchers in Malaysia and the region for measuring the adherence level and predicting the factors that affect the adherence level in HIV/AIDS-positive patients. Another instrument for measuring the adherence level using pharmacy refill data was developed. This is a very simple instrument, which can be used by researchers in clinical pharmacology and medicine. The results of this study can be used in other developing countries where the HIV/AIDS are major health problems.

In summary, this study gives the researchers in Malaysia a point from where they can start when they think about any study on adherence to antiretroviral treatment and on other medication for infectious diseases. Health policy makers can use the finding of this study to formulate a decision regarding the use of antiretroviral treatment and the management of HIV/AIDS in Malaysia.

CHAPTER 2 LITERATURE REVIEW

2.1 Search Strategy

In this chapter and based on our research questions under the title "Factors Affecting Adherence to Highly Active Antiretroviral Treatment", the researcher searched through Science Direct, PubMed database and Google Scholar. The researcher decided not to do a full systematic review due to the availability of current systematic reviews conducted on this research topic (Attia et al., 2009; Falagas, Zarkadoulia, Pliatsika, & Panos, 2008; Mills et al., 2006; Wasti et al., 2011). However, the researcher reviewed and refers to these systematic reviews throughout this chapter. The above-mentioned databases were reviewed for relevant studies similar to our study topic. Studies from two published systematic reviews as indicated in the Evidence Table 2.1 below were examined and referred to in this chapter.

The search terms used were factors, adherence, compliance, Highly Active Antiretroviral Therapy and HIV/AIDS. We downloaded 239 journal articles (described in the flow chart, Figure 2.1 below) using the above databases and search terms. They were found to be relevant to the study topic based on the articles important contents which were relevant to this study and thus used in the review. The majority of the articles examined are survey studies on factors affecting adherence to antiretroviral treatment and other remaining examined qualitative studies on adherence to antiretroviral treatment. The retrieved data is from studies which were carried out in both developed and developing countries, with a few artiles from Malaysia on the epidemiology of HIV and other aspects of HIV treatment but not on measuring adherence to HAART. Table 2.1 below aslo shows the selected relevant studies used in the leterture review in this study. Summmary of the study population, focus of each

study and the country in which the study is carried out is highlighted in table 2.1 below for quick account of these important studies.

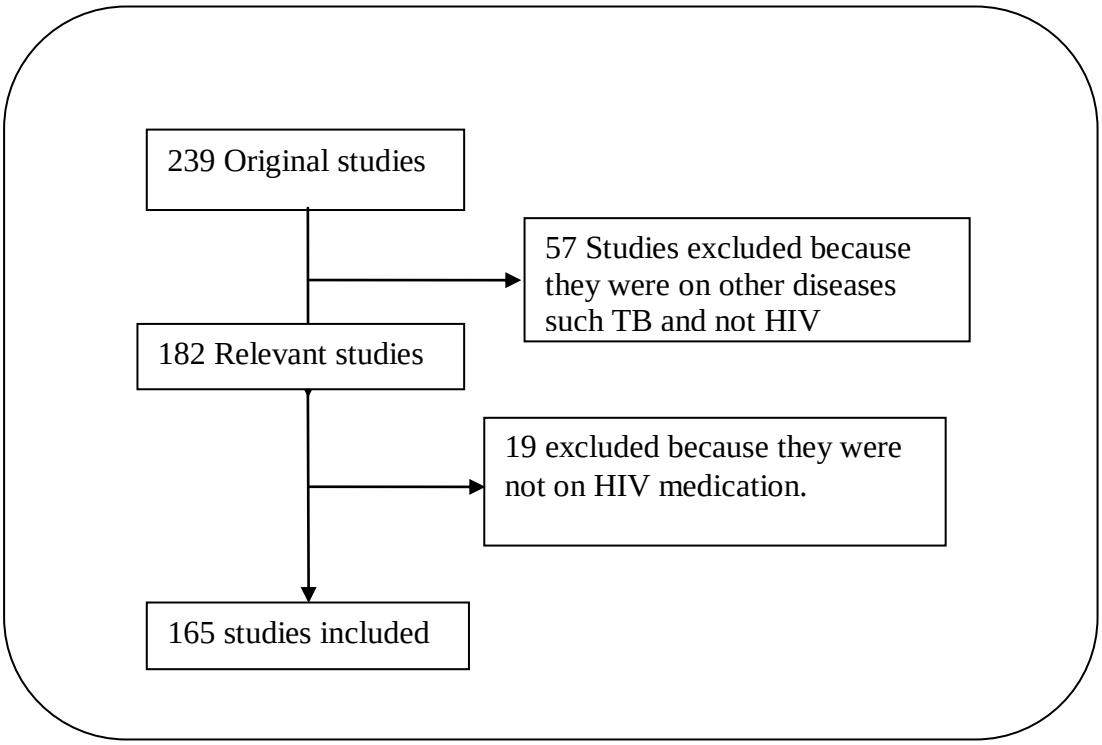


Figure 2-1 Flow chart for studies included in the literature review

Table 2-1: Selected relevant studies for the literature review

Reference	Population	Focus of study	Country	Setting
JOSE A MUNOZ MORENO 2007	530 HIV out-patients on HAART	Assessing Self-Reported Adherence to HIV Therapy Questionnaire the SERAD Study	Spain	Hospital based
C.A.T. Pinheiro1, J.C. 2002	A total of 195 patients participated in the study.	Factors associated with adherence to antiretroviral therapy in HIV/AIDS patients	Italy	Hospital
Hernado knobel 2002	3004 HIV patients on HAART	Validation of simplified medication adherence questionnaire in a large cohort of HIV	US	Hospital based
Abel, 2003	100% women; (2 African-American, 1 Hispanic, 3 white	Factors that influence adherence to ART were explored from perspective of women	US	Clinic
Golin, 2002	16 men/8 women (12 African-American: 12 white)	To understand barriers to ART adherence faced by patients living with HIV in the south-eastern US	US	Clinic
Brigido, 2001	126 men/56 women	To assess if adherence to antiretroviral medication correlates to clinical and laboratory outcomes	Brazil	Clinic
Hills, 2003	78 (no demographic/ ethnicity given specific to study; only general clinic population)	To explore patterns and explanations of adherence to antiretroviral therapies from the patients' perspective	US	Clinic
Johnston-Roberts, 2000	100% women (50% Hispanic, 35% African-American, 15% white)	To explore, from HIV-positive women's own perspectives, the barriers they faced in adhering to combination antiretroviral therapies	US	Journal entries
Kemppainen, 2004	46: 38 men/8 women (12 African-American, 24 white, 5 Hispanic, and 5 mixed)	To identify factors and circumstances that influence the ability of persons with HIV/AIDS and severe mental illness to comply with ART regimens	US	Hospital
Meystre-Agustoni, 2000	37:25 men/12 women(no ethnicity information given)	To explore patients' perceptions of HAART	Switzerland	Clinic

Miller, 2002	30: 23 men/7 women (21 Latino, 7 African- American, 2 white	To assess barriers to adherence to antiretroviral regimens by conducting focus groups and asking patients about their preferences for different aspects of antiretroviral regimens	US	Clinic
Murphy, 2003	81: 45 men/36 women (22% Central American, 61% Mexican, 6% Mexican-American or Chicano, 1% South American, 4% mixed, and 5% other	Three aims: (1) to determine what barriers impede adherence, (2) what strategies facilitate adherence, and (3) investigate the health-care provider–patient relationship and how it may affect adherence	US	Clinic
Murphy, 2000	39; 27 men/12 women (3% Asian/Pacific Islander, 44% African-American, 6% Latino, 3% Native American, 39% white, 6% other or mixed)	To determine what strategies facilitate adherence, what barriers prevent adherence, and investigate the health-care provider–patient relationship and how it may affect adherence	US	Clinic
Oggins, 2003	62; 40 men/22 women (21 African American, 7 Asian, 2 Haitian, 8 Latino/Latina, 9 European American, 11 Native American)	To explore the reasons for low adherence to HIV-medication regimens among ethnic minority groups	US	Private homes, health agencies, or via telephone
Proctor, 1999	39; 27 men/12 women (19 white, 16 African American, 4 Hispanic	To understand the barriers to adherence to HAART faced by people living with HIV/AIDS	US	University medical centers and clinics
Reback, 2003	23; 100% men (87% white, 19% Latino, 4% Native American	To understand the meaning of reported HIV medication adherence among gay and bisexual men who are dependent on or abuse methamphetamine	US	Treatment center

Source: Systematic review for developed and developing countries 2006 and Systematic review 2011 for Asian countries

2.2 Outline of HIV epidemic

Since HIV virus was detected in Malaysia in 1981, more than 32.2 million people are currently living with the disease(Rugalema et al., 2009). The prevalence rate was about 0.5% in the reproductive age group 16-49 years. The prevalence rate is higher in the high risk group such as commercial sex workers and injecting drug users. The main route of infection was through injecting drug use but recently it has become increasingly through the heterosexual route, according to the 2010 Malaysian Ministry of Health report (W. Low, 2009). The 2010 report also predicted the injecting drug use to stabilize while infections via the sexual route (heterosexual and the homosexual route) would increase (W. Low, 2009).

Human Immunodeficiency Virus (HIV), which can spread through body fluids such as blood, breast milk and semen, is the main virus that causes AIDS. Among drug addicts, contaminated needles are considered to be the main route of transmission while sexual route is the main route among high risk groups such as commercial sex workers. At the beginning of the virus infection, the host experiences flu-like illness and will then remain without any other symptoms for about eight years in some cases. Opportunistic infections such as Tuberculosis may start to infect the persons as soon as their immunity depresses.

One of the key components of the immune system is the CD4 cells which measure the effect of the virus on an infected person and measuring the viral load may give the numbers of the HIV virus in the body (Gebo, 2008). When the CD4 count falls beyond 300 to 1000 cells /ul, the person starts to have other opportunistic infections. A CD4 count less than 350 cells will necessitate commencement of antiretroviral treatment.

AIDS patients suffer from many symptoms such as frequent diarrhoea, fever and weight loss which may result in wasting (Hladik et al., 2008).

2.2.1 Virology of HIV

HIV-1 is a retrovirus, which has a single RNA genome and contains about fifteen different types of proteins. There are three types of proteins in HIV-1 virus which are grouped into structural, regulatory and accessory proteins (Demeter et al., 2002). The M group of HIV-1 virus accounts for almost 90% of HIV-1 infections while the other two classes N and O account for the remaining infections (Silvestri, 2008). HIV virus binds its particle (known as virion) to the host cells, which starts when the surface envelope is attached to its receptor. The viral contents such as its genetic material and the protein (reverse transcriptase, or RT) enter the cytoplasm of the host cell resulting in copying of the viral genetic material (Demeter et al., 2002).

2.2.2 Immunology

People infected with HIV virus present two types of antibody immune responses to the virus, which will not stop the progress of infection. The cellular response is mediated through CD4 and CD8 cells which stop the replication of HIV virus by destroying and killing infected cells (Papasavvas et al., 2006). CD4 cells on the other hand responed to the HIV virus through a very complex process resulting in a very low viral load (Seyoum et al., 2006). When the HIV virus is in a resting state, the HAART cannot remove or destroy the virus in the cell leading to continuous infections (Huber & Trkola, 2007).

2.2.3 HIV transmission and risks

In developed countries, the main route of infection is through the homosexual route while 80% of the infection in developing countries is through the heterosexual route of infections with injecting drug use being the second route of infection (Taiwo & Murphy, 2007). The risk of transmitting the virus through the sexual route is increased by the presence of injuries and ulcers in the genital area and it also depends on the viral load (Paltiel et al., 2006). Other methods of viral transmission include blood transfusion, needle injuries, mother-to-child transmission & through the use of infected needles by drug users (Korenromp et al., 2000; Titti et al., 1987).

The risk of transmission from accidental needle injuries is estimated at about 0.4-0.6%. Mother-to-child transmission is very high in developing countries, accounting for 25% newborn babies of HIV infected mothers (Wu, 2008). The transmission in newborn babies is increased mostly during delivery and breast feeding (Kourtis, Bulterys, Nesheim, & Lee, 2001).

2.2.4 Classification of the disease

There are two types of Human Immunodeficiency Virus, namely HIV type 1 and HIV type 2. Both infect the immune system of the host cells which results in leaving the person vulnerable to a lot of opportunistic infections such Pneumonia and Tuberculosis (Ling et al., 2004). When the number of CD4 or helper T cells is less than 600 cells / ul, it means that the immune system is seriously damaged and the infected person is already at risk of opportunistic infection. A CD4 value of more than 1200 cells / ul indicates that the infected person still has a good immune system and such a person may not be required to start HAART. CD 4 of less than 350 cells / ul is a sign of immune impairment and ART can be started, while CD4 of less than 200 cells / ul necessitate

immediate start of the HAART (Lifson et al., 1997; van Baalen et al., 1997). Infection of an individual with the virus is normally followed by a period during which the virus continues to replicate in the body and may render the immune system less functional, resulting in a clinical disease progression.

Untreated HIV disease is chronic and progressive. Primary HIV infection, often marked by a mononucleosis-like acute viral syndrome, is followed by a period of clinical latency typically lasting several years, during which high levels of viral replication and CD4 cells turnover lead to progressive immune dysfunction, eventually resulting in clinical disease progression. The progression of HIV virus in the body and a dysfunctional immune system lead to the development of AIDS which is considered to be the most destructive epidemic of the twenty first century (Goliber, 1999).

2.2.5 Natural course and history of HIV infection

The natural course of the HIV infection has six phases which comprise the acquisition of infection (when the person becomes infected), primary HIV infection, asymptomatic HIV infection, early symptomatic infection, late symptomatic infection (the stage with opportunistic infections) and advanced HIV disease (Lifson et al., 1997). Initial infection of HIV begins with a flu-like illness, which is usually about 3-5 weeks of infection. The infection at this stage is similar to any febrile infection such as Malaria, Typhoid or Dengue fever (Hubert et al., 2000).

About 87% of HIV infected patients come up with the above-mentioned symptoms. According to available data and diagnosis, this is possible only within one or two months after acquiring the infection. Infected persons may have few clinical signs and symptoms at this early stage (Jaffar, Grant, Whitworth, Smith, & Whittle, 2004). The period between HIV infection and the stage of HIV/AIDS may take as long as 10 years. Available data from Zimbabwe indicated that there was no difference in the duration of infection (from the early stage of infection to the stage of HIV/AIDS) between males and females as well as between developed and developing countries (Gregson et al., 2002).

When a patient progresses to AIDS, he or she may survive for about 10 months or more depending on whether he or she is treated or not. This may also vary from one patient to another due to multiple opportunistic infections at this stage (Sterling et al., 2001). HIV/AIDS is classified by either the World Health Organization (WHO) staging or the Center for Disease Control (CDC) classification. The CDC classification has been available since 1982 but has undergone several updates and it now includes measurements as one of its criteria. The WHO staging came to light in 1990 and is fully based on clinical manifestations such as the signs and symptoms of the disease. This staging of the disease is used mostly by poor developing countries in Africa and Asia (Who, 2009).

2.2.6 The laboratory diagnosis of HIV

The diagnosis of HIV is carried out by Enzyme-linked Immune-Sorbent Assay (ELISA) and confirmed by the use of Western blot assay, which can identify HIV antibodies. ELISA is a very specific test and can be used alone for the diagnosis of HIV (Fiscus, Cheng et al. 2006). In HIV infection, antibody production occurs within weeks of infection or less. As such, ELISA testing may be negative if used in the early stages (i.e.

the first few months of infection period, also called the "window period"). The viral load in the window period may be very high and HIV infection can be transmitted during this period (Gibellini, Vitone et al. 2004). HIV infection can be tested on both urine and saliva but this must be followed by serological confirmation.

Home testing for the disease is also available using the HIV rapid serum testing which takes about 30 minutes with 99-100% sensitivity and specificity compared to ELISA testing (Fideli, Allen et al. 2001). In many developing countries, the CD4 count is used for HIV staging since it correlates with the risk of developing opportunistic infections and thus used for the clinical decision making (Finzi, Blankson et al. 1999). Many factors affect the CD4 count and can result in a lot of variation in this count since CD4 is a subset of the white blood cells (T lymphocytes). These factors include other infections that may be available at testing time, malnutrition, use of medication and stressful conditions (Alimonti, Ball et al. 2003).

To differentiate between depletion of the CD4 due to HIV infection and the effect of the above-mentioned factors, we use the CD4 percent and the inversion CD4/CD8 cell ratio (Blanco, Barretina et al. 2001). The viral load measurement in HIV-infected patients is usually made using the Reverse Transcription Polymerase Assay (RT-PCR) which is based on the fact that, the virus is detected when it binds to DNA sequences. The viral load testing results are usually shown in log units, thus a viral log of 10,000 is equal to 4 log units (Mellors, Munoz et al. 1997).

2.3 Antiretroviral Therapy (ART)

Antiretroviral Therapy was first introduced in 1990 and since then has continued to be used by HIV-positive patients worldwide(Shetty, 2008). It helped in reducing mortality in many hospital and treatment centres by improving patients survival rate (Mukherjee, Ivers, Leandre, Farmer, & Behforouz, 2006). In many developing countries, the provision of ART also require patients to be well-educated about the disease, associated opportunistic infections and the need for constant adherence to treatment (C. E. Golin et al., 2002). Patients who have been prescribed ART need to take it for the rest of their lives. The ART if used properly can control and reduce the virus level in HIV patients (J. B. Nachega et al., 2007).

Antiretroviral treatments help in rebuilding the immune system, preventing the virus from multiplying and increasing the duration of a patient's life(Soares & Costa, 2011). The biggest challenges facing the use of antiretroviral in poor countries include poor healthcare infrastructure, high cost of second line treatment and the developing of drug resistance (Gilks et al., 2006; Richard et al., 2004). There are also concerns pertaining to the non-adherence to treatment which will result in failure of treatment and accumulation of strains of highly resistant virus that can promote the spread of drug resistance.

The current treatment of ART is in a combination form known as the Highly Active Antiretroviral Therapy (HAART) (Severe et al., 2005). Three classes of HAART are used in most parts of the world. These include protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNR-TIs) and nucleoside reverse transcriptase inhibitors (NRTIs). All HAART classes have adverse effects which have severe impact on its usage and on patients' adherence to treatment (Dybul, Fauci, Bartlett, Kaplan, &

Pau, 2002). First-line treatments are cheap and easy to use compared to second-line treatments which are very expensive and need to be used only when the first line of treatment fails (Urquhart, 1995).

Some of the significant achievements attributed to HAART are reduction in HIV/AIDS-related mortalities, keeping HIV-positive patients at their homes, helping them to continue with their jobs and emptying hospital wards of HIV/AIDS patients (Akileswaran et al., 2005). The high cost of HAART in many developing countries has made it unavailable to poor patients and necessitated the interventions of WHO and other international organizations to provide the medication (De Cock & De Lay, 2008). The benefits of HAART are great despite its high cost, as it is one of the most useful medication in the fight against infectious diseases in the twenty first century. It is estimated that more than 790,000 deaths would be avoided if the coverage is up to 50%, while the 100% coverage model could avert up to 1,900,000 deaths over the same period (Guimarães et al., 2008).

2.3.1 Type and combination of antiretroviral drugs

HAART combination was developed for the first time in 1996 for the treatment of HIV/AIDS(Cooper et al., 2002). Since that date the combination has contributed significantly in reducing mortality and morbidity among HIV positive patients. The medications have also contributed in emptying hospital words from HIV positive patients. Antiretroviral therapy had the primary aims of improving duration and quality of life, reducing HIV transmission, as well as reducing HIV-related illnesses and deaths. Antiretroviral treatment also has the benefit of reducing the risk of Mother-to-Child HIV Transmission (MTCT) rate when used accurately and at the requested time for the benift of both mother and child (Bogart et al., 2006).

Even though HAART has contributed significantly in fighting against the disease, eradication of the virus is impossible due to the fact that CD4 cells get infected during the acute HIV stage and continues on (Ledergerber, 2004). The goal of maximal viral suppression at the beginning of treatment in some cases may be very difficult due to the resistance strains of the virus. A successful HAART must combine at least two to three drugs from at least 2 different classes of treatment (Carpenter et al., 2000; Struble et al., 2005). Changing from the first line to the second line of treatment may be due to failure of the first line of treatment (Gulick, 2003; Marks & Gulick, 2004).

The most common combination of antiretroviral regimens for treatment in HIV patients generally consists of one NNRTI with two NRTIs or a PI (with or without ritonavir-boosting) with two NR. The antiretroviral treatment (ART) combination of Efavirenz, Stavudine, Lamivudine and Nevirapine is the most frequently used initial regimen in many developing countries including Malaysia. In Malaysia, first-line HAART are provided at no charge by the Ministry Of Health to all patients. Malaysia spends more than USD 3.5 million on HIV/AIDS treatment since the majority of patients are drug users and cannot afford to pay for their medication (Sluis-Cremer & Tachedjian, 2008).

2.3.2 Starting Antiretroviral Therapy

Patients who suffer from an AIDS-defining disease and those whose CD4 cell counts below 200 cells/mm are classified at WHO stage 4 irrespective of their CD4+ cell count. Furthermore, the psychosocial considerations of the patient should be considered before patients are offered ART (Gilks et al., 2006). HIV-positive patients whose CD4 counts are very low and whose clinical status showed progression towards AIDS require immediate start of HAART. In general, the decision to start HAART should be made for the benefit of the patients. Secondary aims of starting antiretroviral treatment include

relieving patients' symptoms, rebuilding and improving the immune system and partial reduction of viral load (Bradley-Springer et al., 2002; Nackchuay, 2009). One of the problems associated with starting or changing antiretroviral treatment is the development of toxicities or side effects to such treatment.

2.3.3 Side effects of antiretroviral drugs

Current HIV treatments need to be administered conteniously to suppress viral replication. HAART, like most other medication, comes with negative aspects such as unwanted drug interactions, drug toxicity, heavy pill burden, pill fatigue and side effects (Rudorf & Krikorian, 2005). Development of resistance to HAART has emerged in all countries worldwide(Mocroft et al., 2001). These toxicities affect most patients undergoing treatment and may result in non-adherence. Complications of HAART include diabetes, renal failure, abnormal blood lipids and liver damage. Other common adverse effects of antiretroviral treatment are vomiting, fever, skin rashes, headache, weight loss and diarrhoea (Bates, 1996). These side-effects of HAART can be classified as acute and long-term, and from mild to severe reactions(Borras-Blasco, Navarro-Ruiz, Borras, & Castera, 2008). This is due to the variability of absorption, distribution and elimination of drugs from patient to patient(Kiertiburanakul & Sungkanuparph, 2009).

Side effects of treatment depend on the type and class of the medication used. NRTIs are commonly used in most countries including Malaysia and they are known to be associated with bone-marrow suppression with subsequent anaemia, peripheral neuropathy, pancreatitis and mitochondrial toxicity, manifesting as myopathy (weakening of the muscles)(Mkhize, 2007). These drugs include d4T, AZT and 3TC (Hofstede, De Marie, Foudraine, Danner, & Brinkman, 2000; Lee, Hanes, & Johnson, 2003). In HAART group, Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) is

the most commonly used group in Malaysia(Lapadula et al., 2008). Efavirenz is the most common drug used by HIV-positive patients in Malaysia and it is known to be associated mostly with adverse effects such as drowsiness, depression and anxiety, which usually results in the patient's refusal of treatment(O'Connor et al., 2007).

The NRTI may cause hepatic toxicity and nevirapine, in particular, is known for its association with skin rash and systemic hypersensitivity (Clarke et al., 2001; De Clercq, 2004). Protease Inhibitors (PI) are known to be very costly and not provided for free in most developing countries including Malaysia and are associated with many side effects (d'Almeida et al., 2008). One of the most common side effects is hyperurisaemia leading to gout, increased risk of cardiovascular events like heart failure, anaemia and elevated liver enzymes (Carr et al., 1998; Riddle, Kuhel, Woollett, Fichtenbaum, & Hui, 2001). Almost all known medications are associated with adverse effects including the new generation of antiretroviral therapy and these could be the main causes of drug resistance and treatment failure (Siripassorn et al., ; Wainberg, Martinez-Cajas, & Brenner, 2007).

2.3.4 Antiretroviral drug resistance

Resistance to treatment in general is a well-established biological process occurring with infectious agents such as viruses, parasites and bacteria (Laing, 2005; Stokes, 2002). In Malaysia, the issue of resistance to HAART is not well studied and there are no published articles on this vital issue. This study will serve as a foundation since we are looking into adherence and also examining the common type of adverse effects to treatment. Resistance to medication in the HIV situation is mostly affected by the very fast replication of the virus and the fact that the virus can easily become inactive and does not respond to HAART (Fumero & Podzamczer, 2003). Adherence to HAART is

highly needed at the commencement of therapy due to high viral load. Non-adherence at the beginning of therapy is more highly associated with development of drug resistance than after six months of therapy due to the fact that the viral load would have been low at this time (Glass et al., 2006; Vlahov & Celentano, 2006).

2.4 Adherence and drug resistance

Adherence is "the extent to which a client's behaviour coincides with the prescribed health care regimen as agreed through a shared decision-making process between the client and the health care provider" (KITSO Manual, 2004; Carter, 2004). The definition of adherence used by the World Health Organization (WHO) is "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendation from a health care provider". The term adherence is viewed to be less judgemental compared to compliance which is the agreement with the recommendations or advice.

Adherence or compliance is still used interchangeably in research although they are not different in definition. Adherence can also be divided into dose, timing and food restriction adherence in the same way as compliance (Södergård, 2006). When drug resistance develops, patients start to suffer from opportunistic infections due to failure of treatment and they transmit the virus with resistance strains to their close contacts. The biggest obstacle that affects patients after they have developed drug resistance is the very expensive second line of treatment that they must undergo, instead of the first line of treatment which is cheaper. The cost of second-line treatment is about 10 times the cost of the first line which is available for free in Malaysia (Cameron, Ewen, Ross-Degnan, Ball, & Laing, 2009). Thus, when the issue of developing drug resistance and

treatment failure is put into consideration, the patient's best option is to ensure a 95% adherence level as recommended by WHO (J.B. Nachega et al., 2007).

2.4.1 Changing Antiretroviral Therapy

Antiretroviral therapy should be changed when there is evidence of treatment failure which is detected in three categories: virological, clinical and immunological. It is well-established that the effects of antiretroviral therapy decrease over time and the main causes of treatment failure are the development of resistance to one or more drugs followed by cross-resistance (Amoroso, Davis, & Redfield, 2002). Non-adherence to treatment is considered to be the most important contributing factor in treatment failure (Jevtovic et al., 2005; van der Ende et al., 2003; Yeni et al., 2002).

Stopping HIV replication using antiretroviral therapy may not be possible due to many reasons and factors which include poor drug absorption, non-adherence leading to drug resistance, low drug dosage due to increased adverse effects and low potency of the antiretroviral used (Sharland, Blanche, Castelli, Ramos, & Gibb, 2004). When there is evidence that viral replication is not in progress despite using HAART, switching from one line of antiretroviral treatment to another should be considered(Colebunders et al., 2006). The most common reasons for changing HAART in any patients are non – adherence, adverse effects of treatment and development of resistance to HAART(Mocroft et al., 2001). Patients who were non-adherent and subsequently developed drug resistance may require more complicated combinations of HAART with different dosing frequencies than the one which he or she had used before (D.A. Murphy, Wilson, Durako, Muenz, & Belzer, 2001). Changing from one antiretroviral therapy to another may be justified if patients prove to have developed some adverse effects to that treatment (Moyle et al., 2008).

2.4.2 Importance of adherence to HAART

Many studies conducted around the world have stated the significance of HAART in the treatment of HIV/AIDS(Uzochukwu et al., 2009). The main objectives of using HAART are to stop the progression of the disease, reduce viral replication hence reducing the viral load, build and restore the immune system thereby increasing the patient's survival rate as well as reduce mortality and morbidity, and in general improve the patient's quality of life by reducing and fighting against opportunistic infections (Wang, Masho, & Nixon, 2006). Many published studies in both developed and developing countries have shown and confirmed the fact that antiretroviral treatment has reduced mortality and improved the quality of life of most patients who adhere to it. In order for treatments to be successful, a very high level of adherence to HAART is required and the combinations of the treatment must be used in the correct quantities as in the prescribed doses (Stewart, Padarath, & Bamford, 2004). Development of drug resistance is always a consequence of increased viral load as a result of either taking the wrong drug at the wrong time, or non-adherence to the prescribed medication.

Adherence also means that the health care provider's instructions for taking the medication are followed. For example, some of the HAART combinations need to be taken with or without food. The right type of food is very important, as avoiding food with excessive amount of fat may play an important role in drug metabolism and drug absorption. Patients on HAART must avoid using other medication - such as alternative or traditional medication - along with their prescribed antiretroviral treatment, as such combinations could have very serious or even fatal interactions (A. Nakiyemba, D. A. Aurugai, R. Kwasa, & T. Oyabba, 2006). Ninety-five percent adherence level can be achieved if patients do not miss more than one dose a month if he is taking once-daily treatment, or missing not more than 3 doses a month if he is taking HAART twice a

day, or missing not more than 4 doses a month if he is taking HAART three times a day (Metcalfe, 2005).

However, most HIV-positive patients on antiretroviral therapy do not achieve 95% adherence level and they end with sub-optimal adherence level, which could be very low. Evidence suggests that greater than 95% adherence level may be necessary to adequately suppress viral replication, produce a durable response and halt disease progression(A. Nakiyemba, D.A. Aurugai, R. Kwasa, & T. Oyabba, 2006). This means that missing more than one dose of a regimen per week may be enough to cause treatment failure. In addition to leading to disease progression, this may result in the development and transmission of drug-resistant viruses, which cannot be treated with first-line (i.e. lower cost) medicines. This will require treatment with second- and/or third-line medicines, which are more expensive, associated with many side-effects and are complex to manage.

The challenge of adherence in the face of potential viral resistance, treatment failure, disease progression and the spread of drug-resistant virus to sexual partners are of great concern. Patients on long-term ART with undetectable levels of HIV still harbour replication-competent virus. For this reason, with current medication, ART is a lifelong process. It should be recognized that adherence to ART is a critical issue, and it is clear from the literature that the factors which influence a patient's ability to adhere are multiple and complex (Fogarty et al., 2002). The consequences of non-adherence are not limited to the patient, which is usually the case in most chronic diseases. If a patient with resistant virus infects another person, the resistant virus is transmitted. This is hence a risk for society in a wider sense, since these patients have limited treatment options (Gazzard, Bernard, & Boffito, 2006).

Among the factors that affect the virological response to HAART are the consequences of previous antiretroviral treatment. Patients with prior treatment are therefore at higher risk for the development of resistance. The time for treatment initiation with antiretroviral therapy has been debated and different approaches have been used for starting HAART in HIV-positive patients (Egger et al., 2002; Paredes et al., 2000).

2.4.3 Theories used to explain adherence

Adherence to HAART remains a significant problem in the clinical reality of the HIV treatment as in other chronic treatments. The theories mainly used have not been well-developed to explain adherent behaviour to drug treatment but rather more on health behaviour in general (Ryan, Patrick, Deci, & Williams, 2008). One of the theories used is the Health Model Theory which states the fact that patients will take action to prevent ill-health conditions, if they feel that they are prone to the vulnerable complications of the disease condition (i.e. they feel that low adherence will result in treatment failure). This is also true if the condition is believed to have serious consequences for the patient (i.e. treatment failure is perceived as bad), and if the patient feels that the action they take will reduce their susceptibility to the condition (i.e. they feel that adherence will reduce the risk for treatment failure). The theory also states that the situation in which the patient feels that the expected barriers (physical, psychological or financial obsticles) to taking the action are more than the perceived benefits and "the conviction that one can successfully execute the behaviour required to produce the outcome" are other concepts that have been added to the model (Becker & Maiman, 1975).

Intention is however influenced by patients' attitudes toward the behaviour and his subjective norms. Attitudes toward the behaviour are a result of weighting (by the individual) the possible outcomes of the action and whether the patient finds these outcomes positive or not. If a patient strongly believes that the outcomes of the behaviour will be negatively valued, this will result in negative attitudes toward the behaviour (Sheeran, 2002).

The Theory of Planned Behaviour deals with the concepts of attitudes toward the behaviour and subjective norms(Ajzen, 2006). It also includes the concept of perceived behavioural control since not all factors influencing behaviour are under the control of the individual. Perceived behavioural control is influenced in turn by control beliefs and perceived power. Control beliefs concern factors that can facilitate or impede the planned behaviour and these factors are weighted by their perceived power (Ajzen & Madden, 1986).

2.4.4 Factors affecting adherence

A range of factors has been found to be related to adherence towards chronic diseases (Ediger et al., 2007). WHO has suggested taxonomy for grouping these factors. The factors are divided into patient-related factors, treatment-related factors, health system-related factors, social and economic factors and condition-related factors (Ismael Escobar et al., 2003). Factors specifically influencing adherence to HIV therapy corresponds well to these categories. Age, gender, marital status and educational level are part of the socio-demographic factors associated with adherence(Arrivillaga, Ross, Useche, Alzate, & Correa, 2009). Other demographic factors include income and educational level which were found to be significantly affecting adherence by some studies. Higher educational level and increase in patient's income have been positively

associated with his adherence level to antiretroviral treatment, which mean patients with a master degree is more adherent to treatment than other with diploma (Kumarasamy et al., 2005). On the other hand ethnicity and religious were found not to affect adherence by other studies(Debra A. Murphy, Roberts, Martin, Marelich, & Hoffman, 2000).

The health care team and health care system can affect adherence levels especially the patient-health care provider relationship together with their access to health care(M. Carrieri et al., 2003). Good nursing care, excellent patients –doctor relationship and good counselling service at some hospitals in western countries were positively affecting the adherence level and resulting in high adherence (Mohammed et al., 2004). On the other hand poor nursing care and non availability of counselling in some poor resource setting led to very low adherence to medications (Loubiere et al., 2009). The complexity of the therapy and adverse effects to treatment are therapy-related factors. Treatment resulting in severe adverse effects such as itching may discharge patients from taking their tablets resulting in low or non-adherent to medication (S. g. n. Duran et al., 2001) When patients run out of pills or high cost of treatment has also been found to be associated with low adherence level. Some other treatment factors such as few prescribed pills, patient's belief in the efficacy of the pills had been found to increase the patient's adherence level (Ammassari et al., 2002).

Health service factors such as long patients waiting time for seen his doctor or collecting his medication and travelling long distances to hospital for treatment and follow up had been shown to discharge patients from visiting these hospital and can cause low adherence level (Hardon et al., 2007). Other important factors such cultural factors (patient's needs to care for other relative) may encourage patients to adhere his treatment, this corresponds with the theory of Health Behaviour Model (Gore-Felton &

Koopman, 2008). The Health Behavioural Model individual tends to adopt a new behaviour when he is faced by a threat, thus patients will adhere to his treatment rather than face the choice of death due to not adhering to his medication. Patient-specific factors such as being busy with other things or being away from home (which results in missing medication), drug or alcohol abuse- related factors, together with motivation are also associated with adherence (Barclay et al., 2007)

2.4.5 Strategies for improving adherence

According to Cochrane reviews which have focused on adherence in chronic disease, several individual interventions or factors have a positive impact on adherence to long-term treatment (Sabaté, 2003). Many adherence-promoting interventions have also been tested in the HIV-infected population. Some randomized controlled trials have evaluated the impact of interventions on adherence (Peterson, Takiya, & Finley, 2003). Two of these studies found no improved adherence, namely Medication Adherence among Community-Dwelling Older Adults: Current Practices and Potential Technology Solution and Cost-related Non-Adherence To Prescribed Medication Therapy Among Medicare Part D Beneficiaries With End-Stage Renal Disease (D.A. Murphy, Lu, Martin, Hoffman, & Marelich, 2002; Ozok, Patel, Wu, & Gurses, 2011).

in 2002 used a multidisciplinary intervention focusing on social support, information and behaviour, while the latter attempted to improve self-efficacy. One of the interventions used cues-dose training (i.e. counsellors trained the patients to find personalized cues for their medicine intake) and money incentives. This intervention enhanced adherence during the intervention but not during the follow-up (Sorensen et al., 2007). An intervention focusing on couples where education about treatment and adherence was the main focus had an impact on adherence during the first period after

the intervention, but showed no difference after 6 months (Haddad et al., 2003). Factors which may contribute and influence an individual's adherence to ART can be divided into the following main categories: Socio-demographic factors, patient factors, treatment factors, factors associated with clinical setting, disease characteristics and patient-provider relationship (García & Côté, 2003; D. A. Murphy, K. J. Roberts, D. Hoffman, A. Molina, & M. C. Lu, 2003; Reynolds et al., 2004).

2.4.6 Conceptual framework

The conceptual framework (Figure 2) below shows factors affecting adherence to HAART. The factors include Socio-demographic factors, patient factors, treatment factors, service factors and cultural factors. In this study, the researcher aims to examine which of the above-mentioned factors affect the adherence level to antiretroviral treatment in Malaysia.

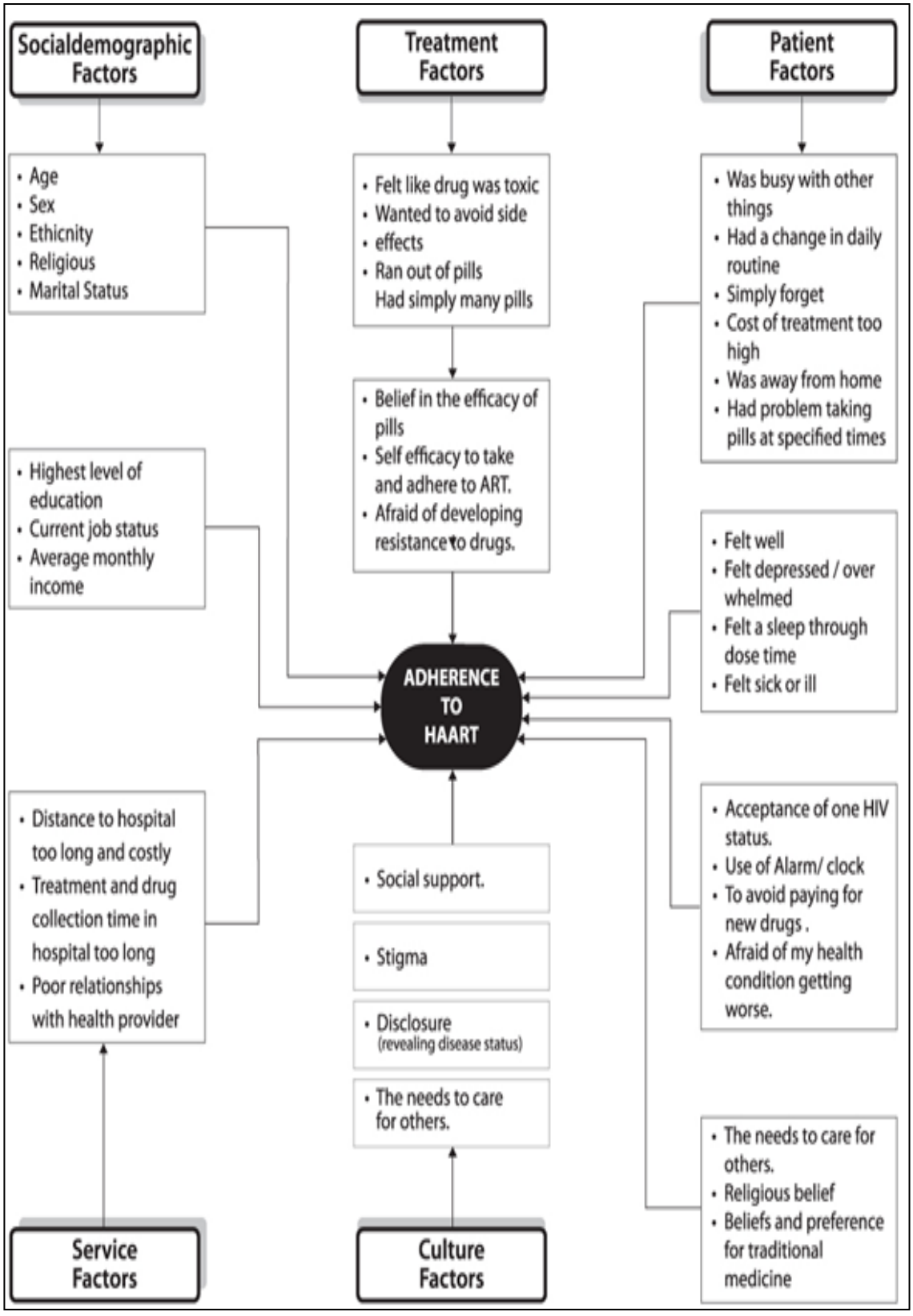


Figure 2-2 Factors affecting adherence to HAART in Sungai Buloh Hospital

2.4.7 Financial constraints

It is logical that the patient's financial status should affect adherence level. Being poor for example, may seriously prevent a patient from either obtaining medication, or transporting oneself to hospital to get treatment. The high cost of medication in some African countries has been found to be a major reason for non-adherence to treatment (Creese, Floyd, Alban, & Guinness, 2002). In Botswana, it was reported that 70% of patients believe that the high cost of treatment is a major reason for non-adherence while 44% of patients believe that the cost of therapy, to some extent, affects their adherence level to HAART(Protopopescu et al., 2009). Apart from the cost of treatment, other costs such as transportation to hospital or health centres and the cost of buying food to be taken along with medication are financial problems which affect most HIV patients in developing countries. In Malaysia, the first-line treatment for HIV is given for free by the Ministry of Health Malaysia in most treatment centres, but the second-line treatment is costly and patients have to pay for their treatment. Other costs such as transportation, hospital charges and food cost definitely play a significant role in adherence to medication in Malaysia.

2.4.8 Social support

Social support is essential for any patient regardless of the type of disease he or she suffers from. Most patients who are surrounded by their loved ones during illness respond better to treatment than those who are staying alone without any social or moral support. Being non–adherent to medication may or may not be associated with social class as shown by some (M. P. Carrieri et al., 2003). Patients who live with their families, sons and very supportive family members are shown to be more adherent than those who do not have children or family support (Given, 2007).

2.4.9 Treatment factors

HIV-positive patients who are on HAART usually face the issue of having to take many pills (up to 5 pills a day), high dosing frequency in one day (ranging from one dose to three doses a day) and also having to comply with particular types of fluids and food. The above-mentioned instructions are always very difficult to follow and can result in non-adherence if patients fail to comply (Brigido et al., 2001). Some studies reported about patients getting tired of taking too many pills. Such patients may refuse to take their medication, resulting in poor or non-adherence (Kleeberger et al., 2001). Adverse effects to HAART such as vomiting, diarrhoea, dry mouth and skin rashes have been shown to lead patients to stop taking medication regularly or even stop taking them completely (Ammassari et al., 2001; S. Duran, M. Sav s et al., 2001). Patients' adherence level decreases with increased dosing frequency, increased amount of pills per day and increase in the severity of side effects to HAART (Ingersoll, 2004). The taste or size of antiretroviral medication may also affect a patient's adherence level (Pontali, 2005). Embarrassing situations in public such as severe itching or sweating and other side effects may result in patients refusing to take medication, leading to non-adherence to treatment.

2.4.10 Patient factors

Studies have shown socio-demographic factors to be associated with adherence level to HAART [150, 151]. For example, a patient's income or completed educational level can positively affect the adherence level. However, some studies showed inconsistent association between adherence level and other factors such as religious belief, use of traditional medicine and use of alternative medicine [152, 153]. Age may influence adherence to highly active therapy; some studies found that elderly patients are more adherent to treatment than their younger counterparts [154].

Another important factor that may affect adherence to treatment is educational level. Some studies showed that those who are highly educated, for instance university graduates, are more adherent to treatment than those with low level of education such as those with merely primary or secondary school education [155]. This is because educated individuals can easily understand the benefit of adherence to HAART and the complications associated with non-adherence. Other socio-demographic factors have also been shown to affect adherence to HAART, such as income, marital status [156].

Patient factors include stigma as a result of disclosure of their HIV status, avoidance of taking prescribed HIV medication in public places, change in daily routine, the feeling of depression, hopelessness, or overwhelmed, falling sick, or being away from home. Other barriers include high costs of treatment and wanting to avoid adverse effects of treatment (Spire et al., 2002). It is important to state that when patients feel that their health condition is getting better or improving, it may negatively affect adherence level since some patients may stop taking their medication (Tuldrà et al., 2000).

2.4.11 Patient provider relationship

Responsibility for successful long-term treatment and adequate viral suppression must lie with the individual who is on antiretroviral therapy. It is equally vital that the selection criteria for antiretroviral therapy be set up and communicated by providers to patients who are in need of such treatment. The relationship between patients and their doctors must be very good for the patients to be satisfied. The best relationship is the one in which patients are included in the decision making process with their care providers (Schneider, Kaplan, Greenfield, Li, & Wilson, 2004). The relationship in which sensitive issues such as race and ethnicity are looked into very carefully by the health care providers when dealing with HIV-positive patients is very important

especially in a country with a multiethnic society like Malaysia (Hasanah, Zaliha, & Mahiran, 2011). In general, a good patient–provider relationship is very important in motivating HIV patients to take their HAART medication, therefore improving the adherence level to treatment.

2.4.12 Health service factor

Hospital setting or service provision has a tremendous effect on a patient's adherence to medication. Among the most important aspects are short waiting time for medication collection, friendly relationship between hospital staff and the patient, warm welcoming by hospital staff, short distance between the hospital and patients' residences, availability of supportive staff and most importantly, the patient's appointment for follow-up should be short and convenient (Architects, 2004; Merten et al.). Likewise, high adherence level of HIV-positive patients on HAART is also associated with maintaining their privacy and confidentiality during interviews, examinations and investigations carried out on patients. Judgemental, unsympathetic and untrained staff with poor human relation may be associated with non-adherence to antiretroviral treatment (G. C. Stone, 1979).

2.4.13 Disease characteristics

Disease characteristics include the impact and severity of HIV on the patients, the effect of other diseases and opportunistic infections on the patient and the ability of the patients in accepting and living with HIV as a disease that has no cure (Tawfik & Kinoti, 2003).

2.4.14 Beliefs and knowledge

Good adherence to antiretroviral therapy could be predicted by a patient's awareness, knowledge, beliefs about the disease and the effectiveness of HAART. It is known that HAART does not cure HIV, but despite this, patients' understanding and belief that HAART can prolong and improve the quality of life is essential in the management of HIV (J. B. Nachega et al., 2005). On the other hand, patients' lack of interest in understanding the disease and being equipped with the knowledge about antiretroviral treatment may eventually lead to non-adherence to treatment. When patients become non-adherent, development of drug resistance and treatment failure will follow.

2.4.15 Depression

Depression is a major predictor of sub-optimal and in most cases non-adherence to prescribed medication. HIV-positive patients suffer from psychiatric illness at one time or another and about 70% of the patients experience depression or anxiety-related illness (Ammassari et al., 2004). This could be due to the fact that HIV/AIDS affect the nervous system, dementia and several forms of central nervous system disorders may even be present in HIV patients. Patients may lose cognitive functions and consequently forget to take medication as prescribed by their health care providers. This will have negative impact of adherence to medication and patients will have sub-optimal adherence or non-adherence to treatment (Tozzi et al., 1999).

2.5. Measuring adherence

Measuring adherence is a problematic and complex procedure, and even though there are many known methods for measuring adherence, there is no 'Gold Standard' (M. A. Chesney, 2006). All of the methods for measuring adherence have their own advantages and disadvantages, and it will be good to use more than one method to measure adherence(Quittner, Espelage, levers-Landis, & Drotar, 2000).

Adherence to antiretroviral therapy can be done either through the direct method or the indirect method. The direct method is more objective and depends on measuring the plasma concentrations of the antiretroviral drugs using therapeutic drug monitoring, whereas the indirect methods rely on less objective measures. The indirect methods mainly include self-reported adherence, such as pill count, pharmacy refill records, Medical Event Monitoring Systems (MEMS), and assessment of adherence by a doctor or nurse (Hugen et al., 2002).

Other indirect methods include reviews of patient charts (documented patient report of adherence to provider), missed clinic visits, Direct Observed Therapy (DOT) and therapeutic outcomes (i.e. viral load, CD4 lymphocyte count and stage of disease progression). The most widely used approach is, however, self-reported adherence, which has its advantages and disadvantages (Knobel et al., 2002; Muñoz-Moreno et al., 2007).

2.5.1 Self-reported adherence

In this method, patients report their adherence level using questionnaires, interviews or diaries, by which a patient reports the number of doses he/she had taken or missed during a specified time interval(Wiener, Riekert, Ryder, & Wood, 2004). This interval differs from one study to another and may be two days, four days, two weeks, four weeks and six weeks. A trusting and very good patient–doctor relationship plays a very important role when using self-reported adherence method to measure adherence level in HIV-positive patients (V. E. Stone et al., 2001). Inquiring about the most recent days of taken and missed doses will give accurate results.

Measuring adherence with self-reporting adherence is used in many countries but it tends to overestimate adherence, and inaccuracies may result from patients' forgetfulness or patients' desires to provide answers which will suit their physicians (Ammassari et al., 2001). Self-reported adherence is believed to be very cheap, fast and easy to administer and more importantly, many studies show an association between self-reported adherence and HIV RNA, which suggests that self-reports may be a valid indicator of adherence (Kerr et al., 2008). Patients reporting to be non-adherent are usually non-adherent indeed (i.e. high specificity) according to pill count. The sensitivity is the probability that patients who are actually being adherent will be categorized as adherent according to the assessment. The disadvantages with the method are that the results are easily affected by recall error (i.e. patients do not remember how many doses they have taken) and social desirability (i.e. patients report the behaviour they think is correct according to the social norms, or in other words they report the behaviour that their health-care personnel want to hear) (Hergenrather, Rhodes, & Clark, 2004).

2.5.2 Pill counts

Using pill counts to measure adherence level is carried out by counting the number of medication remaining in the patients' drug container / bottle during unannounced visits to patients' homes or during patients' hospital visits for follow-up. The adherence level is calculated using the remaining pills, which is assumed to be missed doses(Kalichman et al., 2008). This is easily done if a patient uses a pill organizer in this method of measuring adherence level (Pearson, Simoni, Hoff, Kurth, & Martin, 2007). From another perspective however, patients' privacy and confidentiality may be affected when unannounced visits are conducted, and it may also negatively affect the patient-health care provider relationship(Negash, 2011). Additionally, more human resources are required for home visits and more importantly, patients may even forget to bring their medication with them when visiting the hospital or clinic.

2.5.3 Pharmacy refill data

Measuring adherence to antiretroviral treatment does not depend on physicians or patients alone but also pharmacists who play an important role in supporting HIV patients to adhere to their medication. When patients suffer from problems in their prescribed medication, pharmacists can help in educating them and solve problems associated with taking their prescribed medication (Golin, Isasi, Bontempi, & Eng, 2002). Adherence to treatment can also be measured by pharmacy refill data in which adherent patients are patients who collect their prescribed medication regularly and on due date. Pharmacists help in calculating the adherence level by providing the date in which the antiretroviral medications were dispensed and also the exact number of days between each consecutive refill. If the health care provider obtains the refills according to the prescribed time and medication are collected on the due date, patients are assumed to be taking their medication regularly. On the contrary, if patients have not

taken the prescribed medication as scheduled by their physicians, they are assumed to be missing their medication dose(R. B. Haynes, Ackloo, Sahota, McDonald, & Yao, 2008).

Pharmacy refill data is used in many international studies to calculate adherence level to HAART (J. B. Nachega et al., 2006). A reliable and effective medical record system plays an important role in calculating the adherence level by pharmacy refill data. Calculating the adherence through pharmacy refill data requires patients to obtain their prescribed medication from the same pharmacy all the time. This method is considered to be a non-measure of medication intake by the patients (i.e. patients might not swallow the tablets he collected from the pharmacy, for instance) and therefore have its disadvantages in measuring or calculating adherence (Grossberg, Zhang, & Gross, 2004).

2.5.4 Biological markers

Biological markers such as plasma viral load and CD4 have been used as a very effective indicator of a patient's medication usage in many developing countries including Malaysia. The main objective of antiretroviral treatment is to reduce the plasma viral load, however some studies showed that patients may be taking all of their medication every day and yet their viral load may remain very high (Liu et al., 2001). Using biological markers to monitor adherence in resource-poor settings is found to be very expensive. Other disadvantages of using biological markers such as viral load level is the fact that it causes malabsorption and affects metabolic conditions of the patients. The availability of other infectious diseases and drugs interactions can also lower the plasma viral load, thus giving a false impression that it is due to the antiretroviral treatment. It will be fair to state that these markers are rough indicators of a patient's adherence to HAART and of very limited use(Shiras, 2006).

2.5.5 Medication Events Monitoring System (MEMS)

This method consists of an electronic chip embedded in the lid of the medication bottle. The chip records the opening and closing of the bottle. A computer program downloads the information from the lid and gives a written report. The report shows the exact date and time for each opening of the cap and assumes that the opening concedes with HAART intake. Adherence level is calculated by dividing the number of time-appropriate bottle openings by the number of expected doses over the study period (Samet, Sullivan, Traphagen, & Ickovics, 2001). One of the major disadvantages of this method is it can only access the adherence level on one medication and does not assess the components of the combination therapy such as HAART, other than the fact that the method is expensive. This system is not used in measuring adherence in Malaysia, where most centres depend mainly on physicians using plasma markers as a main method for measuring patients' adherence.

2.5.6 Therapeutic Drug Monitoring (TDM)

There are many ways to measure adherence level, but Therapeutic Drug Monitoring (TDM) is the best objective method for measuring adherence by indicating the concentration of drugs in the serum. TDM has not been used for assessing and measuring adherence level due to the high cost involved in conducting TDM, short half-life of the commonly used HAART medication and the physiology of drug metabolism and drug absorption which affect the use of TDM in measuring the adherence level. At the present time, TDM is only limited to research settings. Many studies have used this method for measuring adherence level. However, this method is very sensitive and expensive to use. It will be discussed in greater detail in chapter three of this thesis.

2.5.7 Combination methods for measuring adherence

Most of the studies conducted on adherence to HAART in HIV-positive patients agree that there is no gold standard for measuring adherence. In addition, most of the methods used for measuring adherence level to antiretroviral treatment have their advantages and disadvantages. For example, the self-reported adherence questionnaire method has the advantage of being cheap and easy to administer, but is associated with recall bias (Muñoz-Moreno et al., 2007). Likewise, pharmacy refill method does not actually prove that the patients actually swallow the pills, rather it merely shows whether a patient has collected the medication or not (C. Golin et al., 2002).

As a result of the above advantages and disadvantages and also the lack of gold standard method for measuring adherence, most studies use a combination of different method (Hill, Kendall, & Fernandez, 2003). Meaning two or more of the above methods are used to assess the adherence level. The most common combination used consists of both the direct and indirect methods for measuring HAART. In this study, we used the self-reported adherence questionnaire, pharmacy refill method and Therapeutic Drug Monitoring (TDM) for measuring the adherence level in HIV-positive patients.

CHAPTER 3 VALIDATION OF LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY (LC-MS-MS) METHOD FOR THE ANALYSIS OF THREE HIGHLYACTIVE ANTIRETROVIRALTREATMENT (HAART) IN HUMAN PLASMA OF HIV/ AIDS POSITIVE PATIENT

3.1 The principle of LC-MS-MS

LC-MS-MS is a combination of two techniques to identify and analyze chemical compounds(Kosjek, Heath, Petrović, & Barceló, 2007). Liquid chromatography can separate a component of a mixture into separate compounds and then characterize them by using mass spectrometry according to their molecular weights. The separation of a mixture by liquid chromatography can be achieved by using a column. A column is normally packed with certain materials from different types of phases, such as the normal phase, reverse phase, ion exchange.

After separation in the column, the samples transferred into the mass spectrometer ion source, where the molecular components are ionized. The mass spectrometer will separate these ions according to the types of their ion charge ratio. For the purpose of simplicity, assume that all ion forms are singly charged; therefore the denominator of the mass-to-charge ratio (m/z) is always 1. Consequently, any ion observed at a particular mass has that mass. Therefore, a compound can be identified either to confirm the presence of the compound, for quantitation by using standard curve or determine the elements within the sample, if unknown.

3.1.1 Experimental

3.1.2 Chemicals

All chemicals obtained for this study are HPLC-grade or reagent-grade. Format and formic acid, ammonium and acetonitrile were obtained from Fisher Scientific, Malaysia. Human plasma which do not contain any drugs was obtained from the University of Malaya Medical Centre blood bank. Antiretroviral drugs such as lamivudine, efavirenz and nevirapine were purchased from Labchem Sdn. Bhd., all with United States Pharmacopeia (USP) grade.

3.1.3 Apparatus

The LC-MS/MS system consisted of an LC-10A UFLC system with a SIL-HT automatic sample injector (Shimadzu, Kyoto Japan) and an API 3200 Q-Trap LC-MS/MS system (Applied Biosystems, Lincoln Centre Drive, Foster City, CA, USA). The LC-MS/MS system was controlled with the Analyst 1.42 software (Applied Biosystems).

3.1.4 Mass spectrometer parameters

The analysis of the drugs in this study was conducted using a mass spectrum with Model API 3200 Q-Trap triple quadrupole mass spectrometer, and operated in ESI mode with positive and negative mode ionization. Analytes were then quantified by Multiple Reactions Monitoring (MRM) (refer to Table 1 for MRM transitions). MRM allows for enhanced selectivity through the measurement of parent and daughter ions simultaneously for each compound of interest. The protonated ion ($M+H^+$) and deprotonated ion ($M-H^-$) of the analytes were then chosen and placed into the collision cell where they separated into product ions. The intensity of the ion was processed and finally maintained and kept by a selected computer system.

Table 3-1: summarised the MRM transition ions and the mode of mass spectrometer analysis

Drug	Ionization mode	MS/MS transition
Lamivudine	Positive	230.20/111.90
Nevirapine	Positive	267.08/226.10
Efavirenz	Negative	313.90/68.90
Zalcitabine	Positive	212.08/112.00

3.2 Chromatographic system

The parameters of the liquid chromatography used in this analysis were a C18 Zorbax column with a diameter of 4.6 mm ID x 100 mm length with 3.5 µm particle sizes packing and Gemini-NX C18 4 mm ID x 2.0 mm length guard column. The assay flow rate was maintained at 0.8 mL/min throughout the process. The mobile phase A was 0.05% formic acid in water and mobile phase B was 10mM ammonium formate in acetonitrile with a pH of 5.8. At the beginning of the assay, the flow gradient was 80:20 v/v of A: B for 0.1 minutes, linearly ramped to 35 % B over 0.5 minutes, and then held at 35% B until 0.8 minutes. The gradient then ramped again to 95% B until 2 minutes and remained for 0.50 minutes. The gradient then returned to 20% B at 2.51 minutes and this condition was maintained and kept constant for about 3.5 minutes.

3.3 Preparation of Mobile Phase

The mobile phase had two phases: Phase A and Phase B. Phase A consisted of 0.05% pure formic acid in deionised water that was well mixed and filtered, and then degassed under vacuum. Mobile phase B was formed by mixing 770 mg ammonium formate in acetonitrile; the pH was adjusted to 5.8 with formic acid before filtration using a 0.45 um membrane and then degassed under vacuum.

3.4 Preparation of standard and control

To prepare lamivudine, nevirapine, and efavirenz stock solution, 2.0 mg of each analyte was weighed and then dissolved in a 10 mL methanol to produce 200µg/mL of each analyte. A diluted concentration was used in spiking the calibration standard. 10mL aliquots of drug-free plasma were spiked with each to obtain a range of concentration from 10 to 500 ng/mL. Frozen Quality Control (QC) pools were prepared at five different concentrations of each analyte using stock solution of each analyte. The analytes contain 200ug/mL in methanol. Zalcitabine was prepared in acetonitrile at 500ng/mL. All samples obtained were kept at -20 ^{0}C in a fridge for future batch analysis.

Table 3-2 Preparation of calibration standards

Analyte concentration (ng/mL)	Volume mix plasma (1ug/mL) µL	Volume free drug plasma (µL)	Total volume (uL)
10	50	4950	5000
25	125	4875	5000
50	250	4750	5000
100	500	4500	5000
250	1250	3750	5000
350	1750	3250	5000
500	2500	2500	5000

Table 3-3 Quality control sample

Analyte concentration (ng/mL)	Volume mix plasma (1ug/mL) µL	Volume free drug plasma (µL)	Total volume (uL)
30	150	4850	5000
240	1200	3800	5000
400	2000	3000	5000

3.5 Extraction procedures

Five hundred microliters of internal standard in acetonitrile solution was mixed with 100uL of plasma (containing an analyte) in 1.5 mL micro centrifuge tubes and vortexed for 20s at high speed. The tube was centrifuged at 14800 rounds per minute for 10 min to turn precipitated proteins into pellet and produce a clear supernatant. Five hundred microliters supernatants was filtered using PHENEX RC 0.25µm syringe filter and transferred to a vial which was inserted and placed in the auto sampler tray which injected it onto the LC column.

3.6 Analyte quantitation

The quantitation of an analyte were achieved using the calibration curve plotted using the area ratio of analyte to internal standard versus known concentration analyte from 10 to 500 ng/mL of plasma with 7 calibrators. All the results were calculated using the y= Ax+B linear regression. The regression coefficient for all the calibration curves obtained were greater than 0.99.

3.7 Method Validation

All the validation procedures and the acceptance criteria used in this study were adapted from the European Agency for the Evaluation of Medicinal Products (EMEA) guideline for method validation (Surapaneni, 2012)and USFDA guideline(Mistri et al., 2007). The frozen plasma samples obtained from HIV positive patients, calibration standards and the quality control samples were first made available for the process and thawed as required. All samples were prepared with the same procedure. The following parameters were studied during method validation.

3.7.1 Specificity

Specificity can be defined as non-interference process between antiretroviral drugs used and internal standard using a pre-determined extraction procedure, LCMS/MS conditions and no cross interference at the retention time when testosterone appear from the endogenous plasma(Owen III, Hidalgo, Li, & Zhang, 2012). Assay specificity was determined by analyzing double blank (plasma sample without analyte and internal standard), blank (plasma sample spike with internal standard only), LLOQ (Lower Limit of Quantification) and ULOQ (Upper Limit of Quantification) sample.

3.7.2 Calibration / linearity

The calibration consists of seven non zero, calibrators assayed in duplicate (nominal values 10, 25, 50, 100,250, 350 and 500ng/mL. Two analyte free samples were analysed, one with the internal standard and one without the internal standard; neither being included when fitting the calibration line. The correlation coefficient (r) between concentration and peak area ratio should be equivalent to, or better than, 0.98. The simplest mathematical model that adequately describes the concentration-response relationship was used.

The following conditions should be met in developing a calibration curve:

- No more than 20% deviation of the LLOQ from nominal concentration.
- No more than 15% deviation of standards other than LLOQ from nominal concentration.

At least 66% of the non-zero standards must meet the above criteria, including the LLOQ and the calibration standard at the highest concentration. Excluding any calibrators should not change the model used.

3.7.3 Inaccuracy and Precision

Inaccuracy was tested by determinations of low, medium and high quality control samples, together with the LLOQ and ULOQ samples. The nominal values for low, medium and high control samples were 30, 240 and 400ng/mL, respectively. The nominal values for the ULOQ and LLOQ were the same nominal concentration as the highest and the lowest calibration standards, respectively.

Assay precision were measured both within-batch and between-batch by the analysis of the three control samples, the LLOQ and the ULOQ. Precision was evaluated as the relative standard deviation of the mean expressed as a percent (coefficient of variation: (CV %). Inaccuracy was expressed as the absolute percent deviation from the theoretically determined concentration (% difference) for within-batch and between-batch precision the LLOQ, ULOQ and the three control samples was each assayed six times in three separate assays. Each assay has an individual calibration curve.

The within- and between-batch mean inaccuracy for the high and medium control sample concentration must be within ±15% of the expected or nominal concentration and within ±20% of the expected or nominal concentration for the lowest control sample. The within-batch and between-batch precision for the high and medium control sample concentration must be within ±15% and within ±20% for the lowest control sample.

At the LLOQ, the mean inaccuracy and imprecision must be within ±20% of the expected or nominal concentration for at least five of the six control samples. At the ULOQ, the mean inaccuracy and imprecision must be within ±15% of the expected or nominal concentration for at least five of the six control samples. At least 66% of the controls must meet the above criteria.

3.7.4 Recovery

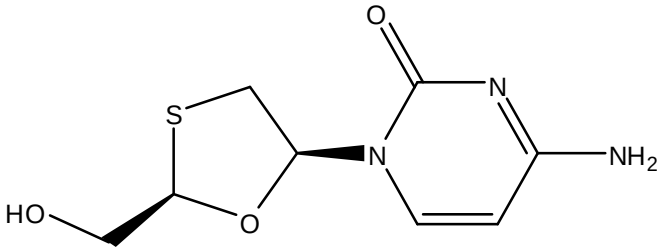
Absolute recovery of the three antiretroviral drugs namely Efavirenz, Lamivudine and Nevirapine was tested using human plasma spiked with other three samples of the above drugs at the same concentrations of the QC samples. Absolute recovery of zalcitabine was obtained at a concentration of 500 ng/mL Peak area measurements produced from the extracted samples were compared to the peak area measurements which were obtained from injection of the test compounds. Statistical parameters such as Mean & SD were calculated from the three measurements at each level.

3.8 Validation Results

3.8.1 Selection of operating protonated ions

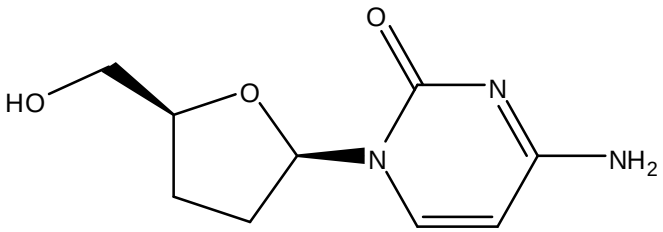
Figure 3.1 shows the chemical structure and the protonated ions of efavirenz lamivudine, nevirapine, and zalcitabine used in this study related to their mass. Major fragment ions at m/z 93.9, 94.9, 100.9, 112.0 and base peak at m/z 229.9 were observed for lamivudine. Whereby, for nevirapine some major fragments ions at m/z 92.9, 104.9, 107.0, 197.7 and base peak at m/z 225.9 were observed. The major fragments ions at m/z for efavirenz were 199.0. 230.0.244.0 and peak at m/z 314.1. The mass spectrum scans for the above two analytes are shown in Figure 3.2, 3.3 and 3.4

Scheme 1: Structures of the drugs



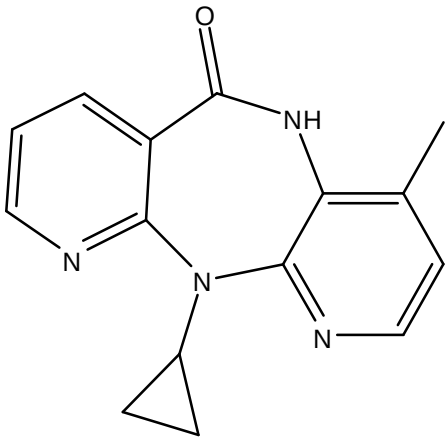
(Lamivudine)

4-amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one



(Zalcitabine)

4-amino-1-((2R,5S)-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one



(Nevirapine)

11-cyclopropyl-4-methyl-5,11-dihydro-6H- dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one

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Figure 3-1 chemical structure efavirenz, lamivudine, nevirapine, and zalcitabine

3.8.2 Specificity

No significant interfering peaks were found at the retention time of efavirenz, lamivudine, nevirapine, and zalcitabine. The signal to noise ratio for all the drugs were both greater than 5. Figure 3.2, 3-3 and 3.4 shows the chromatogram obtained from the blank plasma, blank plasma spiked with 10 ng/mL efavirenz, lamivudine, Nevirapine (The 10 ng/ml was selected because it is the least value at which the LC-MS/MS machine can detect any of the three drugs tested for. This value was determined during the development and validation of the method used for the drug analysis) and blank plasma spiked with 500ng/mL zalcitabine.

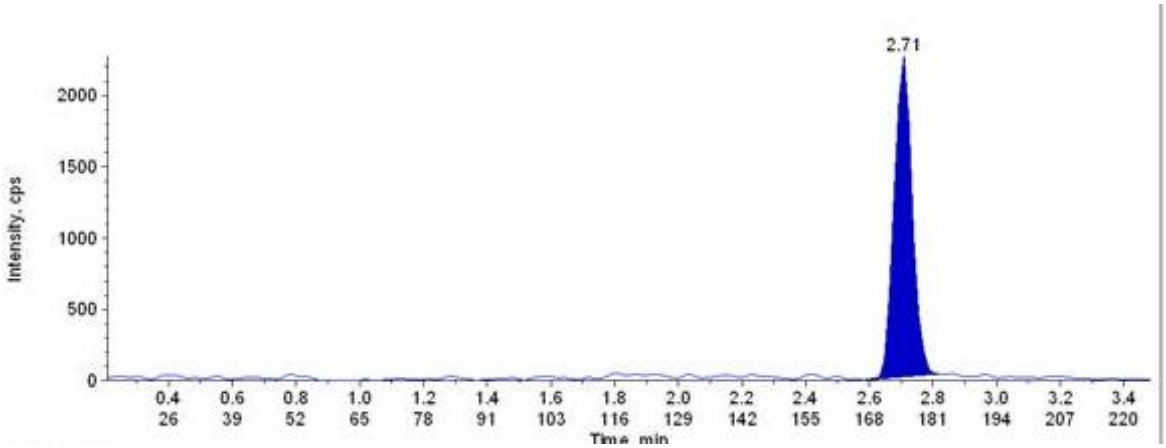


Figure 3-2 Efavirenz

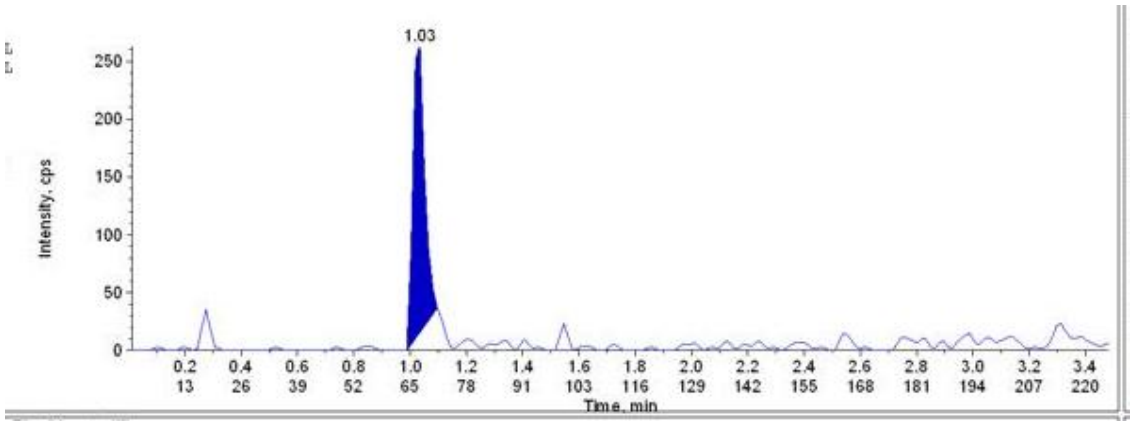


Figure 3-3 Lamivudine

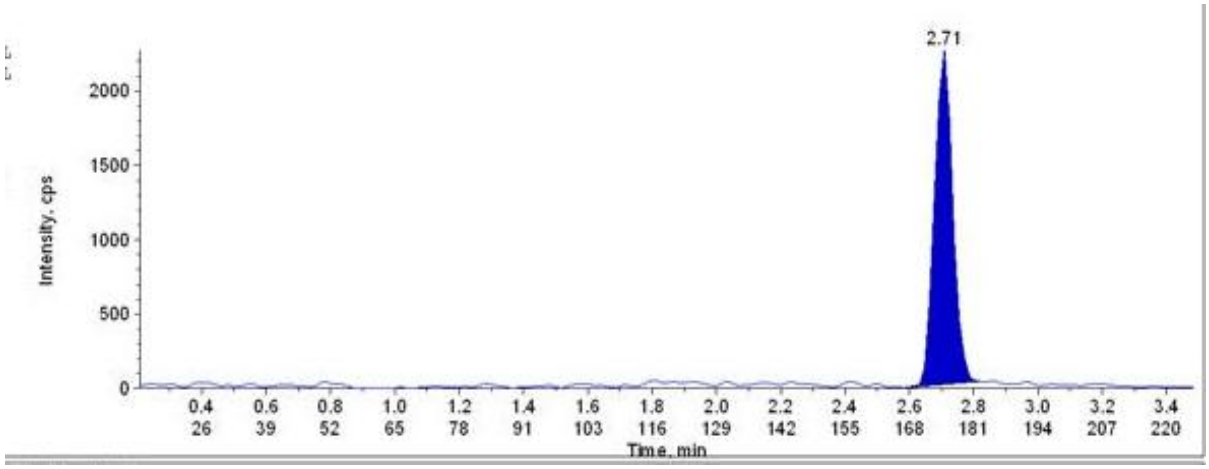


Figure 3-4 Nevirapine

3.8.3 Calibration

The concentration range of efavirenz, lamivudine, nevirapine, measurement was 10 to 500ng/mL to correctly weight the liner regression line for this 500 fold range the residuals were weighted by the reciprocal of the nominal concentration value squared. This achieves an allocation of equal importance to each standard value. That is, a constant coefficient of variation is assumed across the calibration range. The peak area ratio, regression coefficient and the slope of the calibration line etc. were calculated from the peak area data by the analyst program. The regression coefficient for all the calibration curves were greater than 0.99. Mean results obtained from three curves are summarized in Table 3.4

Table 3-4 Regression parameters for three calibration curves during validation

Batch	(C)	(A)	Intercept(B)	r^2
1	6.12 E-6	0.00743	0.000394	0.9965
2	7.75 E-6	0.00772	0.000682	0.9972
3	7.51 E-6	0.00783	0.000210	0.9987

$y = Cx + AX + B$

3.8.4 Imprecision and Inaccuracy

Within-assay reproducibility

The CV% and the percentage for within assay imprecision and inaccuracy including LLOQ and ULOQ were all within the accepted range with ranging from 1.7 to 13% and 0 to 10%, respectively.

Between assay repeatability

The CV% and the percentage for between assay imprecision and inaccuracy including LLOQ and ULOQ were all within the accepted ranges of between 1.9 to 8.3% and 1 to 5%, respectively. Table 3.5 and Table 3.6 summarises the within and between assay imprecision and inaccuracy achieved during the validation study. All the results obtained were below than the limit accepted for validation.

Table 3-5 Within assay imprecision and inaccuracy of efavirenz in plasma

Batch #	Nominal concentrations	Mean n=6	SD	CV	Mean accuracy
	(ng/mL)	(ng/mL)		(%)	(%)
	10 (S/N* ratio > 5)	8.848	0.236685	2.675016	88.48
	30	32.08	1.561089	4.866239	106.9333
1	240	242	0.09 5.787918	2.391702	100.8333
	400	401.4	5.029911	1.253092	100.35
	500	535.6	37.32693	6.969181	107.12
	10 (S/N ratio > 5)	11.02	0.438178	3.976207	110.2
	30	31.64	1.681666	5.314999	105.4667
2	240	205.8	10.28105	4.995651	85.75
	400	333.4	15.25778	4.57642	83.35
	500	470.8	41.32433	8.77747	94.16
	10 (S/N ratio > 5)	11.4	0.158114	1.386964	114
	30	34.24	1.346477	3.932468	114.1333
3	240	241	16.77796	6.96181	100.4167
	400	409.2	7.395945	1.807416	102.3 4
	500	510.6	19.28212	3.776364	102.12

* S/N: Signal to noise ratio

Table 3-6 Between assay imprecision and inaccuracy of efavirenz in plasma

Nominal concentration (ng/mL)	Mean (n=15) (ng/mL)	SD	CV (%)	Mean inaccuracy (%)
10	10.42267	1.196719	11.48188	104.2267
30	32.65333	1.845406	5.651509	108.8444
240	229.6	20.5871	8.966506	95.66667
400	381.3333	36.48418	9.567529	95.33333
500	505.6667	41.89386	8.284876	101.1333

Table 3-7: Within assay imprecision and inaccuracy of Lamivudine in plasma

Batch #	Nominal concentrations (ng/mL)	Mean n=6 (ng/mL)	SD	CV (%)	Mean accuracy (%)
	10 (S/N* ratio > 5)	10.074	0.465167	4.617497	100.74
	30	30.56	1.532319	5.014131	101.8667
1	240	237.4	7.635444	3.216278	98.91667
	400	427.6	17.358	4.0594	106.9
	500	535.6	21.00714	3.92217	107.12
	10 (S/N ratio > 5)	10.77	1.174521	10.90549	107.7
	30	29.96	2.12791	7.102503	99.86667
2	240	233	7.905694	3.393002	97.08333
	400	377.6	15.1096	4.001483	94.4
	500	499	30.11644	6.035359	99.8
	10 (S/N ratio > 5)	11.008	0.786333	7.143289	110.08
	30	34.58	0.460435	1.331505	115.2667
3	240	264.6	11.58879	4.379738	110.25
	400	452	6.442049	1.425232	113
	500	540.4	33.50821	6.200631	108.08

* S/N: Signal to noise ratio

Table 3-8: Between assay imprecision and inaccuracy of Lamivudine in plasma

Nominal concentration	Mean (n=15)	SD	CV	Mean inaccuracy
(ng/mL)	(ng/mL)		(%)	(%)
10	10.61733	0.894926	8.428914	106.1733
30	31.7	2.555945	8.062919	105.6667
240	245	16.79711	6.855963	102.0833
400	419.0667	34.50562	8.233922	104.7667
500	525	32.74577	6.23729	105

Table 3-9: Within assay imprecision and inaccuracy of nevirapine in plasma

Batch #	Nominal concentrations	Mean n=6	SD	CV	Mean accuracy
	(ng/mL)	(ng/mL)		(%)	(%)
	10 (S/N* ratio > 5)	10.62	0.342053	4.617497	100.74
	30	28.62	2.148721	5.014131	101.8667
1	240	222	15.01666	3.216278	98.91667
	400	385.8	15.73849	4.0594	106.9
	500	516.6	47.65816	3.92217	107.12
	10 (S/N ratio > 5)	12.42	0.725948	5.844989	124.2
	30	29.62	1.30269	4.398007	98.73333
2	240	199.4	8.619745	4.322841	83.08333
	400	332.6	19.33391	5.812961	83.15
	500	493.2	50.30606	10.19993	98.64
	10 (S/N ratio > 5)	10.64	0.750333	7.052004	106.4
	30	29.84	0.835464	2.799812	99.46667
3	240	246.8	4.438468	1.798407	102.8333
	400	407.6	4.97996	1.221776	101.9
	500	541.8	16.6343	3.070192	108.36

* S/N: Signal to noise ratio

Table 3-10: Between assay imprecision and inaccuracy of nevirapine in plasma

Nominal concentration	Mean (n=15)	SD	CV	Mean inaccuracy
(ng/mL)	(ng/mL)		(%)	(%)
10	10.64	0.750333	7.052004	106.4
30	29.84	0.835464	2.799812	99.46667
240	246.8	4.438468	1.798407	102.8333
400	407.6	4.97996	1.221776	101.9
500	541.8	16.6343	3.070192	108.36

3.8.5 Recovery

The absolute recovery of efavirenz, lamivudine, nevirapine, and zalcitabine ranged from 84 to 89% and 82 to 86%, respectively. All the values are summarised in Table 3.11 and Table 3.12

3.8.6 Stability

Table 3.13, 3.14, and 3.15 lists the stability data for efavirenz, lamivudine and nevirapine in plasma after three freeze and thaw cycles, after 48 hours at room temperature, and after 48 hours at 4ºC, respectively.Efavirenz, nevirapine and lamivudine were found to be stable at all the conditions tested.

Table 3-11: Percentage of Nevirapine and Lamivudine recovery from plasma

Nevirapine				Lamivudine			
Nominal concentration	Mean area		Recovery	Nominal concentration	Mean area		Recovery
	Extracted samples	Non extracted samples			Extracted samples	Non extracted samples	
(ng/mL)	Peak area	Peak area	(%)	(ng/mL)	Peak area	Peak area	(%)
30	45178	53912	82.5	30	44879	50069	89.6
240	1334923	1499488	89.0	240	1284757	1298722	83.6
400	3866636	4067952	95.1	400	4005169	4309874	92.9

Table 3-12: Percentage of Efavirenz and Zalcitabine recovery from plasma

Efavirenz				Zalcitabine			
Nominal concentration	Mean area		Recovery	Nominal concentration	Mean area		Recovery
	Extracted samples	Non extracted samples			Extracted samples	Non extracted samples	
(ng/mL)	Peak area	Peak area	(%)	(ng/mL)	Peak area	Peak area	(%)
30	45145	53922	83.8				
240	1184957	1399421	84.7	500	3228421	4959878	86.0
400	4166863	4567946	91.2				

Table 3-13: Results of stability tests carried out on efavirenz: values expressed in percentage of the concentration difference between, before and after the test

	Concentration (ng/mL)		
	30	240	400
Time 0 stability data. Mean (n=4)	28.5	235	385
In plasma, after three freeze-thaw cycles. Mean (n=4)	27.1	231	392
Difference (%)	-4.9	-1.7	1.8
In plasma after 48 hours room temperature. Mean (n=4)	25.6	239	380
Difference (%)	-10.1	1.7	-1.3
In plasma after 48 hours at 4ºC. Mean (n=4)	25.9	231	388
Difference (%)	-9.1	0.4	0.8

Table 3-14: Results of stability tests carried out on lamivudine: values expressed in percentage of the concentration difference between, before and after the test

	Concentration (ng/mL)		
Time	30	240	400
Time 0 stability data. Mean (n=4)	29.9	238.7	398.4
In plasma, after three freeze-thaw cycles. Mean (n=4)	27.5	241.0	401.9
Difference (%)	-8.03	0.96	0.88
In plasma after 48 hours room temperature. Mean (n=4)	32.3	239.1	396.9
Difference (%)	8.03	0.17	-0.38
In plasma after 48 hours at 4ºC. Mean (n=4)	30.56	239.9	400.45
Difference (%)	2.21	0.50	0.51

Table 3-15: Results of stability tests carried out on nevirapine: values expressed in percentage of the concentration difference between, before and after the test

	Concentration (ng/mL)		
	30	240	400
Time 0 stability data. Mean (n=4)	31	239.9	399.67
In plasma, after three freeze-thaw cycles. Mean (n=4)	30.68	240.97	398.34
Difference (%)	-1.0323	0.44602	-0.3328
In plasma after 48 hours room temperature. Mean (n=4)	29.86	239.26	401.34
Difference (%)	-3.6774	-0.2668	0.41784
In plasma after 48 hours at 4ºC. Mean (n=4)	32.4	241.32	397.43
Difference (%)	4.51613	0.59191	-0.5605

Table 3-16: Autosampler stability data for efavirenz

Sample type	Expected concentration (ng/mL)	Measured concentration (ng/mL)	Elapsed time (h)
QC1	30	27.91	0
		29.63	4.3
		31.50	8.7
		30.30	17.0
		33.13	22.1
		28.64	24.5
QC 2	240	239.86	0
		241.98	4.3
		238.13	8.7
		236.98	17.0
		240.61	22.2
		242.32	24.6
QC 3	400	398.47	0
		398.99	4.3
		400.57	8.7
		401.09	17.0
		403.00	22.1
		399.52	24.5

Table 3-17: Autosampler stability data for nevirapine

Sample type	Expected concentration (ng/mL)	Measured concentration (ng/mL)	Elapsed time (h)
QC1	30	31.32	0
		30.56	4.3
		29.63	8.7
		32.45	17.0
		30.17	22.1
		27.91	24.5
QC 2	240	239.89	0
		241.52	4.3
		240.28	8.7
		243.04	17.0
		240.17	22.2
		237.18	24.6
QC 3	400	399.03	0
		398.07	4.3
		403.16	8.7
		400.29	17.0
		401.83	22.1
		398.46	24.5

Table 3-18: Autosampler stability data for lamivudine

Sample type	Expected concentration (ng/mL)	Measured concentration (ng/mL)	Elapsed time (h)
QC1	30	29.81	0
		30.83	4.3
		33.56	8.7
		29.13	17.0
		28.71	22.1
		29.91	24.5
QC 2	240	240.63	0
		238.41	4.3
		239.04	8.7
		238.99	17.0
		242.67	22.2
		241.13	24.6
QC 3	400	399.62	0
		397.09	4.3
		398.73	8.7
		401.18	17.0
		400.47	22.1
		403.54	24.5

3.9 Analysis of plasma samples obtained from HIV patients

Blood samples were obtained from 925 patients for analysis. The blood was collected in 2 groups' namely first blood sample and second blood sample. First blood sample was collected with the administration of the self-reported questionnaire, second blood sample was obtained one month after the first sample when patient come to collect his antiretroviral medication. Six ml of blood was drawn from the vein of each patient by a phlebotomist using lithium heparin tube and centrifuged within one hour of collection time. It was then transferred to 2 plain bottles (3ml each) for storage at -80 degrees in the Department of Pharmacology for future batch analysis using the Liquid Chromatography Mass Spectro-Photometery (LC-MS/MS) machine. The number of second blood sample collectd were less than the number of the first blood samples this due to the fact that some patients did not come to give second blood sample. The

researcher has made several telephone calls and sends text massages to ask patients to come for providing second blood sample but still there were some that did not show up.

3.10 Results

Table3.19. below shows the results of lamivudine analysis in the first and second blood samples obtained from HIV-positive patients. Out of 925 samples analysed, 299 (32.3%) of the first blood samples had lamivudine detected while the remaining 197 (21.3%) samples were lamivudine-free. Fifty seven of second blood samples were analyzed. The remaining 868 participants did not provide second blood samples for analysis.

Table 3-19 Analysis of lamivudine in HIV positive plasma samples using LC-MS/MS

Drugs	**Plasma concentration (ng/mL)**			**Detection of the drugs in the plasma samples**	
	Mean	Maximum	Minimum	Positive (%)	Negative (%)
Lamivudine					
1st sample	12±1.1	43029±308	1534.3±31	299 (60.3%)	197 (37.7%)
2nd sample	38±1.7	21057±423	4917.1±27	38 (66.7%)	19 (33.3%)

Note: Sample were diluted prior to analysis from 10 to 100 times dilution

Table III.20 below presents different concentrations of the 243 first blood samples and 38 second blood samples containing lamivudine as detected by LC-MS/MS machine. Thirty one participants' first blood samples had lamivudine concentrations greater than 6001 ng/mL while 12 participants' second blood samples had concentrations greater than 6001. Ninety two or 37.9% of the participants' first blood samples had concentrations ranging from 1 -1000 ng/mLwhile only 6 or 15.8% of the second blood samples contained efavirenz concentrations ranging between 1 ng/mL to 1000 ng/mL.

Table 3-19: Detected Lamivudine concentration in human plasma using LC-MS/MS

Lamivudine in first blood sample			**Lamivudine in second blood sample**		
Con(ng/mL)	**N**	**(%)**	**Con(ng/mL)**	**N**	**(%)**
1--1000	92	37.9	1-- 1000	6	15.8
1001-- 2000	35	14.4	1001-- 2000	4	10.5
2001--3000	33	13.6	2001-- 3000	6	15.8
3001--4000	19	07.8	3001-- 4000	3	7.9
4001--5000	14	05.8	4001-- 5000	3	7.9
5001—6000	19	07.8	5001-- 6000	4	10.5
> 6001	31	12.8	> 6001	12	31.6
Total	**243**	**100**	Total	**38**	**1000**

N = Number of patient. LC-MS/MS = Liquid Chromatography Mass-Spectro-photometry Con = Concentration

Table3.21 below shows the results of efavirenz analysis in the first and second blood samples obtained from HIV-positive patients. Out of 925 samples analysed, 445 (71.2%) first blood samples had efavirenz detected while the remaining 180 (28.8%) samples were negative and three participants did not provide blood for analysis. One hundred and thirty two second blood samples were analyzed. The remaining 793 participants did not provide second blood samples for analysis.

Table 3-21 Analysis of Efavirenz in HIV positive plasma samples using (LC-MS/MS)

Drugs	**Plasma concentration (ng/mL)**			**Detection of the drugs in the plasma samples**	
	Mean	Maximum	Minimum	Positive (%)	Negative (%)
Nevirapine					
1st sample	19±1.4	32100±134	4350.90±91	445 (71.2%)	180 (28.8%)
2nd sample	146±6.1	23450±35	4342.10±29	119 (90.2%)	13 (9.8%)

Table 3.22 presents different concentrations of efavirenz detected in the 346 first blood samples and 119 second blood samples. More than 24% or 84 of the participants' first blood samples had efavirenz concentration above 6001 ng/mL while 21% or 25 of the participants' second blood samples had concentration above 6001 ng/mL. Forty one of the participants' first blood sample had efavirenz concentrations ranging from 1-1000 ng/mL while only 13 participants' second blood samples contained efavirenz concentrations ranging from 1-1000 ng/mLs.

Table 3-20: Detected Efavirenz concentration in human plasma using (LC-MS/MS) machine

Efavirenz in first blood sample			**Efavirenz in second blood sample**		
Con(ng/mL)	**N**	**(%)**	**Con(ng/mL)**	**N**	**(%)**
1—1000	41	11.8	1-- 1000	13	10.9
1001-- 2000	45	13.0	1001-- 2000	10	8.9
2001--3000	59	17.1	2001-- 3000	28	23.5
3001--4000	52	15.0	3001-- 4000	22	18.5
4001--5000	32	09.2	4001-- 5000	10	8.4
5001--6000	3309.5		5001-- 6000	11	9.2
> 6001	84	24.3	> 6001	25	21.0
Total	**346**	**100**	**Total**	**119**	**100**

N = Number of patient. LC-MS/MS = Liquid Chromatography Mass-Spectro-photometry Con = concentration

Table 3.23 below shows the results of nevirapine as analyzed in the first and second plasma samples obtained from HIV-positive patients. Out of 925 samples analyzed, 394 (69.6%) first blood samples had nevirapine detected while the remaining 172 (30.4%) samples were negative and two participants did not provide blood for analysis. Ninety five second blood samples were analyzed. The remaining 830 participants did not provide second blood samples for analysis.

Table 3-21: Analysis of Nevirapine in HIV positive plasma samples using (LC-MS/MS)

Drugs	**Plasma concentration (ng/mL)**			**Detection of the drugs in the plasma samples**	
	Mean	Maximum	Minimum	Positive (%)	Negative (%)
Nevirapine					
1st sample	11±1.2	11650±12	2734.17±121	394 (69.6%)	172 (30.4%)
2nd sample	44±2.3	12566±40	3853.3±29	82 (86.3%)	13 (13.7%)

Table 3.24 below presents the different concentrations of 269 first blood samples and 82 second blood samples containing nevirapine as detected by the LC-MS/MS machine. Thirty six participants' first blood samples had nevirapine concentrations greater than 6001 ng/mL while 15 participants' second blood samples had concentrations greater than 6001. Ninety five or 35.3% of the participants' first blood samples had concentrations ranging from 1-1000 ng/mL while only 12 or 14.6% of the second blood samples contain nevirapine concentrations between 1 ng/mL to 1000 ng/mL.

Table 3-22: Detected Nevirapine concentration in human plasma using (LC-MS/MS) machine

Nevirapine in first blood sample			**Nevirapine in second blood sample**		
Con(ng/mL)	**N**	**(%)**	**Con(ng/mL)**	**N**	**(%)**
1--1000	95	35.3	1-- 1000	12	14.6
1001-- 2000	34	12.6	1001-- 2000	7	8.5
2001--3000	41	15.2	2001-- 3000	13	15.9
3001--4000	24	08.9	3001-- 4000	15	18.3
4001--5000	22	08.2	4001-- 5000	13	15.9
5001--6000	17	06.3	5001-- 6000	7	8.5
> 6001	36	13.4	> 6001	15	18.3
Total	**269**	**100**	**Total**	**82**	**100**

N = Number of patient. LC-MS/MS = Liquid Chromatography Mass-Spectro-photometry Conc = Concentration

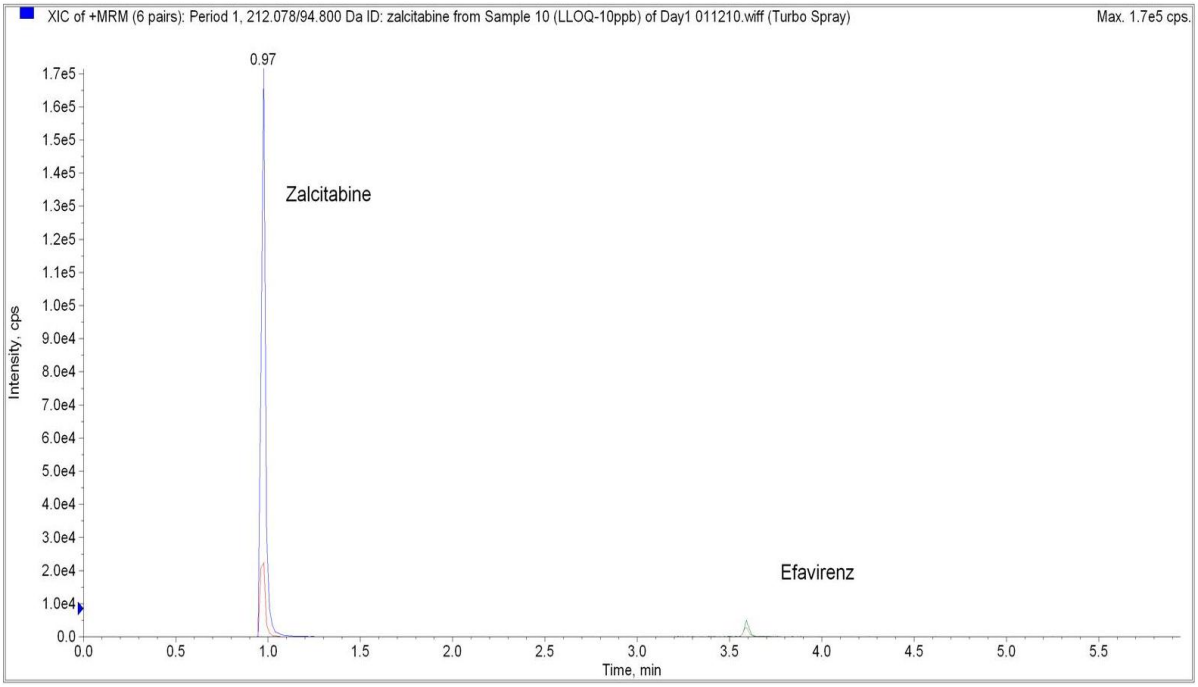


Figure 3-5 Spectra for Efavirenz

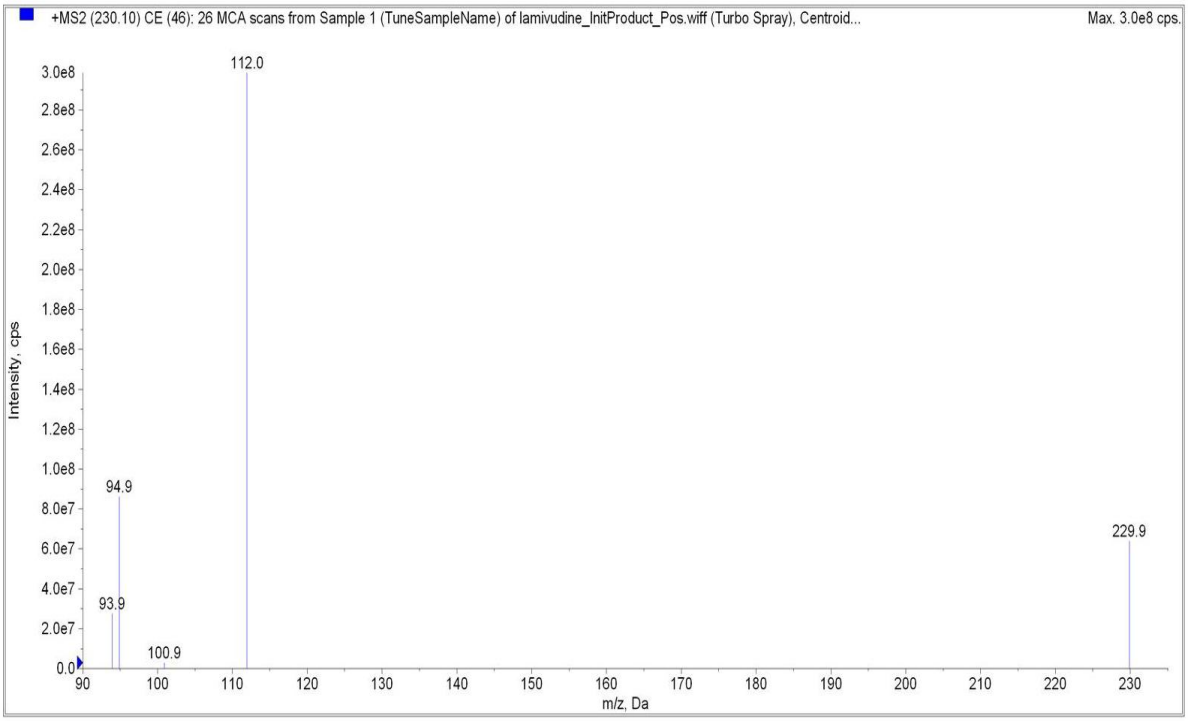


Figure 3-6 Spectra for Lamivudine

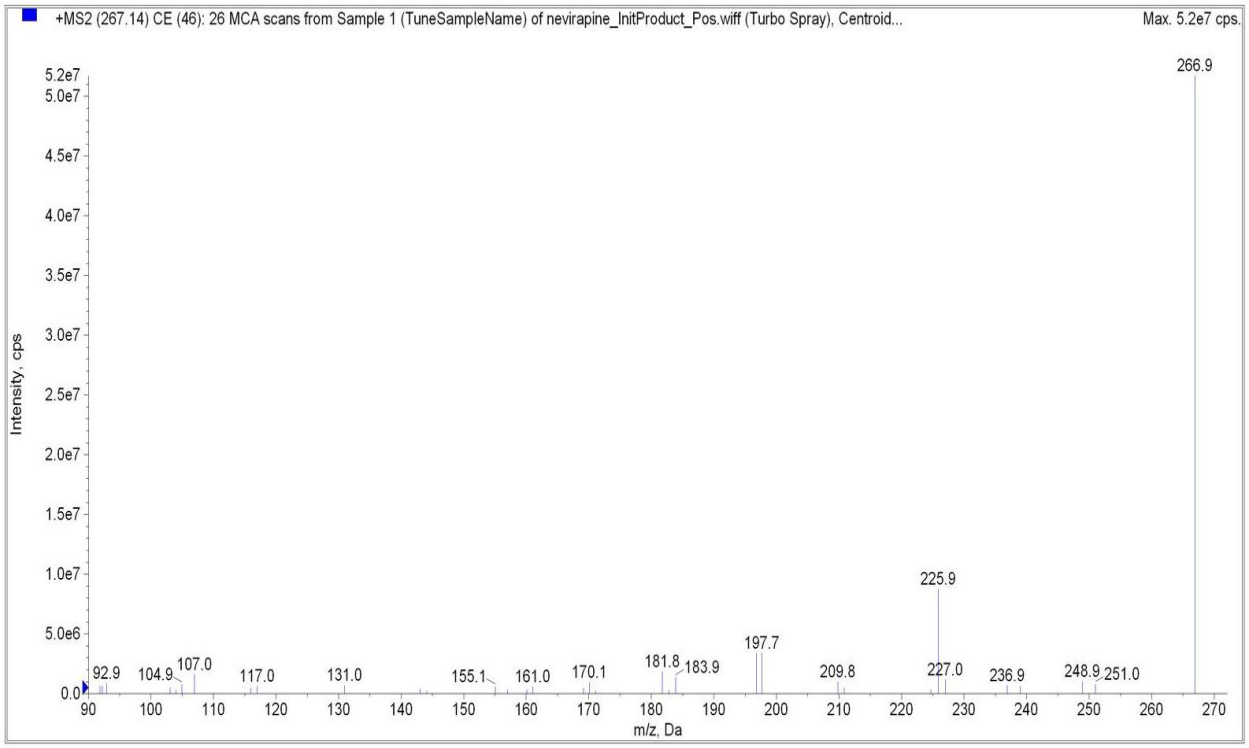


Figure 3-7 Spectra for Nevirapine

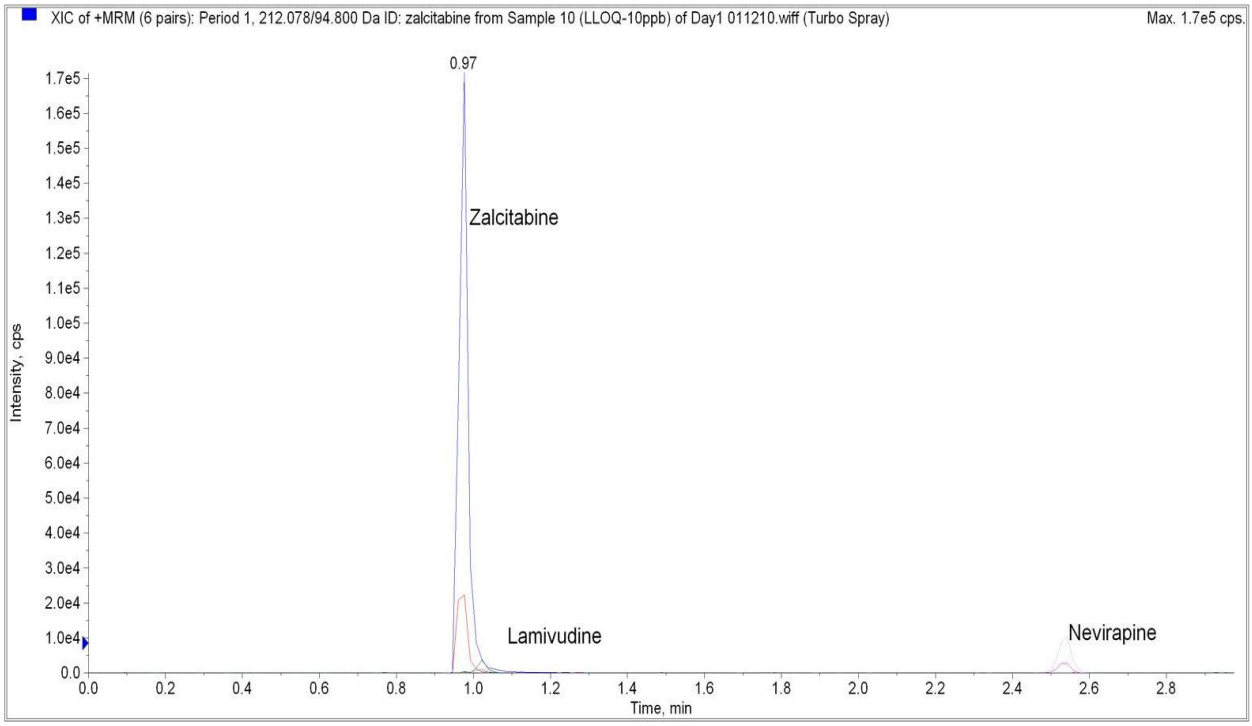


Figure 3-8 Spectra for both Nevirapine and Lamivudine

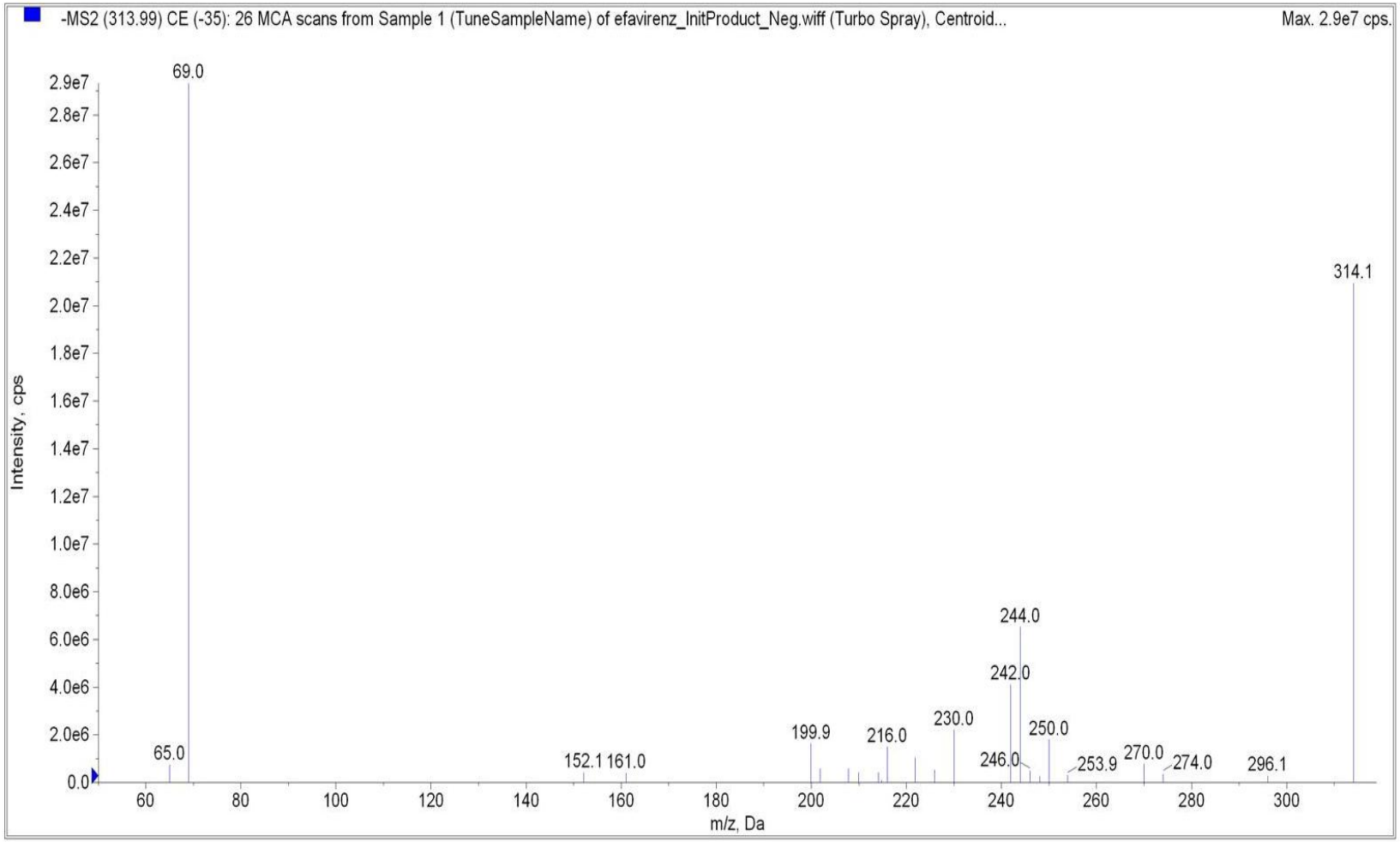


Figure 3-9 Spectra for Efavirenz

CHAPTER 4 METHODOLOGY

4.1 Study design

This section provides the overall plan of the study; it briefly covers the following four main issues: the strategy of the study, its conceptual framework, data collection and the methods of analysis used. This study is intended to describe factors affecting adherence to antiretroviral treatment in HIV-positive patients in Malaysia. The best method that was selected to carry out this study and address the research question is through a bidirectional cohort (both prospective and retrospective) study, which consists of two components. Prospective cohort study design usually describe a group of patients and follow them from the present time to the future while in retrospective cohort patients records are obtained from the present time to specific years in the past.

First, patients were monitored for a period of one year *(Nov 2009 – Oct 2010)*. During this period, blood samples were collected twice after the administration of the self-reported questionnaires, and pharmacy record data were collected for the preceding six months from online hospital record data. All investigation results such as biological marker (viral load), immune reconstruction makers (CD4, CD8), liver function tests and other haematological investigation results had been collected. These two components were carried out simultaneously and at the end of the first year, all of the blood samples collected was analyzed in the pharmacology lab using the LC-MS-MS machine.

The machine determined the antiretroviral drug levels in the plasma using Therapeutic Drug Monitoring method. The LC-MS/MS was used because it is more accurate and has the ability to analyze more than one drug in a very short time compared to the old Liquid Chromatography machine. The research team (i.e. researcher and data collectors) administered a self-reported adherence questionnaire to collect information about the reasons that facilitate patients to adhere to treatment as well as barriers for missing medication. We collected pharmacy data and results of clinical tests done at the same time from online clinical records. Cohort studies have several advantages. They are useful to ascertain both incidence and natural history of a disease. In addition, they are also important in investigating multiple outcomes that might occur after a single exposure. The cohort study design is suitable for studying rare exposures, and it reduces the risk of survivor bias. Cohort studies also allow calculation of incidence rates, relative risks, and other outcome measures such as survival analyses.

However, cohort studies also have their own disadvantages. These include selection bias which happen when patients were selected to participate in the study. Moreover, loss to follow-up can be a problem, and cohort studies are not suitable for studying rare diseases. Before-after cohort studies have significant limitations. An investigator takes a measurement, exposes participants to an intervention, repeats the measurements, and then compares them. The first limitation is regression to the mean (which refers to a phenomenon where if a variable is extreme on the first measurement, later measurements may tend to be closer to the centre of distribution) because lower mean values will arise at follow-up. The second limitation is that secular trends - such as seasonal changes in disease frequency - can affect results. In principle, a cohort study could be used to estimate average risks, rates, or occurrence times. This requires that the whole cohort remain at risk and under observation for the entire follow-up period. In

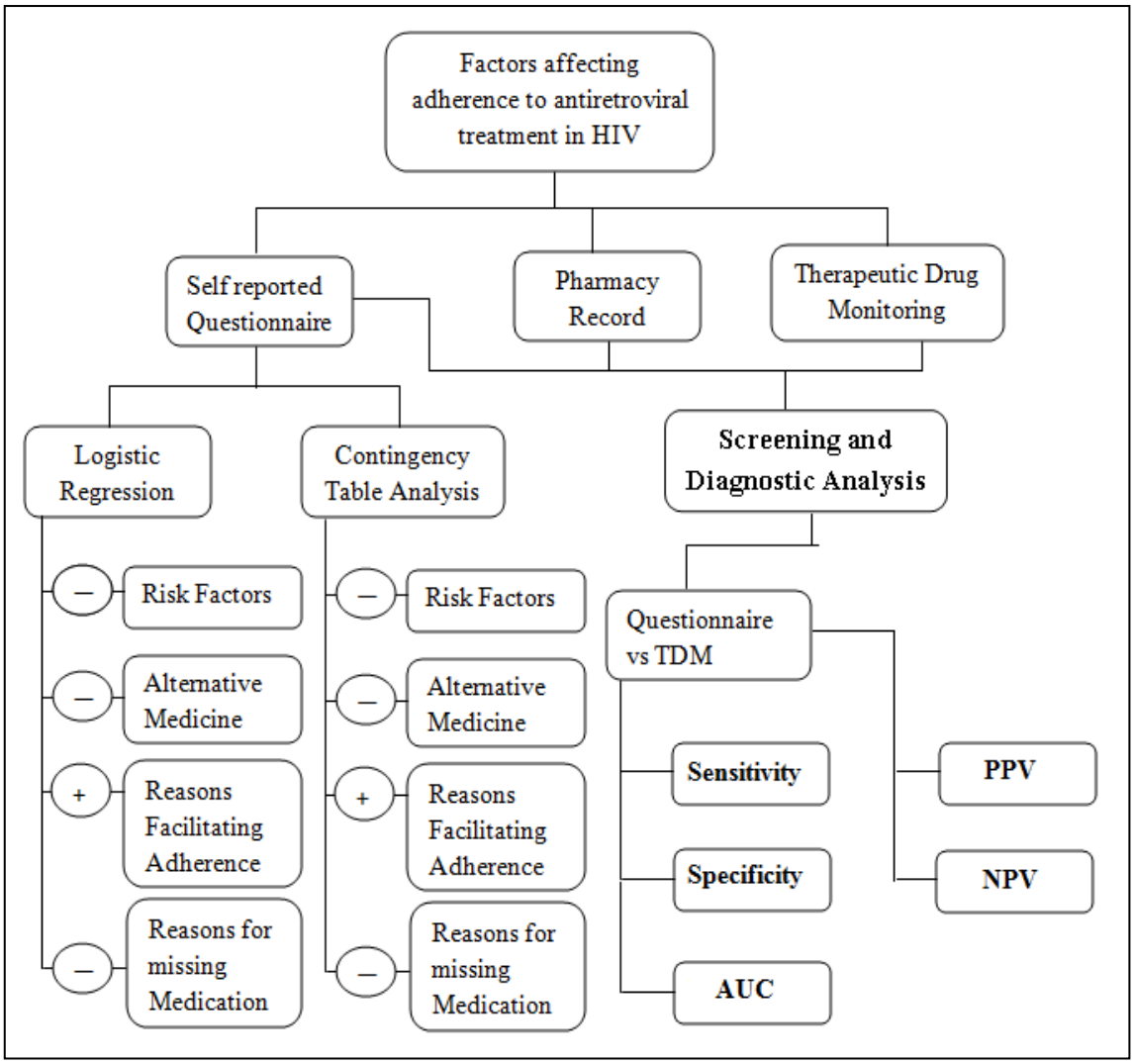
practice, patients may be lost, transferred, or die of competing causes. When losses or competing risks occur, one may still estimate the incidence rate using survival methods.

Figure 4.3 illustrates the conceptual framework of the study. It outlines the different ways of analyzing factors affecting adherence to antiretroviral treatment among HIV-positive patients. As shown by the figure, three different measures of 'adherence to antiretroviral treatment' were used: first is through self-reported adherence questionnaire, second is through pharmacy refill from online electronic records and the last one is by obtaining the drugs level using Therapeutic Drug Monitoring (TDM).

The self-reported questionnaire consists of 48 dichotomous questions that can be divided into four main groups as follows:

1) Risk factors of HIV treatment;
2) Alternative medications to HIV patients;
3) Reasons facilitating the adherence to treatment; and
4) Reasons for missing HIV medications.

With the exception of 'reasons for facilitating' variables, all variable groups have a negative relationship with adherence.



AUC = Area under the curve
PPV = Positive predictive value
NPV = Negative predictive value

Figure 4 2 Conceptual framework

As we would see in the data analysis and modeling section, the study uses different methods of analyzing factors affecting adherence to antiretroviral treatment in HIV. They include logistic regression analysis, contingency table analysis (descriptive/odd ratio), and screening & diagnostic test analysis. In order to achieve the desired results, this study was executed in the following phases:

Phase 1: Instrument Development and Validation, June 2009 – Oct 2009

During this phase, a self-reported study instrument for measuring overall adherence was developed. This involved pre-testing on fifteen participants with different educational level and backgrounds, forward and backward translation into Bahasa Malaysia, Mandarin and Tamil as well as a test-retest to check for reliability. Figure 4.3 outlines the translation process of the modified AACTG questionnaire from English languages into Malay, Chinese and Tamil languages.

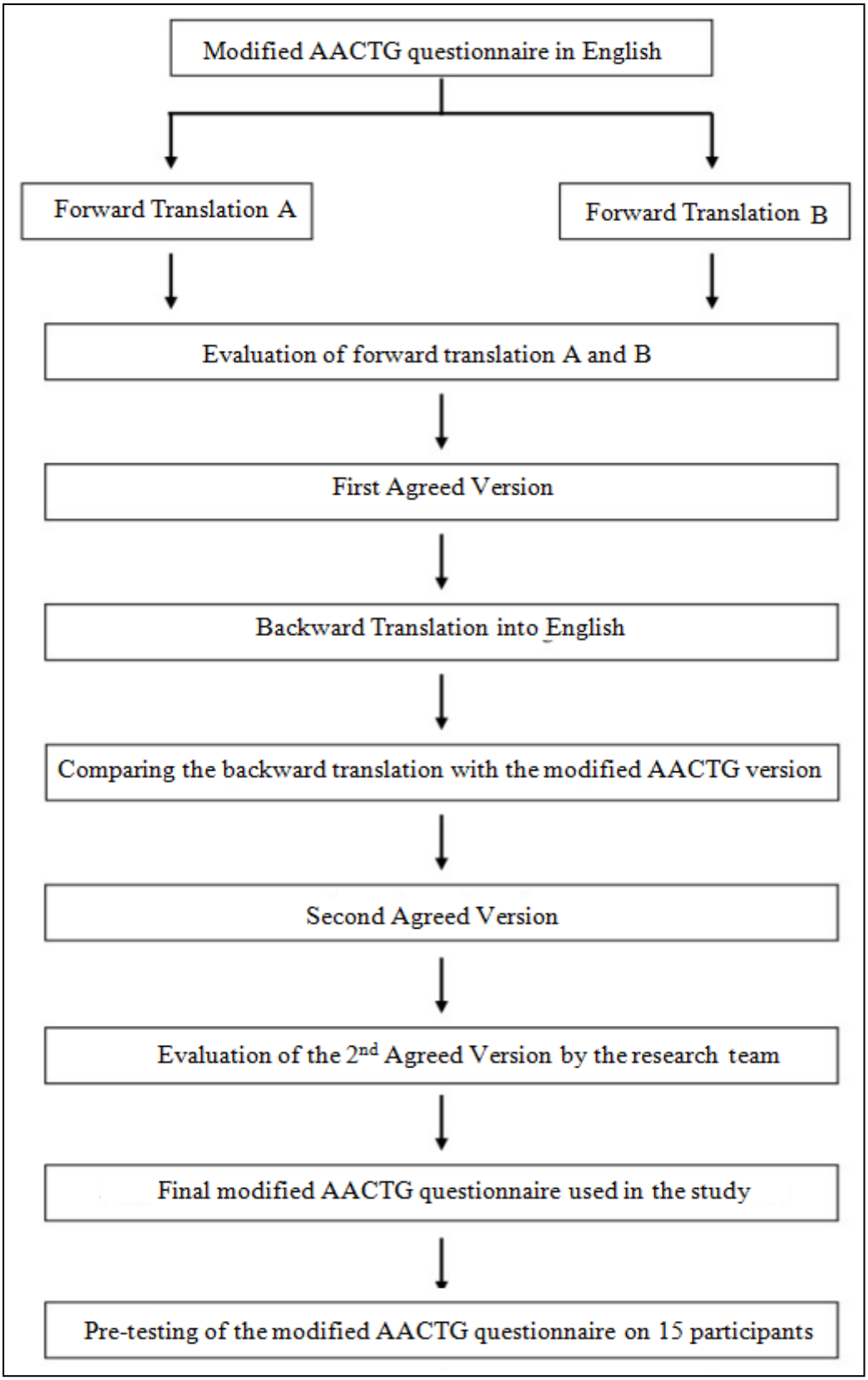


Figure 4-1 Forward and backward translation from English into Bahasa Malayu and Chinese.

Phase 2: Data Collection and Refinement, Nov 2009 – Oct 2010

The pharmacy refill instruments were applied to the study population over a 1-year period (Nov 2009 –Oct 2010). This was accompanied by blood taking in order to check for therapeutic drug concentration. Blood was frozen at between -20 to -80 degrees Celsius for future batch analysis.

Phase 3: Method Development and Validation using LC-MS/MS, Oct 2010 – March 2011

All chemicals and drugs for the LC-MS/MS therapeutic drug monitoring machine (Nevirapine, Lamivudine, Efavirenz and Zalcitabine) were obtained from Labchem Sdn. Bhd. in Kuala Lumpur. They were used in human plasma to develop standards for checking therapeutic drug concentration. This method was developed and validated using the LC-SM/MS machine first; then, the frozen plasma obtained from HIV-positive patients was used to check for the concentration of the drugs. Drugs tested for were Lamivudine, Efavirenz, and Nevirapine which are used by the Ministry of Health as part of the HAART regimen. The batch anlaysis and testing for drugs in human plasma was completed by April 2011.

Phase 4: Data Analysis and Report Writing, March 2011 – April 2012

The researcher culturally adopted, developed and validated the Adult AIDS Clinical Trials Group (AACTG) adherence questionnaire. The pharmacy refill counts were obtained from the online pharmacy records in Sungai Buloh Hospital. The collected data was entred into SPSS between Nov 2010- Feb 2011.Then, the findings were analysed (Feb 2011- June 2011) and presented in a few conferences. IT illustrates the flow chart of the study process starting from the proposal development through data collection till the report writing. It showed the duration for each step.

4.2 Study area and population

This study was carried out in Hospital Sungai Buloh, (a tertiary-level hospital in the Malaysian state of Selangor) which is located about 25 km from Kuala Lumpur, the capital of Malaysia. The hospital covers an area of 130 acres and has a capacity of 620 beds. It was built to meet the needs of the growing and crowded population in the district of Gombak, providing various medical services and tertiary services. Sungai Buloh Hospital has been identified as a centre of excellence for Infectious Diseases such as HIV/AIDS. The infectious diseases clinic operates 3 days a week from 8 a.m. to 5 p.m., catering for the treatment and follow-up of HIV/AIDS patients. It is the largest infectious disease hospital in Malaysia. Most of the data in this hospital are entered into an online electronic medical record system for all the patients and thus the data stored are easy to access and more accurate than the traditional medical record system and filing used in other hospitals.

The study population consists of patients who visited the HIV /AIDS clinic in Sungai Buloh Hospital for treatment and follow-up between November 2009 and October 2010. Prior to the establishment of this hospital in 2006, most of these patients went to Hospital Kuala Lumpur for their treatment and follow-up. The HIV patients came from three districts – Gombak, Petaling and Kuala Selangor. These three catchment areas have a total population of almost one million residents. A few other HIV patients came from the other areas of Kuala Lumpur.

4.3 Sample size

Researchers rarely survey or analyze the entire population; instead, they select a sample which is expected to explain the phenomenon under study for the entire population. Determining sample size is a very important issue, since samples that are too large may

waste time, resources and money, while samples that are too small may lead to inaccurate results. The sample size in this cohort study is based on their exposure status. The study subjects should be at risk of the outcome under investigation (adherent or non-adherent) at the beginning of the cohort study and as the cohort is followed through time to assess their later outcome.

The sample size for this research was calculated by using the Formula 3.1 below (Araoye, 2003) . The following assumptions were considered: first, the sample was representative; second, the sampling error was small; third, the sample was viable in the context of funds available for the research study; fourth, systematic bias was controlled in a better way; and finally, results from the sample study will be generalizable.

$$n = \frac{z^2\, p\, q}{e^2} \text{ ---------- } 3.1$$

Where: z= standard variate (1.96) which corresponds to 95% confidence interval

p = proportion of HIV and AIDS patients on ARV treatment who did not adhere

q = 1 – p

e = the desired marginal error (precision of measurement)

p = 0.20 (was found from previous similar studies (Talam et. al., 2008 and Aroaye, 2003).

q = 0.80

e = 0.026 (e is the margin of error which is the tolerable amount of error and usually standard of error of equal or less than 0.05 is acceptable).

$$n = \frac{1.96^2\ x\ 0.20\ x\ 0.80}{(0.026)^2} = 909 \approx 925$$

Thus, based on the values z = 1.96, p = 0.20, q = 0.80, and e = 0.026. The sample size, denoted by n, equals to 909 patients which is almost equal to 925.

4.4 Sampling procedure

Convenience sampling technique was applied and it was drawn from a group of patients undergoing antiretroviral treatment in Hospital Sungai Buloh, Malaysia who satisfied the inclusion criteria. Convenience sampling was used considering the problem of consent and poor response rate in HIV/ AIDS studies.

4.4.1 Inclusion criteria

The inclusion criteria were Malaysian nationals, adults (18 years and above) of either sex who were HIV-positive (person detected to have the human immunodeficiency virus HIV), used HAART for at least two month, obtained their treatment from the hospital pharmacy and gave written consent to participate in the study. Patients must actually be taking the following antiretroviral treatment drugs: lamivudine and /or efavirenz and /or nevirapine. They were selected based on the fact that most of the patients in Sungai Buloh Hospital were prescribed this combination by their physicians.

4.4.2 Exclusion criteria

Individuals who were either very ill or unable to complete the study questionnaire, those who are less than 18 years of age, pregnant women (due to changes in a pregnant woman's mental and physical health from pregnancy through six months postpartum), patients who refused to give a written informed consent, eligible patients who participated in the pre-testing and test-retest of the questionnaire, patients who were not on the three selected HAART medications used in this study and patients who were not

Malaysian by nationality were excluded from this study since we wanted to restrict generalize our results within the Malaysian populations only.

4.4.3 Ethical consideration

This study is approved by both the University of Malaya Medical Centre Research Ethics Committee and Ministry of Health Malaysia (Reference number 714.14, see Appendix J). Individual written informed consent form (Appendix F) was distributed to each participant in their preferred language and it was clearly stated that participation was voluntary and that the participant could withdraw from this study at any time. The consent form was signed after the purpose & benefits of the study had been explained to the participants. Privacy & confidentiality were maintained throughout the study period.

4.5 Study variables

This study on factors affecting adherence to antiretroviral treatment has 48 variables which can be categorized into two main groups: dependent variables and independent variables.

4.5.1 Dependent variable

The dependent variable of this study is called 'Adherence to antiretroviral treatment'. It is defined as having adherence level of more than 95% as measured by either of the following methods. The adherence level was assessed within aperiod of two weeks, four weeks and sex weeks respectively using overall self-reported adherence. Patients with 95% adherence level mean those patients had missed 5% of their prescribed dose. Adherence will then be categorized into high adherence (>95%), moderate adherence (75% to 95%) and lower adherence (<75%). The researcher used the WHO standard which requires a minimum adherence level of 95% or more for patients to be adherent

& avoid treatment failure [222, 223]. This variable was measured using self-reported adherence questionnaire, pharmacy refill from online electronic records and objectively by obtaining the drug level using Therapeutic Drug Monitoring (TDM).

4.5.2 Independent variables

Table 4-1: Independent variables

Group	**Variables**
Demographic	age, race, ethnicity, marital status, employment status, income level and level of education
Disease factors (side effects)	HIV transmission route, duration of HIV infection, Age, Sex, Marital Status, Vomiting, Diarrhoea, Loss of appetite, Dry mouth, Itching, Tiredness, Rashes, Fever, and Headache.
Treatment factors	duration of treatment, medication side effects, drug dose frequency and number for missed doses in preceding 4days.number of missed doses in 2 weeks, 4 weeks and 6 weeks.
Reasons for missing medications	distance to hospital too long and costly, was busy with other things, treatment and drug collection time in hospital too long, had a change in daily routine, felt well did not want others to notice you taking medications, simply forget was, away from home, felt depressed / over whelmed, religious belief, had problem taking pills at specified times, felt a sleep through dose time, cost of treatment too high, felt like drug was toxic, wanted to avoid side effects, poor relationships with health provider, ran out of pills, beliefs and preference for traditional medicine, felt sick or ill and had simply many pills
Reasons facilitating adherence to treatments	acceptance of one HIV status, use of Alarm/ clock, belief in the efficacy of pills, the needs to care for others, social support, self efficacy to take and adhere to ART, to avoid paying for new drugs, afraid of my health condition getting worse, afraid of developing resistance to drugs, disclosure revealing disease status).

Patients were asked to report the adverse effects of treatment such as itching, loss of appetite if such symptoms were felt only after taking their medications (this is to distinguish between symptoms due to disease and symptoms due to medication side effects)

4.6 Description of the study instruments used in this study

4.6.1 Self-reported questionnaire

Instead of choosing to develop and validate new instruments to use in this study, the researcher decided to translate, culturally adapt and use an instrument which is already validated in many developed countries and used in many international studies on measuring adherence to antiretroviral treatment. This is to avoid the high cost, huge resources and long time required for the development and validation of a new instrument. The researcher used the Adult AIDS Clinical Trials Group (AACTG) adherence questionnaire (see Appendix 1) which is designed and tested by the Center for AIDS Prevention Studies (CAPS) and made available free of charge at the following website: http://www.caps.ucsf.edu/tools/surveys/. This is for the benefit of HIV researchers, evaluators, prevention program planners and designers.

The AACTG questionnaire has been translated and used in some developing countries such as India, South Africa, Kenya, Pakistan and some other African countries (Balakrishnan et al., 2005; J. Nachega et al., 2004). Before translating the study instrument into Malaysian languages, the study team - after reviewing all items in the questionnaire - decided to exclude some items from the questionnaire and modified others that are not suitable to be used in Malaysia. The team members applied their clinical experience of working with HIV/AIDS-positive patients for many years in modifying the AACTG questionnaire and obtaining the final version to fit in the context of Malaysian society.

The AACTG questionnaire used in this study consists of two parts. The first part contains the introduction and questions about socio-demographic characteristics such as age, sex and marital status. The second part of the questionnaire includes questions related to the number of missed doses in the preceding days, 2 weeks, 4 weeks and 6 weeks, twenty questions on the reasons for missing medications and ten questions on reasons facilitating adherence to antiretroviral treatment. It also contains questions on prescribed medications as well as the number of doses taken and missed.

The total number of doses missed was assessed by first asking the patients to state whether or not they had missed any medication. Those who had missed medication were asked to choose the number of doses they missed (between one, two or three doses) over the specified period of four days, two weeks, four weeks and six weeks. Other questions on the adverse effects of treatment, use of alternative medicine such as yoga and use of traditional medicine are also included (see Appendix A). All questions are closed-ended questions. The True or False choices represent the frequency of experiencing a specific item during the last one month and answers are assigned a rating of 1 and 2 respectively.

Based on the study population in Sungai Buloh Hospital (study area), the study team decided to translate the new instrument into three languages - Malay, Chinese and Tamil - in addition to the English version. The guidelines used by WHO for translating and adapting study instruments in health was used. This guidline consisted of foreword transilation, backword transilation, pre-testing of the questionnaire and cognitive interviewing before obtaining the final version of the questionnaire. Three very well-experienced independent bilingual translators (who speak English and Malay, English and Chinese and English and Tamil) were selected to make a forward and backward

translation from English to Malay, Chinese and Tamil languages. The translators did a semantic translation and the instrument was then checked for the accuracy of translation. After this initial step, three bilingual translators and two monolingual reviewers participated in a back-translation process. Two of the back translators were from the original transilators who performed the forword transilation. After a repetition of the back-translation process to correct errors in translation, the target version of the final questionnaire was obtained. The questionnaire was then pretested on fifteen participants (due to the constraints in the available resources and the fact that there is no specific number for testing a questionnaire on) with different educational backgrounds and levels. They included three teachers, four general workers, two unemployed individuals and six students. The purpose of pretesting was to explore the feasibility of using this new instrument in the HIV/AIDS population in Sungai Buloh Hospital, and more importantly for accuracy, interpretability and to identify any problem associated with the new version of the questionnaire.

The researcher and two research assistants performed a test-retest reliability assessment on 40 HIV/AIDS-positive patients in the Infectious Disease Clinic of Sungai Buloh Hospital three months before the commencement of the main study. The questionnaire was administered twice with a two-week interval between the first and second sessions to avoid recall bias. A two-week interval was considered not too long enough for changes that could potentially affect responses to occur and not too short enough to enable the recall of previous responses (Brazier et al., 1992; Jackson et al., 1996).

All of the participants' identification numbers were listed and kept for future exclusion from the main study. The questions listed in the questionnaire were delivered in Malay, Chinese and English. Subjects were asked to attempt to answer all of the questions. The results were entered into the SPSS version 16 for analysis (Carver & Nash, 2006).

4.6.2 Pharmacy refill data instrument

In Sungai Buloh Hospital, HIV/AIDS-positive patients visit the pharmacy departments monthly to collect their prescribed medications. We decided to obtain information on the patients' last six visits to the pharmacy to collect their medications using the instrument (see Appendix E). A patient's most recent visit to obtain his/ her medication from the pharmacy is considered to be the last refill visit. This is for the purpose of comparison with other instruments used in this study. The research assistant retrieved data on the preceding six refill visits for each patient from the Pharmacy Information System and filled in the information on the instrument for each visit and medication.

The form used was designed by the researcher to collect data from the online pharmacy record in the pharmacy department of Sungai Buloh Hospital. The form was completed by a research assistant who was working in the above-mentioned department and had the experience of obtaining such information for other studies in the past. Data collected includes the patient's hospital number and date of visit. Each instrument was labelled with a number for the purpose of identification.

On each patient's refill visit, information such as the refill status (whether or not the patients collected a particular medication), number of pills prescribed per day, number of pills dispensed on each refill visit, specific date on which medication was dispensed and the exact number of days between each refill visit and its consecutive refill visit was

calculated. Since all participants in this study must be on one of the three drugs (Lamivudine, Efavirenz, or Nevirapine) a table was provided for each medication with a space for the above-mentioned information.

The adherence level for each medication was calculated using the following formula which is used in many international studies (Grossberg & Gross, 2007; Saberi, Caswell, Amodio-Groton, & Alpert, 2008).

Adherence = (pills dispensed/pills prescribed per day) / (days between refills) x 100%

4.6.3 Instrument for collecting investigation results

The test results for all the investigations carried by HIV/AIDS-positive patients participating in this study were obtained from the Laboratory Information System (LIS) by a research assistant, who completed the specific designed instrument (see Appendix E). The instrument contains the following information: patient's hospital number, date of collection, instrument number, patient's age and date of birth as well as method of exposure to the disease.

Investigation results that were obtained from the patient's electronic records include the baseline (after diagnosis of the disease), pre-treatment investigations (before the commencement of HAART) and most recent investigations done (at most six months before or during the current index visits) for each patient. Test results included haemoglobin level, white blood cells, CD4, CD8, viral load and detailed liver function test such as total protein, albumin and bilirubin levels. Other clinic information obtained includes the patient's baseline, pre-treatment and most recent weight (in kg). The

patient's disease history and past medical history were also obtained and filled in the instrument. The date for each of the above tests is filled in the space provided.

Table 4-2: Instruments used in the study

#	Description	Appendix
1	AACTG) questionnaire in English language	Appendix A
2	AACTG) questionnaire in Malay language	Appendix B
3	AACTG) questionnaire in Chinese language	Appendix C
4	Instrument for data collection from online records	Appendix D
5	Instrument designed for collection of data from hospital electronic medical records for both drugs and investigations tests results	Appendix E
6	Written inform consent form for obtaining patients consent	Appendix F
7	First blood collection instrument for Therapeutic Drug Monitoring	Appendix G
8	Second blood collection instrument for TDM	Appendix H
9	Pharmacy refill data instrument for number of drugs doses, time, date of collection and drug side effects	Appendix I
10	University of Malaya Medical Centre Research Ethics Committee approval form for conducting the study	Appendix J

4.6.4 Therapeutic Drug Monitoring (TDM) instrument

Monitoring drug concentration in humans to optimize efficacy and reduce toxicity is not a new concept in clinical pharmacology. It is also considered the most objective method for measuring adherence to antiretroviral treatment. In this study, blood samples were drawn by a phlebotomist after the patient had completed the self-reported questionnaire, and was on any of the following HIV drugs: Lamivudine, Nevirapine, and Efavirenz. The data collection instrument used for this procedure provides information such as detailed instructions for the blood sample collection, patient hospital number, date of collection, time of blood collection and time it was centrifuged.

Other information includes the name of the prescribed medications, dosage, date and time when the last dose was taken and number of doses administered per day (See Appendix D). Six ml of blood was drawn from the vein of each patient by a phlebotomist using lithium heparin tube and centrifuged within one hour of collection time. It was then transferred to 2 plain bottles (3ml each) for storage at -80 degrees in the Department of Pharmacology for future batch analysis using the Liquid Chromatography Mass Spectro-Photometery (LC-MS/MS) machine. The process of development and validation of the method for analysis of the above drugs is discussed in detail in Chapter 2 of this thesis.

4.6.5 Overall self-reported adherence

The self-reported questionnaires were then administered to patients who satisfy the inclusion criteria by two well-trained data collectors. Atrained interviewer was not employed to collect the data so as to reduce the cost which may arise since the sample size was large and extra-funding was required for the expensive labrotory work. The data collectors were two counsellors who attended a two-day training course given by the researcher on how to introduce the study to participants, administer the self-reported questionnaires, and fill in the blood forms. All of the information collected was based on the patient's self-report. The primary adherence measure is based on patients recall. Mean adherence level was calculated by asking participants to answer the following 4 questions (A to D) with a **Yes** or **No** response: A- Do you sometimes find it difficult to remember to take your medicine?; B-When you feel better, do you sometimes stop taking your medicine?; C-Thinking back over the past four days, have you missed any of your doses?; D-Sometimes if you feel worse when you take the medicine, do you stop taking it?

We then assessed adherence by counting the number of **No** answers to questions A to D. If all 4 answers were **No,** the patient was classified as being highly adherent, but if there was 1 **Yes** answer, the patient was classified as being moderately adherent. If there were 2 or more **Yes** answers, the patient was classified as having low adherence level (T. Barfod, Hecht, Rubow, & Gerstoft, 2006; TS Barfod, Sørensen, Nielsen, Rodkjær, & Obel, 2006).

The 4 questions were designed so that an adherent patient would need to give a **No** response since it has been observed that in many studies participants tended to answer **Ye**s to questions posed to them by their health care providers in order to please them (Nieuwkerk & Oort, 2005; G. Wagner & Miller, 2004). In order to measure the adherence level over longer periods of time (such as the preceding two weeks, four weeks and six weeks) from the day the questionnaire was administered, the percentages of medication actually reported to have been taken by the patients were calculated and regarded as the adherence level for each patient at the stated period of two weeks, four weeks and sex weeks accordingly. Adherence level was then categorized into high adherence (>95%), moderate adherence (75% to 95%) and low adherence (<75%). For analysis by logistic regression we dichotomized adherence level to define high adherence as >95% and lower adherence as <95%.

4.7 Data collection and entry

The following four methods were used to collect the data:

1- A self-reported questionnaire to measure adherence to therapy.

2- Collecting data from pharmacy records of drugs dispensed.

3- Instrument to obtain measure of response to therapy such as viral loads, CD4 cell counts, adverse events, nutritional status (i.e. BMI, body fat), and biochemical measures like haemoglobin, white blood cells and liver function tests.

4- Therapeutic drug monitoring using the LC-MS/MS method.

The above-listed methods were used to collect the required data for this study. Qualitative and quantitative data were collected using a pretested self-reported questionnaire (Appendix A-D) which was developed and culturally adapted for this purpose. The questionnaires were administered to eligible patients by two research assistants on their appointment days (usually on Mondays, Wednesdays and Fridays) after the patients' vital signs and weight had been recorded by the nurses. The questionnaire was administered in a private room after each patient had completed a written informed consent form (Appendix F).

The research assistants explained the importance and significance of the study to the participants. Participants were informed of their right to continue or withdraw from the study at any time and were asked to answer all the questions in the questionnaire and reminded that there were no right or wrong answers. The participants were encouraged to choose the most suitable questionnaire based on their language preference (i.e. English, Malay, Chinese or Tamil). Most participants completed their questionnaires in an average of five to ten minutes after which they were sent to an adjacent laboratory room.

Six ml of blood was drawn from each patient by a trained phlebotomist under a safe and sterile condition. The blood sample was collected in a lithium heparinised tube, labelled as the first blood sample and the blood collection instrument (Appendix G) was filled. The collected blood was then sent to the Haematology lab within one hour for centrifuging. It was stored in a refrigerator at -20 degrees Celsius and kept for batch transportation by the research officer to the Pharmacology Department. There, the blood was kept at a temperature of -80 degrees Celsius for future analysis using the Liquid Chromatography - Mass Spectrometry (LC-MS-MS) machine to determine the drug level.

Before each patient left the phlebotomy room, a second form (see Appendix H) for providing the second blood sample (one month after the first one) was given to them. For convenience, the second blood sample was collected when the patients came to collect their medications from the hospital pharmacy in the following month. Before starting the data collection, the researchers had conducted a training workshop for the data collectors to train them on aspects such as introducing the study to participants, administering the self-reported questionnaire, etc. Thus, a trained research assistant used the pharmacy refill data instrument (Appendix I) to obtain information on the type of drugs used, dosing frequency, number of pills taken per day and adverse drug effects) from the online electronic medical record. This was done in a private room in the Pharmacy Department three times a week after obtaining the hospital registration number of each patient who participated in the study in the previous week.

The completed instruments were collected by the researcher who compared the hospital number and instrument number of each patient and added them to the patients' self-reported questionnaires which were stored for future use. Another trained medical record clerk collected investigations and test results twice a week after obtaining the patients' hospital numbers from the list of patients who participated in the study using the provided instrument (Appendix E). All three of the above-mentioned instruments were kept by the researcher for data entry purpose.

Data was entered into an SPSS version 16 data file. Every categorical variable in the study instrument was given a name that identified its place in the data set, and for each variable every possible value is coded with a number. To ensure accuracy, the researcher did a double data entry at different times, making two complete sets of data with a similar structure. The two sets were then exported to Epi-Info for Windows version 3.4.3 and were validated using Epi-Info Compare. Some differences in the two sets of variables were noticed and the researcher went back to the original source of data to check for the correct answers and corrected them accordingly. Thirty five participants (3.6% from a total of 978 participants) had missing variables in the data and had to be removed from the data sets since their presence could have adversely affected the analysis. A final data set which was used for the analysis was then generated.

4.8 Data management

The data set was then imported into SPSS version 16 for analysis. Before analysis, data was cleaned and pre-processed which involved accuracy checking, treatment of missing values, recategorization and recoding of fields. Data was checked for accuracy and missing values were identified and rechecked for value correction based on the questionnaire which the participants had previously completed. Missing values of less than 5% were found, and this was due to a data entry error. The missing values which could not be corrected were removed from the data sets so as to avoid the analysis from being adversely affected. Finally, a total of 48 variables related to adherence among HIV-positive patients were analyzed.

4.9 Test- Retest, Reliability and Validity

The researcher and two research assistants performed a test-retest reliability assessment on 40 HIV/AIDS-positive patients in the Infectious Disease Clinic of Sungai Buloh Hospital three months prior to the commencement of the main study. The questionnaire was administered twice with a one week-interval between the first and second sessions to avoid recall bias. One week is considered not too long enough for changes that could potentially affect responses to occur and not too short enough to enable the recall of previous responses (Kalton & Schuman, 1982; Nieuwkerk & Oort, 2005). Questions listed in the questionnaire were delivered in Malay, Chinese and English. Subjects were asked to attempt to answer all of the questions. The results were entered into the SPSS version 16 for analysis (Carver & Nash, 2006).

The items in the questionnaire were binary-item scales to measure the level of adherence to antiretroviral treatment among HIV-positive patients in Malaysia. The questionnaire consists of 48 dichotomous questions, which measured the level of adherence to antiretroviral treatment among HIV-positive patients in Malaysia. These 48 questions were subdivided into the following 4 main groups: (1) Adverse effects of HIV treatment (9 questions); (2) Use of alternative medicine by HIV-positive patients (9 items); (3) Reasons facilitating adherence to treatment (10 questions); and (4) Reasons for missing HIV medication (20 items). All items in the questionnaire were binary-item scales.

To determine the accuracy and trustworthiness of the data, Cronbach and Split-half tests were used to test for internal consistency in order to check the repeatability of the scale as a whole. The face validity and construct validity were used to check if items in the instrument are right and valid.

4.9.1 Reliability Analysis

Reliability is the instrument's ability to provide consistent results in repeated uses (Rahman, 2001). Another way to look at reliability is by the following analogy: two people who are equal in terms of the construct being measured should get the same score. There are so many ways to test reliability but this study uses only the most common measures for reliability which are Cronbach's alpha, split-half reliability and inter-rater reliability (Grilo et al., 2001).

Cronbach's alpha is the basic measure for reliability; it is used to determine internal consistency between questionnaires. The value of the Cronbach Alpha coefficient ranges between 0 and 1. The closer the value is to 1, the higher the level of consistency is among the items. A commonly accepted rule of thumb is that 0.7-0.8 is an acceptable value for Cronbach's Alpha; values less than 0.7 are considered weak and unreliable; and reliabilities of higher than 0.95 are not necessarily desirable (Baessler, O'Neill, Maher, & Battistutta, 2010).

Split-half methodology is one of the measures to test internal consistency. This method splits the items in the data into two sets. A score for each instrument is calculated based on each half of the scale. If there is consistency in the data, the mean value between the two split parts should be similar, and the two halves of the questionnaire should also correlate perfectly – with large correlation being a sign of reliability. The final method for testing reliability of our data is by using inter-rater reliability (interclass correlation) on the binary items in the questionnaire that checks whether or not two or more raters are consistent (Boyer & Verma, 2000).

4.9.2 Validity Analysis

After reliability test, the next step is to test validity of the instrument measurements. This is important because it provides confidence that the empirical findings accurately reflect the proposed constructs. This study uses several measures of validity of the self-reported adherence questionnaire. The first one is the face validity which concerns the appearance of the questionnaire measurements. Several people who are well-versed in the field were asked about the validity of instruments in the questionnaire (S. N. Haynes, Richard, & Kubany, 1995). The second method for testing the validity of the data is convergent validity, which checks whether or not the items in an instrument

converge to the same intent. (Blackburn, Donnelly et al. 2004). The final method for testing the validity of instruments in the self-reported adherence questionnaire is Cronbach validity which is simply the square of the Cronbach reliability.

4.9.3 Test retest analysis

Test-retest analysis is one of the simplest ways of testing the stability and reliability of an instrument over time. As mentioned in above the data collection was performed twice in two different occasions. This is to check the stability and reliability of an instrument over time, if the results of the two periods differed by a great deal, then it is suspected that the measure was inaccurate. If the Spearman rank correlation (which is used for binary items) between separate administrations of the test is high (0.7 or higher), then it has good test-retest reliability (Rousson, Gasser, & Seifert, 2002).

4.10 Data analysis

After gathering data through the questionnaire, the researcher analyzed the data using SPSS version 16. All statistical values were considered significant at $P \leq 0.05$ with the exception of entry into the logistic regression model. For the latter, we chose p-value < 0.25 (Bendel & Afifi, 1977 and Mickey & Greenland, 1989). The researcher made sure the data were normally distributed. The following were used in analysing the collected data: descriptive analysis, comparative analysis of contingency tables, sensitivity, specificity, positive predictive value, negative predictive value, and receiver operating characteristic (ROC) curves to compare between SRA and TDM and logistic regression analysis. Four multivariate regression models between the dependent variables and independent variables were developed. Paired t –test was use to determine the factors affecting adherence. Cross tabulation of the HIV adherence predictors (independent

variables) with overall self-reported adherence questionnaire was prefored and odd ratio was used to report the results.

4.10.1 Descriptive statistics:

Descriptive statistics were used to analyze socio-demographic characteristics, calculate percentages of adherent and non-adherent patients (using the self-reported adherence questionnaire) for overall adherence level and calculate adherence level for individual medication using pharmacy records. Calculation of percentages of reasons for missing medication, reasons facilitating adherence, medication side effects, as well as the type of alternative medicine used for the treatment of HIV/AIDS was described by means of descriptive statistics such as calculation of frequency distributions and percentages as well as the use of appropriate statistical graphs.

The overall adherence level calculated by the self-reported questionnaire was then dichotomized into adherent for participants with adherence level equal to or greater than 95% and not adherent for participants with adherence level less than 95%. The operational definition of adherence level as adherent and not adherent was based on the fact that WHO requires 95% adherence level to antiretroviral therapy for successful treatment, avoidance of resistance development and treatment failure.

4.10.2 Comparative analysis of contingency tables:

This section is on comparison of adherence level to the different independent variables using cross tabulation analysis with odds ratio and chi-square analysis. A cross tabulation analysis is useful to show how respondents answered to two or more questions at the same time; hence, this would give us greater insights. The Crosstabs

procedure forms two-way and multiway tables and provides a variety of tests and measures of association for two-way tables.

Specifically, we would make a cross tabulation of four different classification schemes in adherence to antiretroviral therapy (overall adherence level measured by self-reported questionnaire, adherence to HIV medication as measured by TDM for Efavirenz, adherence to HIV medication as measured by TDM for Nevirapine, and adherence to HIV medication as measured by TDM for Lamivudine) versus HIV adherence to HAART predictors (socio-demographic characteristics, adverse effects of treatment, alternative medication used for HIV treatment, reasons facilitating adherence to HAART and reasons for missing HAART medication).

4.10.3 Sensitivity, Specificity and Predictivities of Self Reported Adeherence versus TDM

To be certain about the results of our instrument and tests (TDM levels for three medications vs Self-reported adherence level) we need to do evaluation of screening or diagnostic test using sensitivity, specificity, positive and negative predictive values as well as diagnostic accuracy (all with 95% confidence intervals). Contingency table of 2 x 2 serves as a basis of our analysis of diagnostic tes; Table 4.3 which is 2 x 2 contingency table provides the outcome of two test on a sample of n subjects. According to the table, test positive people would be a+b, and test negatives would be c+d. The true positive were in cell ‘a’ and those true negative were in cell d. From this table, we calculated the sensitivity, specificity, and predictive value using the formulas bellow the table.

Table 4-3: 2 x 2 contingency table

	Test 2 positive	Test 2 negative	Row total
Test 1 positive	*a*	*b*	*a + b*
Test 1 negative	*c*	*d*	*c + d*
Column total	*a + c*	*b + d*	*n*

From the above table, we calculated the sensitivity, specificity, and predictive value using the formulas bellow the table.

- Sensitivity is the proportion of test positives and is found by = a/(a+c).
- Specificity is the proportion of test negatives in those who are without disease and is found by = d/(b+d).
- Positive Predictive value (PPV) is the proportion of people who tested positive on the screening test who are actually sick = a/(a+b).
- Negative predictive value is the proportion of people who are tested negative on the screening test who are actually not sick = d/(c+d

4.10.4 Multiple logistic regression techniques:

Four logistic regression models were used to determine the effect of independent variables on the dichotomized adherence level measured by: 1) self-reported adherence questionnaire; 2) TDM level for Efavirenz using the LC-MS/MS machine; 3) TDM level for Nevirapine using the LC-MS/MS machine; and 4) TDM level for Lamivudine using the LC-MS/MS machine. In this modelling, 48 independent variables were used to determine the predictors of adherence to treatment such as 'reasons facilitating adherence', 'reasons for missing medications', 'socio-demographic characteristics', 'adverse effects of treatment to antiretroviral medications' and 'use of alternative medicine for HIV/AIDS treatment by HIV-positive patients on HAART'. The researcher would make a comparison between the outcomes of the four regression

models besides indicating which independent variables may be good predictors of HIV patients' adherence to HAART.

The specification method of prediction was "Enter" by which the researcher specifies the variables that will go into the regression equation and the stage at which they go in. The results were interpreted using the odds ratios and 95% confidence intervals (Bendel & Afifi, 1977; Greenland, 1989). P-values of <0.25 were used to decide variables for initial entry into the model; the last category was used as a reference for all binary variables. Overall, this study uses the identification scheme and modelling techniques of Hosmer-Lemeshow.

The logistic regression model is expressed as follows [3]:

$$\ln(ODDS) = \ln\left(\frac{\hat{Y}}{1-\hat{Y}}\right) = a + bX$$

Where:

$\hat{Y}$ is the predicted probability of the event which is coded with 1 (Adherent) rather than with 2 (Non-Adherent),

$1-\hat{Y}$ is the predicted probability of the other decision, and

X_i is our predictor variables.

Logistic regression predicts the log odds of the dependent event. The "event" is a particular value of y, the dependent variable. By default, the event is y = 1 for binary dependents coded 0, 1, and the reference category is 1. The natural log of the odds of an event equals the natural log of the probability of the event occurring divided by the probability of the event not occurring:

ln(odds(Adherence)) = ln(prob(adherence)/prob(non-adherence)). The logistic regression equation itself is:

$$\text{Log}(y) = \beta_0 + \beta_1 * X_1 + \beta_2 * X_2 + \beta_3 * X_3 + \beta_i * X_k.$$

$$\text{Log}\left\{\frac{P}{1- P}\right\} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots \beta_i X_k$$

$$\frac{P}{1 - P} = exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots \beta_i X_k)$$

$$P = \frac{exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots \beta_i X_k)}{1 + exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots \beta_i X_k)}$$

$$exp(\beta_0) = Odds\ Ratio$$

Where y is the log odds of the dependent variable = ln(odds(adherence));

β_0 is the constant; and

there are k independent (X) variables.

The "y" is the logit, also called the log odds.

The " β " terms are the logistic regression coefficients/ parameter estimates.

Exp(b) = the odds ratio for an independent variable = the natural log base e raised to the power of b. The odds ratio is the factor by which the independent increases or (if negative) decreases the log odds of the dependent.

In Multivariate Linear Regression, the model (b coefficients) is determined by the "least-square" method but in logistic, the model is determined by the "maximum likelihood" method. Therefore, in logistic, b coefficients are called maximum likelihood estimators (MLE). The logistic and linear regression models differ in assumptions. In linear regression, we interpret b coefficients but in logistic regression, the exp (b) which is Odds Ratio is interpreted. An odds ratio of 1 indicates no difference in risk between the groups, i.e. the odds in each group are the same. If the odds ratio of an event is >1, the rate of that event is increased in patients who have been exposed to the risk factor. If <1, the rate of that event is reduced. Odds ratios are frequently given with their 95% CI – if the CI for an odds ratio does not include 1 (no difference in odds), it is statistically significant.

The following are the steps that the researcher had followed for modelling logistic regression. The first step was to explore the data (Descriptive Statistics). Next, the researcher did a simple (binary) logistic regression modelling, and the third step was to conduct variable selection & checking "linearity in the logit". Then, in the fourth step, the researcher checked whether there was an interaction & multicollinearity effect. The fifth step was to check model assumptions and outliers. Lastly, the final step was the interpretation of the final model.

Initial model building starts with a model of intercept and one explanatory variable. Then, the construction of multivariate model starts by adding variables into the model one by one until the newly added variable does not improve to the prediction power of the model. This is tested through the G statistic (difference in -2 Log likelihood ratio for the overall model with a nested model), Hosmer-Lemshow test, Omnibus test, and Wald statistic. For more information and discussion on the practical model building steps, see Chapter Four and Five, the results and discussion.

G statistics is analogous to the F test of linear regression models (Chow, 1960). G statistic is compared with the chi-square table, and if the G > the Chi-square, the null hypothesis is rejected and it is concluded that at least and perhaps all p coefficients are different from zero at $\alpha = 0.05$.

This means that the inclusion of the new variable into the model has improved it. Another statistic of the measure of goodness of fit is Hosmer and Lemeshow chi-square test; this test is the recommended test for overall fit of a binary logistic regression model (Hosmer, Hosmer, Le Cessie, & Lemeshow, 1997).

A finding of non-significance corresponds to the conclusion that the model adequately fits the data. Another way to justify the fitness of the model is by looking the Omnibus test; which tests whether or not the explained variance in a set of data is significantly greater than the unexplained variance. A finding of significance corresponds to the conclusion that there is adequate fit of the data to the model, meaning that at least one of the predictors is significantly related to the response variable.

Checking linearity in logit for numerical independent variables:

In our independent variables in the model, only age is a numerical variable. Here, the researcher tested whether age is linear in logit (of outcome) or not. There is more than one method to check this assumption. However, the researcher used the design variable based quartiles method. The following steps were followed to check the linearity problem: First, the researcher categorized the variable in quartiles (4 levels); second, he calculated the midpoints of the quartile groups; third, he fit the model with the 4-level categorical variable and finally, the researcher plotted the midpoints to observe the linearity. If non-linear, the assumption of "linear in logit" is not satisfied. This means that the numerical variable is not appropriate. The solution to this problem is to use categorized variable instead of using numerical variable. However, as you would see in the results chapter, we found the age variable as linear.

Checking Interactions:

An interaction occurs when the effect of one independent variable on the dependent variable is influenced by (or depends on, or interacts with) another independent variable. To assess whether an interaction is present or not, all possible two-way interactions were checked (one at a time), then the researcher added the created interaction terms to the "main effect model" as additional independent variables and ran the model again using the “Enter” method. If an interaction term is significant ($P<0.25$), it means that there is an interaction between the two variables. Thus, the appropriate model is the main effect variables plus the significant interaction term.

CHAPTER 5 RESULTS

5.1 Sample information

Figure 5.1 is a flow chart for the sample information during the study period. Those who had complete data and included in the analysis were a total of 925 or 94.6% of the all HIV-positive patients recruited for the study. More than 381 patients or 41.8% had been on HAART for more than three years while 238 or 25.8% of the patients had been on HAART for one year or less.

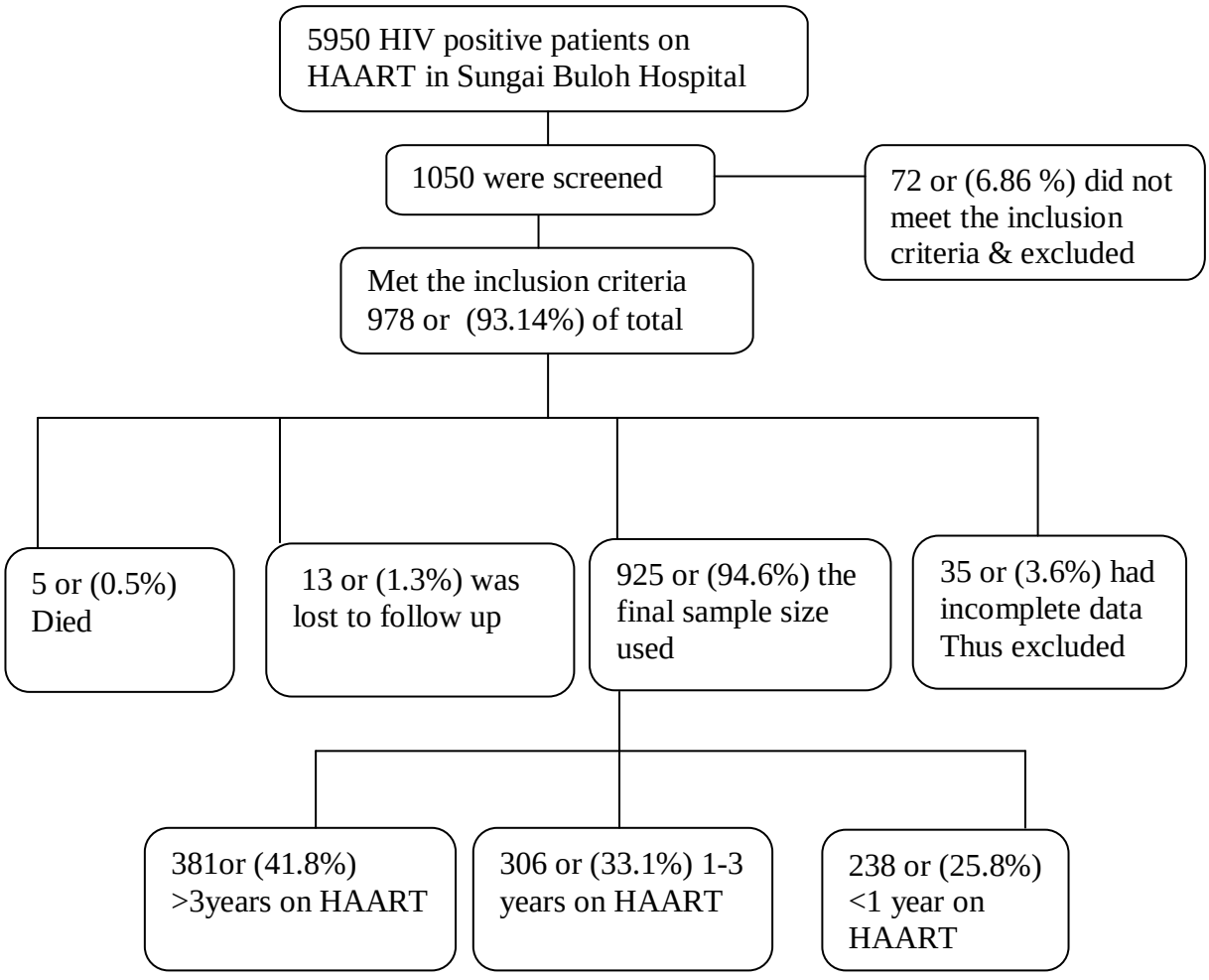


Figure 5-1 Flow chart of study participants (n=925)

5.2 Socio -demographic variables

This section provides a description of demographic variables included in the logistic regression analysis and contingency table analysis to investigate the research questions. At the beginning, a total of 5950 patients were identified as having HIV infection. Out of these, 1050 patients were screened, of which 978 patients met the inclusion criteria and responded to the distributed questionnaires, the remaining 72 patients did not met the intial screening and were excluded.

The socio-demographic and baseline characteristics of the participants are shown in Table 5.1 and 5.2 below. Out of the 978 patients who fulfilled the inclusion criteria, 925 patients had correctly filled the questionnaires. A total of 53 (5%) patients were identified as having incomplete data, 13 (1.3%) of the participants were lost to follow up while 5 (0.5%) of the participants died. The remaining 35 or 3.6% respondents had missing values in their data and had to be removed in order to not affect the analysis, since the study has a big sample of 925 patients.

The highest percentage of the participants consists of those who were educated with secondary school level and above (658 or 71.2%), while 49 or 16% had primary school education.The educated with secondary school level is noticed to be high this could be due to bias since the questionnaire is self-administered. Only 118 or 12.8% of the participants had no formal education. More than half of them (505 or 54.6%) were employed, 193 or 20.9% were unemployed and 58 or 6.3% were retired. About 366 or 39.6% of the participants had an average monthly income of less than RM1500 (USD480) per month, 242 or 26.2% had a monthly income between RM 1501 and RM2500 (USD480-USD800) per month, while only 26 or 2.3% had an average monthly income of more than RM6500

(USD2080) per month. Less than half of the participants (451 or 48.8%) were exposed to HIV infection through the heterosexual route, followed by 278 (30.1%) who were infected through injecting drug use. 140 (15.1%) of them were infected via the homosexual route.

Table 5-1: Socio-Demographic characteristics (n =925)

Variable	N	%
Gender		
Female	219	23.68
Male	706	76.32
Race / Ethnicity		
Malay	250	27.03
Chinese	585	63.24
Indian	72	7.78
Others (Dayak , Kadazan)	18	1.95
Age group in years		
18—30	330	35.68
31—44	338	36.54
45 or more	257	27.78
Religion		
Islam	258	27.89
Buddhism	448	48.43
Hinduism	53	5.73
Christianity	97	10.49
Taoism	55	5.95
Others	14	1.51
Completed Education		
No formal schooling	118	12.8
Primary school	149	16.1
Secondary school up to form 3	251	27.1
Secondary school up to form5	215	23.2
High school(form 6 / A level)	60	6.5
Diploma	41	4.4
Degree	91	9.8
Current job status		
Not employed	193	20.9
Employed	505	54.6
Self employed	146	15.8
Retired	58	6.3
Retired but re-employed	23	2.5

Table 5-2 : Socio-demographic characteristics (continued)

Variable	N	%
Average monthly income		
< RM 1500	366	39.57
RM1501—2500	242	26.16
RM2501 – 3500	152	16.43
RM3501—4500	60	6.49
RM4501—5500	50	5.41
RM5501—6500	29	3.14
RM6501 or more	26	2.81
Marital status		
Single	373	40.32
Married	440	47.57
Separated (Married but not living together)	21	2.27
Divorced	39	4.22
Widow / Widower	52	5.62
Number of children		
0 (No child)	500	62.5
1—3	279	30.2
4—6	127	13.7
>6	19	2.1
Number of children living with patients		
0 (No child)	58	62.9
1—3	265	28.6
4—6	68	7.4
>6	10	1.1

Table 5.3 shows the exposure risk of HIV-positive patients on HAART. The most common exposure risk was through the heterosexual route, followed by injecting drug use. The least common exposure risk was through received blood or blood products. Nine out of the 925 participants' exposure risks were unknown.

Table 5-3: Exposure risk of HIV positive patients (n = 925)

Variable	N	%
Bisexual	7	0.8
Homosexual	140	15.1
Heterosexual	451	48.8
Heterosexual / Homosexual through IDU	35	3.8
Injecting drug use	278	30.1
Received blood / blood product	1	0.1
Unknown	9	1.0
Others	2	0.2

5.3 Test, test-retest, reliability and validation

This section is about findings of the test-retest, reliability and validity of the study. Reliability test consists of the following three different ways of testing: Cronbach alpha, split-half and inter-rater reliability. For the validity test, the study uses three types of testing validity of the study: face validity, convergent validity and Cronbach validity. The last part of this section provides findings of the test-retest

5.3.1 Reliability

A) Cronbach Alpha

This test was employed to determine internal consistency between items within each domen. Table 5.4 provides the values of Cronbach's alpha of the above-mentioned four item groups (adverse effects of HIV treatment, alternative medicine used by HIV-positive patients, reasons facilitating adherence to treatment, and reasons for missing HIV medication). The results show that the Cronbach's Alpha reliability coefficient for all variables were above the acceptable limit of 0.70 and only one alpha is slightly above 0.8.

Table 5-4: Reliability Statistics: Internal consistency by Alpha Cronbach

Group of Variables	Cronbach's Alpha	Cronbach's Alpha Based on Standardized Items	N
Adverse effects of HIV treatment	.826	.828	9
Use of alternative medicine	.777	.779	8
Reasons facilitating adherence	.813	.812	10
Reasons for missing HIV medications	.873	.875	20

N = Number of iteams in each category

Tables 5.4 to 5.7 provide a column labelled 'Cronbach's Alpha if Item deleted'. This refers to the value of the overall alpha if that item is not included in the calculation. It was found that each of the 47 items on the adherence level scale has a smaller Cronbach's Alpha value than its corresponding calculated scale alpha mentioned in Table 5.4. This implies that no single item in the scale suppresses its corresponding alpha level. Therefore, the self-reported questionnaire of this study can be considered as a reliable measure of adherence level to antiretroviral treatment in HIV-positive patients.

Table 5-5: Item-Total Statistics of Adverse effects of HIV treatment

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Cronbach's Alpha if Item Deleted
Vomiting	1.45	4.151	.517	.342	.810
Diarrhoea	1.43	3.789	.745	.760	.783
Appetite	1.38	3.984	.507	.380	.811
Dry Mouth	1.40	3.836	.653	.680	.793
Itching	1.43	4.251	.394	.276	.822
Tiredness	1.33	4.020	.430	.385	.822
Rash	1.40	4.195	.397	.321	.823
Fever	1.40	3.990	.540	.442	.806
Headache	1.40	3.887	.615	.591	.798

Table 5-6: Item-Total Statistics of Use of alternative medicine

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Cronbach's Alpha if Item Deleted
Alcohol	1.22	2.846	.532	.468	.745
Alternative med	1.22	3.051	.351	.228	.773
Herbal med	1.22	2.999	.395	.242	.766
Yoga	1.12	2.830	.408	.383	.768
Acupuncture	1.20	2.779	.544	.623	.742
Dietary	1.22	2.897	.485	.636	.752
Mind	1.20	2.779	.544	.469	.742
Religious treatment	1.20	2.728	.589	.444	.734

Table 5-7: Item-Total Statistics of Reasons facilitating adherence

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Cronbach's Alpha if Item Deleted
RFA_Acceptance	7.23	4.999	.476	.308	.798
RFA_Discosure	7.28	4.871	.497	.297	.796
RFA_Alam	7.25	4.859	.529	.545	.792
RFA_Beleif	7.20	5.036	.487	.425	.797
RFA_Care	7.25	4.654	.653	.640	.777
RFA_Social	7.23	4.794	.601	.525	.784
RFA_Afraid	7.23	5.102	.415	.273	.805
RFA_Resistance	7.18	5.071	.505	.432	.795
RFA_paying	7.20	5.138	.423	.268	.803
RFA_Efficacy	7.20	5.292	.330	.379	.813

RFA = Reason Facilitating Adherence. RFA – Acceptance = Acceptance of HIV Status as a Reason facilitating adherence to treatment

B) Inter-rater Reliability

The values of inter-rater are reported in Table 5.8. This table provides a single measure of Inter-rater Correlation for each of the four item groups. It was found that the intra-class correlation of each of the four item groups of adherence has a correlation score of 0.3 which is acceptable; this indicates reproducibility of the data (Fleiss, et al. 1979).

The following is the intra-class reliability of the four variable groups. On average, 'Adverse effects of HIV treatment' has an intra-class correlation of 0.827 with an interval of 0.744 to 0.897 and 95% confidence level while the 'Use of alternative medicine' has an intra-class correlation of 0.780 with an interval of 0.659 to 0.870 an 95% confidence. The variable group 'Reasons facilitating adherence' has an average intra-class correlation of 0.815 and an interval of 0.716 to 0.890 and 95% confidence. Next, 'Reasons for missing medication' has an average intra-class correlation of 0.875 with an interval of 0.811 to 0.925 and 95% confidence. In summary, the reliability estimates produced under the intra-class correlation models are numerically identical, suggesting a moderate agreement of the data.

Table 5-8: Intra-class Correlation Coefficient

Variable groups	Intra-class Correlation	95% Confidence Interval		
		Lower Bound	Upper Bound	Value
Adverse effects of HIV treatment				
Single Measures	.347	.234	.493	5.733
Average Measures	.827	.734	.897	5.733
Use of alternative medicine				
Single Measures	.307	.194	.455	4.490
Average Measures	.780	.659	.870	4.490
Reasons facilitating adherence				
Single Measures	.305	.202	.448	5.343
Average Measures	.815	.716	.890	5.343
Reasons for missing medications				
Single Measures	.259	.176	.381	6.224
Average Measures	.875	.811	.925	6.224

C) Split half methodology

The final method of testing reliability of the questionnaire instrument is the split-half methodology. This methodology splits items into two groups and then compares these groups as if they were two separate administrations of the same survey. Table 5.9 below provides the results for split-half reliability. For each of the four item groups, the scale of the first half split (Part 1) is similar to the other half split (Part 2) as their mean scores and alpha did not differ much; besides that, for each of the two, half splits show a high correlation coefficient, which suggests a high internal consistency of the instruments.

Table 5-9: Results for split-half reliability

Description	Part 1			Part 2			
	Mean	Alpha	Items	Mean	Alpha	#	Correlation
Adverse effects of treatment	0.80	0.761	5	0.77	0.629	4	0.692
Use of alternative medicine	0.70	0.542	4	0.67	0.720	4	0.626
Reasons facilitating adherence	3.93	0.730	5	4.10	0.632		0.682
Reasons for missing	1.92	0.756	10	1.95	0.762	10	0.855

5.3.2 Validity Analysis

The validity of the adherence level of HIV medication scale was measured through face validity analysis and Cronbach validity analysis.

A) Face validity: The study instruments were checked by three public health consultants in the department who believed that the self-reported adherence questionnaire appears to measure what it is supposed to measure and because of this, it is valid (Nevo 1985). In summary, as seen in the different methods of reliability analysis and validity statistics of the above tables, all items seem to be contributing well to the scale's reliability and validity.

B) Cronbach validity: The third approach that is used to test the validity of the questionnaire instrument is the Cronbach validity. This test is the square root of Cronbach Alpha that was previously mentioned. Table 5.10 provides the results of Cronbach Validity (square root of the alpha) which is a measure of the extent to which the results and findings can be generalized. As the table shows, each of the four item groups that measure adherence level of antiretroviral treatment in HIV-positive patients has an acceptable coefficient alpha.

Table 5-10: Reliability Statistics: Internal consistency by Alpha Cronbach

Group of Variables	Square root of Cronbach's Alpha	Sqrt Cronbach's Alpha Based on Standardized Items	N of Items
Adverse effects of HIV treatment	0.909	0.910	9
Use of alternative medicine	0.881	0.883	8
Reasons facilitating adherence	0.902	0.901	10
Reasons for missing HIV medications	0.934	0.935	20

5.3.3 Test retest analysis

Test-retest analysis is the simplest method of testing the reliability of a study. In this analysis, the survey is administered twice to the same group of people and then the two sets of results are correlated. In other words, test-retest reliability is the correlation between the same tests administered at two time points (Weir 2005). The following table provides the correlation coefficient of the test-retest variables. As shown in Table 5.11, almost all of the test-retest Spearman correlations of the 4 group variables (side effects of treatment, use of alternative medicine, reasons facilitating adherence and reasons for missing HIV

medication) are greater than 0.3, thus the instrument is said to have a good test-retest reliability (Fleiss, et al. 1979).

Table 5-11: Spearman Correlation analysis of test-retest data

Adverse effects of HIV treatment			Use of alternative medicine		
#	Variables	Value	#	Variables	Value
1	Vomiting 1 and 2	0.314286	1	Alcohol 1 and 2	0.899735
2	Diarrhoea 1 and 2	0.315063	2	Alternative med 1 and 2	0.359313
3	Appetite 1 and 2	0.218750	3	Herb med 1 and 2	0.688033
4	Dry Mouth 1 and 2	0.263181	4	Yoga 1 and 2	0.341882
5	Itching 1 and 2	0.411765	5	Acupuncture 1 and 2	0.307359
6	Tiredness 1 and 2	0.404226	6	Dietary 1 and 2	0.215686
7	Rash 1 and 2	0.427669	7	Mind 1 and 2	0.480519
8	Fever 1 and 2	0.382088	8	Relig_treatment 1 and 2	0.653680
9	Headache 1 and 2	0.263181	9		

Reasons facilitating adherence			Reasons for missing HIV medications		
#	Variables	Value	#	Variables	Value
1	RFA_Acceptance 1 and 2	0.188982	1	RMM_Away 1 and 2	0.539650
2	RFA_Disclosure 1 and 2	0.290929	2	RMM_busy 1 and 2	0.329276
3	RFA_Alam 1 and 2	0.382088	3	RMM_forget 1 and 2	0.452061
4	RFA_Beleif 1 and 2	0.134199	4	RMM_manypills 1 and 2	0.375000
5	RFA_Care 1 and 2	0.628619	5	RMM_effects 1 and 2	0.518476
6	RFA_Social 1 and 2	0.218750	6	RMM_stigma 1 and 2	0.359313
7	RFA_Afraid 1 and 2	0.098693	7	RMM_routine 1 and 2	0.653680
8	RFA_Resistance 1 and 2	0.359313	8	RMM_toxic 1 and 2	0.223814
9	RFA_paying 1 and 2	0.359313	9	RMM_asleep 1 and 2	0.359313
10	RFA_Efficacy 1 and 2	0.263181	10	RMM_sick 1 and 2	0.264628
			11	RMM_depressed 1 and 2	0.427669
			12	RMM_well 1 and 2	0.490098
			13	RMM_nopills 1 and 2	0.592157
			14	RMM_specific 1 and 2	0.665133
			15	RMM_religous 1 and 2	0.250000
			16	RMM_waiting 1 and 2	0.375000
			17	RMM_distance 1 and 2	0.375000
			18	RMM_relation 1 and 2	0.134199
			19	RMM_cost 1 and 2	0.458333
			20	RMM_tradional 1 and 2	0.427669

5.4 Measuring Adherence Level

The adherence level was measured subjectively by the overall self-reported adherence questionnaire and pharmacy records method, and objectively by testing for HAART drug level in human plasma through Therapeutic Drug Monitoring (TDM) using the LC-MS/MS machine.

5.4.1Measuring adherence using over all self-reported adherence questionnaire

Figure 5.2 below shows the number of HIV-positive patients who missed their medication in the last 2 weeks, 4 weeks, and 6 weeks before the study as well as the number of medication doses they had missed. In the last 2 weeks before the study, only 22 or 2.3% patients missed two or more doses, compared to 48 or 5.2% in the last 4 weeks and 62 or 6.7% participants in the last 6 weeks before the study. The results in this table revealed that participants missed more doses of their medication as the number of weeks increased.

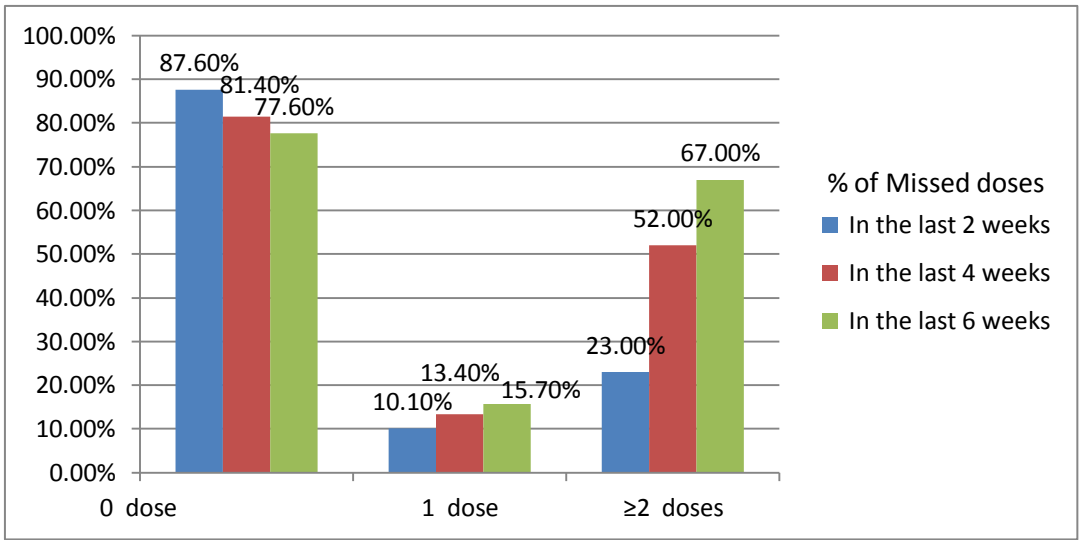


Figure 5-2 Number of HIV positive patients missing their medications (n =925)

Table 5.12 displays the adherence level to antiretroviral treatment using the self-reported questionnaire. Four questions (A to D, as mentioned below) were designed to obtain information on the time of taking HAART medication, number of doses missed over the past days and whether or not a patient will stop taking medication when he/she feels better or worse**.**

Table 5-12: Assessing adherence to Highly Active Antiretroviral Treatment in HIV positive patients in Sungai Buloh Hospital using overall self-reported adherence questionnaire (n =925)

Questions	**YES (%)**	**NO (%)**
A	123 (13.3)	802 (86.7)
B	28 (3.0)	897 (97.0)
C	40 (4.3)	885 (95.7)
D	37 (4.0)	888 (96.0)

A-Do you sometimes find it difficult to remember to take your medicine?
B-When you feel better, do you sometimes stop taking your medicine?
C-Thinking back over the past days, have you missed any of your doses?
D-Sometimes if you feel worse when you take the medicine, do you stop taking it?

Table 5.13 below reveals the results of adherence level as measured using the overall self-reported adherence questionnaire. Out of 925 participants, 756 or 81.7% of them had adherence level equal to or greater than 81.7% and were classified as adherent, whereas 169 or 18.3% were classified as not adherent. This means that the adherence level is high, although the figure is less than the required 95% adherence level by the World Health Organization (WHO).

Table 5-13: Adherence level measured by overall self-reported adherence questionnaire (n = 925)

Adherence status	N	%
Adherent(≥95% adherence level)	756	81.7
Not adherent (< 95% adherence level)	169	18.3
Total	925	100

95% adherence level is operational definition used because it is WHO requirement for the definition of adherent to HAART**.**

5.4.2 Measuring adherence using pharmacy records

Table 5.14 below describes the type of HAART used by each HIV-positive patient based on the information obtained from the online electronic pharmacy record. The results show that patients were on combined medication. The most common type of drug used was Efavirenz, followed by Nevirapine. The least commonly used drug was Lamivudine.

Table 5-14: Number of HIV positive patients on each antiretroviral drug used in HAART (n =925)

Drug name	Yes (%)	No (%)
Efaviranz (DMP-266)	791 (85.5)	134 (14.5)
Nevirapine	653 (70.6)	272 (29.4)
Lamivudine (3TC)	594 (64.2)	331 (35.8)

Table 5.15 below shows the group of HAART used by participants, the HAART medication used, the number of medication taken per day, number of pills or tablets taken per day and the duration of HAART used (in years). The results reveal the following: 872 out of 925 participants were on NRTI+NNRTI; the most common combination used

contained ZDV-3TC-EFV (431 out 925 participants); the highest number of medication taken per day was 3-4 medications (522 or 56.4% of the participants); the highest number of tablets or pills taken per day was 4-6 pills per day (557 or 60.2%); and the longest duration on HAART was < 3 years (380 or 44.1%).

Table 5-15: Description of HAART used by HIV patients during study period (n=925)

HAART DETAILS	**N**	**%**
HAART group		
1= NRTI	35	3.8
2=NNTRI	18	1.9
3=NRTI+NNRTI	872	94.3
Total	925	
HAART medications used		
1= ZDV-3TC-EFV	431	46.6
2= ZDV-3TC-NVP	192	20.8
3=ZDV-3TC-d4T	9	1.0
4=d4T-3TC-EFV	170	18.1
5=d4T-3TC-NVP	61	6.6
6= ZDV-3TC	11	1.2
7= Others	51	5.5
Total	925	
Number of HAART medications taken per day		
1—2	401	43.4
3—4	522	56.4
>4	02	0.2
Total	925	
Number of HAART pills / tablets taken per day		
1—3	361	39
4—6	557	60.2
>6	7	0.8
Total	925	
Duration of HAART used in years		
< 1	238	25.8
1—3	307	33.1
>3	380	44.1
Total	925	

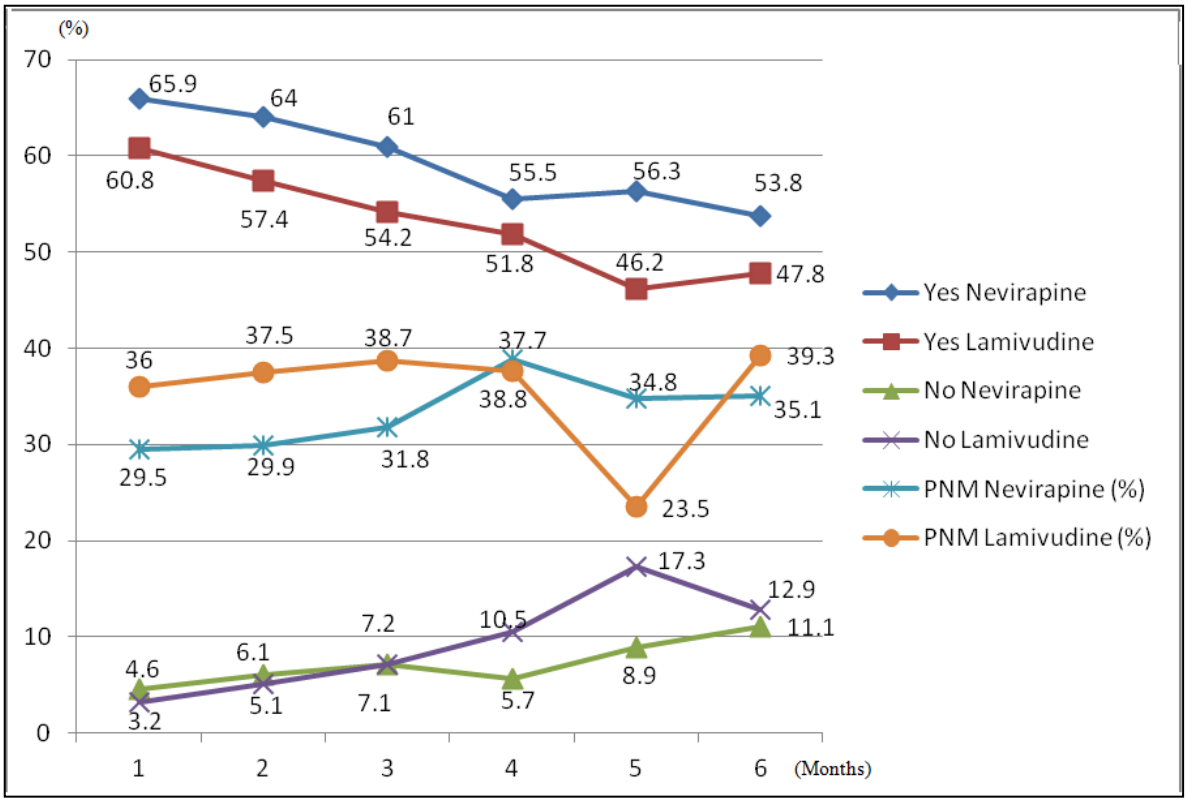
Eventhough ZDV is the most common in the above HAART combination, but it is not commonly used in Sungai Buloh that is why it is not analysed in this study

HAART= Highly Active Antiretroviral Treatment, ZDV = Zidovudine

NNRTI= Non-nucleoside Reverse Transcriptase Inhibitor, 3TC = Lamivudine
NRTI = Nucleoside Reverse Transcriptase Inhibitor, EFV = Efaviranz
NVP = Nevirapine, d4t = Stavudine

Figure 5.3 below describes the dispensation of Lamivudine and Nevirapine based on the online pharmacy record in the previous 6 months from the interview date for HIV-positive patients. The results revealed the number of patients who had collected their prescribed medication, patients who missed their prescribed medication and the number of patients who are not prescribed any of the two types of medication mentioned above.

The results describe the 6 refill statuses, starting from the interview date as the first refill and going retrospectively to the 6^{th} refill as the last refill from the pharmacy record. In the first refill for Nevirapine, out of 925 patients, 610 (65.9%) patients collected their prescribed medication, 43 (4.6%) patients did not collect their medication and 272 (29.5%) were not prescribed Lamivudine by their doctors. For the first refill for Lamivudine, 559 (60.8%) patients had collected their prescribed medication, 30 (3.2%) did not collect their medication and 333 (36%) out of the total 925 patients had been prescribed Lamivudine by their doctors. As seen in the graph, the number of patients collecting their prescribed medication decreases with time, while the number of missed medication shows an increasing trend as time passes.



Yes = Patient has collected prescribed medication
No = Patient missed their prescribed medication
PNM= Patient is Not on this Medication

Figure 5-3 Online pharmacy records for Lamivudine and Nevirapine dispensation in the last 6 month for HIV positive patients (n= 925)

Figure 5.4 below describes the dispensation of Nevirapine and Efavirenz in the past 6 months from the interview date based on the online pharmacy record for HIV-positive patients. The results reveal the number of patients who had collected their prescribed medication, patients who missed their prescribed medication and the number of patients who were not prescribed any of the two medications above.

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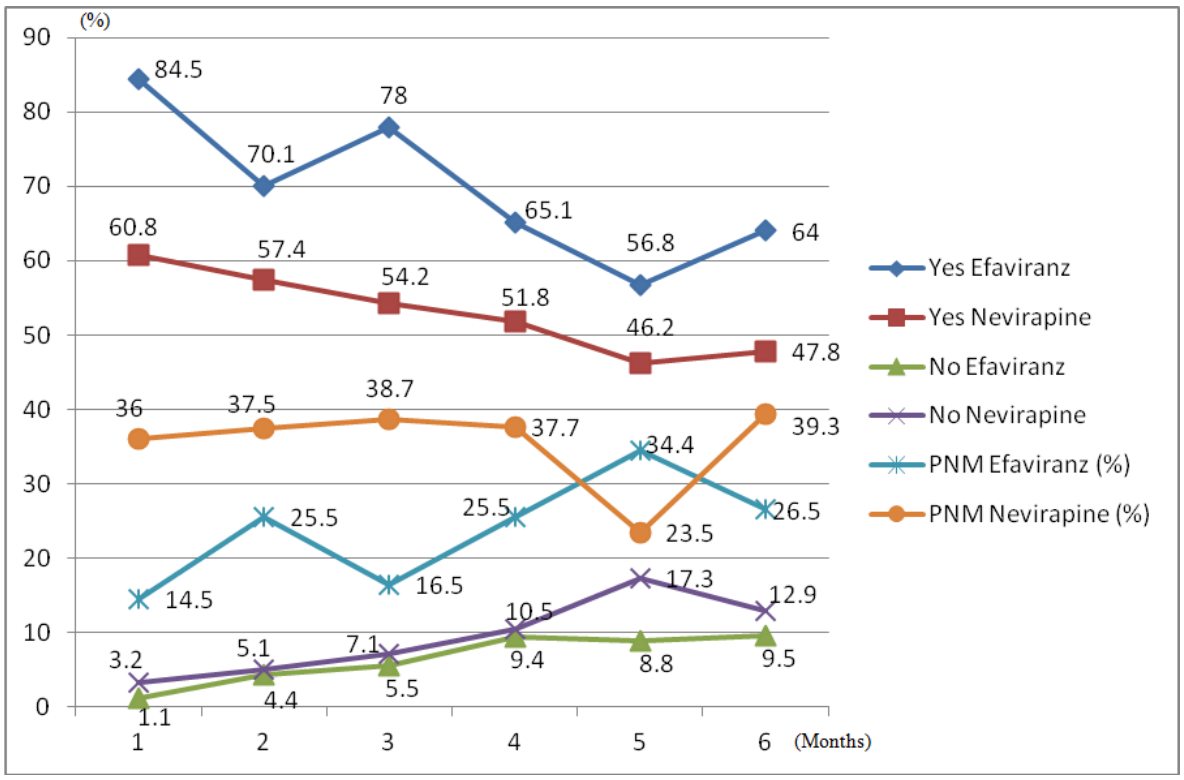

Figure 5-4 Online pharmacy record for Nevirapine and Efaviranz dispensation in the last 6 month for HIV positive patients (n= 925)

Yes = Patient has collected prescribed medication
No = Patient missed prescribed medication
PNM= Patient is Not on this Medication

Table 5.16 shows the adherent and non-adherent patients for each medication listed below as measured by the pharmacy refill data.Participants on Efavirenz (73.2% adherent) and Nevirapine (68.5% adherent) were mainly adherent to their medication. Patients on Lamivudine had the lowest adherence level (53.1%) as calculated by pharmacy refill method and they were the most likely to switch drugs.

Table 5-16: Adherence level for antiretroviral drug in HIV positive patients based on pharmacy refill data

	Adherence level		
	(≥ 95%) Adherent	**(≤95%)Not –adherent**	
Drug name			Total
Efaviranz	579 (73.2)	212 (26.8)	791 (100)
Nevirapine	407 (68.5)	189 (31.5)	594 (100)
Lamivudine	347(53.1)	306 (46.9)	653 (100)

The calculation above is based on the following formula:
Adherence= (pills dispensed /pills prescribed per day) / days between refills) x 100 %

5.4.3 Measuring adherence level via Therapeutic Drug Monitoring (TDM)

Table 5.17 describes the detected and not detected drugs in the first and second blood samples for participants as tested by the LC-SM/SM machine. It also shows the total number of participants whose blood was unavailable for testing in both the first and second blood samples. Each blood sample contained more than one drug as they were tested for multiple drugs. The number of first blood samples for each drug was much more than their second blood samples. Blood samples were unavailable for more than 75% of the second blood samples for each drug since these patients did not come to provide second blood samples the researcher and his data collectors attempted several times to call the patients to participate.The drug which was most detected in the first blood samples was Efavirenz and the least detected was Lamivudine. In the second blood samples, Efavirenz was the most detected drug followed by Nevirapine and Lamivudine as the least detected.

Table 5-17: Blood sample analyzed by LC-MS/MS using Therapeutic Drug Monitoring (TDM) method in HIV positive patients on HAART (n=925)

Drug name	Yes (%)	No (%)	NA (%)
Efaviranz in 1st blood sample	445 (48.1)	180 (19.5)	300 (32.4)
Efaviranz in 2nd blood sample	120 (13)	13 (1.4)	792 (85.6)
Nevirapine in 1st blood sample	394 (42.6)	172 (18.6)	359 (38.8)
Nevirapine in 2nd blood sample	82 (8.9)	13 (1.4)	850 (89.7)
Lamivudine in 1st blood sample	299 (32.3)	197 (21.3)	429 (46.4)
Lamivudine in 2nd blood sample	42 (4.5)	19 (2.1)	864 (93.4)

Yes = Drug is detected by the LC-SM/MS machine
No = Drug is Not detected by the LC-MS/MS machine
NA= Blood is not available for analysis by LC-MS/MS machine
N = Number of patients

Table 5.18 below shows the test results for three antiretroviral drugs in human plasma using the LC-MS/MS machine. The medication was in a combined format. Efavirenz was detected in 71.2 % of the participants, Nevirapine in 69.6% of them and Lamivudine in 60.3% of the participants, at the quantity of 10ng/ml or more(the least value at which the drugs were detected.

Table 5-18: Blood sample analyzed by LC-MS/MS using Therapeutic Drug Monitoring (TDM) method in HIV positive patients on HAART

	TDM level as tested by LC-SM/SM machine		
Drug name	**Positive (%)**	**Negative (%)**	**Total**
Efaviranz	445 (71.2)	180 (28.8)	625 (100)
Nevirapine	394 (69.6)	172 (30.4)	566 (100)
Lamivudine	299 (60.3)	197 (39.7)	496 (100)

Positive= Means drug is detected at 10 ng/ml or more by the LC-MS/MS machine.
Negative= Means drug was not detected at 10 ng/ml or more

5.5 Descriptive results of HIV adherence predictors

Table 5.19 below shows the results on reasons for missing medication among HIV-positive patients as given by the participants in the overall self-reported adherence questionnaire. Participants assigned the answer "Yes" if they agreed with the reason given for missing medication and assigned a "No" as an answer if they did not agree. The table contains 20 reasons for missing medication with "Yes" and "No" responses for 925 participants. The most frequent reasons for missing medication were: beliefs and preference for traditional medicine, ran out of pills, simply forgot and cost of treatment too high. The least frequent reasons for missing medication were felt a sleep through dose time, felt sick or ill, felt like drug was toxic and poor relationship with health care providers

Table 5-19: Reasons for missing medications in HIV positive patients (n =925)

Reason(s) for missing treatment dose(s)	**Yes (%)**	**No (%)**
Beliefs and preference for traditional medicine	372 (40.2)	553 (59.8)
Ran out of pills	351 (37.9)	574 (62.1)
Simply forgot	317 (34.3)	608 (65.7)
Cost of treatment too high	297 (32.1)	628 (67.9)
Was busy with other things	292 (31.6)	633 (68.4)
Distance to hospital too long and costly	269 (29.1)	656 (70.9)
Religious belief	258 (27.9)	667 (72.1)
Wanted to avoid side effects	255 (27.6)	670 (72.4)
Was away from home as reason for missing medications	253 (27.4)	672 (72.6)
Felt well	241 (26.1)	684 (73.9)
Had a change in daily routine	237 (25.6)	688 (74.4)
Had problem taking pills at specified times	236 (25.5)	689 (74.5)
Treatment and drug collection time too long	232 (25.1)	693 (74.9)
Had simply many pills	232 (25.1)	693 (74.9)
Stigma	230 (24.9)	695 (75.1)
Felt depressed / overwhelmed	230 (24.9)	695 (75.1)
Poor relationships with health provider	228 (24.6)	697 (75.4)
Felt like drug was toxic	227 (24.5)	698 (75.5)
Felt sick or ill	218 (23.6)	707 (76.4)
Felt a sleep through dose time	200 (21.6)	725 (78.4)

Table 5.20 below reveals the results of 10 factors which are believed to facilitate the adherence to HAART among HIV-positive patients. Participants assigned "Yes" as a response if they agreed with the factors as factors facilitating adherence and assigned a "No" response if they did not agree. The most common factors facilitating adherence were disclosure, belief in the efficacy of pills, afraid of developing resistance to drugs and afraid of my health condition getting worse.The least common factors facilitating adherence to HAART were the use of alarm/clock, to avoid paying for new drugs and the need to care for others.

Table 5-20: Factors facilitating adherence to HAART in HIV positive patients (n =925)

Reasons facilitating adherence	Yes (%)	No (%)
Disclosure (revealing disease status)	714 (77.2)	211 (22.8)
Belief in the efficacy of pills	693 (74.9)	232 (25.1)
Afraid of developing resistance to drugs.	672 (72.6)	253 (27.4)
Afraid of my health condition getting worse.	659 (71.2)	266 (28.8)
Acceptance of one's HIV status.	655 (70.8)	270 (29.2)
Afraid of my health getting worse.	652 (70.5)	273 (29.5)
Self-efficacy to take and adhere to ART.	651 (70.4)	274 (29.6)
The need to care for others.	648 (70.1)	277 (29.9)
To avoid paying for new drugs	524 (56.6)	401 (43.4)
Use of Alarm/ clock	421 (45.5)	504 (54.5)

ART = Antiretroviral Treatment

Table 5.21 below shows the results of 6 types of alternative medicine used by HIV-positive patients who were on HAART. The most common types of alternative medicine used are herbal medicine, mind-body therapies and yoga. The least commonly used types of alternative medicine are dietary supplements, religious treatment and acupuncture.

Table 5-21: Alternative medicine used for HIV treatment in HIV positive patients on HAART

Alternative medicine	**Yes (%)**	**No (%)**
Herbal medicine	335 (36.2)	590 (63.2)
Mind-body therapies	215 (23.2)	710 (76.8)
Yoga	210 (22.7)	715 (77.3)
Acupuncture	190 (20.5)	735 (79.5)
Dietary supplements	190 (20.5)	735 (79.5)
Religious treatment	190 (20.5)	735 (79.5)

Table 5.22 below reveals the results of clinical investigations carried out by HIV-positive patients before they started undergoing HAART and 6 months or more after they have undergone HAART. This is the same for all 925 participants. Investigations included the CD4, CD8 and viral load tests. Six hundred and forty out of 925 participants had pre-treatment CD4 > 300 cells/ul with and overall mean value of 254.91 for pre-treatment CD4. Two hundred seventy eight participants had post-treatment CD4 value of less than 300 cells /ul, with overall mean value of 450.21 for post treatment CD4. This result shows that there was an increase in the pre-treatment CD4 value after the participants had undergone HAART treatment for at least 6 months. The mean pre-treatment viral load was very high (151416.2 copies/ml) while the mean post-treatment viral load value was 117. The role of pre-treatment analysis was to show if there is improvement of the values after patients start their medication (post-treatment).

Table 5-22: Clinical investigation results in HIV positive patients (n=925)

Variable	Pre-treatment			Post-treatment		
	N (%)	Mean	Median	N (%)	Mean	Median
CD8 cells /ul						
<300	39 (4.2)	1119.59	945.00	38 (4.1)	1396.47	8700
301--600	161 (17.4)			177 (19.1)		
601--900	222 (24.0)			262 (28.3)		
901--1200	204 (22.1)			233 (25.2)		
1201--1500	141 (15.2)			116 (12.5)		
1501--1800	91 (10.2)			55 (5.9)		
1801--2100	48 (5.2)			30 (3.2)		
>2100	16 (1.7)			14 (1.5)		
Total	925 (100)			925 (100)		
Viral load copies /ml						
<50	381 (41.2)	151416.2	327.00	797 (86.2)	117.00	
50-- 1000	153 (16.3)			98 (10.6)		
>1000	391 (42.3)			30 (3.2)		
Total	925 (100)			925 (100)		
Log viral load						
<3	692 (75.0)			846 (91.5)		
3--4.5	123 (13.1)			54 (5.8)		
>4.5	110 (11.9)			25 (2.7)		
Total	925 (100)			925 (100)		

Pre-treatment = before the start of HAART
Post-treatment= First investigation done after 6 month or more after the commencement of HAART. This same for all participants

Table 5.23 below describes the HIV-positive patients' disease history on the day they were interviewed by their doctors in the clinic for the first time. Out of 925 patients, 556 or 60.1% did not have any other diseases apart from being HIV-positive. One hundred and thirty eight (14.9%) had co-existing infectious diseases such as TB or PCP, and 96 or 10.6% had both liver and renal diseases. Nine patients had both renal and co-existing infectious diseases.

Table 5-23: Diseases history of HIV positive patients while on HAART (n=925)

Past medical history	**N**	**%**
No history of any other disease except HIV	556	60.1
Co-existing infectious disease such as TB or PCP	138	14.9
Has both liver and renal disease	96	10.6
Associated liver disease only	65	7.0
Associated renal disease only	35	3.8
Has both liver disease and co existing infectious disease	26	2.8
Has both renal disease and co existing infectious disease	9	1.0

Past medical history = Patients past history on the day they were interviewed by their doctor in the clinic for the first time.
PCP = Pneumocystis pneumonia
TB= Tuberculosis

Table 5.24 below shows the results of the comparison between biological markers for pre-treatment and post-treatment status in HIV- positive patients. The mean pre-treatment CD4 values are significantly different from the mean post-treatment CD4 value at 95% CI of -129.623, 82.653 whereas the mean CD8 pre-treatment count shows no significant difference with the mean post-treatment CD8 level at 95% CI of -1104.279, 550.521. Regarding the viral load and log10 viral load, both show significance difference before and after treatment at 95% CI of 109296.03, 188394.52 and 0.211, 0.304 respectively.

Table 5-24: Comparison between biological markers for HIV patient pre-treatment and post-treatment using paired t test (n=925)

Variable		N	Mean	Standard Deviation	95% Confidence Interval
CD4	Pre-treatment	925			
	Post-treatment	925	-195.296	363.952	(-129.623, 82.653)
CD8	Pre-treatment	925			
	Post-treatment	925	-276.879	12822.4	(-1104.279, 550.521)
Viral load	Pre-treatment	925			
	Post-treatment	925	148,800	612903	(109296.03, 188394.52)
Log_{10}	Pre-treatment	925			
Viral load	Post-treatment	925	0.257	0.721	(0.211, 0.304)

5.6 Comparing three specific drug levels as detected by TDM using LC-MS/MS machine vs. Overall adherence level measured by self-reported questionnaire

This section is on comparison between the various measures of Therapeutic Drug Monitoring (TDM) with the overall adherence level as measured by the self-reported questionnaire. Only participants who actually took Efavirenz, Lamivudine and Nevirapine had their therapeutic drug level tested. Patients indicated which drug they were on before they start answearing the self-reported questionnaire and this was also confirmed from their pharmacy records. We compared the drug levels detected in human plasma via TDM using the LC-MS/MS machine with the adherence level calculated by the self-reported questionnaire.

Table 5.25 below shows the results of overall adherence level that was measured by the self-reported questionnaire in comparison with the Efavirenz level as detected by TDM using the LC-MS/MS machine. Overall the adherence level as measured by SRA was 0.80, 0.76 and 0.71 for Efavirenz, Nevirapine and Lamivudine (Table 5.25). This contrasted with the overall adherence measured using TDM of 0.71, 0.70 and 0.60 for the same drugs

respectively. For the true positive values detected by both the SRA and TDMs were 0.94, 0.92 and 0.89 for Efavirenz, Nevirapine and Lamivudine. While, the true negative values of both the SRA and TDMs were 0.55, 0.62 and 0.56 for the same drugs respectively.

Table 5-25: Adherence levels by SRA and TDM and Sensitivity and specificity of SRA versus TDM for each drug tested using TDM as the gold standard

Drug	**SRA adherence (%)**	**TDM adherence (%)**	**SRA/TDM adherence**	**SRA/TDM non-adherence**
Efavirenz	501/625 (80.2)	445/625 (71.2)	421/445 (94.6)	100/180 (55.6)
Nevirapine	430/566 (76.0)	394/566 (69.6)	366/394 (92.9)	108/172 (62.8)
Lamivudine	352/496 (71.0)	299/496 (60.3)	267/299 (89.3)	112/197 (56.9)

Table 5.26 displays the sensitivity, specificity, positive and negative predictive values for the 3 drugs. SRA sensitivity was highest for Efavirenz (0.95; 95% CI 0.92, 0.96) and lowest for Lamivudine (0.89; 95% CI 0.85, 0.92). SRA specificity ranged between 0.56 and 0.63 and was highest for Nevirapine. PPV for SRA ranged between 0.76 (Lamivudine) and 0.84 (Efavirenz). A similar pattern was seen for NPV. Overall diagnostic accuracy ranged between 0.76 (Lamivudine) and 0.84 (Nevirapine). For the diagnostic accuracy, all the the three drugs (Efavirenz, Nevirapine and Lamivudine) have an acceptable area of under the curve which is above 0.70.

Table 5-26: PPV, NPV and diagnostic accuracy of SRA versus TDM for each drug tested using TDM as the gold standard

Drug	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**Diagnostic accuracy (95% CI)**
Efavirenz	0.95 (0.92, 0.96)	0.56 (0.48, 0.63)	0.84 (0.81, 0.87)	0.81 (0.73, 0.87)	0.83 (0.80, 0.86)
Nevirapine	0.93 (0.90, 0.95)	0.63 (0.55, 0.70)	0.85 (0.81, 0.88)	0.79 (0.72, 0.85)	0.84 (0.80, 0.87)
Lamivudine	0.89 (0.85, 0.92)	0.57 (0.50, 0.64)	0.76 (0.71, 0.80)	0.78 (0.70, 0.84)	0.76 (0.72, 0.80)

5.7 Cross tabulation of overall adherence level as measured self-reported questionnaire and selected independent variables

Bivariate analysis was conducted to determine if there was any statistically significant association between the dependent and independent variables**.** In this part of the analysis, we examined the quantifiable relationship between the measured overall self-reported adherence levels, which has been dichotomized into those who are adherent to treatment with those who are non-adherent to treatment. We defined those who were adherent as patients who had adherence level equal to or more than 95% (using the self-reported questionnaire), while those who were not-adherent were defined as patients who had adherence level less than 95%. We used the 95% cut-off point since it is the WHO requirement for adherence to HAART among HIV/AIDS-positive patients.

Table 5.27 provides an insight to the socio-demographic factors and self-reported adherence level. Seven demographic factors were examined (gender, religion, ethnicity, education, marital status, average monthly income, and age group in years). Out of these factors, education level, marital status, average monthly income and age in years were statistically significant with the overall adherence level as measured by the self-reported questionnaire. Among the married participants, 92.2% were adherent to HAART while 7.8% of them were not adherent. On the other hand, almost two thirds of the unmarried respondents (64.5%) were adherent to their medication compared to 35% of them who were not adherent to the HAART. In short, married patients have higher odds ratio of 6.503 (95% CI 4.469, 9.462) compared to the reference group of the unmarried.

Among the income categories, those with an income range of RM 1,501 – 2,500 have the highest adherence level; this group had an OR of 7.708 (95% CI 4.148, 14.323) which was the highest compared to the rest of the income categories. The patient's age showed an increasing trend with the adherence level of the patient, as the age categories of 31 – 44 and 44 and above have at least more than 10 times higher adherence level compared to those aged 18 – 30, where their odds ratio were 10.877 (95% CI 4.944, 23.927) and 21.379 (95 CI 9.446, 48.386) respectively. Among the patients educational level categories, the categories 'Secondary level IV', 'Secondary level V' and 'Degree level' have at least more than 9 times higher adherence level compared to the other education categories as indicated by their Odds ratio of 26.924 (95% CI 11.009, 65.848), 9.71 (95% CI 3.618, 26.064) and 6.574 (95% CI 2.018, 21.42) respectively. Other socio-demographic characteristics such as gender, religion and ethnicity were not statistically significant with the adherence level as measured by the overall self-reported questionnaire.

Table 5-27: Cross-tabulation of socio-demographic characteristics of adherent and non-adherent HIV positive patients using overall adherence self-reported questionnaire (n=925)

Variable	Adherent (%)	Not Adherent (%)	Total (%)	OR (95%CI)
Gender				
Female	171 (78.1)	48 (21.9)	219 (23.7)	Reference category
Male	585 (82.9)	121 (17.1)	706 (76.3)	0.736 (0.506, 1.072)
Total	756 (81.7)	169 (18.3)	925 (100)	
Religion				
Islam	215 (83.3)	43 (16.7)	258 (27.9)	Reference category
Buddhism	368 (82.1)	80 (17.9)	448(48.4)	0.794 (0.171, 3.692)
Hinduism	40 (75.5)	13 (24.5)	53 (5.7)	0.270 (0.034, 2.117)
Christianity	82 (84.5)	15 (15.5)	97 (10.5)	1.232 (0.234, 6.478)
Taoism	39 (70.9)	16 (29.1)	55 (5.9)	0.312 (0.056, 1.725)
Others	12 (85.7)	2 (14.3)	14 (1.5)	0.794 (0.082, 7.651)
Total	756 (81.7)	169 (18.3)	925 (100)	
Ethnicity				
Malay	209 (83.6)	41 (16.4)	250 (27.0)	Reference category
Chinese	474 (81.0)	111 (19.0)	585 (63.2)	1.154 (0.245, 5.433)
Indian	57 (79.2)	15 (20.8)	72 (7.8)	2.356 (0.304, 18.272)
Others	16 (88.9)	2 (11.1)	18 (1.9)	7.678 (0.715, 82.402)
Total	756 (81.7)	169 (18.3)	925 (100)	
Completed Education level				
No formal schooling	55 (46.6)	63 (53.4)	118 (12.8)	Reference category*
Primary school	108 (72.5)	41 (27.5)	149 (16.1)	8.544 (3.490, 20.914)
Secondary school – 3	222 (88.4)	29 (11.6)	251 (27.1)	26.924 (11.009, 65.848)
Secondary school – 5	200 (93.0)	15 (7.0)	215 (23.2)	9.71 (3.618, 26.064)
High school (form6 level)	51 (85.0)	9 (15.0)	60 (6.5)	4.053 (1.225, 13.41)
Diploma	36 (87.8)	5 (12.2)	41 (4.4)	5.454 (1.161, 25.630)
Degree	84 (92.3)	7 (7.7)	91 (9.8)	6.574 (2.018, 21.42)
Total	756 (81.7)	169 (18.3)	925 (100)	
Marital status				
Single	225 (64.5)	124 (35.5)	349 (37.7)	Reference category*
Married	531 (92.2)	45 (7.8)	576 (62.3)	6.503 (4.469, 9.462)
Total	756 (81.7)	169 (18.3)	925 (100)	
Average monthly income				
≤RM 1,500 / Month	228 (62.3)	138 (37.7)	366 (39.5)	Reference category*
RM 1,501—2,500	227 (93.8)	15 (6.2)	242 (26.2)	7.708 (4.148, 14.323)
RM 2,501—10,000	301 (95.0)	16 (5.0)	317 (34.3)	2.488 (1.127, 5.490)
Total	756 (81.7)	169 (18.3)	925 (100)	
Age group in years				
18—30	210(63.6)	120 (36.4)	330 (35.7)	Reference category*
31—44	312 (92.3)	26 (7.7)	338 (36.5)	10.877 (4.944, 23.927)
45 or more	234 (91.1)	23 (8.9)	257 (27.8)	21.379 (9.446, 48.386)
Total	756 (81.7)	169 (18.3)	925 (100)	

Demographic factors examined – gender, religion, ethnicity, completed educational, marital status average monthly income and age group in years.

* Statistically significant

Table 5.28 shows the cross-tabulation of adverse effects to treatment and the overall adherence level as reported by the self-reported adherence questionnaire. The variables 'vomiting', 'diarrhoea', 'loss of appetite', 'itching', 'tiredness', 'rash' and 'fever' were found to be statistically significant with the overall adherence level as measured by the self-reported questionnaire. The variables 'diarrhoea', 'vomiting', 'tiredness' and 'loss of appetite' had shown bigger odds ratio among the adverse effect variables, with an odds ratio of 0.107 (95% CI 0.074, 0.155), 0.100 (95% CI 0.068, 0.144), 0.296 (95% CI (0.210, 0.418) and 0.185 (95% CI 0.130, 0.264) respectively.

Patients who had these adverse effects were less likely to be adherent to treatments. The variables 'rash', 'itching' and 'fever' had relatively smaller odds ratio among the adverse effect variables; these three variables had demonstrated a similar pattern of odds ratio which is 0.027 (95% CI 0.017, 0.043), 0.055 (95% CI 0.037, 0.082) and 0.092 (95% CI 0.064, 0.134) respectively. In general, all of these adverse effects variables had shown an odds ratio approximately less than one, which indicates that adverse effects (i.e. side effects) of treatment would decrease the adherence level towards HIV medication.

Other variables such as 'dry mouth' and 'headache' were found to be not statistically significant with the overall adherence level according to the overall self-reported questionnaire.

Table 5-28: Adverse/Side effects of treatment and overall adherence level as measured using self-reported questionnaire (n =925)

VARIABLE	Adherent (%)	Not Adherent (%)	Total	OR (95%CI)
Rash				
Yes	62 (36.7)	107 (63.3)	169 (18.3)	0.027 (0.017, 0.043)*
No	694 (91.8)	62 98.2)	756 (81.7)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Itching				
Yes	83 (41.5)	117 (58.5)	200 (21.6)	0.055 (0.037, 0.082)*
No	673 (92.8)	52 (7.2)	725 (78.4)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Loss of Appetite				
Yes	148 (60.7)	96 (39.3)	244 (26.4)	0.185 (0.130, 0.264)*
No	608 (89.3)	73 (10.7)	681 (73.6)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Dry mouth				
Yes	165 (82.1)	36 (17.9)	201 (21.7)	1.031 (0.687, 1.549)
No	591 (81.6)	133 (18.4)	724 (78.3)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Diarrhoea				
Yes	113 (51.8)	105 (48.20	218 (23.6)	0.107 (0.074, 0.155)*
No	643 (90.9)	64 (9.1)	707 (76.4)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Tiredness				
Yes	184 (67.6)	88 (32.4)	272 (29.4)	0.296 (0.210, 0.418)*
No	572 (87.6)	81 (12.4)	653 (70.6)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Vomiting				
Yes	99 (49.3)	102 (50.7)	201 (21.7)	0.100 (0.068, 0.144)*
No	657 (90.7)	67 (9.3)	724 (78.3)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Fever				
Yes	104 (49.3)	107 (50.7)	211 (22.8)	0.092 (0.064, 0.134)*
No	652 (91.3)	62 (8.7)	714 (77.2)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Headache				
Yes	110 (81.5)	25 (18.5)	135 (14.6)	0.980 (0.613, 1.570)
No	646 (81.8)	144 (18.2)	693 (85.4)	
Total	756 (81.7)	169 (18.3)	925 (100)	

Adverse effects of treatment analysed -rash, itching, loss of appetite, dry mouth, diarrhoea, vomiting, fever and headache. Reference category is No

* Statistically significant

Table 5.29 below shows the cross-tabulation of alternative medication used and overall adherence level as measured by the self-reported adherence questionnaire. The following alternative medication variables were found to be statistically significant with the overall adherence level as measured by the self-reported questionnaire: ‘use of herbal medicine’, ‘use of body mind therapy’, ‘use of dietary supplements’, ‘use of religious treatment’ and ‘use of acupuncture’.

The variables ‘use of religious treatment’, ‘use of dietary supplements’, and ‘use of acupuncture’ had relatively small odds ratio compared to the other alternative medication variables; their odds ratio were 0.071 (95% CI 0.049, 0 .105), 0.072 (95% CI 0.049, 0.107) and 0.073 (95% CI 0.050, 0.108) respectively. Conversely, variables such as ‘use of body mind therapy’ and ‘use of herbal medicine’ had bigger odds ratio compared to the other variables; the odds ratio of these variables were 0.093 (95% CI 0.064, 0.135) and 0.302 (95% CI 0.214, 0.426) respectively. In general, all of these alternative medication variables had shown approximately an odd ratio of less than one, which indicates that, the use of alternative medication causes patients not to adhere to their HIV medication. Only the variable ‘use of Yoga’ was found as not having a statistically significant effect to the overall adherence level based on the self-reported questionnaire.

Table 5-29: Alternative medicine used by HIV positive patients and overall adherence level calculated by self-reported questionnaire (n=925)

Variables	**Adherent** (%)	**Non-Adherent (%)**	**Total (%)**	**OR (95%CI)**
Use of dietary supplements				
Yes	83 (43.7)	107 (56.3)	190 (20.5)	0.071 (0.049, 0.105)*
No	673 (91.6)	62 (8.4)	735 (79.5)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Use of Religious treatment				
Yes	84 (43.7)	107 (56.3)	190 (20.5)	0.072 (0.049, 0.107)*
No	672 (91.6)	62 (8.4)	735 (79.5)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Use of Yoga				
Yes	100 (85.5)	17 (14.5)	117 (12.6)	1.363 (0.791, 1.347)
No	656 (81.2)	152 (18.8)	808 (87.4)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Use of Acupuncture				
Yes	85 (43.7)	107 (56.3)	190 (20.5)	0.073 (0.050, 0.108)*
No	671 (91.6)	62 (8.4)	735 (79.5)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Use of body mind therapy				
Yes	107 (49.8)	108 (50.2)	215 (23.2)	0.093 (0.064, 0.135)*
No	649 (91.4)	61 (8.6)	710 (76.8)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Use of Herbal Medicine				
Yes	234 (69.9)	101 (30.1)	335 (36.2)	0.302 (0.214, 0.426)*
No	522 (88.5)	68 (11.5)	590 (63.8)	
Total	756 (81.7)	169 (18.3)	925 (100)	

Alternative medication examined - use of herbal medicine, use of alcohol, use of religious treatment, use of body mind therapy, use of dietary supplements, use of yoga & use of acupuncture. Reference category is No

* Statistically significant values

Table 5.30 below shows the cross-tabulation of reasons facilitating adherence to HAART and the overall adherence level as measured using the self-reported adherence questionnaire. The following variables were found to be statistically significant with the overall adherence level according to the self-reported questionnaire: 'Use of alarm/ clock', 'Acceptance of HIV status', 'Belief in efficacy of the pills', 'Self-efficacy to take & adhere to medication', 'Afraid of my health getting worse', 'Afraid of developing drug resistance', and 'Disclosure about HIV status'.

The variables ‘Use of alarm/clock’, ‘Acceptance of HIV status’, ‘Afraid of my health getting worse’ and ‘Afraid of developing drug resistance’ had relatively small odds ratio compared to the other variables for factors of facilitating adherence; their odds ratio were 7.057 (95% CI 4.445, 11.205), 5.686 (95% CI 3.989, 8.106), 6.782 (95% CI 4.729, 9.728), and 7.210 (95% CI 5.025, 10.348) respectively. On the other hand, variables such as ‘Belief in efficacy of the pills’, ‘Self-efficacy to take medication’ and ‘Disclosure about HIV status’ had bigger odds ratio compared to the other reasons facilitating adherence; the odds ratio of these variables were 8.711 (95% CI 6.036, 12.575), 12.527 (95% CI 8.459, 18.551), and 10.819 (95% CI 7.435, 15.744) respectively.

Table 5-30: Reasons facilitating adherence to HAART and their overall adherence level as measured using self-reported questionnaire (n=925)

Variable	Adherent (%)	Not Adherent (%)	Total (%)	OR (95% CI)
Use of Alarm/ clock				
Yes	398 (94.5)	23 (5.5)	421 (45.5)	8.234 (5.108, 11.205)*
No	358 (71.0)	146 (29.0)	504 (54.5)	
Total	756 (81.7)	169 918.3)	925 (100)	
Acceptance of HIV status				
Yes	590 (90.1)	65 (9.9)	655 (70.8)	5.686 (3.989, 8.106)*
No	166 (61.5)	104 (38.5)	270 (29.2)	
Total	756 (81.7)	169 (18.3)	925 (100)	
To avoid paying for new drugs				
Yes	461 (82.6)	97 (17.4)	558 (60.3)	1.159 (0.827, 1.627)
No	295 (80.4)	72 (19.6)	367 (39.7)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Belief in the efficacy of pills				
Yes	631 (91.1)	62 (8.9)	693 (74.9)	8.711 (6.036, 12.575)*
No	125 (53.9)	107 (46.1)	232 (25.1)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Self-efficacy to take & adhere to medication				
Yes	609 (93.5)	42 (6.5)	651 (70.4)	12.527(8.459, 18.551)*
No	147 (53.6)	127 (46.4)	274 (29.6)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Afraid of health getting worse				
Yes	593 (91.0)	59 (9.0)	652 (70.5)	6.5230 (4.729, 9.617)*
No	163 (59.7)	110 (40.3)	273 (29.5)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Afraid of developing drug resistance				
Yes	610 (90.8)	62 (9.2)	672 (72.6)	7.210 (5.025, 10.348)*
No	146 (57.7)	107 (42.3)	253 (27.4)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Disclosure of HIV				
Yes	652 (91.3)	62 (8.7)	714 (77.2)	10.819 (7.435, 15.744)*
No	104 (49.3)	107 (50.7)	211 (22.8)	
Total	756 (81.7)	169 (18.3)	925 (100)	
The need to care for dependents				
Yes	516 (83.1)	97 (17.4)	613 (66.3)	1.298 (0.927, 1.853)
No	295 (80.4)	72 (19.6)	367 (33.7)	
Total	756 (81.7)	169 (18.3)	925 (100)	

Reasons facilitating adherence examined - use of Alarm/ clock, acceptance of HIV status, to avoid paying for new drugs, belief in the efficacy of pills, the need to care for others, afraid of my health getting worse, afraid of developing drug resistance, disclosure and self-efficiency to take & adhere to medication. Reference category is No

*statistically significant

Table 5.31 shows the cross-tabulation of reasons for missing medication and the overall adherence level as reported by the self-reported adherence questionnaire. The following variables of reasons for missing medication were found to be statistically significant with the overall adherence level measured by the self-reported questionnaire: 'Simply forgot', 'Cost of treatment too high', 'Distance to hospital too long and costly', 'Ran out of pills' and 'Away from home' The variables 'Simply forgot', 'Cost of treatment too high' and 'Away from home' had relatively small odds ratio compared to the other variables of reasons of missing medication; their odds ratio were 0.160 (95% CI 0.111, 0.230), 0.171 (95% CI 0.119, 0.244) and 0.097 (95% CI 0.199, 0.199) respectively.

Variables such as 'Distance to hospital too long and costly' and 'Ran out of pills' had relatively bigger odds ratio compared to the other reasons for missing medication; the odds ratio of these variables were 0.240 (95% CI 0.170, 0.340) and 0.449 (95% CI 0.321, 0.630) respectively. In general, the odds ratio for the above reasons of missing medication was less than one, which indicates that these reasons were negatively associated with the overall adherence level. In other words, these factors would decrease the level of adherenc to HAART. Only the variable 'Busy with other things' was found to be insignificantly associated with the overall adherence to HAART.

Table 5-31: Reasons for missing medications and overall adherence level using self-reported questionnaire (n=925)

Variable	Adherent (%)	Not Adherent (%)	Total (%)	OR (95%CI)
Simply forget				
Yes	200 (63.1)	117 (36.9)	317 (34.3)	0.160 (0.111, 0.230)*
No	556 (91.4)	52 (8.6)	608 (65.7)	
Total	756 (81.7)	169 (18.3)	925 (1000	
Cost of treatment too high				
Yes	186 (62.6)	111 (37.4)	297 (32.1)	0.171 (0.119, 0.244)*
No	570 (90.8)	58 (9.2)	628 (67.9)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Distance to hospital too long and costly				
Yes	175 (65.1)	94 (34.9)	269 (29.1)	0.240 (0.170, 0.340)*
No	581 (88.6)	75 (11.4)	656 (70.9)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Busy with other things				
Yes	176 (83.0)	36 (17.0)	212 (22.9)	1.121 (0.748, 1.681)
No	580 (81.3)	133 (18.7)	713 (77.1)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Run out of pills				
Yes	260 (74.1)	91 (25.9)	351 (38.0)	0.449 (0.321, 0.630)*
No	496 (86.4)	78 (13.6)	574 (62.0)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Away from home				
Yes	146 (57.7)	107 (42.3)	253 (27.4)	0.097 (0.199, 0.199)*
No	610 (90.8)	62 (9.2)	672 (72.6)	
Total	756 (81.7)	169 (18.3)	925 (100)	

Reasons for missing medications examined- simply forget, cost of treatment too high, distance to hospital too long and costly, busy with other things, run out of pills, away from home and wanted to avoid side effects. The reference category is No.
* statistically significant

Table 5.32 below presents the cross-tabulation of another group of reasons for missing medications and the overall adherence level as measured using the self-reported adherence questionnaire. The following variables were found to be statistically significant with the overall adherence level as measured by the self-reported questionnaire: 'Had simply many pills', 'Fell asleep during dose time', 'Did not want others to notice taking medication' 'Had a change in daily routine' and 'Wanted to avoid side effects'.

The variables 'Fell asleep during dose time' and 'Did not want others to notice taking medication' have relatively small odds ratio compared to the other factors of missing medication; their odds ratio were 0.084 (95% CI 0.058, 0.123) and 0.073 (95% CI 0.050, 0.108) respectively. On the other hand, variables such as 'Had simply many pills', 'Had a change in daily routine' and 'Wanted to avoid side effects' have bigger odds ratio compared to the other factors of missing medication; the odds ratio of these variables were 0.115 (95% CI 0.080, 0.166), 0.353 (95% CI 0.249, 0.501) and 0.121 (95% CI 0.084, 0.174) respectively. This indicates that these reasons[2] were negatively associated with the overall adherence level and thus may result in patients being less adherent to their medication. Other reasons for missing medication were found to be not significantly associated with the overall adherence to HAART as calculated by the self-reported adherence questionnaire. These reasons include 'Felt like drug was toxic', 'Felt sick or ill', 'Had problems taking medicine at specific times' and 'Religious belief'.

Table 5-32: Reasons for missing medications and overall adherence level using self-reported questionnaire (n=925)

Variable	Adherent (%)	Not-Adherent (%)	Total (%)	OR (95%CI)
Had simply many pills				
Yes	125 (53.9)	107 (46.1)	232 (25.1)	0.115 (0.080, 0.166)*
No	631 (91.1)	62 (8.9)	693 (74.9)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Fell asleep during dose time				
Yes	94 (7.0)	106 (53.0)	200 (21.6)	0.084 (0.058, 0.123)*
No	663 (91.3)	63(8.7)	725 (78.4)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Did not wanted others to notice taking medicine				
Yes	83 (43.9)	106 (56.1)	189 (20.4)	0.073 (0.050, 0.108)*
No	673 (91.4)	63 (8.6)	736 (79.6)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Had a change in daily routine				
Yes	163 (68.8)	74 (31.2)	237 (25.6)	0.353 (0.249, 0.501)*
No	593 (86.2)	95 (13.8)	688 (74.4)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Felt like drug was toxic				
Yes	83 (85.6)	14 (14.4)	97 (10.5)	1.365 (0.755, 2.470)
No	673 (81.3)	155 (18.7)	828 (89.5)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Wanted to avoid side effects				
Yes	125 (54.3)	105 (45.7)	230 (24.9)	0.121 (0.084, 0.174)*
No	631 (90.8)	64(9.2)	695 (75.1)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Felt sick or ill				
Yes	69 (82.1)	15 (17.9)	84 (9.1)	1.031 (0.574, 1.851)
No	687 (86.7)	154 (18.3)	841 (90.9)	
Total	756 (81.7)	169 (18.3)	925 (100)	

Table 5.33 below presents the cross-tabulation of the third group of reasons for missing medication and the overall adherence level as measured using the self-reported adherence questionnaire. The variables ‘Felt depressed’, ‘Felt well’, ‘Treatment and drug collection time too long’ and ‘Poor relationship with health provider’ were found to be statistically significant with the overall adherence level based on the self-reported questionnaire.

The variable ‘Poor relationship with health provider’ has relatively bigger odds ratio compared to the other reasons of missing medication; it has an odds ratio of 0.323 (95% CI 0.230, 0.453). On the other hand, the variables ‘Felt depressed’, ‘Felt well’, and ‘Treatment and drug collection time too long’ have relatively small odds ratio compared to the ‘Poor relationship with health provider’ as reasons for missing medications. Their odds ratio were 0.117 (95% CI 0.081, 0.168), 0.106 (95% CI 0.074, 0.152) and 0.136 (95% CI 0.095, 0.196) respectively. In general, the odds ratio for the above reasons for missing medication was less than one, which indicates that these reasons were negatively associated with the overall adherence level. In other words, these factors would decrease the level of adherence to HAART. The variables ‘Had problems taking medicine at specific time’, ‘Religious belief’ and ‘Beliefs & preference for traditional medicine’ were found to be insignificantly associated with the overall adherence to HAART according to the self-reported adherence.

Table 5-33: Reasons for missing medications and overall adherence level using self-reported questionnaire (n=925)

Variable	Adherent (%)	Not-Adherent (%)	Total (%)	OR (95%CI)
Felt depressed				
Yes	124 (53.9)	106 (46.1)	230 (24.9)	0.117 (0.081, 0.168)*
No	632 (90.9)	63 (9.1)	695 (75.1)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Felt well				
Yes	124 (51.5)	117 (48.5)	241 (26.1)	0.106 (0.074, 0.152)*
No	632 (92.4)	52 (7.6)	684 (73.9)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Had problems taking medicine at specific time				
Yes	93 (84.5)	17 (15.5)	110 (11.9)	1.254 (0.726, 2.166)
No	663 (81.3)	152 (18.7)	815 (88.1)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Religious belief				
Yes	71 (82.6)	15 (17.4)	86 (9.3)	1.064 (0.594, 1.908)
No	685 (81.6)	154 (18.4)	839 (90.7)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Treatment and drug collection time too long				
Yes	130 (56.0)	102 (44.0)	232 (25.1)	0.136 (0.095, 0.196)*
No	626 (90.3)	67 (9.7)	693 (74.9)	
Total	756 (81.7)	169 (18.3)	925 (100)	
Poor relationships with health provider				
No	262 (70.4)	110 (29.6)	372 (40.2)	
Yes	494 (89.3)	59 (10.7)	553 (59.8)	0.323 (0.230, 0.453)*
Total	756 (81.7)	169 (18.3)	925 (100)	
Beliefs and preference for traditional medicine				
Yes	52 (81.2)	12 (18.8)	64 (6.9)	
No	704 (81.8)	157 (18.2)	861 (93.1)	0.702 (0.442, 1.114)
Total	756 (81.7)	169 (18.3)	925 (100)	

Reasons for missing medications examined - had simply many pills, fell asleep during dose time, felt depressed, felt well, treatment and drug collection time too long, poor relationships with health provider, beliefs and preference for traditional medicine. Reference category is No

*statistically significant

5.8 Cross-tabulations of HIV adherent predictors vs. three specific drug levels as measured by TDM using LC-MS/MS machine

This section is on the cross-tabulation of three specific drug levels as detected by TDM versus adherence determinants (adverse effects of treatment, alternative medication, reasons facilitating adherence to HAART and reasons for missing medication). Table 5.34 shows the results of cross tabulation analysis of the adverse effects of treatment and TDM method for detecting Efavirenz, Nevirapine and Lamivudine level using the LC-MS/MS machine. The variables 'Rash', 'Itching', 'Diarrhoea', 'Vomiting' and 'Fever' were found to be statistically significant with the TDM level of all the three drugs mentioned above.

These variables had shown similar odds ratios across all three drugs, with the exception of variables 'Rash' and 'Itching' which had shown relatively small odds ratios compared to the other factors of adverse effects to treatment. The odds ratios of these variables (rash and itching) were 0.204 (95% CI 0.133, 0.312) and 0.235 (95% CI 0.158, 0.350) for Efavirenz; 0.212 (95% CI 0.138, 0.324) and 0.207 (95% CI 0.138, 0.310) for Nevirapine; 0.263(95% CI 0.171, 0.404) and 0.266 (95% CI 0.177, 0.401) for Lamivudine. Likewise, the variables 'Vomiting' and 'Fever' in TDM for Nevirapine had shown smaller odds ratios of 0.239 (95% CI 0.159, 0.360) and 0.281 (95% CI 0.189, 0.419) respectively.

The variables 'Dry mouth' and 'Headache' were found to be insignificant in all three TDM drugs. Variables 'Loss of appetite' and 'Tiredness' were found insignificant in Lamivudine and Nevirapine data, respectively. The rest of the variables (diarrhoea, vomiting and fever) of almost all three TDM drugs had shown an odds ratio between 0.281 and 0.399. In other words, patients suffering from the above side effects are more likely to be non-adherent to their medication compared to patients who did not suffer from them.

Table 5-34: Comparing the TDM level of three specific antiretroviral medications with their adverse effects. (n =925)

Factor	TDM status of Efavirenz			TDM status of Nevirapine			TDM status of Lamivudine		
	Positive	**Negative**	**OR (95% CI) (Efaviranz)**	**Positive**	**Negative**	**OR (95% CI) (Nevirapine)**	**Positive**	**Negative**	OR (95% CI) (Lamivudine)
Rash									
Yes	48 (41.7)	67 (58.3)	0.204 (0.133, 0.312)	50 (41.7)	70 (58.3)	0.212 (0.138, 0.324)	44 (36.1)	78 (63.9)	0.263 (0.171, 0.404)
No	397(77.8)	113 (22.2)		344 (77.1)	102 (22.9)		255 (68.2)	119 (31.8)	
Itching									
Yes	64 (46.0)	75 (54.0)	0.235 (0.158, 0.350)	60 (42.9)	80 (57.1)	0.207 (0.138, 0.310)	52 (37.4)	87 (62.6)	0266 (0.177, 0.401)
No	381 (78.4)	105 (21.6)		334 (78.4)	92 (21.6)		247 (69.2)	110 (30.8)	
Appetite									
Yes	110 (62.5)	66 (37.5)	0.567 (0.391, 0.823)	77 (51.3)	73 (48.7)	0.329 (0.223, 0.487)	93 (58.9)	65 (41.1)	0.917 (0.624, 1.347)
No	335 (74.6)	114(25.4)		317 (76.2)	99 (23.8)		206 (60.9)	132 (39.1)	
Dry Mouth									
Yes	82 (68.3)	38 (31.7)	0.844 (0.549, 1.299)	109 (74.7)	37 (25.3)	1.395 (0.912, 2.135)	73 (63.5)	42 (36.5)	1.192 (0.775, 1.835)
No	363 (71.9)	142 (28.1)		285 (67.9)	135 (32.1)		226 (59.3)	155 (40.7)	
Diarrhoea									
Yes	72 (50.7)	70 (49.3)	0.303 (0.205, 0.449)	75 (50.7)	73 (49.3)	0.319 (0.215, 0.472)	62 (43.7)	80 (56.3)	0.383 (0.257, 0.570)
No	373 (77.2)	110 (22.8)		319 (76.3)	99 (23.7)		237 (66.9)	117 (33.1)	
Tiredness									
Yes	118 (62.4)	71 (37.6)	0.553 (0.384, 0.798)	113 (65.7)	59 (34.3)	0.770 (0.525, 1.130)	79 (51.0)	76 (49.0)	0.571 (0.389, 0.840)
No	327 (75.0)	109 (25.0)		281 (71.3)	113 (28.7)		220 (64.5)	121 (35.5)	
Vomiting									
Yes	71 (50.7)	69 (49.3)	0.305 (0.206, 0.453)	59 (44.7)	73 (55.3)	0.239 (0.159, 0.360)	52 (39.4)	80 (60.6)	0.308 (0.204, 0.465)
No	374 (77.1)	111 (22.9)		335 (77.2	99 (22.8)		247 (67.9)	117 (32.1)	
Fever									
Yes	76 (51.4)	72 (48.6)	0.309 (0.210, 0.455)	69 (48.3)	74 (51.7)	0.281 (0.189, 0.419)	63 (44.4)	79 (55.6)	0.399 (0.268, 0.594)
No	369 (77.4)	108 (22.6)		325 (76.8)	98 (23.2)		236 (66.7)	118 (33.3)	
Headache									
Yes	56 (62.9)	33 (37.1)	0.641 (0.401, 1.026)	62 (69.7)	27 (30.3)	1.003 (0.613, 1.641)	44 (62.0)	27 (38.0)	1.086 (0.648, 1.822)
No	389 (72.6)	147 (27.4)		332 (69.6)	145 (30.4)		255 (60.0)	170 (40.0)	

Adverse effects analysed included, rash, itching, dry mouth, Diarrhoea, Tiredness, Vomiting, Fever and Headache.

Table 5.35 shows the results of cross tabulation between the alternative use of medication and TDM method for detecting Efavirenz, Nevirapine and Lamivudine level using the LC-MS/MS machine. The following variables of alternative medication were found to be statistically significant with all three TDM levels as measured by the LC-MS/MS machine: 'Use of dietary supplements', 'Use of Religious Treatment, 'Use of Acupuncture, 'Use of Body Mind Therapy' and 'Use of Herbal Medicine'.

The variables 'Use of Dietary Supplement', 'Use of Religious Treatment', as well as 'Use of Acupuncture' had relatively smaller and similar odds ratios between 0.210 and 0.310. On the other hand, the variable 'Use of Herbal medicine' had a relatively bigger odds ratio compared to the other alternative medication variables; the odds ratio of this variable is 0.602 (95% CI 0.421, 0.862) for Efavirenz, 0.585 (95% CI 0.406, 0.841) for Nevirapine and 0.570 (95% CI 0.395, 0.824) for Lamivudine. The variable 'Use of Body Mind Therapy' had shown significance only in TDM Efavirenz with an odds ratio of 0.310 (95% CI 0.210, 0.458). In general, all of the significant alternative to medication variables had shown approximately an odds ratio of less than one, which indicates that the use of alternative to medication causes patients not to adhere to their HIV medication. Only 'Use of Yoga' variable was found to not have a statistically significant effect to all three TDM levels as measured by the LC-MS/MS machine.

Table 5-35: Alternative medicine used by HIV positive patients and TDM status for three specific drugs as detected by LC-MS/MS machine (n =925)

Factor	TDM status of Efavirenz			TDM status of Nevirapine			TDM status of Lamivudine		
	Positive	**Negative**	**OR (95% CI) (Efaviranz)**	**Positive**	**Negative**	OR (95% CI) (Nevirapine)	**Positive**	**Negative**	OR (95% CI) (Lamivudine)
Use of Dietary supplement	59 (44.7)	73 (55.3)	0.224	59 (44.7)	73 (55.3)	0.239	50 (38.5)	80 (61.5)	0.294
Yes	386 (78.3)	107 (21.7)	(0.150, 0.336)	335 (77.2)	99 (22.8)	(0.159, 0.360)	249 (68.0)	117 (32.0)	(0.194, 0.445)
No									
Use of Religious treatment	60 (45.8)	71 (54.2)	0.239	59 (44.7)	73 (55.3)	0.239	49 (38.0)	80 (62.0)	0.287
Yes	385 (77.9)	109 (22.1)	(0.160, 0.358)	335 (77.2)	99 (22.8)	(0.159, 0.360)	250 (68.1)	117 (31.9)	(0.189, 0.435)
No									
Use of Yoga	49 (70.0)	21 (30.0)	0.937	62 (71.3)	25 (28.7)	1.098	46 (66.7)	23 (33.3)	1.275
Yes	396 (71.4)	159 (28.6)	(0.544, 1.613)	332 (69.3)	147 (30.7)	(0.664, 1.816)	253 (59.3)	174 (40.7)	(0.804, 2.352)
No									
Use of Acupuncture	64 (47.8)	70 (52.2)	0.264	54 (42.2)	74 (57.8)	0.210	49 (38.3)	79 (61.7)	0.293
Yes	381 (77.6)	110 (22.4)	(0.177, 0.394)	340 (77.6)	98 (22.4)	(0.139, 0.319)	250 (67.9)	118 (32.1)	(0.193, 0.445)
No									
Use of body mind therapy	75 (50.7)	73 (49.3)	0.310	84 (63.2)	49 (36.8)	0.674	82 (42.8)	70 (57.2)	0.675
Yes	370 (77.6)	107 (22.4)	(0.210, 0.458)	310 (71.6)	123 (28.4)	(0.447, 1.015)	217 (67.5)	125 (32.5)	(0.458, 0.994)
No									
Use of Herbal Medicine	136 (64.2)	76 (35.8)	0.602	139 (62.6)	83 (37.4)	0.585	101 (52.1)	93 (47.9)	0.570
Yes	309 (74.8)	104 (25.2)	(0.421, 0.862	255 (74.1)	89 (25.9)	(0.406, 0.841)	198 (65.6)	104 (34.4)	(0.395, 0.824)
No									

Adverse effects analysed included, rash, itching, dry mouth, Diarrhoea, Tiredness, Vomiting, Fever and Headache.

Table 5.36 shows the results of cross tabulation between reasons facilitating adherence to HAART and TDM method for detecting Efavirenz, Nevirapine and Lamivudine level using the LC-MS/MS machine. The following reasons facilitating adherence to HAART were found to be statistically significant with the all the three TDM levels as measured by LC-MS/MS machine: 'Afraid of my health getting worse', 'Use of alarm/clock', 'Belief in the efficacy of pills', and 'Self-efficacy to take & adhere to medication'.

These significant variables had shown similar pattern of odds ratios across all of the three drugs, with the exception of the 'Use of alarm/clock' variable which had shown relatively bigger odd ratios – in two out of the three TDM models – compared to the other facilitating factors; the odds ratios of this variable were 4.929 (95% CI 3.173, 7.659) for Nevirapine and 4.622 (95% CI 3.060, 6.983) for Lamivudine. The variables 'Afraid of my health getting worse', 'Acceptance of HIV status', 'Belief in the efficacy of pills', 'Self-efficacy to take & adhere to medication', 'Afraid of developing drug resistance', and 'Disclosure' had smaller and similar odds ratios which are in between 0.25 and 0.36.

The variable 'Acceptance of HIV status' was found insignificant in Efavirenz and Lamivudine data, while the variables 'Afraid of developing drug resistance' and 'Disclosure or revealing of one's HIV status' were found insignificant in the models of Nevirapine and Lamivudine respectively. The variables 'To avoid paying for new drugs' and 'The need to care for others' were found to be insignificant in all three TDM levels as measured by the LC-MS/MS machine. In general, the odds ratio for the above reasons facilitating adherence was greater than one, which indicates that these reasons were positively associated with the overall adherence level. In other words, these factors would increase the level of adherence to HAART.

Table 5-36: Reasons facilitating adherence to HAART and TDM status for three specific drugs as detected by LC-MS/MS machine (n =925)

Factor	TDM status of Efavirenz			TDM status of Nevirapine			TDM status of Lamivudine		
	Positive	**Negative**	**OR (95% CI) (Efaviranz)**	**Positive**	**Negative**	OR (95% CI) (Nevirapine)	**Positive**	**Negative**	OR (95% CI) (Lamivudine)
Afraid of my health getting worse									
Yes	347 (77.3)	102 (22.7)	2.708 (1.870, 3.921)	291 (78.4)	80 (21.6)	3.249 (2.234, 4.725)	224 (68.7)	102 (31.3)	2.782 (1.897, 4.079)
No	98 (55.7)	78 (44.3)		103 (52.8)	92 (47.2)		75 (44.1)	95 (55.9)	
Use of Alarm/ clock									
Yes	250 (83.3)	50 (16.7)	3.333 (2.288, 4.855)	201 (87.0)	30 (13.0)	4.929 (3.173, 7.659)	164 (80.0)	41 (20.0)	4.622 (3.060, 6.983)
No	195 (60.0)	130 (40.0)		193 (57.6)	142 (42.4)		135 (46.4)	156 (53.6)	
Acceptance of HIV status									
Yes	313 (76.9)	120 (23.1)	1.186 (0.818, 1.718)	307 (77.7)	88 (22.3)	3.368 (2.298, 4.936)	200 (63.1)	117 (36.9)	1.381 (0.952, 2.005)
No	132 (58.3)	60 (41.7)		87 (50.9)	84 (49.1)		99 (55.3)	80 (44.7)	
To avoid paying for new drugs	260 (69.9)	112 (30.1)	0.853 (0.598, 1.217)	238 (68.8)	108 (31.2)	0.904 (0.625, 1.308)	179 (60.1)	119 (39.9)	0.978 (0.677, 1.412)
Yes	185 (73.1)	68 (26.9)		156 (70.9)	64 (29.1)		120 (60.6)	78 (39.4)	
No									
Belief in the efficacy of pills									
Yes	365 (78.2)	102 (21.8)	3.489 (2.383, 5.109)	313 (76.3)	97 (23.7)	2.988 (2.027, 4.404)	232 (67.1)	114 (32.9)	2.521 (1.703, 3.732)
No	80 (50.6)	78 (49.4)		81 (51.9)	75 (48.1)		67 (44.7)	83 (55.3)	
Self-efficiency to take & adhere to medication									
Yes	339 (79.2)	89 (20.8)	3.270 (2.271, 4.709)	297(79.0)	79 (21.0)	3.604 (2.471, 5.257)	220 (68.8)	100 (31.2)	2.701 (1.848, 3.948)
No	106 (53.8)	91 (46.2)		97 (51.1)	93 (48.9)		79 (44.9)	97 (55.1)	
Afraid of developing drug resistance									
Yes	342 (77.6)	99 (22.4)	2.717 (1.882, 3.922)	267 (77.3)	100 (22.7)	1.443 (0.996, 2.090)	229 (67.4)	111 (32.6)	2.535 (1.719, 3.738)

No	103 (56.0)	81 (44.0)		127 (51.5)	70 (48.5)		70 (44.9)	86 (55.1)	
Disclosure									
Yes	371 (77.9)	105 (22.1)	3.581 (2.431, 5.275)	323 (76.7)	98 (23.3)	3.435 (2.311, 5.106)	215 (67.6)	126 (32.4)	1.442 (0.981, 2.119)
No	74 (49.7)	75 (50.3)		71 (49.0)	74 (51.0)		84 (41.3)	71 (58.7)	
The Need to care for others	304 (71.4)	122 (28.6)	1.025	267 (71.8)	105 (28.2)	1.342	203 (62.5)	122 (37.5)	0.982
Yes	141 (70.9)	58 (29.1)	(0.707, 1.485)	127 (65.5)	67 (34.5)	(0.925, 1.946)	96 (56.1)	75 (43.9)	(0.683, 1.413)
No									

Table 5.37 shows the results of cross tabulation of reasons for missing HIV medication and TDM method for detecting Efavirenz, Nevirapine and Lamivudine level using the LC-MS/MS machine. The variables 'Simply forgot', 'Cost of treatment too high', 'Away from home', 'Had simply many pills', 'Distance to hospital too long and costly', 'Ran out of pills', and 'Busy with other things' were found to be statistically significant with the TDM level of the three TDM drugs (Efavirenz, Nevirapine and Lamivudine).

The variables 'Simply forgot', 'Cost of treatment too high', 'Away from home' and 'Had simply many pills' significantly contributed to all of the thee TDM drugs (Efavirenz, Nevirapine and Lamivudine), while other variables were found partially significant in some of the TDM drugs. For example, 'Distance to hospital too long & costly' and 'Ran out of pills' were not statistically significant in Nevirapine and Lamivudine data, and 'Busy with other things' was not statistically significant in Efavirenz data. We can also see that the odds ratio in Nevirapine model was approximately 0.35, while the odds ratio of Lamivudine model was slightly bigger, with an odds of approximately 0.4.

Odds ratios of less than one were shown for the Efavirenz model, as follows: 0.319 (95% CI 0.223, 0.458) for the variable 'Simply forgot'; 0.349(95% CI 0.243, 0.500) for 'Cost of treatment too high'; 0.499 (95% CI 0.346, 0.720) for 'Distance to hospital too long and costly'; 0.431 (95% CI 0.298, 0.624) for 'Ran out of pills'; 0.397 (95% CI 0.274, 0.574) for 'Away from home'; and 0.353 (95% CI 0.242, 0.515) for the variable 'Had simply many pills'. In general, all of the significant reasons for missing HIV medication had shown odds ratios of approximately less than one, which indicates that the presence of these reasons causes patients not to adhere to their HIV medication.

Table 5-37: Reasons for missing medications and TDM status for three specific drugs as detected by LC-MS/MS machine (n =925)

Factor	TDM status of Efavirenz			TDM status of Nevirapine			TDM status of Lamivudine		
	Positive	**Negative**	**OR (95% CI) (Efaviranz)**	**Positive**	**Negative**	OR (95% CI) (Nevirapine)	**Positive**	**Negative**	OR (95% CI) (Lamivudine)
Simply forget									
Yes	125 (55.8)	99 (44.2)	0.319	117 (55.7)	93 (44.3)	0.359	97 (49.0)	101 (51.0)	0.452
No	320 (79.8)	81 (20.2)	(0.223, 0.458)	277 (77.8)	79 (22.2)	(0.248, 0.519)	202 (67.8)	96 (32.2)	(0.312, 0.654)
Cost of treatment too high									
Yes	115 (56.1)	90 (43.9)	0.349	107 (56.3)	83 (43.7)	0.340	81 (46.3)	94 (53.7)	0.407
No	330 (78.6)	90 (21.4)	(0.243, 0.500)	287 (76.3)	89 (23.7)	(0.275, 0.580)	218 (67.9)	103 (32.1)	(0.279, 0.594)
Distance to hospital too long and costly									
Yes	113 (60.8)	73 (39.2)	0.499	112 (63.3)	65 (36.7)	0.654	82 (52.6)	74 (47.4)	0.628
No	332 (75.6)	107 (24.4)	(0.346, 0.720)	282 (72.5)	107 (27.5)	(0.448, 0.954)	217 (63.8)	123 (36.2)	(0.428, 0.922)
Busy with other things									
Yes	93 (66.4)	47 (33.6)	0.748	105 (70.5)	44 (29.5)	0.010	83 (64.3)	46 (35.7)	1.261
No	352 (72.6)	133 (27.4)	(0.499, 1.119)	289 (69.3)	128 (30.7)	(0.008, 0.014)	216 (58.9)	151 (41.1)	(0.832, 1.912)
Run out of pills									
Yes	103 (58.2)	74 (41.8)	0.431	200 (71.2)	81 (28.8)	1.158	112 (54.9)	92 (45.1)	0.684
No	342 (76.3)	106 (23.7)	(0.298, 0.624)	194 (68.1)	91 (31.9)	(0.809, 1.658)	187 (64.0)	105 (36.0)	(0.475, 0.985)
Away from home									
Yes	100 (56.8)	76 (43.2)	0.397	89 (53.3)	78 (46.7)	0.352	70 (45.2)	85 (54.8)	0.403
No	345 (76.8)	104 (23.2)	(0.274, 0.574)	305 (76.4)	94 (23.6)	(0.240, 0.515)	229 (67.2)	112 (32.8)	(0.273, 0.594)
Had simply many pills									
Yes	88 (54.3)	74 (45.7)	0.353	75 (49.3)	77 (50.7)	0.290	65 (43.6)	84 (56.4)	0.374
No	357 (77.1)	106 (22.9)	(0.242, 0.515)	319 (77.1)	95 (22.9)	(0.196, 0.429)	234 (67.4)	113 (32.6)	(0.252, 0.554)

Table 5.38 shows the results of cross tabulation of reasons for missing HIV medication and TDM method for detecting Efavirenz, Nevirapine and Lamivudine level using the LC-MS/MS machine. Variables 'Fell asleep during dose time', 'Did not want others to notice taking medicine', 'Had a change in daily routine', 'Wanted to avoid side effects', and 'Felt depressed' were found to be statistically significant with the TDM level of the three TDM drugs (Efavirenz, Nevirapine and Lamivudine). Variables 'Felt like drug was toxic' and 'Felt sick or ill' were found to not have a statistically significant effect to all the three TDM levels as measured by LC-MS/MS machine. The variables 'Had a change in daily routine' and 'Wanted to avoid side effects' were not statistically significant in analysis of Nevirapine, & Lamivudine data.

Lamivudine model has the most number of non-significant variables (four). Nevirapine, with three non-significant variables, is at the second spot while Efavirenz has the smallest number of non-significant variables (two). The variables 'Fell asleep during dose time' and 'Did not want others to notice taking medicine' had shown relatively smaller and similar odds ratios of around 0.2 to 0.3. On the other hand, the variable 'Felt depressed' had a slightly bigger odds ratio compared to the other reasons for missing medication; the odds ratio of this variable was 0.320 (95% CI 0.219, 0.468) for Efavirenz, 0.268 (95% CI 0.181, 0.397) for Nevirapine and 0.331 (95% CI 0.222, 0.493) for Lamivudine.

In general, all significant reasons for missing HIV medication had shown approximately odds ratios of less than one, which indicates that these reasons were negatively associated with the overall adherence level. In other words, these factors would decrease the level of adherence to HAART.

Table 5-38: Reasons for missing medications and TDM status for three specific drugs as detected by LC-MS/MS machine (n =925)

Factor	TDM status of Efavirenz			TDM status of Nevirapine			TDM status of Lamivudine		
	Positive	**Negative**	**OR (95% CI) (Efaviranz)**	**Positive**	**Negative**	OR (95% CI) (Nevirapine)	**Positive**	**Negative**	OR (95% CI) (Lamivudine)
Fell asleep during dose time	61 (42.4)	83 (57.6)	0.186	64 (45.7)	76 (54.3)	0.245	51 (38.9)	80 (61.1)	0.301
Yes	384 (79.8)	97 (20.2)	(0.125, 0.277)	330 (77.5)	96 (22.5)	(0.164, 0.366)	248 (67.9)	117 (32.1)	(0.199, 0.455)
No									
Did not wanted others to notice taking medicine	61 (45.9)	72 (54.1)	0.238	58 (43.6)	75 (56.4)	0.223	49 (38.3)	79 (61.7)	0.293
Yes	384 (78.0)	108 (22.0)	(0.159, 0.356)	336 (77.6)	97 (22.4)	(0.148, 0.337)	250 (67.9)	118 (32.1)	(0.193, 0.445)
No									
Had a change in daily routine	87 (60.8)	56 (39.2)	0.538	107 (65.2)	57 (34.8)	0.752	73 (54.1)	62 (45.9)	0.703
Yes	358 (74.3)	124 (25.7)	(0.363, 0.797)	287 (71.4)	115 (28.6)	(0.511, 1.108)	226 (62.6)	135 (37.4)	(0.471, 1.049)
No									
Felt like drug was toxic	42 (68.9)	19 (31.1)	0.883	47 (67.1)	23 (32.9)	0.877	36 (60.0)	24 (40.0)	0.987
Yes	403 (71.5)	161 (28.5)	(0.498, 1.565)	347 (70.0)	149 (30.0)	(0.514, 1.497)	263 (60.3)	173 (39.7)	(0.569, 1.712)
No									
Wanted to avoid side effects	96 (56.5)	74 (43.5)	0.394	96 (59.3)	66 (40.7)	0.528	90 (57.3)	67 (42.7)	0.836
Yes	349 (76.7)	106 (23.3)	(0.271, 0.572)	298 (73.8)	106 (26.2)	(0.360, 0.772)	209 (61.7)	130 (38.3)	(0.569, 1.227)
No									
Felt sick or ill	39 (68.4)	18 (31.6)	0.864	37 (68.5)	17 (31.5)	0.945	32 (65.3)	17 (34.7)	1.269
Yes	406 (71.5)	162 (28.5)	(0.480, 1.556)	357 (69.7)	155 (30.3)	(0.516, 1.729)	267 (59.7)	180 (40.3)	(0.684, 2.354)
No									
Felt depressed	85 (53.5)	74 (46.5)	0.320	73 (48.0)	79 (52.0)	0.268	61 (41.5)	86 (58.5)	0.331
Yes	360 (77.3)	106 (22.7)	(0.219, 0.468)	321 (77.5)	93 (22.5)	(0.181, 0.397)	238 (68.2)	111 (31.8)	(0.222, 0.493)
No									

Table 5.39 shows other results of cross tabulation of reasons for missing HIV medication and TDM method for detecting Efavirenz, Nevirapine and Lamivudine level using the LC-MS/MS machine. The variables 'Felt well' and 'Treatment & drug collection time too long' were found to be statistically significant with the TDM level of the three TDM drugs (Efavirenz, Nevirapine and Lamivudine). The variable 'Beliefs and preference for traditional medicine' was found as not statistically significant in all three TDM levels based on the LC-MS/MS machine. Variables 'Had problems taking medicine at specific time', 'Poor relationship with health provider' and 'Religious belief' were reported as not statistically significant in Nevirapine & Lamivudine.

Lamivudine and Nevirapine models have the highest number of non-significant variables (four), while Efavirenz has the smallest number of non-significant variables. The variable 'Treatment & drug collection time too long' had relatively bigger odds ratio compared to other reasons for missing medication; the odds ratio of this variable was 0.410 (95% CI 0.281, 0.597) for Efavirenz, 0.345 (95% CI 0.234, 0.508) for Nevirapine and 0.382 (95% CI 0.257, 0.566) for Lamivudine. In general, all significant reasons for missing HIV medication in this table had shown approximately odds ratios of less than one, which indicates that these reasons were negatively associated with the overall adherence level. In a nutshell, these factors would decrease the level of adherence to HAART.

Table 5-39: Reasons for missing medications and TDM status for three specific drugs as detected by LC-MS/MS machine (n =925)

Factor	TDM status of Efavirenz			TDM status of Nevirapine			TDM status of Lamivudine		
	Positive	**Negative**	**OR (95% CI) (Efaviranz)**	**Positive**	**Negative**	OR (95% CI) (Nevirapine)	**Positive**	**Negative**	OR (95% CI) (Lamivudine)
Felt well									
Yes	87 (52.4)	79 (47.6)	0.311	81 (48.5)	86 (51.5)	0.259	64 (40.8)	93 (59.2)	0.486
No	358 (78.0)	101 (22.0)	(0.213, 0.453)	313 (78.4)	86 (21.6)	(0.176, 0.381)	235 (69.3)	104 (30.7)	(0.307, 0.769)
Had problems taking medicine at specific time									
Yes	43 (66.2)	22 (33.8)	0.768	55 (68.8)	25 (31.2)	0.954	39 (56.5)	30 (43.5)	0.835
No	402 (71.8)	158 (28.2)	(0.445, 0.278)	339 (69.8)	147 (30.2)	(0.572, 1.590)	260 (60.9)	167 (39.1)	(0.499, 1.396)
Religious belief									
Yes	33 (55.0)	27 (45.0)	0.264	38 (65.5)	20 (34.5)	0.811	29 (56.9)	22 (43.1)	0.854
No	412 (72.9)	153 (27.1)	(0.264, 0.780)	356 (70.1)	152 (29.9)	(0.457, 1.440)	270 (60.7)	175 (39.3)	(0.476, 1.535)
Treatment and drug collection time too long									
Yes	92 (56.8)	70 (43.2)	0.410	83 (52.5)	75 (47.5)	0.345	65 (43.9)	83 (56.1)	0.382
No	353 (76.2)	110 (23.8)	(0.281, 0.597)	311 (76.2)	97 (23.8)	(0.234, 0.508)	234 (67.2)	114 (32.8)	(0.257, 0.566)
Poor relationships with health provider									
Yes	133 (67.9)	112 (32.1)	0.297	129 (71.9)	102 (28.1)	0.334	136 (62.4)	82 (37.6)	1.170
No	272 (73.2)	68 (26.8)	(0.206, 0.428)	265 (67.8)	70 (32.2)	(0.231, 0.484)	163 (58.6)	115 (41.4)	(0.814, 1.683)
Beliefs and preference for traditional medicine									
Yes	25 (62.5)	15 (37.5)	0.655	30 (65.2)	16 (34.8)	0.8036	21 (58.3)	15 (41.7)	0.917
No	420 (71.8)	165 (28.2)	(0.337, 1.273)	364 (70.0)	156 (30.0)	(0.426, 1.516)	278 (60.4)	182 (39.6)	(0.460, 1.824)

Table 5.40 below presents the summary of the results of cross-tabulations for four methods of assessing the level of adherence to HAART (HIV adherence predictors): 1) adherence level measured by overall self-reported questionnaire; 2) adherence level measured by TDM level for Efavirenz; 3) adherence level measured by TDM level for Nevirapine; and 4) adherence level measured by TDM level of Lamivudine.

The side effect variables - 'Rash', 'Itching', 'Diarrhoea', 'Vomiting' and 'Fever' - are significant predictors for adherence to HAART based on all four models. The variables 'Loss of appetite' and 'Tiredness' were found to be insignificant in TDM for Lamivudine method and TDM for Nevirapine method respectively. Variables 'Dry mouth' and 'Headache' were found to be insignificant according to all four methods of assessing the adherence level of HIV medication (HAART). Regarding the use of alternative medication by patients, variables 'Use of dietary supplement', 'Use of religious treatment', 'Use of acupuncture' and 'Use of herbal medicine' were found to be significant predictors for adherence to HAART based on all four methods. On the other hand, the variable 'Use of body mind therapy' was found to be significant only in the self-reported questionnaire and insignificant in the other three TDM methods. Only the variable 'Use of Yoga' as an alternative medication to HAART was found as insignificant in all four methods of assessing the adherence level to HIV medication (HAART).

The cross-tabulation results of the reasons facilitating adherence to HAART using the four methods of assessing adherence level mentioned previously are as follows: the variables 'Use of alarm clock', 'Belief in the efficacy of pills', and 'Self-efficacy to adhere to medication' were found to be significant predictors to all four methods of assessing the adherence level to HIV medication. The variable 'Acceptance of HIV status' was found to be insignificant in TDM for Efavirenz and TDM for Lamivudine, while the variables 'Afraid of drug resistance' and 'Disclosure about HIV status' were found to be insignificant in TDM Nevirapine and TDM Lamivudine respectively. The variables 'Avoid paying for new drugs' and 'The need to care for others' were found to be insignificant in all of the 4 methods of assessing adherence level of HAART.

Table 5-40: Factors affecting adherence to HAART (adherence predictors) using four different methods (n =925)

Categories	Factor	OSRAQ	TDM Efaviranz	TDM Nevirapine	TDM Lamivudine	Sign. Level
Adverse effect of treatment	Rash	Yes	Yes	Yes	Yes	4
Adverse effect of treatment	Itching	Yes	Yes	Yes	Yes	4
Adverse effect of treatment	Appetite	Yes	Yes	Yes	No	3
Adverse effect of treatment	Dry Mouth	No	No	No	No	0
Adverse effect of treatment	Diarrhoea	Yes	Yes	Yes	Yes	4
Adverse effect of treatment	Tiredness	Yes	Yes	No	Yes	3
Adverse effect of treatment	Vomiting	Yes	Yes	Yes	Yes	4
Adverse effect of treatment	Fever	Yes	Yes	Yes	Yes	4
Adverse effect of treatment	Headache	No	No	No	No	0
Use of Alternative Medication	Use of Dietary supplement	Yes	Yes	Yes	Yes	4
Use of Alternative Medication	Use of Religious treatment	Yes	Yes	Yes	Yes	4
Use of Alternative Medication	Use of Yoga	No	No	No	No	0
Use of Alternative Medication	Use of Acupuncture	Yes	Yes	Yes	Yes	4
Use of Alternative Medication	Use of body mind therapy	Yes	No	No	No	1
Use of Alternative Medication	Use of Herbal Medicine	Yes	Yes	Yes	Yes	4
Reasons Facilitating Adherence	Use of Alarm/ clock	Yes	Yes	Yes	Yes	4
Reasons Facilitating Adherence	Acceptance of HIV status	Yes	No	Yes	No	2
Reasons Facilitating Adherence	To avoid paying for new drugs	No	No	No	No	0
Reasons Facilitating Adherence	Belief in the efficacy of pills	Yes	Yes	Yes	Yes	4
Reasons Facilitating Adherence	Self-efficiency	Yes	Yes	Yes	Yes	4
Reasons Facilitating Adherence	Afraid of drug resistance	Yes	Yes	No	Yes	3
Reasons Facilitating Adherence	Disclosure	Yes	Yes	Yes	No	3
Reasons Facilitating Adherence	The need to care for others	No	No	No	No	0
Total 'Yes:		18	16	15	14	

OSRAQ = Overall Self-Reported Adherence questionnaire, TDM for Efavirenz =Therapeutic Drug Monitoring for Efavirenz, Adverse effect = Adverse effect to HAART
TDM for Nevirapine = Therapeutic Drug Monitoring for Nevirapine, TDM for Lamivudine =Therapeutic Drug Monitoring for Lamivudine
4 = Variable is predictor of adherence level to HAART by all the four methods above, 3 = variable is predictor of adherence to HAART by 3 methods
2 = Variable is predictor of adherence level to HAART by two methods, 1 = variable is predictor of adherence to HAART by one method only. 0 = variable is not predictor of adherence

Table 5.41 below shows the cross tabulation results of the reasons for missing medication and also four methods to assess the level of adherence to HAART. The variables 'Simply forgot', 'Cost of treatment too high', 'Away from home', 'Had many pills', 'Fell asleep during dose time', 'Stigma', 'Felt depressed', 'Felt well', and 'Drug collection time too long' were found to be significant predictors of all the four methods of assessing the level of adherence to HAART. The variables 'Wanted to avoid side effects' and 'Poor relationship with health care provider' are significant in only the following three methods: overall self-reported questionnaire, TDM for Efavirenz and TDM for Nevirapine.

The variables 'Distance to hospital too long', 'Ran out of pills', and 'Had a change in daily routine' are found to be insignificant in two models – TDM for Nevirapine and TDM for Lamivudine methods. The variables 'Had problems at specific time', and 'Religious belief' are not significant in the following three methods: overall self-reported questionnaire, TDM for Nevirapine and TDM for Lamivudine data. The variables 'Busy with other things', 'Felt like drug was toxic', 'Felt sick or ill', and 'Beliefs of traditional medicine' were found to be insignificant in all four methods of assessing the adherence level to HIV medication.

The result of the cross-tabulation of 43 factors with four different methods of measuring adherence to HAART shows the following: Twenty-three factors were strong predictors of adherence as measured by all four methods of measuring adherence to HAART; four factors were predictors of adherence according to three methods; four other factors were predictors of adherence as confirmed by two methods and other eight factors were shown not to be predictors of adherence to HAART as they were found insignificant by all four methods of measuring adherence.

Table 5-41: Factors affecting adherence to HAART (adherence predictors) using four different methods (n =925)

Categories	Factor	OSRAQ	TDM Efaviranz	TDM Nevirapine	TDM Lamivudine	Sign. Level
Reasons for missing medic.	Simply forget	Yes	Yes	Yes	Yes	4
Reasons for missing medic.	Cost of treatment too high	Yes	Yes	Yes	Yes	4
Reasons for missing medic.	Distance to hospital too long	Yes	Yes	No	No	2
Reasons for missing medic.	Busy with other things	No	No	No	No	0
Reasons for missing medic.	Run out of pills	Yes	Yes	No	No	2
Reasons for missing medic.	Away from home	Yes	Yes	Yes	Yes	4
Reasons for missing medic.	Had simply many pills	Yes	Yes	Yes	Yes	4
Reasons for missing medic.	Fell asleep during dose time	Yes	Yes	Yes	Yes	4
Reasons for missing medic.	Stigma	Yes	Yes	Yes	Yes	4
Reasons for missing medic.	Had a change in daily routine	Yes	Yes	No	No	2
Reasons for missing medic.	Felt like drug was toxic	No	No	No	No	0
Reasons for missing medic.	Wanted to avoid side effects	Yes	Yes	Yes	No	3
Reasons for missing medic.	Felt sick or ill	No	No	No	No	0
Reasons for missing medic.	Felt depressed	Yes	Yes	Yes	Yes	4
Reasons for missing medic.	Felt well	Yes	Yes	Yes	Yes	4
Reasons for missing medic.	Had problems at specific time	No	Yes	No	No	1
Reasons for missing medic.	Religious belief	No	Yes	No	No	1
Reasons for missing medic.	Drug collection time too long	Yes	Yes	Yes	Yes	4
Reasons for missing medic.	Poor relationships with provider	Yes	Yes	Yes	No	3
Reasons for missing medic.	Beliefs of traditional medicine	No	No	No	No	0
Total Yes		14	16	11	9	

OSRAQ = Overall Self-Reported Adherence questionnaire, TDM for Efavirenz =Therapeutic Drug Monitoring for Efavirenz,
TDM for Nevirapine = Therapeutic Drug Monitoring for Nevirapine, TDM for Lamivudine =Therapeutic Drug Monitoring for Lamivudine
Reasons for missing medic = Reasons for missing HIV medications. 4 = Variable is predictor of adherence level to HAART by all the four methods above, 3 = variable is predictor of adherence to HAART by 3 methods. 2 = Variable is predictor of adherence level to HAART by two methods, 1 = variable is predictor of adherence to HAART by one method only. 0 = variable is not predictor of adherence

5.9 Multiple logistic regressions models

This section is about the interpretation & reporting of four logistic regression models. These models assessed the factors that affect adherence towards HIV medication using the following dependent variables: overall self-reported adherence questionnaire, TDM level for Efavirenz, TDM level for Nevirapine and TDM level for Lamivudine. The independent variables used were: socio-demographic characteristics, reasons for missing medication, factors facilitating adherence, use of alternative medication and adverse effects of HIV treatment. Table 5.42 below shows the model building stages of the first model; this model was the best-fit model that could be used to explain the dependent variable 'Adherence of HIV medication as measured by the overall self-reported adherence questionnaire'. This table uses the forward variable selection technique, which sequentially selects variables with the smallest log likelihood ratio and an acceptable Hosmer –Lemshow statistic.

Table 5-42: Forward Adding Model building stages for adherence / non-adherence as measured by overall self-reported questionnaire (n =925)

Variable	2 Log likelihood	Difference	Hosmer-Lemshow	
			Chi-Square	Sig.
Diarrhoea	731.417			
Vomiting	659.369	72.048	1.535	0.464
Use of religious treatment	540.612	118.757	5.126	0.275
Use of herbal medicine	467.124	73.488	8.53	0.129
Use of Alarm/ Clock	422.917	44.207	14.088	0.051
Acceptance of HIV status	386.465	36.452	3.747	0.808
Self-efficiency	370.433	16.032	5.88	0.661
Simply forgot	321.734	48.699	14.734	0.065
Distance to hospital too long & costly	300.392	21.342	7.266	0.508
Educational level	273.285	27.107	1.889	0.984
Age	250.914	22.371	2.903	0.94
Income	224.971	25.943	7.59	0.474

Self-efficacy = Self-efficiency to take & adhere to medication

Table 5.43 below goes into the heart of the results. After evaluating the forward adding variable, the best and most parsimonious model of the overall adherence/non-adherence to HIV medication as measured using the overall self-reported adherence questionnaire is summarized in table 5.43. In the beginning, we evaluated 48 variables in our modeling. Then, after making adjustments based on the Hosmer-Lemshow approach, we obtained twelve variables that actually had effect and improved the fitness of the model. The twelve variables in the table are the final multivariate variables that can explain the overall adherence / non-adherence of HIV medication as measured by the self-reported adherence questionnaire. The variables were 'Diarrhoea', 'Vomiting', 'Use of religious treatment', 'Use of herbal medicine', 'Use of alarm /clock', 'Acceptance of HIV status', 'Self-efficacy to take & adhere to medication', 'Simply forgot', 'Distance to hospital too long and costly', 'Education', 'Age of the patient in categories' and 'Income status'.

Based on our findings, patients who experienced side effects such as diarrhoea and vomiting which resulted from antiretroviral treatment were less likely to be adherent to HIV medication with an OR of 0.081, (95% CI 0.034, 0.192) and OR of 0.131, (95% CI 0.058, 0.294) respectively. Also, patients using alternative medication such as religious treatment and herbal medicine were less likely to be adherent to the antiretroviral drugs with an OR of 0.067 (95% CI 0.027, 0.165) and OR of 0.227 (95% CI 0.103, 0.501) respectively. Reasons facilitating adherence to treatment such as 'Use of alarm /clock', 'Self-efficacy to adhere' and 'Acceptance of HIV status' all had a positive relationship with adherence to antiretroviral medication with OR values as follows: 6.712 (95% CI 2.747, 16.397), 4.711 (95% CI 2.062, 10.76), and 4.727 (95% CI 1.96, 11.403)

respectively. This positive relationship means that these facilitating factors increase patients' level of adherence to HAART.

The variables 'Simply forgot' and 'Distance to hospital too long and costly' were significant reasons for missing medication; these variables had a negative relationship with the adherence towards HIV antiretroviral drugs with an OR of 0.08 (95% CI 0.033, 0.197) and 0.264 (95% CI 0.111, 0.632) respectively. The negative relationship means that these two reasons will decrease the level of adherence to HAART in patients who consider them as reasons for missing medication.

Among the demographic variables, educational level , patients who belong to the 31 – 44 years of age and patients whose income are in the 1,500 – 2,500 and 2,501 – 10,000 categories were more likely to be adherent with OR of 1.43 (95% CI 1.108, 1.844), 5.119 (95% CI 2.159, 12.14), 6.139 (95% CI 2.289, 16.465) and 9.993 (95% CI 3.175, 31.454) respectively. This implies that the above-mentioned factors increase the level of adherence to HAART. Besides the twelve variables, there are 36 other factors which are found to be significant in the univariate analysis but not significant in the multivariate analysis. These variables were reported in the cross-tabulation section earlier (Section 5.7).

The researcher had checked all possible two-way interactions one at a time, and found no significant interaction effect in the above model. Thus, the variables in Table 5.42 or Table 5.43 best explain the dependent variable 'Adherence of HIV medication as measured by the overall self-reported questionnaire'. Interpretation of the independent variables was based on the right most columns in Table 5.38, labelled "Exp (B)". More information about the interpretation and discussion are presented in Chapter 6 (discussion).

Table 5-43: Model I overall adherence/non-adherence measured by self-reported questionnaire (n =925)

Variables (Yes versus No)	**Crude odd ratio**	**Adjusted Odds ratio (95% CI)**
Diarrhoea (Yes versus No)	0.107 (0.074, 0.155)	0.081 (0.034, 0.192)
Vomiting (Yes versus No)	0.099 (0.068, 0.144)	0.131 (0.058, 0.294)
Use of religious treatment (Yes versus No)	0.071 (0.049, 0.105)	0.067 (0.027, 0.165)
Use of herbal medicine (Yes versus No)	0.302 (0.214, 0.426)	0.227 (0.103, 0.501)
Use of Alarm /Clock (Yes versus No)	7.057 (4.445, 11.205)	6.712 (2.747, 16.397)
Self efficacy to adhere (Yes versus No)	12.527 (8.459, 18.551)	4.711 (2.062, 10.761)
Acceptance of HIV status (Yes versus No)	5.687 (3.989, 8.106)	4.727 (1.960, 11.403)
Simply forget (Yes versus No)	0.160 (0.111, 0.230)	0.080 (0.033, 0.197)
Distance to travel too long (Yes versus No)	0.240 (0.170, 0.340)	0.264 (0.111, 0.632)
Education level (Yes versus No)	0.986 (0.898, 1.084)	1.430 (1.108, 1.844)
Age 18 – 30	Reference Group	Reference Group
Age 31 – 44	5.765 (3.554, 9.352)	5.119 (2.159, 12.14)
Age 45 or more	0.880 (0.492, 1.575)	1.077 (0.388, 2.990)
Income $\leq$ RM 1,500 / month	Reference Group	Reference Group
Income RM 1,501 – 2,500	3.109 (1.620, 5.192)	6.139 (2.289, 16.465)
Income RM 2,501 – 10,000	4.088 (2.151, 7.152)	9.993 (3.175, 31.454)
Constant		3.673

Self-efficacy to adhere = Self-efficacy to take & adhere to medication
Distance to travel too long = Distance to hospital too long and costly

Figure 5.5 shows the ROC curve of the logistic regression model using the Overall Self-Reported Questionnaire results; it offers an excellent visual comparison of the models' performances. As we can observe, the curve is above the diagonal line, which indicates that the model performs well. The area under the curve (AUC) of this model was approximately 0.92 (95% CI 0.895, 0.941). This means that the model can predict 92% of the outcomes correctly. In other words, the predicted logistic regression model reports more adherence level compared to the threshold of self-reported questionnaire reports. The ROC curve tells us how well the model predicts adherence.

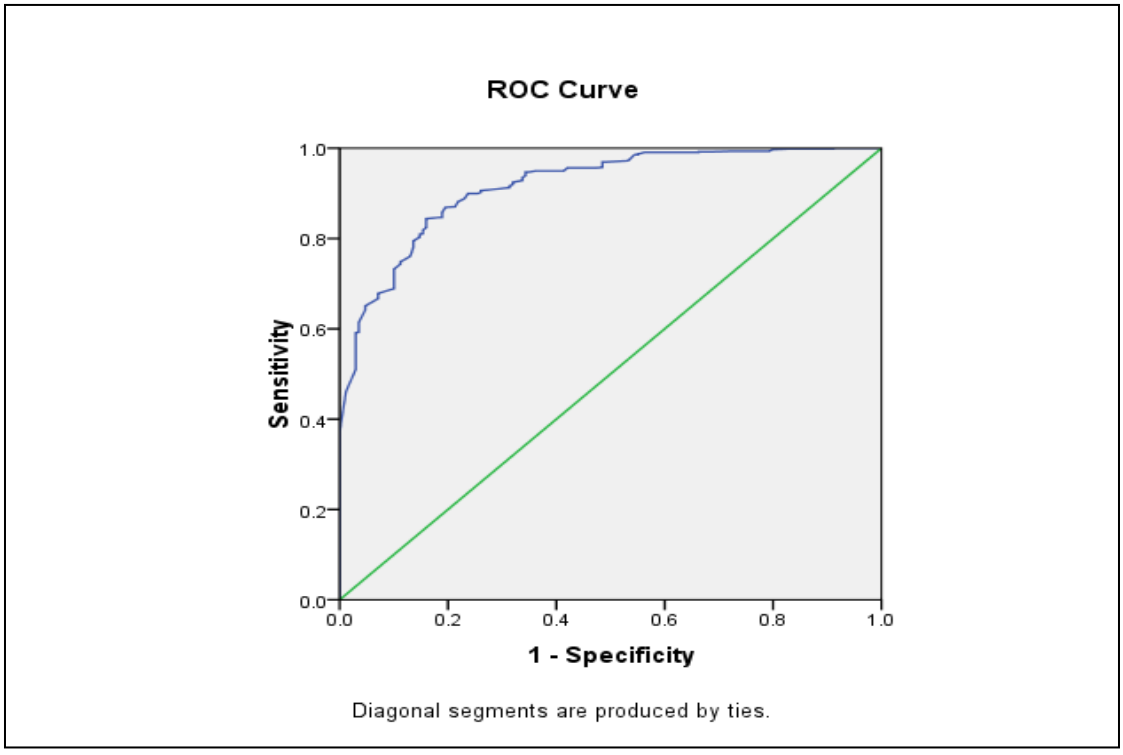

Figure 5-5 Receiver Operating Characteristic curve of the logistic regression for comparing the models' performance of overall self-reported adherence questionnaire

Table 5.44 below shows the model building stages of the second model; it uses the forward adding variable technique which sequentially selects the variables with the smallest log likelihood ratio and an acceptable Hosmer –Lemshow statistic. This model is the best-fit model to explain the dependent variable 'Adherence to HIV medication as measured by TDM for Efavirenz using the LC-MS/MS machine'. The table provides the following information: description of the variables, -2 log likelihood ratio, deviance, and Hosmer-Lemshow statistics (chi-square value and its corresponding significance level).

Table 5-44: Forward Adding Model building stages of Adherence / non-adherence as measured by TDM for Efaviranz (n = 791)

			Hosmer-Lemshow	
Variable	**2 Log likelihood**	**Difference**	Chi-Square	Sig.
Diarrhoea	715.119			
Vomiting	701.389	13.73	0.151	0.927
Use of Religious treatment	675.384	26.005	1.511	0.68
Use of Dietary supplement	658.649	16.735	5.961	0.202
Use of Alarm / Clock	644.373	14.276	7.218	0.301
Belief in efficiency	625.489	18.884	5.921	0.549
Simply forget	604.729	20.760	9.529	0.300
Felt sleep during dose time	583.994	20.735	12.864	0.117
Age	557.429	26.565	7.832	0.45

RFA –Belief = Belief in the efficacy of pills,

After the evaluation of the forward adding variable of model II, the best and the most parsimonious model of the adherence/non-adherence of HIV medication as measured by TDM level of Efavirenz was summarized in Table 5.44. In the beginning, we evaluated 48 variables in the modeling, but after making adjustments based on Hosmer-Lemshow approach, we obtained nine variables that have effects on the model. These nine variables presented in the table are the final multivariate variables that can explain the adherence/

non-adherence of HIV medication as measured by TDM level of Efavirenz. The variables are 'Diarrhoea', 'Vomiting', 'Use of religious treatment as alternative treatment for HIV', 'Use of dietary supplements as alternative treatment', 'Use of alarm/clock', 'Belief in the efficacy of pills', 'Simply forgot', 'Felt asleep during dose time' and 'Age of the patient in categories'.

It was found that when patients have considered diarrhoea and vomiting as adverse effects of antiretroviral drugs, they were less likely to be adherent to HIV medication with an OR of 0.667 (95% CI 0.393, 1.134) and 0.613 (95% CI 0.36, 1.046) respectively. Also, Patients using alternative medication such as religious treatment and dietary supplements as an alternative treatment are less likely to be adherent to their antiretroviral drugs with an OR of 0.547 (95% CI 0.321, 0.934) and 0.812 (95% CI 0.458, 1.34) respectively. Reasons facilitating adherence such as 'Use of alarm/clock' and 'Belief in the efficacy of pills' have a positive relationship with adherence to the HIV antiretroviral drugs with an OR of 2.107 (95% CI 1.336, 3.323) and 2.169 (95% CI 1.357, 3.468) respectively. This implies that these reasons increase patient's adherence level to their antiretroviral treatment.

The variables 'Simply forgot' and 'Felt asleep during dose time' were shown to be significant reasons for missing medication; these variables have a negative relationship with the adherence towards HIV antiretroviral drugs with an OR of 0.501 (95% CI of 0.319, 0.787) and 0.323 (95% CI of 0.198, 0.526) respectively. This negative relationship means that these reasons will decrease patients' level of adherence to HAART. Among

the demographic variables, patients who belonged to the categories of 18 – 30 and 31 – 44 years significantly contributed towards the adherence to HIV medication. Patients aged 31 – 44 were more likely to be more adherent with an OR of 2.457 (95% CI 1.451, 4.159) compared to the base age group, 18 – 30 years. Age group III (45 years and above) did not significantly contribute towards the adherence to HIV medication. There were 39 factors which were significant in the univariate analysis but not significant among the nine significant factors in the multivariate analysis. These variables were also reported in the above cross-tabulation, Section 5.7.

Table 5-45: Forward Adding Model (III) building stages of Adherence / non-adherence as measured by TDM level for Efaviranz (n =791)

Variables (Yes versus No)	**Crude Odds ratio (95% CI)**	**Adjusted Odds ratio (95% CI)**
Diarrhoea (Yes versus No)	0.303 (0.205, 0.449)	0.667 (0.393, 1.134)
Vomiting (Yes versus No)	0.305 (0.206, 0.453)	0.613 (0.360, 1.046)
Religious treatment (Yes versus No)	0.239 (0.160, 0.358)	0.547 (0.321, 0.934)
Dietary supplement (Yes versus No)	0.224 (0.15, .336)	0.812 (0.458, 1.340)
RFA-Use of Alarm / Clock (Yes versus No)	3.333 (2.288, 4.855	2.107 (1.336, 3.323)
RFA-Belief in efficiency (Yes versus No)	3.489 (2.383, 5.109)	2.169 (1.357, 3.468)
RMM-Simply forgot (Yes versus No)	0.320 (0.223, 0.458)	0.501 (0.319, 0.787)
RMM-Slept during dose time (Yes versus No)	0.186 (0.125, 0.277)	0.323 (0.198, 0.526)
Age 18 – 30	Reference Group	Reference Group
Age 31 – 44	2.286 (1.510, 3.460)	2.457 (1.451, 4.159)
Age 45 or more	0.622 (0.389, 0.994)	1.109 (0.671, 1.832)
Constant		2.139

RFA – Belief = Belief in the efficacy of pills,
RMM –Slept= Felt asleep during dose time.

Figure 5.6 shows the ROC curve of the logistic regression model using the results of TDM level for Efavirenz model. It offers an excellent visual comparison of the models' performances. As we can observe, the curve is above the diagonal line, which indicates that the model performs well. This means that 79% of the patients would have a higher chance of adhering to their HIV medication (as indicated by the predicted model of the overall self-reported questionnaire) than not adhering to it. The area under the curve (AUC) of this model is approximately 0.79 (95% CI of 0.773, 0.852). This means the model is able to predict 79% of outcomes accurately.

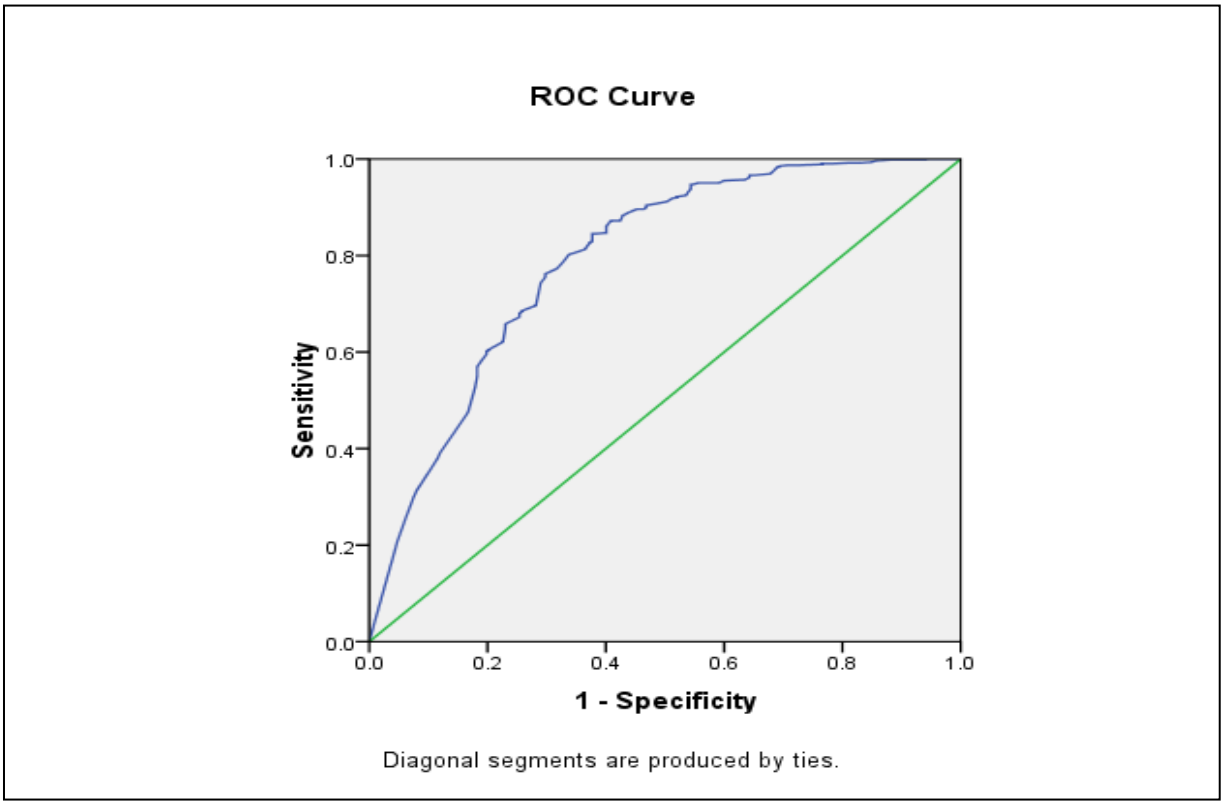

Figure 5-6 Receiver Operating Characteristic curve of the logistic regression for comparing the models' performance of TDM level for Efaviranz (n =791)

Table 5.46 below shows the model building stages of the third model; it uses the forward adding variable technique which sequentially selects the variables with the smallest log likelihood ratio and an acceptable Hosmer –Lemshow statistic. This model is the best-fit model to explain the dependent variable of 'Adherence of HIV medication as measured by TDM level for Nevirapine'. The table provides the following information: description of the variables, -2 log likelihood ratio, deviance, and Hosmer-Lemshow statistics (chi-square value & its corresponding p-value).

Table 5-46: Forward Adding Model (III) building stages of Adherence / non-adherence as measured by TDM level for Nevirapine (n=653)

			Hosmer-Lemshow	
Variables	**2 Log_likelihood**	**Difference**	Chi-Square	Sig.
Diarrhoea	662.781			
Vomiting	638.69	24.091	0.263	0.877
Use of Religious treatment	613.804	24.886	1.017	0.907
Use of Dietary supplement	602.158	11.646	5.285	0.259
Use of Alarm / Clock	585.590	16.568	5.976	0.309
Afraid of my health getting worse	563.119	22.471	8.577	0.284
RMM_ Felt asleep during dose time	540.625	22.494	4.928	0.669
Income	501.660	38.965	11.835	0.159
Marital status	479.637	22.023	7.920	0.246

Acceptance of HIV = Acceptance of HIV status,
RMM – Slept = Felt asleep during dose time.

After an evaluation of the forward adding variable of model III, the best and the most parsimonious model of the adherence /non-adherence to HIV medication as measured by TDM level of Nevirapine was summarized in Table 5.46. In the beginning, we evaluated 48 variables in the modeling, but after making adjustments based on the Hosmer-Lemshow approach, we obtained nine variables that have effects on the model. These nine variables are the final multivariate variables that can explain the adherence/non-adherence to HIV medication as measured by TDM level of Nevirapine. The variables are 'Diarrhoea', 'Vomiting', 'Use of religious treatment as alternative treatment for HIV', 'Use of dietary supplements as alternative treatment', 'Use of alarm/clock', 'Acceptance of HIV status', 'Fell asleep during dose time', 'Income' and 'Marital status'.

Based on our findings, when patients considered diarrhoea and vomiting as side effects of antiretroviral drugs, they were less likely to be adherent to HIV medication with an OR of 0.590 (95% CI 0.346, 1.006) and 0.454(95% CI 0.261, 0.788) respectively. This means that diarrhoea and vomiting decrease patients' adherence to their antiretroviral treatment. Patients using alternative medication such as religious treatment and dietary supplements as an alternative treatment are less likely to be adherent to the antiretroviral drugs with an OR of 0.389 (95% CI 0.224, 0.676) and 0.729 (95% CI 0.413, 1.087) respectively. This implies that the use of these types of alternative medication decreases the level of adherence to HAART. Reasons facilitating adherence such as 'Use of alarm/clock' and 'Afraid of my health getting worse' have a positive relationship with the adherence to HIV antiretroviral drugs with an OR of 2.612 (95% CI 1.607, 4.244) and 3.996 (95% CI

2.367, 6.747) respectively. This positive relationship means that the above-mentioned facilitating reasons increase patients' adherence level to their medication.

The variable 'Fell asleep during dose time' is the only significant reason for missing medication in Model (III) of adherence/non-adherence as measured by TDM level for Nevirapine. This variable had a negative relationship with the adherence level of antiretroviral drugs with an OR of 0.223 (95% CI 0.133, 0.374). It implies that this reason decreases the level of adherence to HAART.

Among the demographic variables, a patient's marital status and income significantly contributed towards the adherence to HIV medication. Patients who belonged to the income categories II and III (RM 1,500 – RM 2,500 and RM 2,501 – RM 10,000 respectively) were more likely to be adherent to the HIV medication with an OR of 0.220 (95% CI 0.126, 0.385) and 0.216 (95% CI 0.111, 0.419) compared to the base income group (less than RM 1,500). As for the marital status, married patients were more likely to adhere to their HIV medication as shown by an OR of 2.931 (95% CI 1.307, 3.814). Other 39 factors were significant in the univariate analysis but not significant in the multivariate analysis. These variables are also reported in the above cross-tabulation (Section 5.7).

Table 5-47: Forward Adding Model (III) building stages of Adherence / non-adherence as measured by TDM level for Nevirapine (n = 653)

Variables (Yes versus No)	**Crude Odds ratio (95% CI)**	**Adjusted Odds ratio (95% CI)**
Diarrhoea (Yes versus No)	0.319 (0.215, 0.472)	0.590 (0.346, 1.006)
Vomiting (Yes versus No)	0.239 (0.159, 0.360)	0.454 (0.261, 0.788)
Religious treatment (Yes versus No)	0.239 (0.159, 0.360)	0.389 (0.224, 0.676)
Dietary supplement (Yes versus No)	0.239 (0.159, 0.360)	0.729 (0.413, 1.087)
Use of Alarm / Clock (Yes versus No)	4.930 (3.173, 7.659)	2.612 (1.607, 4.244)
RFA_ Afraid of health (Yes versus No)	3.249 (2.234, 4.725)	3.996 (2.367, 6.747)
RMM_ asleep (Yes versus No)	0.245 (0.164, 0.366)	0.223 (0.133, 0.374)
Income $\leq$ RM 1,500 / month	Reference Group	Reference Group
Income RM 1,501 – 2,500	1.472 (0.964, 2.247)	0.220 (0.126, 0.385)
Income RM 2,501 – 10,000	1.405 (0.855, 2.308)	0.216 (0.111, 0.419)
Marital status (Yes versus No)	0.784 (0.548, 1.123)	2.931 (1.307, 3.814)
Constant		4.836

RFA Afraid = Afraid of my health getting worse,
RMM asleep = Felt asleep during dose time

In addition, the researcher checked all possible two-way interactions one at a time and found no significant interaction effect in the above model. Thus, the variables in Table 5.46 and 5.47 best explain the dependent variable of 'Adherence of HIV medication as measured by TDM for nevirapine'. The interpretation of the independent variables is based on the right most columns in Table 5.47, labelled "Adjusted odd ratio". More information about the interpretation and discussion are presented in Chapter 6 (discussion).

Figure 5.7 shows the ROC curve of the logistic regression model using the results of the TDM level for Nevirapine model; it offers an excellent visual comparison of the models' performances. As we can observe, the curve is above the diagonal line, which indicates that the model performs well. The area under the curve (AUC) of this model is approximately 0.77(95% CI of 0.725, 0.817). This means the model can predict 77% of the outcomes accurately.

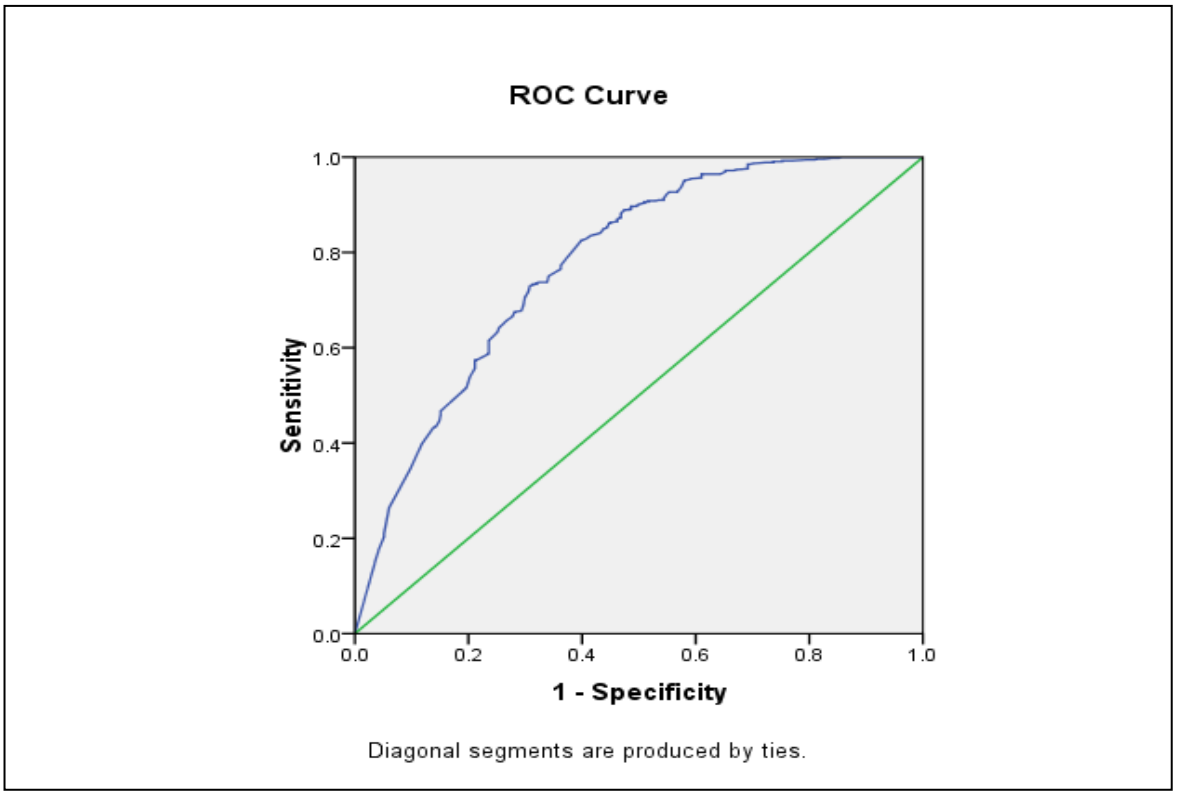

Figure 5-7 Forward Adding Model (III) building stages of Adherence / non-adherence as measured by TDM level for Nevirapine (n =653)

Table 5.48 below shows the model building stages of the fourth model; it uses the forward adding variable technique which sequentially selects the variables with the smallest log likelihood ratio and an acceptable Hosmer –Lemshow statistic. This model is the best-fit model to explain the dependent variable of 'Adherence to HIV medication as measured by TDM for Lamivudine using the LC-MS/MS machine'. The variables selected in this model had the smallest Log likelihood ration and a good Hosmer – Lemshow statistic. The table provides the following information: description of the variables, -2 log likelihood ratio, deviance, and lastly Hosmer-Lemshow statistics.

Table 5-48: Forward Adding Model building stages of Adherence / non-adherence as measured by TDM level for Lamivudine (n= 594)

Variable	**2 Log likelihood**	**Difference**	**Hosmer-Lemshow**	
			Chi-Square	Sig.
Diarrhoea	643.819		Chi-Square	Sig.
Vomiting	627.697	16.122	0.894	0.640
Use of Acupuncture	605.317	22.38	2.307	0.511
RFA -Acceptance	592.802	12.515	6.938	0.327
RMM_ Asleep	578.055	14.747	7.46	0.280
Busy with other things	560.834	17.221	3.024	0.883
Marital status	542.834	18.000	14.531	0.069

RFA –Acceptance = Acceptance of HIV status
RMM-Asleep = Felt asleep during dose time,

After the evaluation of the forward adding variable of model IV, the best and the most parsimonious model of the adherence/non-adherence to HIV medication as measured by TDM level of Lamivudine was summarized in Table 5.49. In the beginning, we evaluated 48 variables in the modelling, but after making adjustments based on the Hosmer-Lemshow approach, we obtained seven variables that have effects on the model. These seven variables shown in the table were the final multivariate variables that can explain

the adherence/non-adherence of HIV medication as measured by TDM level of Lamivudine. The variables were 'Diarrhoea', 'Vomiting', 'Use of acupuncture as alternative medication', 'Acceptance of HIV status', 'Fell asleep during dose time', 'Busy with other things', 'Distance to hospital too long and costly' and 'Marital status'.

It was found that patients who had diarrhoea and vomiting as adverse effects of antiretroviral drug were less likely to be adherent to HIV medication with an OR of 1.55(95% CI 0.964, 2.513) and OR of 1.889, (95% CI 1.155, 3.091) respectively. The use of acupuncture as an alternative treatment was the only alternative medicine that was significant in Lamivudine model. It indicates that patients using acupuncture as an alternative treatment were less likely to be adherent to the antiretroviral drugs with an OR of 2.491 (95% CI 1.552, 3.997). The variable 'Acceptance of HIV status' was the only reason that facilitated adherence to antiretroviral drugs. In other words, 'Acceptance of HIV status' had a positive relationship with adherence to HIV antiretroviral drugs with an OR of 0.52 (95% CI 0.339, 0.797).

The variables 'Fell asleep during dose time' and 'Busy with other things' were the common and significant reasons for missing medication. These variables had a negative relationship with the adherence to the HIV antiretroviral drugs with an OR of 2.227, (95% CI 1.402, 3.539) and 2.227 (95% CI 1.402, 3.539) respectively. This means that the variables may decrease the adherence level to antiretroviral treatment. Among the demographic variables, only marital status significantly contributed towards the adherence to HIV medication with an OR of 0.774 (95% CI 0.511, 1.173). There were

41other factors which were significant in the univariate analysis but not significant in the multivariate analysis. These variables are also reported in the above cross-tabulation, Section 5.7.

Table 5-49: Model IV of Adherent versas not adherent as measured by TDM level for Lamivudine (n = 594)

Variables (Yes versus No)	**Crude Odds ratio (95% CI)**	**Adjusted Odds ratio (95% CI)**
Diarrhoea (Yes versus No)	0.383 (0.257, 0.570)	1.556 (0.964, 2.513)
Vomiting (Yes versus No)	0.308 (0.204, 0.465)	1.889 (1.155, 3.091)
Use of Acupuncture (Yes versus No)	0.293 (0.193, 0.445)	2.491 (1.552, 3.997)
RFA_Acceptence (Yes versus No)	2.512 (1.712, 3.686)	0.520 (0.339, 0.797)
RMM_asleep (Yes versus No)	0.301 (0.199, 0.455)	2.227 (1.402, 3.539)
Busy with other things (Yes versus No)	0.344 (0.232, 0.509)	1.791 (1.167, 2.749)
Marital status (Yes versus No)	0.836 (0.583, 1.198)	0.774 (0.511, 1.173)
Constant		0.197

RFA-Acceptance = Acceptance of HIV status
RMM- asleep = Felt asleep during dose time

As done in the above modelling, after checking all possible two-way interactions, the researcher found no significant interaction effect in the above model. Thus, the variables in Table 5.48 and 5.49 best explain the dependent variable of 'Adherence of HIV medication as measured by TDM for lamivudine'. More information about the interpretation and discussion are presented in Chapter 6 (discussion).

Figure 5.8 shows the ROC curve of the logistic regression model using the results of TDM level for Lamivudine model; it offers an excellent visual comparison of the models' performances. As we can observe, the curve is above the diagonal line, which indicates that the model performs well. The area under the curve (AUC) of this model is approximately 0.75 (95% CI of 0.708, 0.796). This means that the model accurately predicts 75% of the outcomes correctly.

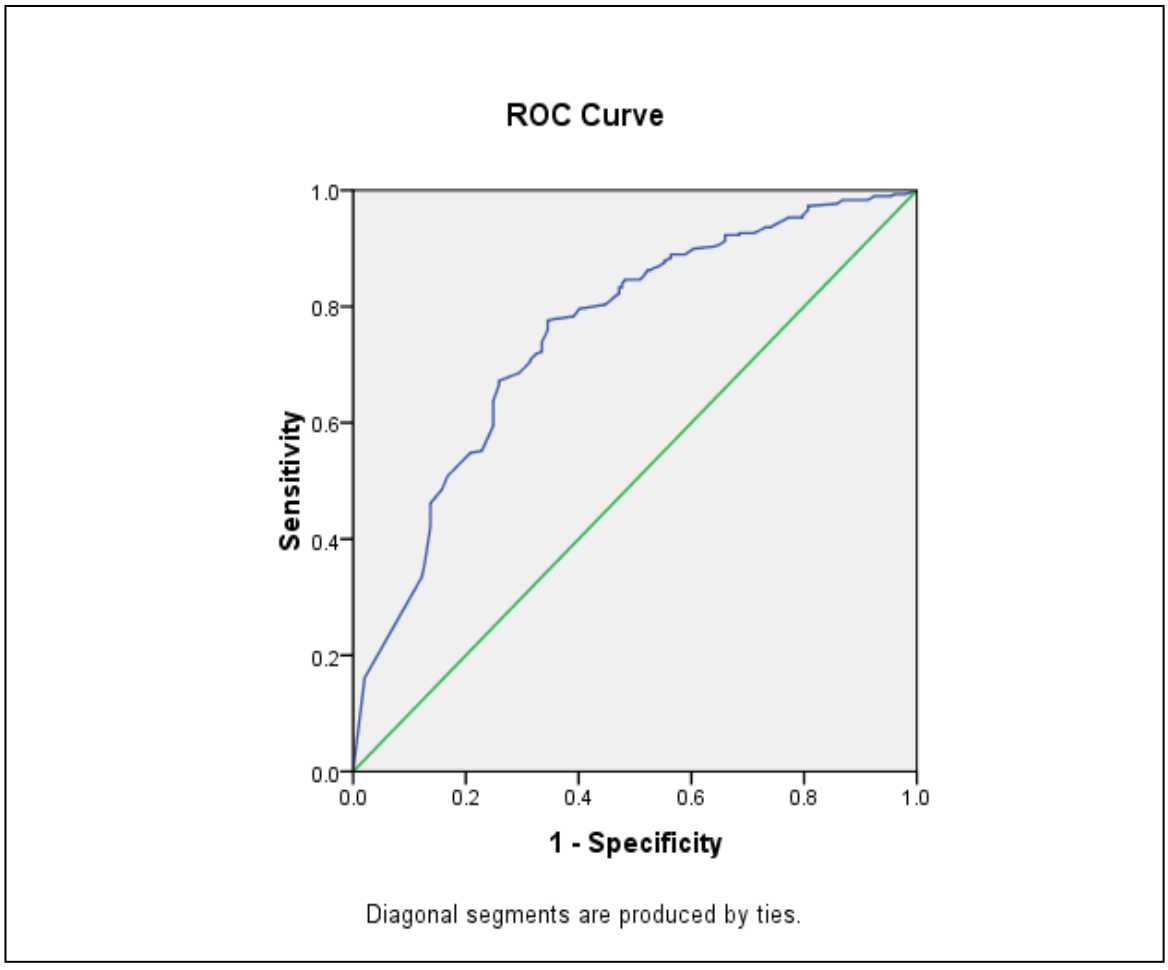

Figure 5-8 Receiver Operating Characteristic curve of the logistic regression for comparing the models' performance of TDM level for Lamivudine (n =594)

Table 5.50 below presents the summary of four logistic regression models of adherence level to HIV medication (HIV adherence predictors) as measured by the overall self-reported questionnaire and TDM for three[3] Highly Active Antiretroviral Treatment (HAART). As the table shows, model one of the 'Overall adherence measured by self-reported questionnaire' had the most significant variables compared to the other three models[4], it had 12 significant adherence predictors that can predict the level of adherence to HAART and 7 non-significant predictors.

Model two of adherence level as measured by TDM level for Efavirenz had the second highest number of significant variables with 10 significant predictors and 9 non-significant predictors. While model three of adherence level measured by TDM level for Nevirapine had the third highest number of significant variables that can predict the level of adherence to HAART, with 8 significant factors and 11 non-significant factors. Finally, model four of adherence level measured by TDM level for Lamivudine had the least number of significant variables that can predict the level of adherence to HAART; it contained 7 significant factors and 12 non-significant factors.

The variables of 'Diarrhoea' and 'Vomiting' (adverse effects to treatment) were significant predictors for adherence to HAART based on all four models. The variables 'Use of religious treatment as alternative medication' and 'Use of alarm/clock as reason facilitating adherence' were significant in three models (Model 1, 2 and 3). 'Fell asleep during dose time' as a reason for missing medication was significant in Model 2, 3, and

[3] Three TDM drugs 1) Efavirenz, 2) Nevirapine and 3) Lamivudine)
[4] Adherence measured by TDM Efavirenz method, TDM Nevirapine method and TDM Lamivudine method.

4. The following variables had a significant effect on two models: 'Use of dietary supplements as alternative treatment' had effect on Model 2 and Model 3, 'Acceptance of HIV status' as a facilitating factor had an effect on Model 1 and Model 4, while the variable of 'Simply forgot' as a reason for missing medication had an effect on Model 1 and Model 2. Finally, among the demographic variables, age, income and marital status of the patient had a significant effect on two models: age in Model 1 and 2; income in Model 1 & 3; and marital status in Model 3 & 4.

The variables 'Use of herbal medicine', 'Self-efficacy to take & adhere to medication', 'Distance to hospital too long and costly' and 'Education level' were found as significant only in Model 1 of the overall self-reported adherence questionnaire. The following variables were found to be not significant in Model 1 of the overall adherence level measured by the self-reported questionnaire: 'Use of dietary supplements', 'Use of acupuncture', 'Belief in the efficacy of pills', 'Afraid of my health getting worse', and 'Fell asleep during dose time'.

Table 5-50: Comparing the results of four different multivariate regression models for adherence to HAART (n =925)

#	Categories	Variable	SRA	TDM_Efv	TDM_Nev	TDM_Lam
1	Adverse effect to HAART	Diarrhoea	Yes	Yes	Yes	Yes
2	Adverse effect to HAART	Vomiting	Yes	Yes	Yes	Yes
3	Use of alternative medication	Use of religious treatment as alt treatment for HIV	Yes	Yes	Yes	No
4	Use of alternative medication	Usage of Herbal medicine	Yes	No	No	No
5	Use of alternative medication	Use of dietary supplements as alternative treatment	No	Yes	Yes	No
6	Use of alternative medication	Use of Acupuncture as alternative treatment	No	No	No	Yes
7	Reasons facilitating adherence	Use of Alam/ clock	Yes	Yes	Yes	No
8	Reasons facilitating adherence	Acceptance of HIV status	Yes	No	No	Yes
9	Reasons facilitating adherence	Self-efficacy to take & adhere to medication	Yes	No	No	No
10	Reasons facilitating adherence	Belief in the efficacy of pills	No	Yes	No	No
11	Reasons facilitating adherence	Afraid of my health getting worse	No	Yes	No	No
12	Reasons for missing medication	Simply forget	Yes	Yes	No	No
13	Reasons for missing medication	Distance to hospital too long and costly	Yes	No	No	No
14	Reasons for missing medication	Felt asleep during dose time	No	Yes	Yes	Yes
15	Reasons for missing medication	Was busy with other things	No	No	No	Yes
16	Socio-demographic variables	Education	Yes	No	No	No
17	Socio-demographic variables	Age of patient	Yes	Yes	No	No
18	Socio-demographic variables	Income of patient	Yes	No	Yes	No
19	Socio-demographic variables	Marital status of patient	No	No	Yes	Yes
		Total Yes	**12**	**10**	**8**	**7**

SAR: Multivariate regression model for overall adherence using self-reported adherence questionnaire.
TDM_Efv: Multivariate regression model for Therapeutic Drug Monitoring (TDM) of Efaviranz level using LC-MS/MS machine
TDM_Nev: Multivariate regression model for Therapeutic Drug Monitoring (TDM) of Nevirapine level using LC-MS/MS machine
TDM_Lam: Multivariate regression model for Therapeutic Drug Monitoring (TDM) of Lamivudine level using LC-MS/MS machine
Yes = The variable is significant, No = The variable is not significant

CHAPTER 6 Discussion

6.1 Study methods and Sampling information

This study assesses the adherence level towards the Highly Active Antiretroviral Therapy (HAART) using a variety of measures and methods; using combination methods of analysis is more reliable than using individual method. In this respect, this study is deemed to be a study with multiple methods ascompared to most of the earlier studies with limited methods. The study sample was drawn from a cross-section of HIV/AIDS patients in Sungai Buloh Hospital. The sampling method applied in the study was simple convenience sampling in order to ensure no preference in the selection process which may introduce selectivity bias. Each patient in our sample had an equal probability of being selected from a list of all population units (Kothari, 2003). The sample size formula used in the study was sufficiently adequate (n=925) as most of the other similar studies used samples which were comparatively less in size; in general, the greater the sample size, the more precise the estimates are. In terms of the power of the test, the study had used 80% of power at the 0.05 level of significance (two sided), and other similar studies had used same power test. This is rather significant since the greater the power of the test, the higher the probability of not committing Type II error.

6.2 Descriptive statistics of socio- demographic variables

Findings of socio-demographic variables (age, gender, race, educational, religion and income) in the adherence towards antiretroviral treatment is inconsistent. Some researchers find association between socio-demographic variables of the patient and the adherence level of antiretroviral treatment, while others find no association between the two. In this section, we discuss the effects of the following socio-demographic factors on the adherence level of antiretroviral treatment: age, gender, race, educational, religion and income level.

The majority of respondents in this study were male; this is probably due to the fact that females were not willing to participate in the study. This difference may also contribute to the fact that the prevalence of HIV infection is more predominant among men in South East Asian countries (UNAIDS, 2002). In Malaysia, men represent the majority (92%) of HIV cases while women and girls account for less than 10% of this total (Taylor, Nadchatram, & Faisal, 2007). This contradicts the findings of Nyambura (2003) that – in his study of factors that influence non-adherence to antiretroviral therapy among HIV and AIDS patients in Kenya – found more female respondents compared to the males. In terms of the respondents' age, the majority of patients belong to the younger age group, as younger people are always more vulnerable to the HIV epidemic than older people, and this result is similar to other studies that were conducted.

As shown by the results of the study, the majority of HIV-positive patients in this study were Chinese, followed by Malays, and the least were Indians. This could be due to bias since the questionnaire is self-administered. Perhaps this inconsistency can also be explained by the fact that the majority of people living near the study site are Chinese This result is contrary to previous similar studies and reports, which show that the Malay ethnic group makes up the majority of HIV-positive patients in Malaysia.. Correspondingly, in terms of religion, Buddhists made up the majority of the respondents, followed by Muslims and Hindus. This pattern can also be given a similar explanation as in the case with the ethnic group. Regarding marital status, there was not a big difference in number between the married and singles in our study findings. In some other studies, HIV/AIDS is more likely to be prevalent among the unmarried compared to the married ones (unfpa, 2012).

Patients who received less than primary education were the majority respondents in this study. The more educated and skilled people are, the more likely they tend to protect themselves and the less prone they would be to engage in risky sexual behaviour. Similarly, patients with a monthly income level of less than RM 3,500 made up more than half of the respondents; this may indicate that prevalence of HIV/ AIDS is higher among people with low income. According to (Bartelmus, 2005; Grainger, Webb, & Elliott, 2001) HIV affects mainly those who are usually less economically active in jobs & vocations; hence, HIV is more prevalent among the less skilled and less educated patients (UNAIDS, UNFPA, & UNIFEM;, 2012). Domestically and internationally, it was proven that HIV/AIDS is more prevalent among patients with lower levels of socioeconomic status (Siti et. al., 2007).

Lastly, we found that the heterosexual route was the most common route of transmission with (48.8%) of the participants acquiring their infection through this route. This may indicate that there is a huge shift in the mode of infection which used to be through the injecting drug use in the past 15 years (Siti N. Z et al., 2007). The prominence of heterosexual transmission in this study may be due to the dominance of Chinese respondents (63.24%) in our study. Siti et. al., (2007) had reported that heterosexual transmission of HIV is more common among Chinese Malaysians, in contrast to Malay and Indian Malaysians for whom the IDU transmission predominates by far (Siti N. Z et al., 2007).

The second route of infection according to our results findings was injecting drug use (30.1%). This used to be the highest route of infection and the reduction in number of people who get infected through this route could be due to the successful harm reduction program implemented in the country in the past 10 years. Based on the Malaysian HIV epidemic report, injecting drug use is the predominant mode of HIV transmission (72.7%), followed by heterosexual intercourse (15.3%) and homosexual (1.7%) (Taylor et al., 2007).

According to Munoz-Moreno et. al., (2007), a study done on 11 Spanish hospitals found that intravenous drug use was the most prevalent route of HIV/AIDS transmission (33%), heterosexual intercourse came second with 32%, followed by blood product transfusion of HIV/AIDS with a 5% score. In Canada, injection drug use exposure accounted for 17.7% of cumulative adult HIV case reports in the year 2008 (Public Health Agency of Canada, 2010). Heterosexual sex was estimated to account for one-third of total new diagnoses in Alabama 2006 (Sawires, Szekeres, & Cooates, 2007).

Usually, homosexual sex has a higher risk in the transmission of HIV/AIDS than the heterosexual route in most parts of the western world. Similar results were found in this study as it was shown that heterosexual route is the main contributor of HIV AIDS, which account for 48.8% cases compared to the homosexual route of transmission which comprises 15.1%. Homosexuality is not acceptable to the majority of the Malaysian society as they are restricted by religious and cultural values. However, it has shown an increasing trend in the recent years compared to the past few years. In summary, our findings in terms of age, sex, marital status, education level, race and religion were similar with some studies and not similar with others which were conducted in the developed world, as shown above.

6.3 Measuring Adherence Level

Measuring the adherence level of high antiretroviral treatment is very important in determining the outcome of a patient's treatment. In this study, we measured the adherence level using three different methods to ensure that we would obtain an accurate and reliable measure. Three methods were also used due to the fact that there is no gold standard in measuring the adherence level and it has been suggested in many studies to use more than one method to measure adherence level (Paterson, Potoski, & Capitano, 2002; J. Wagner et al., 2001). First, the researcher used the overall self-reported adherence level to determine the adherence level as reported by the HIV-positive patients on HAART. This was based on the number of doses missed and the time interval. Secondly, the researcher calculated the adherence level based on the online pharmacy records for HAART collected by the patients. Thirdly, we measured the adherence level based on the tested drug level in patients' blood using the LC-MS/MS machine, which is the most accurate machine to detect medication level.

6.3.1 Measuring Adherence level using over all self-reported Adherence Questionnaire

In this section, adherence level was measured using the overall self-reported adherence questionnaire. The calculation of the adherence level was based on the number of missed doses in the last 2 weeks, 4 weeks and 6 weeks. This interval was used to determine whether there is significant difference in the adherence level measured in a long and short time basis. It was noticed that the adherence level in the last two weeks was greater than the adherence level in the last 4 weeks. This could be due to the fact that participants filling in the questionnaire in the last 2 weeks tended to remember the number of doses they missed within the 2 weeks more than in the last 4 weeks.

Participants also missed more medication doses in the last 6 weeks compared to the last 4 and 2 weeks. Many studies have shown that recall bias tends to underestimate the level of adherence to HAART and thus the adherence level measured by self-reported questionnaires is mostly reduced as patients may not remember the date he had taken his medication, leading to low adherence level as in Ethiopia (Balcha, Jeppsson, & Bekele, 2011; Sreeranga, 2010). The overall adherence level calculated in our study was 81.7% which was less than the adherence level calculated in other developing countries. The adherence level calculated in South Eastern Nigeria by Ukwe and team members was 86.1% (Ukwe, Ekwunife, Udeogaranya, & Iwuamadi, 2011), and the one calculated in South Africa using the self-reported questionnaire was 88% (J. Nachega et al., 2004). However, the overall adherence level calculated in this study is considered to be high (81.7%) compared with other developing countries (I. Escobar, M. Campo, J. Martín et al., 2003).

Adherence level measured via self-reported questionnaire in some developed countries such as France was found to be 78.1% (Moatti et al., 2000), which is less than the adherence level measured in Malaysia. Haug *et al.* In United States found the adherence level as reported by the self-reported questionnaire to be 76.7% which is also less than the level obtained in our study (Malta, Strathdee, Magnanini, & Bastos, 2008). The self-reported adherence level obtained in USA by Hinkin and team members was 80.7% (Hinkin et al., 2004) and this figure is almost equal to the level calculated in this study. Based on the few examples mentioned above, adherence level measured by the self-reported questionnaire may not depend on whether a country is developed or developing, even though it makes more sense for the level to be higher in developed countries than developing countries.

Developed countries usually have excellent infrastructure, very good transportation system, as well as more treatment centres compared to developing countries. More importantly, hospital waiting time for patients receiving HAART in those countries is less than in developing countries, and nutritional and financial status of the patients are also much better. All of the above-mentioned reasons will definitely make the level of adherence to HAART much better in developed countries compared to developing countries.

In Section 6.3, the adherence level was found to be high among educated patients with high income. This could be due to the fact that educated patients may know and understand the HIV/AIDS and the level of adherence to HAART more than the patients with less education or the non-educated. High income contributed positively towards adherence level as patients have money to spend on treatment, nutrition, better housing; all this helps patients with high income to be more adherent to treatment than patients with lower income. Adherence level of 81.7% is considered to be a good level even though it is less than the 95% level requested by the World Health Organization (WHO). In our study, the adherence level is either similar to or slightly higher than the level obtained by some studies conducted in other developed parts of the world. The overall adherence level measured by the self-reported questionnaire was 81.7%. This is less than the 95% adherence required by WHO to prevent the development of resistance, cross resistance and treatment failure (Bartlett, 2002).

6.3.2 Measuring adherence level using pharmacy records

Participants in this study were included if they were on a combination of antiretroviral treatment. Only patients on Efavirenz, Nevirapine and Lamivudine were included in this study since these were the most commonly prescribed HIV medication by their physicians and the most commonly used drugs by the patients receiving treatment in the hospital.

The patients' pattern of medication collection behavior over the preceding six months showed a decreasing trend as illustrated in Chapter 6 (Figure 5.3). This means that patients collected more medication in the first month than in the second or third month, and the quantity collected decreased with time. Consequently, it definitely decreased their adherence level as times goes on; this could be either because they were becoming tired of collecting their medication, or they were unhappy with their medication or both. Patients can become reluctant to collect their medication due to severe adverse effects, depression and long distance to hospital (Ammassari et al., 2001; Carlucci et al., 2008; Starace et al., 2002).

The adherence level measured by pharmacy refill records revealed that Efavirenz had the highest adherence level (73.2% with 95% CI of 69.3 to 0.76.1 of adherence) among the three drugs. This could be due to the fact that the drug is given once daily at bedtime, which is also a very convenient time to take the medication since patients will be at home. In addition, Efavirenz is also prescribed as a single drug, not in a combination form as the other two (Nevirapine and Lamivudine). Adverse effects are much less in single drugs than in combined forms (Vanni et al., 2007); thus, patients may prefer Efavirenz to the other two drugs.

Nevirapine, on the other hand, had an adherence level of 68.5%, which was a little less than Efavirenz. This could be due to the fact that the drug is given in a combined form with other antiretroviral drugs and it is associated with many adverse effects due to its combination with other medication as reported by several studies (Carr & Cooper, 2000; Harding, Molloy, Easterbrook, Frame, & Higginson, 2006). Nevirapine could also be prescribed twice daily at the time during which patients are most likely to be at work or busy with other things. Taking Nevirapine during working time could result in patients forgetting their medication at home.

Patients on Lamivudine had the lowest adherence level (53.1%) as calculated by the pharmacy refill method. This reduction in adherence level could also be due to the adverse effects associated with the medication prescribed in combined forms (Qurishi et al., 2003). Compared to Efavirenz, this drug is taken twice daily and without food restrictions, which could result in other adverse effects.

In general, adherence level for the above three drugs (Efavirenz, Nevirapine and Lamivudine) as measured by the pharmacy refill method was much less than the overall adherence level measured using the self-reported adherence questionnaire for the above three medications which was found to be 81.7%. This could be due to the fact that self-reported adherence using a questionnaire is over estimated as shown in other similar studies (Adams, Soumerai, Lomas, & Ross-Degnan, 1999; Fong et al., 2003; Miller et al., 2002).

6.3.3 Measuring adherence level using TDM

First and second blood samples collected from HIV-positive patients were analyzed with the LC-MS/MS machine to detect three antiretroviral drugs: Efavirenz, Nevirapine and Lamivudine in both samples. Table 5.17 (in the results chapter) shows that participants on Efavirenz were more adherent (71.2% adherent) compared to those on Nevirapine (69.6% adherent) and Lamivudine (60.3% adherent). These findings are affected by the dose frequency, dose time, adverse effects of each drug and the availability of each medication (in single or combined form) as discussed earlier in this section. It is important to acknowledge other factors that can reduce the amount of medication detected by the LC-MS/MS machine such as drugs metabolism and drug interactions with other substances in the body. Abnormal metabolism due to any disease or any of the above factors will lead to the reduction of level of adherence to HAART. The adherence level would be low when the amount of drug detected by the machine is low. If there is an abnormality in the renal system for example, much of the drug may be excreted, thus resulting in a low level of HAART in the blood and consequently low adherence level.

This method of measuring adherence level is objective and is the most accurate method since drug levels are detected in the patients' blood using a very sensitive machine. Before the blood samples were collected, patients with other diseases except HIV had been excluded; patients with abnormal liver and renal tests had also been excluded from this study. There were no published studies on measuring the level of adherence to HAART in Malaysia and South East Asia using the LC-MS/MS machine, and therefore the findings from this study could be used as a reference for similar future studies.

6.4 Comparing the three specific drug levels as detected by TDM using LC-MS machine vs. Overall adherence level measured by self-reported questionnaire

This is the first ever reported study in South East Asia to validate a locally and culturally adapted self-reported adherence (SRA) questionnaire with detected levels of three anti-retroviral medications in human plasma using LC-MS/MS. As expected, SRA adherence levels were slightly higher than those obtained by TDM. Social desirability bias could probably account for some for this difference but it was less than we expected. The levels of sensitivity and PPV of SRA in Malaysia are comparable to levels obtained elsewhere (Godin, Gagné, & Naccache, 2003). We have also determined that SRA is surprisingly sensitive but not very specific and this has been shown by other researchers (Biadgilign, Deribew, Amberbir, Deribe, & Berhane, 2010). This is to be expected given that high sensitivity is often accompanied by low specificity. The high PPV levels are not actually that surprising given that the actual adherence to medication is high, naturally giving rise to high PPV. The fairly high diagnostic accuracy is probably a result of fairly high discriminative ability of the SRA instrument to decide who has adhered or not adhered to medication. This is backed up with the fairly high AUC values of SRA, which has been shown elsewhere by other researchers (Duong et al., 2001).

TDM is expensive and requires complex machinery and trained personnel to perform (Rakhmanina, Van Den Anker, & Soldin, 2004). These factors make it rather unsuitable for use in resource-poor environments. With this kind of profile, this begs the question whether SRA could therefore be trusted enough to replace TDM in measuring adherence and the answer is in the affirmative. When high sensitivity and PPV are required, SRA can be relied upon to check adherence. We hope that this piece of research will help answer the question whether SRA could reliably be used to measure adherence in HAART patients in a resource-poor environment.

Limitations of this study include recall bias and social desirability bias (Shi et al., 2010). Recall bias was minimized by ensuring proper definition and articulation of the research question and improving the quality of the questionnaire. Social desirability bias was minimized by engaging a research assistant who was not directly involved in the HIV clinic to collect the data. In summary, SRA is a surprisingly accurate instrument for measuring HAART adherence compared to TDM and can be reliably used in practice in a resource-poor setting.

6.5 Cross tabulation of the HIV adherence predictors (independent variables) with overall self-reported adherence questionnaire

This section discusses the findings of cross tabulation of factors affecting adherence to Highly Active Antiretroviral Therapy (HAART) and the adherence level as measured by the overall self-reported adherence questionnaire. This cross tabulation analysis helps us to understand the adherence behaviour and factors that affect people's adherence to antiretroviral drugs. Table 5.27 (in the results chapter) shows the cross tabulation of seven[5] socio-demographic factors and the overall self-reported adherence

[5] Gender, religion, ethnicity, education, marital status, income and age

level. Based on our results, four out of the seven socio-demographic variables (patient's level of education, marital status, average monthly income and age group in years) significantly influenced the level of adherence to HAART.

The study results did not show whether an increase or decrease in the pattern of educational level corresponds with an increase or decrease in the adherence level. However, level three of secondary school had the biggest odds ratio compared to the other levels of education; this signifies that patients with level three of secondary school are more likely to adhere to ARV medication. Other studies had found significant relationship between high education level and correspondingly high adherence level (Talam et. al.,2008). In the case of this study, education and adherence did not show a pattern; it is not clear why those with level 3 of secondary school had higher odds ratio compared to patients with diploma and degree. This setting is totally different from the findings of other similar studies. This difference may be possibly due to the fact that those with formal education are more aware of the side effects of antiretroviral treatment and the fact that there is no cure for HIV/AIDS; thus, they may decide to rationalize this point and therefore are less likely to adhere to ARV medications (Uzochukwu et al., 2009). According to other studies on chronic diseases, patient's education is the most important tool that can contribute to adherence towards medication of chronic diseases such as hypertension, diabetes, cardiovascular diseases etc., and thereby reduces the morbidity and mortality rates of these conditions (Shiri, 2007).

Similarly, the relationship between income categories and adherence level did not show a pattern. Patients with an income Level II (RM 1,501 – RM 2,500) had the biggest odds ratio compared to Levels I and III (≤RM 1,500 and RM 2,501 – 10,000 respectively). Similar studies show that there is positive association between adherence level and the income level; Kleeberfer et. al., (2001) had mentioned that low income is indirectly associated with low adherence to antiretroviral drugs. In this study, the reason behind the lack of pattern between adherence level and patient's income level cannot be explained. Thus, based on the income status of respondents, income is not a good predictor of adherence to antiretroviral treatment. On the other hand, results of the study show that married patients were more likely to adhere to their antiretroviral medications compared to the unmarried ones. This can be justified by the fact that married individuals may help to remind their spouses to take their medication or even put pressure on their spouses to take their medication in order to live longer. This type of relationship is also supported by other studies: (Gallant & Block, 1998; Uzochukwu et al., 2009).

For the age variable, the study findings show that older patients were more adherent to their medication compared to their younger counterparts; for instance, patients aged 45 years and above had the biggest odds ratio compared to patients aged below 45 years who had smaller odds ratio. This can best be explained by the fact that older patients are most likely married and have children, and therefore would want to live longer to care for them. Older people are also usually wiser than the young and may accept their HIV status more easily as well as take their HIV medications in order to stay alive. Many studies have also found association between adherence level and older age, and are thus consistent with our study findings (Montessori et al., 2000; Salami et. al.,2010; Wenger et al., 1999). For those under the age of 30 years, their non-adherence could be as a

result of the fact that they are most likely unmarried and unemployed or with low income (Uzochukwu et al., 2009). Similar results were found in multivariate logistic analysis developed in Section 6.8.

The above cross tabulation reveals no differences between HIV medication adherence level measured by the overall self-reported questionnaire and other socio-demographic characteristics such as religion, gender and ethnicity. As mentioned earlier, the study had used sufficient sample size (precision) and power. Other similar studies have shown that socio-demographic variables are inconsistent in influencing adherence and the scholars agreed that many of the demographic factors are not good predictors of adherence to antiretroviral treatment (Williams & Friedland, 1997).

6.5.1 Adherence and Side Effect

A side effect is usually regarded as an undesirable secondary effect which occurs in addition to the desired therapeutic effect of a drug or medication. In this study, participants were provided a list of 9 side effects associated with HAART, and asked to check those that applied to them using a binary scale of "yes" and "no". Table 5.28 in the results chapter shows the cross tabulation results of nine side effect variables (rash, itching, loss of appetite, dry mouth, diarrhoea, tiredness, vomiting, fever and headache) with overall level of adherence to antiretroviral drugs as measured by the self-reported questionnaire. Adverse effects including vomiting, diarrhoea, tiredness and loss of appetite were the most common side effects in our study. According to the odds ratio, these side effect variables decreased by at least 10% of the level of adherence to antiretroviral drugs. Among these, variables 'dry mouth' and 'headache' were found as not significant in the adherence to antiretroviral drugs.

The variables ‘rash’ and ‘itching’ were reported to have smaller odd ratios compared to the above-mentioned side effects; according to their odds ratio, these variables decrease the adherence level by 3% and 6% respectively. In contrast to this finding, the literature reports that the most common side effects of antiretroviral drugs are ‘rash’ and ‘itching’. Studies that found significant association between adherence and side effects include: Ammassari et al., (2001), Harzke et al., (2004), Giacomet et al., (2003), Moahmmed et al., (2004), Nachega et al., (2004), Van Oosterhout et al., (2005) and many others.

In many studies, it was reported that medication side effects were the most common reason for non-adherence (Duran et. al., 2001 and Chesney et. al., 2000). These studies have shown that there is inverse relationship between medication side effects and adherence. In other words, when patients experience side effects, they tend to stop undergoing treatment or take it irregularly (S. Duran, M. Savès et al., 2001). Chesney et al., (2000) found that 24% of patients reported that wanting to avoid side effects was a reason for their failure to take medication as prescribed.

6.5.2 Factors facilitating adherence to antiretroviral treatment

Factors facilitating adherence help patients to take their antiretroviral medications regularly and are also referred to as adherence motivators. Usually when these factors exist, patients are more likely to adhere to the HAART regimen than those who lack these factors. This implies that there is direct relation between factors facilitating adherence and patients’ level of adherence to treatment. Table 5.30 provides nine factors that facilitate adherence to antiretroviral drugs. Among these, seven variables were significantly related to the adherence to antiretroviral drugs, whereas the remaining two factors were found to be insignificant. The discussion in this section only revolves around the variables that were found to be significant.

Acceptance of HIV status enhances patients' level of adherence to antiretroviral drugs, extant literature indicate that the lack of acceptance of HIV status and the disease implications would lead to poor level of adherence to antiretroviral drugs (Johnson et al., 2003). This study found that patients who accept their HIV status would have higher adherence level compared to patients who do not accept it. Non-acceptance of the disease may also exacerbate symptoms and lead to poorer overall mental and physical health. Belief in antiretroviral treatment is an essential component of good adherence, as shown in Table 5.30 (in the results chapter), patients who believe in the efficacy of HAART and have faith in the treatment have a greater likelihood to adhere to the ARV medications compared to those who do not believe in them.

Adherence to medication has also been shown to be determined by self-efficacy to take and adhere to the medication. Self-efficacy is a person's belief or confidence in their ability to carry out a target behaviour successfully; it enhances a person's confidence in their ability to overcome barriers and succeed in change. This study found that the presence of self-efficacy would increase the patient's level of adherence level to ARV by a factor of 12.52 with a 95% CI of (8.459, 18.551). The fear of their health getting worse and the development of drug resistance have shown to be prevalent among HIV/AIDS patients (Meng et al., 2008). The study results had shown that the fear of health deterioration and drug resistance had a positive significant relationship with the behaviour of adherence to HAART. Patients who feared health deterioration and drug resistance have more chances of adhering to HIV medication compared to those who do not. The results of this study are consistent with the literature and logic. Some studies reported that awareness of the role of medication in avoiding severe illness and drug resistance would considerably contribute to high adherence (Colber et. al., 2006). Thus,

awareness programmes would provide practical and effective help in improving the rate of adherence to antiretroviral drugs.

Disclosure of HIV status to family members and friends was seen as essential to successful adherence. Even though it is difficult, literature and experience revealed that disclosure is very important and thus HIV patients should disclose their condition to relatives and family members. Disclosure encourages support to be given to the patients and it plays a vital role in encouraging good adherence. Our study results, for instance, showed that patients who disclosed their HIV status to family members or friends had bigger odds in adhering to their medication compared to patients who did not disclose their status.

On the other hand, the use of alarm or clock also has an important role in promoting good adherence to ART. The study results showed significant differences in the level of adherence to HAART among patients who used alarm clock and those who do not use it. The use of alarm clock would increase the adherence level of a patient on ARV by a factor of 7.06 with a 95% CI of (4.445, 11.205). In summary, the results of factors facilitating HAART in this study are consistent with other studies, as most respondents indicated that the above-mentioned facilitating factors were a major contributing cause that increased their level of adherence to medication.

6.5.3 Reasons for missing medications

In Tables 5.31 to 5.33 the researcher provided twenty reasons for missing antiretroviral drugs. They include forgetfulness, high cost of treatment, ran out of pills, had simply many pills, did not want others to notice them taking medicine, had a change in daily routine, depression, and poor relationship with the provider, among others. Out of the twenty reasons for missing medication, only six variables are non-significant in influencing the level of adherence to antiretroviral drugs. The results showed that each reason for missing medication had an odds ratio of less than one; thus, they were expected to have a negative relationship with the level of adherence. In general, reasons for missing medication would make patients less adherent to their medication regimens.

This study found that forgetfulness as a reason for missing antiretroviral medication is a main cause of poor adherence to HAART; it decreased the patients' level of adherence to antiretroviral drugs by 16% compared to patients who did not forget their medication. This could be due to many reasons such as the complications of HIV/AIDS affecting the enter brain or the memory centre, and short -term memory loss is one of the symptoms of HIV/ AIDS. Another possible reason is participants' low level of intelligence, since most of the participants were non-educated or had low levels of education. Side effects of some HAART medications may also cause severe headache. Patients who forget to take their medication may find it difficult to maintain a schedule, keep track of time, eat and drink on a regular basis, and do other daily life routines; therefore, their adherence to HAART during drug use is irregular. Forgetfulness does not always occur in isolation; other factors can also contribute to it, including memory deficits, emotional stress, oversleeping, etc.

Similarly, it was reported in other studies that forgetfulness was the principal reason reported for skipping doses, and the following papers had found that forgetfulness is the main reason for missing ARV medications: Tiyou et. al., (2010); Ostrop et. Al., (1998); Barfod et. Al., (2006); Molassiotis et. al., (2002) and several others.

This study had found 'stigma' to be one of the reasons that caused individuals to not take their medication on time. In the context of this study, stigma refers to the condition where patients do not want others to notice them taking their HIV/AIDS medication, which makes it as a contributor to non-adherence. Taking HAART is an indication of being HIV-positive, and many HIV positive patients prefer not to take such medications in order to avoid being identified by friends and relatives as an HIV /AIDS-positive patient.

As shown in Table 5.32, stigma may reduce the adherence level of antiretroviral drugs by 7.3%. When patients have this fear of stigma, they are more likely to have frequent treatment interruptions since the tablets must be hidden and eventually not taken at all in the presence of others for fear of being stigmatized (Uzochukwu et al., 2009). Not taking medications in front of other people - especially if it is during dosing time - may result in patients missing their medications. When medication is missed or its consumption is interrupted, it may reduce the adherence to HAART and can even result in non-adherence. Studies that had found stigma as significant and a prominent factor in decreasing adherence are plenty, and the following are some which are worth mentioning: Chongo (2011); Peretti, et. al. (2006); Canadian aboriginal AIDS network (2004); and Rintamaki et. al. (2006).

Depression, as a reason for missing HIV medication, significantly affected the level of adherence to antiretroviral drugs among HIV/AIDS-positive patients. The results in Table 5.33 illustrates that depression could reduce the adherence level of antiretroviral drugs by 11.7%. Although depression is not medically certified, depressive symptoms were self-reported by patients living with HIV; several studies indicated that depressive symptoms are associated with disease progression and death (Chongo, 2011). Depression is negatively associated with adherence level of antiretroviral drugs. This means that when patients are depressed they do not properly adhere to their medications, which promotes disease progression and increased mortality rate (Simpson et al., 2006). Several studies had found that depression is negatively associated with adherence, these studies include: Barfod et al., (2005); Farinpout et al., (2003); Cupsa et al., (2000); Catz et al., (2000); and (Chongo, 2011), among many others.

Some participants in this study also complained about the high cost of treatment as a reason for missing HIV medications. According to the study results, this particular reason for missing medication may reduce the level of adherence to antiretroviral drugs by 17.1% as opposed to patients who did not consider such as a reason as a factor for missing HIV medications. Although the first line of antiretroviral drugs is free in Malaysia, the cost of transportation to obtain antiretroviral drugs might be a reason given for non-adherence, as the majority of the study respondents had an average monthly income of less than RM 1500 (US $480). Complaints about the cost of transportation by respondents indicates that the patients came from far to collect their medications, hence it is necessary to reallocate the location of the centres that currently provide antiretroviral drugs to the highly prominent HIV locations.

Malaysian government provides free drugs for the first line of Highly Active Antiretroviral Treatment (HAART), but the second-line treatment is very costly and has to be paid by the patients themselves (Vicknasingam et al.,2010). The result on the cost of treatment being a barrier to the adherence towards antiretroviral drugs has also been reported in other studies (Yu et al., 2007). Daniel et al., (2004). The inability to afford medication has been one of the most frequently reported reasons for non-adherence. It has also been noted that in poor countries in Africa and other developing countries, the cost of antiretroviral treatment is one of the major causes of non-adherence. (Uzochukwu et al., 2009).

Poor relationship with health care providers such (i.e. doctors or nurses) is a big obstacle and decreases the adherence level of HIV-positive patients to their antiretroviral treatment. Respondents in this study supported the fact that poor relationship with health care providers is a barrier to the adherence towards HAART. Conceptually, it was expected that poor relationship with health care providers has a negative relationship with patients' level of adherence to antiretroviral treatment. The study found that patients who had poor relationship with their health care providers may have 32% chances of reduced level of adherence to antiretroviral drugs. Several studies had reported that non-adherence was caused by lack of confidence and trust between the health care provider and the patient (Van Servellen et al.,2002). The findings of this study had also been reported in other studies including: Witteveen et al., (2002); Malcolm et al., (2003); Powell-Cope et. al., (2003); Remien et al., (2003) and others.

The results showed that it is hard for the patients to take their HIV medications when their usual daily routine had changed or was disturbed. Chaotic schedules or disruption of daily routine is thought to be a barrier to adherence and it may result in missed doses.

Weekends and holidays represent a change in routine from the more structured activity on weekdays. Traveling from place to place in searching for support may cause difficulty for the patients to attend their monthly reviews and drug collections. According to this study, patients who complained about changes in their daily routine could have 35% less adherence rate compared to the patients who did not complain about them. Conceptually, a change in daily routine is negatively related with the level of adherence to antiretroviral drugs. Adamian et. al., (2004) and Graney et. al., (2003) found that having a fixed routine would contribute to the adherence level of HIV-positive patients on ARV medication. On the other hand, it was also reported that having many pills was also a contributor to non-adherence.

The study results in Table 5.33 show that patients who complained about having many pills may have 11% less adherence rate compared to those who do not complain about it. Theoretically, having many pills is negatively associated with the level of adherence to antiretroviral drugs. Patients are often concerned that taking medication may accidentally reveal their HIV status to their friends; therefore, single daily dosing is an important issue in improving adherence rate (Uzochukwu et al., 2009). Based on our study, the average number of pills per day was between three to six pills. For those on single medication, they would have less than 4 pills per day which is not a large amount and not an issue of concern.

Running out of antiretroviral pills was one of the reasons for missing medication according to this study. The study shows that running out of antiretroviral pills reduced the adherence level by 45% among HIV-positive patients on antiretroviral treatment. Running out of antiretroviral drugs is associated with poor level of adherence to antiretroviral drugs; thus, this would promote the development of resistance to drugs, cross resistance, worsening of patients' health status, treatment failure and also increases the risk of transmission of other opportunistic infections (Uzochukwu et al., 2009). The findings of this study are consistent with those found by Iliyasu et. al., (2005) and Mukhtar-Yola (2006).

As previously mentioned, this study found that six out of twenty reasons of missing medication were insignificant in affecting the level of adherence among HIV patients who are on antiretroviral drugs. These reasons were: busy with other things, felt like drug was toxic, felt sick or ill, had problems taking medicine at specific times, religious beliefs, and beliefs & preference for traditional medicine. The results of these variables are inconsistent with some of the earlier studies that found these reasons to produce significant results in missing medications. This could be due to the fact that participants in our study were not affected by these reasons for missing medications and therefore did not consider them as being significant. Participants in the other studies might have considered other elements, for example religious treatment and preference to traditional medicine (if they are religious and have a strong belief in traditional medicine), contrary to those in our study and vice versa.

For example, studies by Mohammed et al., (2004); and Murphy et al., (2003) found that the variable 'drug was toxic/harmful' was a significant reason for missing medication, whereas the variable 'busy with other things' was reported as a major reason for missing medication by Catz et al., (2000); Ferguson et al., (2002); Stout et al., (2004) and many other studies. Other similar studies reported feeling sick or worse as an important reason for missing medication. However, on the contrary, we found that all six of the above-stated reasons to be insignificant based on our findings in Chapter 6. The studies of Catz et al., (2000) and Byakika-Tusiime et al., (2005) found feeling sick as a significant reason for missing HIV medication.

In summary, most of the reasons for missing medication presented in this study are consistent with the findings of other similar studies. Almost all of the reasons for missing HIV medication reported in this study had an odds ratio of less than one, which indicates that it is negatively related to Highly Active Antiretroviral Treatment (HAART) adherence levels in HIV-positive patients.

6.6 Comparison of HIV adherent predictors vr three specific drug levels as measured by TDM using LC-MS/MS machine And Overall adherence as measured by self-reported questionnaire

Since adherence is a complex behaviour and difficult to evaluate; we used different techniques to measure the level of adherence to antiretroviral drugs. As mentioned earlier, Therapeutic Drug Monitoring (TDM) was one of the methods used to determine the level of adherence to antiretroviral treatment, and the overall self-reported adherence questionnaire to calculate the adherence level. Thus, in this section we discuss the comparisons of three specific drug levels as detected by TDM versus factors affecting adherence (adherence predictors) to Highly Active Antiretroviral Therapy (HAART).

6.6.1 Side Effects variables

Table 5.34 shows results of the cross tabulation of adverse effects of treatment and TDM method for detecting Efavirenz, Nevirapine and Lamivudine levels. The following side effects were found to be statistically significant with the TDM level for all three drugs (Efavirenz, Nevirapine and Lamivudine): 'Rash', 'Itching', 'Diarrhoea', 'Vomiting' and 'Fever'. This finding indicates that patients who experience the above side effects would most likely be non-adherent to the specific medication associated with that particular adverse effect. These side effects are the most common and most serious adverse effects associated with antiretroviral medications used to treat HIV infection (Hawkins, 2010; Remien et al., 2003). Moreover, these side effects were reported to be significant based on the measurement by the overall self-reported adherence questionnaire.

Although dry mouth and headache were found as insignificant in all three TDMs (Efavirenz, Nevirapine and Lamivudine), it was reported as significant by other similar studies, stating that these side effects are common adverse effects among patients. Similarly, we found that these two side effects were insignificant in the overall self-reported questionnaire adherence level. Other adverse effects such as loss of appetite and tiredness were less common among patients who used the three drugs above. In this study, almost all adverse effects of antiretroviral treatment were found to be negatively associated with the level of adherence to treatment.

This negative relationship means that patients who suffered these adverse effects would be uncomfortable and reluctant to take any medications associated with such symptoms. Thus, adverse effects reduce patients' level of adherence to antiretroviral treatment. This reduction in adherence level or even non-adherence to antiretroviral medication may result in the development of drug resistance, cross resistance and treatment failure. It would be vital for health care providers, physicians or pharmacists to identify the adverse effects to HAART in order to help patients by either changing the medication or provide treatment for such side effects.

6.6.2 Alternative Medication and self-reported adherence level

Table 5.35 displays the results of cross tabulation between the use of alternative medication and TDM method for detecting Efavirenz, Nevirapine and Lamivudine level using the LC-MS/MS machine. The table shows that using alternative medication such as dietary supplements, religious treatment, acupuncture and herbal medicine were found to be statistically significant with all three TDM levels as measured by the LC-MS/MS machine. Many patients with HIV status use alternative medication as a treatment for HIV/AIDS. The broad realm of alternative medication comprises herbal remedies, spiritual practices/prayers, traditional medicines, acupuncture, mind body therapy and numerous others. The reasons for using alternative medicine include stress reduction, relief of side-effects and symptoms (i.e. dermatological disorders, nausea, depression, insomnia, weakness etc) and pain relief (Tamuno, 2011).

According to other studies, the use of acupuncture and herbal medications has become one of the most commonly used alternative therapies for AIDS (Peltzer et. al., 2010). Likewise, this study shows that the use of acupuncture and herbal medicine was significant in all four methods of measuring adherence level for Efavirenz, Nevirapine Lamivudine using the LC-MS/MS machine as well as the overall adherence level based on the self-reported adherence questionnaire. The use of acupuncture and herbal medications decreased the adherence to antiretroviral drugs, and this may be due to the usually "powerful" status and beliefs attributed to traditional medicine. The above alternative medications used were found to decrease adherence level according to both the self-reported questionnaire and TDM monitoring for the three above-mentioned drugs. A possible explanation to this is when patients get tired from undergoing HAART or feel that the drugs do not have an effect on them, they may decide to go for herbal medicine or religious treatment. The use of dietary supplement was insignificant in all four methods of measuring adherence level (based on Efavirenz, Nevirapine Lamivudine and Self-reported Questionnaire). According to a UNICEF report (2010), the use of dietary supplement is very important for people living with HIV/AIDS because the body has to fight the virus and opportunistic infections (UNICEF, 2010). Insufficient nutrition can increase vulnerability to HIV infections and also promote the progression from infection to illness (Chongo, 2011). This study had shown that the use of dietary supplement reduced the adherence level as indicated by its small odds ratio (less than one).

Theoretically, the use of complementary and alternative medicines decrease adherence to HAART among HIV-positive patients; this may be due to the usually "supreme" status and beliefs attributed to traditional medicine used in a multi-cultural society like Malaysia. This strong belief in alternative or complimentary medicine may cause some patients to be careless with their antiretroviral treatments (Tamuno, 2011). As reported by Owen Smith et. al.(2007), patients using complementary and alternative medicines, relative to non-alternative medicine users, were 1.69 times more likely to report missing HAART doses in the last 30 days (CI: 1.02-2.80; P=.041) even after adjusting for age, education, race, religion and income.

Table 5.36 displays the results of cross tabulation between reasons facilitating adherence to HAART and TDM method for detecting Efavirenz, Nevirapine and Lamivudine levels using the LC-MS/MS machine as well as self-reported adherence as measured by the questionnaire. The table shows that the following reasons of facilitating adherence to HAART were found significant in all three TDM levels as measured by the LC-MS/MS machine: 'afraid of my health getting worse', 'use of alarm/clock', 'belief in the efficacy of pills', and 'self-efficacy to take & adhere to medication'. Many studies have shown that these facilitating factors play a variety of important roles in influencing adherence to HAART. There are evidences that self-efficacy in taking medication and the use of alarm clock as a reminder to patients to take their medications would improve medicines adherence (Müller, 2009).

Murphy et al. (2003) and Witteveen et al. (2002) found significant relationship between patients' adherence level and the use of reminder tool and self-efficacy to take medication as facilitating factors. The use of alarm clock and belief in efficacy of the pills were also found to be significant according to the self-reported questionnaire. This was indicated by the participants who believed that these two facilitating reasons helped them to adhere to their antiretroviral medications.

It is believed that the variables 'fear of health deterioration' and 'belief in the efficacy of antiretroviral treatment' have positive relationship with adherence to antiretroviral treatments; many qualitative studies have reported this type of relationship (Fassinou et al., 2004) and Powell-Cope et. al., (2003). On the other hand, the variable 'needs to care for others' is the only variable that was found to be insignificant in all three TDMs (Efavirenz, Nevirapine and Lamivudine). Likewise, it was found insignificant in the overall self-reported adherence level using the questionnaire, as discussed earlier. Thus, the 'need to care for others' is not a good predictor of adherence as it is not significant in all of the four methods of measuring adherence (Efavirenz, Nevirapine Lamivudine and self-reported questionnaire).

Tables 5.37 through 5.39 provide the results of cross tabulation between reasons missing HARRT medications and TDM method for detecting Efavirenz, Nevirapine and Lamivudine level using the LC-MS/MS machine. Reasons for missing medication were negatively associated with patients' level of adherence to antiretroviral drugs. These tables analyze 20 reasons for missing medications, and among these, 11 of them were significantly related with adherence of HAART. These significant variables are: 'simply forgot', 'cost of treatment too high', 'away from home', 'had many pills', 'fell asleep during dose time', 'stigma', 'felt depressed', 'felt well', and 'drug collection time too

long'. They were found to be significant predictors by all four methods of assessing the level of adherence to HAART. These findings are consistent with the results of other studies like the following: Adamian et. al., (2004); Graney et. al., (2003); (Uzochukwu et al., 2009); Iliyasu et. al., (2005); and Mukhtar-Yola (2006).

The following reasons for missing medications were found to be insignificant in all four methods of measuring the level of adherence to antiretroviral drugs (Efavirenz, Nevirapine Lamivudine and Self-reported Questionnaire): 'felt like drug was toxic', 'felt sick or ill' 'busy with other things' and 'beliefs for traditional medicine'. According to the respondents, these reasons were not significant in influencing their adherence to HAART. These results are inconsistent with the findings of similar earlier studies in this field including: Mohammed et al., (2004); Murphy et al., (2003); Catz et al., (2000); Ferguson et al., (2002); Stout et al., (2004); Byakika-Tusiime et al., (2005).

The variables 'distance to hospital too long', 'ran out of pills', and 'had a change in daily routine' were found to be insignificant based on two models – TDM for Nevirapine and TDM for Lamivudine methods – but they are significant based on the overall self-reported questionnaire and TDM for Efavirenz. The long distance to hospital may discourage patients to come and obtain their medication as it might exhaust them. It may also cause patients to postpone their visit to the hospital, which will eventually result in the patients defaulting from treatment. This was particularly true in the case of patients who lived further away and had no other choice but to walk, but often these patients were unable to find the time and energy to make a trip to the hospital. This discussion may be true in our study as most of our respondents had low income. To address this problem, intervention designers or ARV distribution system

would allow patients to pick up drugs from any health facility in order to help those patients who are complaining from distance to hospital (Skoval et. al.,2006).

While the variable 'ran out of pills' was a significant barrier to adherence, this variable is significant based on the overall self-reported adherence and TDM of Efavirenz. The problem of running out of antiretroviral drugs would result in resistance to drugs, cross resistance, worsening of the health status of the patients, leading to treatment failure and increases the risk of transmission of other opportunistic infections (Uzochukwu et al., 2009). The findings of this study are consistent with those found by Iliyasu et. al., (2005) and Mukhtar-Yola (2006).

The following two reasons for missing medications were not significant according to the overall self-reported questionnaire, TDM for Nevirapine and TDM for Lamivudine: 'Had problems at specific times', and 'religious belief'. Other reasons for missing HIV medications such as 'busy with other things', 'felt like drug was toxic', 'felt sick or ill', and 'beliefs of traditional medicine' were found to be insignificant in all four methods of assessing the level of adherence to HIV medication (HAART). Reasons that were insignificant in this section are negatively associated with the level of adherence to HAART and thus decrease the level of adherence to treatment.

In summary, the comparison of 43 adherence predictors of HIV using four different methods of measuring adherence to HAART had shown the following: Twenty-three factors are strong predictors of adherence based on all four methods of measuring adherence to HAART. These 23 factors were significant by all four methods used in this study and as such can be regarded as factors that affect patients' adherence to antiretroviral treatment. Four other factors are predictors of adherence according to

three methods, and another four are predictors of adherence as confirmed by two methods for measuring the level of adherence to HAART. The remaining eight factors were shown not to be predictors of adherence to HAART as they were not significant by all of the four methods of measuring adherence level.

6.7 Multiple logistic regressions models

A logistic regression model was constructed for each of the following four methods of measuring adherence as reported in Chapter Five: Overall self-reported adherence questionnaire, TDM level for Efavirenz, TDM level for Nevirapine and TDM level for Lamivudine. These logistic regression models were intended to identify factors associated with adherence to Highly Active Antiretroviral Treatment (HAART). The variables assessed in these four models were categorized into five groups: side effect variables, alternative medication variables, facilitating factors, missing medication factors and lastly demographic factors.

6.7.1 Logistic regression model one: Self-reported questionnaire

In regression model one of the overall adherence/non-adherence as measured by the self-reported questionnaire, diarrhoea and vomiting were side effects identified to be negatively associated with the adherence to antiretroviral treatment. Generally, antiretroviral drugs may cause undesirable side effects that would complicate the maintenance of good adherence to medication. As reported by Sherman and Fish (2000), diarrhoea is prevalent in 30 -70% of HIV-infected patients at some point during their illness. Similarly, according to other studies, vomiting is a troubling side effect experienced by many patients on antiretroviral treatment which causes discontinuity of antiretroviral therapy. Thus, these side effects contribute to non-adherence of the medication and consequently may cause resistance towards HIV medications, resulting

in treatment failures, opportunistic infections, loss of financial resources and many other problems (Ruiz-Pérez et al., 2006). Many similar studies have shown that these side effects were consistently associated with decreased adherence level.

Among the alternative medication variables, this study found that the use of religious treatment and herbal medicine were significant in the logistic regression model with a decreasing effect of adherence to antiretroviral treatments. According to results of other studies, the role that religion plays in adherence to medical treatment is a complex and varied one; some researchers found that alternative medications such as religious treatment and herbal medicine have a positive influence on health behaviours and health outcomes (Parspns et. al., 2006; and Walis, 1996), while others indicated that the use of herbal medicine has a negative influence on health behaviours (Pargament et. al., 1998 and Pargament et. al., 2003).

The facilitating factors such as the use of alarm clock, acceptance of HIV status, and self-efficacy were identified to be significantly associated with the improvement of adherence to ART. Similar to other studies, these facilitating factors were found to increase the adherence to antiretroviral treatments. In our sample, the use of alarm clock was the primary factor that facilitated adherence; according to Yao et. al., (2010), 69.4% of the study respondents stated that using a watch and/or an alarm clock would help them to remember the time of drug intake.

The second significant facilitating factor found in the logistic regression was self efficacy. Self-efficacy refers to patients' beliefs about their capabilities and their ability to exercise personal control. The following studies have indicated the significance of self-efficacy in adherence to antiretroviral drugs: Kgatlwane et. al.,

(2006); Adam et. al., (2003); and Laws et. al., (2000) among many others. Lastly, in the logistic regression model of the overall self-reported questionnaire, we found that the acceptance of HIV status was significant with an improving effect on adherence to antiretroviral treatment. Many similar studies have agreed that patients' acceptance of HIV status is necessary for both adherence to medication and good health outcomes of HIV-positive patients (Abel & Painter, 2003; Kgatlwane et al., 2006; Remien et al., 2003; Witteveen & van Ameijden, 2002).

Reasons for missing medications that include forgetfulness and long travel distance were found to be significantly related with non-adherence in the logistic regression model one of the self-reported adherence questionnaire; these reasons have a decreasing effect on the adherence to antiretroviral treatments. According to similar studies, the most common reason for missing medication is forgetfulness; the following studies have reported forgetfulness as a reason for missing medication: (Harzke et al., 2004; Kgatlwane et al., 2006; Marhefka et al., 2004; Mohammed et al., 2004; Molassiotis et al., 2002). Kgatlwane, et. al., (2006) reported in their study that 2 out of every 10 patients missed taking their medication because of forgetfulness. Distance to travel was found to be significant with an odds ratio of less than one; this indicates that long travel distances may discourage patients to adhere to antiretroviral treatments as some of them might feel tired of traveling to the hospital, postponing it and eventually forgetting to collect them. As reported by many studies, patients on antiretroviral drugs are burdened by the cost of transportation even though their governments are providing ARVs for free.

Among the demographic variables, level of education, age and income level of the patient showed a significant association with the adherence to antiretroviral treatments. Educated patients have more chances of adhering to their antiretroviral treatments compared to patients with lower level of education. The association of education on the adherence to antiretroviral treatments is inconsistent, some researchers found association between patients' education and level of adherence to antiretroviral treatment, while others found no association between the two (Kgatlwane et al., 2006; Uzochukwu et al., 2009).

On the other hand, the study results show an increasing trend in the patients' income level was associated with an increase in adherence level; this suggests that patients with higher income are more likely to adhere to treatment. This type of relationship is also supported by Gallant & Block, 1998 and Uzochukwu, et al., 2009. Similarly, the study also shows an increasing trend or dose-response relationship between a patient's age and adherence rate. The effect of age on the adherence is also controversial as some researchers found a positive association between adherence rate and age of the patient, while others found either a negative association or no association at all (Kgatlwane et al., 2006). In general, the results of this logistic regression model of the overall adherence level as measured by the self-reported questionnaire supports the previous empirical evidence on factors affecting adherence level of antiretroviral treatments.

6.7.2 Logistic regression model two: TDM for Efaviranz

In regression model two of adherence/non-adherence as measured by TDM for Efavirenz, diarrhoea and vomiting were side effects that were identified to be negatively associated with the adherence to antiretroviral treatment. According to model two of adherence/non-adherence as measured by TDM for Efavirenz, two alternative medication variables were found to be significant in this logistic regression model - 'use of religious treatment' and 'use of dietary supplement'. These two variables have a decreasing effect on adherence to antiretroviral treatments. According to results of other studies, the role that religion plays in adherence to medical treatment is a complex and varied one; some researchers have found that alternative medications (such as religious treatment and herbal medicine) have a positive influence on health behaviours and health outcomes (Parspns et. al., 2006; and Walis, 1996) while others have indicated that the use of dietary supplement have a negative influence on health behaviours (UNICEF, 2010 and (Chongo, 2011).

The second significant facilitating factor found in the logistic regression was belief in the efficacy of the medications. The study results indicate that patients who believed in their antiretroviral treatment (i.e. that it will cure the illness or help to control the progression of the disease) have more chances of adhering to their antiretroviral treatments. The following studies have indicated the importance of belief in the efficacy of the medications in adherence to antiretroviral drugs: Powell-Cope et. al., (2003); Kgatlwane et. al., (2006); Abel and Painter (2003); (Witteveen & van Ameijden, 2002); and (Remien et al., 2003), among others.

Among the reasons for missing medication, forgetfulness and falling asleep during dose time were found to be significantly related with non-adherence in the logistic regression model two of adherence/non-adherence as measured by TDM for Efavirenz. These reasons have a decreasing effect on the adherence to antiretroviral treatments.

In addition to that, falling asleep during dose time was also found to have negative association in the adherence to antiretroviral treatment. According to the logistic regression results of Model II, sleeping through dose time was a major cause of non-adherence to antiretroviral treatment. Other similar studies have reported falling asleep as a barrier to the adherence towards antiretroviral treatments. Studies that established this relationship include: (Mohammed et al., 2004); (Monreal, Cunha, & Trinca, 2002); (Stout et al., 2004) and several others.

From the list of demographic variables, only the patient's age showed a significant association with the adherence to antiretroviral treatments. The effect of age on the adherence to antiretroviral treatments is inconsistent; some researchers found an association between the patient's age and level of adherence to antiretroviral treatment, while others have found no association between the two. As regression model II of TDM for Efavirenz shows, middle aged patients (31-44 years) reported higher adherence compared to the younger ($\leq$ 30 years) and older ($\geq$ 45 years) patients. Although it is not very clear why middle aged patients were more adherent than the other age groups, this may be due to the fact that middle aged patients desire to improve their health because of the sense of obligation towards their family as a majority of this age group (31-44 years) had children under the age of 18. Watt et. al., (2009) stated that these patients are always more concerned about their children and elderly parents.

6.7.3 Logistic regression model three: TDM for Nevirapine

In regression model three of adherence/non-adherence as measured by TDM for Nevirapine, diarrhoea and vomiting were identified to be side effects that were negatively associated with the adherence to antiretroviral treatment. Generally, antiretroviral drugs may cause undesirable side effects that set hurdles in maintaining good adherence to antiretroviral medication.

According to model three of adherence/non-adherence as measured by TDM for Nevirapine, two alternative medication variables were found significant in this logistic regression model - 'Use of religious treatment' and 'Use of dietary supplement'. These two variables had a decreasing effect on adherence to antiretroviral treatments. According to results of other studies, the role that religion plays in adherence to medical treatment is an intricate and varied one; some researchers found that alternative medications (such as religious treatment and herbal medicine) have a positive influence on health behaviours and health outcomes (Parspns et. al., 2006; and Walis, 1996) while others indicated that the use of dietary supplement have a negative influence on health behaviours (UNICEF, 2010 and (Chongo, 2011).

Factors facilitating adherence to HAART such as the use of alarm and acceptance of HIV status were identified as being significantly associated with improving adherence to ART. Similar to other studies, these facilitating factors increase the adherence to antiretroviral treatments. The use of alarm clock was the primary factor that facilitated adherence in our sample. According to Yao et. al., (2010), 69.4% of the study respondents stated that using a watch and/or an alarm clock would help them to remember the time of drug intake.

The second significant facilitating factor found in the logistic regression was the fear of health deterioration; this variable had a positive relationship with adherence to antiretroviral treatments. In other words, the fear of their health getting worse would encourage patients to be more adherent to the antiretroviral treatments in order to improve their health and prolong their lives. The studies of Powell-Cope et. al., (2003) and (Fassinou et al., 2004) found that the fear of health deterioration is a significant facilitator in adherence to antiretroviral drugs.

Among the reasons of missing medication, only falling asleep during dose time was found to have an impact on adherence to antiretroviral treatment. According to the logistic regression results of model II, sleeping through dose time is a major cause of non-adherence to antiretroviral treatment; thus, patients' level of adherence to treatment would be reduced. Other similar studies reported falling asleep as a barrier to the adherence towards antiretroviral treatment. Among the studies that found this relationship are: (Mohammed et al., 2004); (Monreal et al., 2002); and (Stout et al., 2004). When patients undergoing HAART fall asleep, they tend to miss their dosing time and thus will have low adherence level compared to patients who do not fall asleep.

As for the demographic variables, the age and income level of a patient showed a significant association with the adherence to antiretroviral treatments. Patients with higher income status have more chances of adhering to their antiretroviral treatments compared to patients with lower level of income. The effect of income on the adherence to antiretroviral treatments is disputed; some researchers found the association between the income status of a patient and level of adherence to antiretroviral treatment (Gallant

& Block, 1998; Uzochukwu, et al., 2009) whereas others found no association between the two (Kgatlwane et al., 2006; Uzochukwu et al., 2009).

Finally, marital status of the patient was found to singly contribute to the level of adherence to antiretroviral treatment. As the regression model three of TDM for Nevirapine shows, married patients were almost 3 times more adherent to their antiretroviral treatment than the unmarried ones. A possible explanation is that married patients may have children and therefore desire to stay alive longer to care for their children. Another possibility is that married patients may help to remind each other to take their prescribed medications, support each other morally (Uzochukwu et al., 2009).

6.7.4 Logistic regression model four: TDM for Lamivudine

In regression model three of adherence/non-adherence as measured by TDM for Nevirapine, diarrhoea and vomiting were identified to be side effects that were negatively associated with the adherence to antiretroviral treatment. Generally, antiretroviral drugs may cause undesirable side effects that set hurdles in maintaining good adherence to antiretroviral medication. According to model three of adherence/non-adherence as measured by TDM for Nevirapine, two alternative medication variables were found significant in this logistic regression model - 'Use of religious treatment' and 'Use of dietary supplement'. These two variables had a decreasing effect on adherence to antiretroviral treatments. According to results of other studies, the role that religion plays in adherence to medical treatment is an intricate and varied one; some researchers found that alternative medications (such as religious treatment and herbal medicine) have a positive influence on health behaviours and health outcomes (Parsons et al., 2006) while others indicated that the use of dietary supplement have a negative influence on health behaviours (Chongo, 2011).

Factors facilitating adherence to HAART such as the use of alarm and acceptance of HIV status were identified as being significantly associated with improving adherence to ART. Similar to other studies, these facilitating factors increase the adherence to antiretroviral treatments. The use of alarm clock was the primary factor that facilitated adherence in our sample. According to Yao et. al., (2010), 69.4% of the study respondents stated that using a watch and/or an alarm clock would help them to remember the time of drug intake.

The second significant facilitating factor found in the logistic regression was the fear of health deterioration; this variable had a positive relationship with adherence to antiretroviral treatments. In other words, the fear of their health getting worse would encourage patients to be more adherent to the antiretroviral treatments in order to improve their health and prolong their lives. The studies of Powell-Cope et. al., (2003) and (Fassinou et al., 2004) found that the fear of health deterioration is a significant facilitator in adherence to antiretroviral drugs.

Among the reasons of missing medication, only falling asleep during dose time was found to have an impact on adherence to antiretroviral treatment. According to the logistic regression results of model II, sleeping through dose time is a major cause of non-adherence to antiretroviral treatment; thus, patients' level of adherence to treatment would be reduced. Other similar studies reported falling asleep as a barrier to the adherence towards antiretroviral treatment. Among the studies that found this relationship are: (Mohammed et al., 2004); (Monreal et al., 2002); and (Stout et al., 2004). When patients undergoing HAART fall asleep, they tend to miss their dosing time and thus will have low adherence level compared to patients who do not fall asleep.

As for the demographic variables, the age and income level of a patient showed a significant association with the adherence to antiretroviral treatments. Patients with higher income status have more chances of adhering to their antiretroviral treatments compared to patients with lower level of income. The effect of income on the adherence to antiretroviral treatments is disputed; some researchers found the association between the income status of a patient and level of adherence to antiretroviral treatment (Gallant & Block, 1998; Uzochukwu, et al., 2009) whereas others found no association between the two (Kgatlwane et al., 2006; Uzochukwu et al., 2009).

Finally, marital status of the patient was found to singly contribute to the level of adherence to antiretroviral treatment. As the regression model three of TDM for Nevirapine shows, married patients were almost 3 times more adherent to their antiretroviral treatment than the unmarried ones. A feasible explanation is that married patients may have children and therefore desire to stay alive longer to care for their children. Another possibility is that married patients may help to remind each other to take their prescribed medications, support each other morally (Uzochukwu et al., 2009).

6.8 Recommendations

In this chapter, the researcher makes recommendations based on the findings of the study. The following recommendations should be considered in an attempt to improve the level of adherence to antiretroviral treatment among HIV-positive patients in Malaysia. The recommendations are grouped into the following categories: Recommendations to the Ministry of Health Malaysia; recommendations to Health care professionals such as doctors, pharmacists, counsellors and nurses; recommendations to patients, family members and caregivers; and recommendations to Non –governmental Organizations (NGOs).

6.8.1Recommendations to Ministry of Health Malaysia:

Based on the findings of this study, the following recommendations are presented in order to improve the level of adherence to antiretroviral treatment among HIV positive patients in Malaysia.

- The overall level of adherence to HAART measured by the self-reported questionnaire in Sungai Buloh Hospital was 81.7%. This may seem high compared to the level obtained in other developing countries, however, it is much less than the expected 95% adherence level proposed or required by the World Health Organization (WHO) to avoid treatment failure. This shows that a large number of participants do not abide by their medication regimens. They need to be educated, counselled, motivated and encouraged to take their antiretroviral treatment. To achieve this target, patients should be informed about HAART usage and its adverse effects, given counselling about the disease and most importantly the significance of high adherence level.
- Since first-line antiretroviral treatment is currently available for free in most hospitals in the country, the Government should provide second-line treatment at a subsidized rate or completely free. This will be of great help for patients who have been shifted from the first line of treatment to the second line of treatment due to treatment failure.
- Three methods were used to measure the level of adherence to HAART in this study – the self-reported Adherence questionnaire, Therapeutic Drug Monitoring (TDM) using the LC-MS/MS machine and pharmacy refill method. Each had its advantages and disadvantages. The researcher would like to recommend the TDM as a method to measure adherence level as it is more accurate and objective. The Ministry of Health should encourage major hospitals in the country to

conduct regular research and use TDM to determine the adherence level among their HIV-positive patients.

- Self-reported adherence questionnaire is a method which is simple, fast, easy to use and cost effective. It should be recommended to only be used in health facilities which have not yet measured the level of adherence. This will be good in obtaining an estimated level of adherence to HAART due its associated bias.
- Based on the findings of this study, the researcher will not recommend the pharmacy refill method due to its limitations. This method only provides information about a patient's drugs collection records but does not show whether the medication has actually been consumed or not.
- Our findings show more than thirty factors that could predict adherence to Highly Active Antiretroviral Treatment (HAART) as measured and confirmed by more than one method. These factors were grouped into four groups: reasons for missing medications, factors facilitating adherence, adverse effects of treatment and the use of alternative medicine.

  The researcher recommends these significant factors to be compiled in a booklet and distributed by the Ministry of Health to all health centres and hospitals in the country. This booklet should be used by physicians, pharmacists and nurses to inform patients about the predictors of adherence to HAART.

  Patients receiving HAART in any hospital should come together and form a peer support group to exchange information and learn from each other's experiences. They can also learn self-care skills from each other e.g how to improve adherence such as use of alarm clock as reminders as this strategy has been found to increase the odds of adherence marketly.
- Most patients complained that the distance to travel to hospitals for the purpose of obtaining their treatment is too far and costly. This affected their adherence

level and to solve this problem, the Ministry of Health should open more treatment centres for HIV-positive patients.

- The use of religious treatment and herbal medicine by HIV-positive patients on HAART was highly significant in our findings. It affected their adherence level and because of this, the Ministry of Health should try to bring traditional medicine and Western medicine together and put more light on the importance of adhering to HAART. Patients should be educated about HAART and discouraged from combining other alternative medicines with HAART.
- The Ministry of Health Malaysia and the HIV/AIDS Council should provide full support in terms of food, cost of transportation, and cost of second-line treatment for poor patients undergoing HAART and cannot afford the treatment. This will play a big role in increasing the adherence level since these are big barriers to adherence.
- Waiting time for follow-up and obtaining medication in hospitals is still long as indicated by participants in this study. This is due to the shortage of human resources in hospitals and treatment centres in Malaysia, which is a very serious and vital problem. Urgent attention is needed if patients' adherence to medication is to be improved. For example, few doctors are managing a huge number of HIV patients, resulting in their inability to provide quality services.

6.8.2 Recommendations to Health care Professionals:

Medical doctors and pharmacists should take enough time to educate their patients about HIV /AIDS, antiretroviral treatment and adherence to their medications. Patients should be informed about the consequences of non-adherence and the required high level of adherence to HAART in order to avoid the development of drugs resistance and treatment failure. This information may encourage patients to take their medication regularly, resulting in high level of adherence. Health care providers should also take time to listen to patients' problems related to the antiretroviral treatment, side effects, social problems as well as psychological problems that they encounter while undergoing HAART. Sympathy and respect should be imparted when attending to patients.

In addition, health care providers should provide psychological support to HIV-positive patients. Health care practitioners should explain to patients in a language that they can understand and do it with extreme care to improve patient-doctor relationship which is a very important factor in improving the level of adherence.

Doctors should be well-trained to ensure that they are able to identify adverse effects of HAART, advise their patients and find proper solutions to such side effects in order to avoid patients from stopping to take their medication. Health care professionals such as doctors should ensure that their patients are well-educated about the disease and HAART before prescribing the medications to them. They should provide detailed information and counselling, which should include the following:

- Establishment of a social support team which includes patients and suitable health care providers such as counsellor and nurses. This social support team should meet every one or two weeks. The group should hold discussions on issues related to their treatment and group members should be given the opportunity to learn from each other. They should discuss the importance of

adherence to treatment, factors facilitating adherence and factors leading to missing HAART medications.

- Patients should be encouraged to use any kind of suitable reminding devices that can help to remind them of their medication time, such as the use of an alarm clock which is found to be a very import tool in this study. Use of calendars, stop watches and mobile phones as reminders should also be encouraged. Patients should know that a high level of adherence to HAART (95% or more) is essential for their treatment to work effectively.

6.9 Limitations of the study

One of the limitations expected in this study was selection bias, which may arise as motivated or well patients might be more likely to accept participation and thereby be over represented. In addition, social desirability bias may affect the correct measurements of variables. This occurs when patients report the behaviour they think is correct according to the social norm. In other words, they would report what their health care provider wants to hear. This was minimized by engaging a research assistant who was not directly involved in the HIV clinic to obtain consent, distribute and collect questionnaires. Recall bias is associated with self –reported adherence questionnaire as some patients may not remember their medication doses. It was minimized by ensuring proper definition and articulation of the research question and improving the quality of the questionnaire. As the questionnaire was sel-administered there would be selection biaswith those who are educated and can read and write responding to the question.

This is done by ensuring that the questions asked during the interview were clear and well-understood by the participants. Another general limitation is the use of many different types of questionnaires developed to measure adherence, making comparison of results between studies difficult. However this was minimized in this study by adopting the AACTG adherence questionnaire that has been used in various multi-national studies on adherence. Since only adult patients (18 years and above) have participated in the study, the results can only be generalized to adults. The reasons for non-participation in the study should have been listed in the exclusion criteria but the researcher did not included this because it was noted after the study have been completed and the author aknoledeged this limitation.

Due to the unavailability of sufficient funds, this study was conducted in only one hospital, which could also affect the generalizability of the study. Most of the patients came from the out-patients department for treatment and follow-up. We did not include patients who were admitted into the wards due to the fact that they were very ill, and in general we might miss many patients (this is common in any hospital-based study). However, patients in the wards are more likely to be more adherent as they would be forced to take their medications.

The researcher acknoledeged limitations in using some vague terms in the questionnaire such as using social support in question 20 of the questionnaire, acceptance of ones HIV status which may have other meaning –may mean a fatalistic belief i.e ihave HIV/AIDS. Using the term efficacy of pills may not be understood as it is a technical term. These limitations were noticed after the completion of the study and it was regratable that it will not be corrected.

The second blood samples collected for the three drugs (efavirenz , nevirapine and lamivudine) were less than the requested sample size because ,most of the participants did not come back to donate the second blood samples. The research team has send SMS massages to remind the participants but only few have shown up. The second blood sample was collected with the aim to be used for confirmation and also as a backup for the first blood sample. Since the second blood samples were not complete the researcher did not analyzed these samples or used them with other results but reported them as obtained.

The researcher did not compare the adherence as measured with pharmacy refill data with other methods for measuring adherence such self-reported adherence or TDM because it was not one of the objectives of the study and prefer to compare the TDM levels with the self reported questionnaire since this was the third specific objective of the study. It was also known that measuring adherence using pharmacy refill data just provide information on whether the patients has collected his medication or not but may not tell if the patients has swollen the collected tablets. Based on this the researcher concentrated on measuring adherence using TDM and SRA. Therefore, this point may be considered for future studies.

CHAPTER 7 CONCLUSION

7.1 Measurement of Adherence

In this study, the adherence level was measured using three different methods to ensure the accuracy and reliability of the measurement. The first measurement used was the self-reported adherence questionnaire. The second was calculation of the adherence level based on the online pharmacy records for the Highly Antiretroviral Treatment collected by the patients. The final method of measurement of adherence level was based on testing drug levels in patients' blood using the LC-MS/MS machine. Among these three methods, the self-reported questionnaire had the highest adherence level compared to the other measurements of adherence; pharmacy refill records show the second highest adherence level to antiretroviral treatments and the least level of adherence was shown by the drug therapeutic measurement method.

The adherence level measured by Therapeutic Drug Monitoring revealed that Efavirenz had the highest adherence level among the three drugs; Nevirapine was at the second spot, showing a slightly lower level than Efavirenz and patients on Lamivudine had the lowest adherence level. Similar results were found in pharmacy refill records which revealed that patients on Efavirenz were more adherent compared to those on Nevirapine and Lamivudine. The self-reported adherence questionnaire was found to show the highest adherence level among all methods of measuring adherence (TDM and pharmacy refill records being the other two methods). This could be due to the fact that a self-reported adherence questionnaire is subjective and is more likely to report an overestimation. In summary, based on the above measurements of adherence levels, it is clearly shown that the level of adherence in Malaysia is much less than the adherence level recommended by the World Health Organization (WHO).

7.2 Comparative analysis of contingency tables

In this study, a comparison was made between the levels of adherence as measured by the four methods (self-reported questionnaire, TDM Efavirenz, TDM Nevirapine and TDM Lamivudine) and 48 factors affecting adherence to Highly Antiretroviral Treatments (HAART). These factors were classified into the following four groups: adverse effects of medications, reasons for missing medications, factors facilitating adherence and alternative medications used for HIV treatment. The results of cross tabulation analysis were interpreted using the odds ratios and 95% confidence intervals. Results indicate that both the self-reported questionnaire and TDM level of Efavirenz had the most number of significant variables affecting the level of adherence level to antiretroviral treatments compared to the other adherence methods. Each of them had 32 significant adherence predictors and 11 non-significant predictors of the level of adherence to HAART. TDM level of Nevirapine is at the second place with 26 significant factors and 17 non-significant factors. Finally, TDM level of Lamivudine had the least number of significant variables that could predict the level of adherence to HAART with 23 significant factors and 20 non-significant factors.

According to the cross-tabulation results, twenty-three factors were found to be strong predictors of adherence to HAART based on all four methods of measuring adherence. These factors are as follows: rash, itching, diarrhoea, vomiting, fever, use of dietary supplement, use of religious treatment, use of acupuncture, use of herbal medicine, use of alarm clock, belief in the efficacy of pills, self-efficacy to adhere to medication, forgetfulness, cost of treatment too high, being away from home, had many pills, fell asleep during dose time, stigma, felt depressed, felt well, and drug collection time was too long.

This result is interesting and is supported by both logic and the literature; as measuring adherence by the level of drug detection in the human plasma using Therapeutic Drug Monitoring machine is considered to be close to the gold standard for measuring adherence.

7.3 Logistic Regression Analysis

In this study, 48 determinants of the level of adherence to antiretroviral treatment were assessed using four logistic regression models; 19 out of the 48 variables were at least found to be significant in one of the four logistic regressions. Model one assessed determinants of adherence measured by the self-reported questionnaire. It had the highest number of significant variables compared to the other three models with 12 significant adherence predictors and 7 non-significant predictors. Model two assessed determinants of adherence measured by TDM level for Efavirenz, and this model had the second highest number of significant variables with 10 significant predictors and 9 non-significant predictors.

Model three assessed determinants of adherence measured by TDM level for Nevirapine. This model had the third highest number of significant variables that could predict the level of adherence to HAART, with 8 significant factors and 11 non-significant factors. Lastly, model four assessed the determinants of adherence level measured by TDM level for Lamivudine; this model had the least number of significant variables that could predict the level of adherence to HAART, with 7 significant factors and 12 non-significant factors.

The variables ‘Diarrhoea’ and ‘Vomiting’ (adverse effects to treatment) were found to be significant predictors of adherence to HAART by all four models. The use of religious treatment as an alternative medication and the use of alarm clock as a reason facilitating adherence were found significant in three models (models 1, 2 and 3). Falling asleep during dose time as reason for missing medication was found significant in models 2, 3, and 4. The four above-mentioned logistic regression models were the best-fit models that could explain different measures of adherence to antiretroviral treatment. Thus, it is necessary to consider the predictors in order to improve the treatment of HIV/AIDS.

7.4 VALIDATION OF LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY (LC-MS-MS) METHOD

First method was developed and then validated using human plasma free of any medications using LC-MS/MS method. Three highly active antiretroviral treatments namely efavirenz, nevirapine and lamivudine were tested for in human plasma sample of 925 patients. The first blood sample collected from 925 participants was tested for detection of the three HAART medications using LC-MS/MS method at 10ng/ml. The detected concentrations were transferred into SPSS for analysis. The adherence level measured using overall self-reported adherence questionnaire was validated against the detected TDM level for the three medications. Even though TDM was objective and more accurate, but it was found to be more complex and very expensive. Measuring adherence level using SRAQ was cheap, fast and easily conducted, this is very suitable and useful for measuring adherence level in developing countries.

7.4 Future Research

Based on our findings, research is urgently needed to explore other methods for measuring the level of adherence to HAART such as Medication Events Monitoring System (MEMS). An investigation on the issue of developing resistance and cross resistance leading to treatment failure would be greatly called for.

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APPENDIX A

Self Reported Adherence Questionnaire

Instrument No: ----------

Patient SB NO: ..... Assessment Date [DD/MM/YYYY]: .....
Administrator: .....

Introduction:

My name is Dr Umar Yagoub Mohammed. I'm a postgraduate student in public health at the Department of Social and Preventive Medicine, Faculty of Medicine University Malaya, under the supervision of Prof Awang Bulgiba Awang Mahmud. I'm conducting a research on factors affecting adherence to antiretroviral treatment in HIV positive patients in Hospital Sungai Buloh, Malaysia. I would appreciate if you would complete this brief questionnaire, which will take about Five to Ten minutes to fill out. Participation in this project is completely voluntary. All information that you provide through your participation in this study will be kept confidential. Further, you will not be identified in the thesis or in any report or publication based on this research. I would like to assure you that this study has been reviewed and received ethical clearance. Your participation represents available contribution to medical research and we thank you in advance for your participation.

INSTRUCTIONS:

Please answer the following questions in part one and part two below by ticking "✔". **ONLY ONE box** for the answer you think is correct.

Part One: Socio-demographic characteristics.

1. Gender :
   □--Male □--Female

2. Religion:
   □--Islam □--Buddhism □--Hinduism □--Christianity □--Taoism
   □--Others: [Specify]…….....
3. Ethnic Group:
   □--Malay □--Chinese □--Indian
   □--Others: [Specify]…….....
4. Marital status:
   □--Single □--Married □--Separated [Married but not living together]
   □--Divorced □--Widow/widower
5. Do you have any children?
   □--Yes □--No
   If yes how many children do you have? ----------
   How many of them are staying with you? ----------
6. What is your highest level of education?
   □--No formal schooling □--Primary school
   □--Secondary School up to Form 3-[PMR/SRP/LCE]
   □--Secondary School up to Form 5 [SPM/MCE/O-Levels]
   □--High School [Form 6/ A--levels/Matriculation]
   □--Diploma □--Degree
   □--Others: [Specify]…….....

7. Current job status:
   □--Not employed □--Employed □--Self employed
   □—Retired □--Retired and re-employed
8. What is your average monthly income from ALL sources including paid job, public assistance/welfare?
   □--Less than RM 1500 per Month □--RM 1501--- 2500
   □--RM 2501--- 3500 □--RM 3501--- 4500
   □--RM 4501--- 5500 □--RM 5501--- 6500
   □--RM 6501 or more

   9- Do you face any the following adverse events (any unexpected, unfavourable or dangerous reaction to a drug e.g. Itching) because of your HIV treatment in the last 3 month? Please circle **1or 2** in the space below.

	Adverse ef ect	**Yes**	**N**
□--	Vomiting	1	2
□--	Diarrhoea	1	2
□--	Loss of appetite	1	2
□--	Dry Mouth	1	2
□--	Itching	1	2
□--	Tiredness	1	2
□--	Rash	1	2
□--	Fever	1	2
□--	Headache	1	2

Part Two: Adherence grading and factors affecting adherence.

10- Do you currently use medicines that have not been prescribed for you by your

Your doctor?

□—Yes □-- No

11- Do you currently drink so much alcohol that it prevents you from taking your HIV medicines? □—Yes □-- No

12-Have you ever used any of the following Traditional / Alternative medicine for the treatment of HIV / AIDS? Please circle **1 or 2** in the space below.

	Yes	**No**
□-- Herbal Medicine (The use of plants)	1	2
□--Yoga (is the practice of breathing exercises, postures, stretching exercises)	1	2
□--Acupuncture (involves the relatively painless insertion of extremely thin needles into the skin at specific points)	1	2
□-- Dietary Supplements (Vitamins, Minerals)	1	2
□-- Mind-body Therapies (Meditation uses deep breathing or other focusing techniques)	1	2
□--Use of any Religious Treatments (drinking prayer water, take part in prayer for treatment)	1	2

13- When did you start taking HIV medicine for the first time? (Modern/Western medicine only).
Month ……..... Year: …….....

14- How many different HIV medicines are you taking every day?
□--2 □--3 □--4 □--5 □--6 □--7 □--8

15- How many HIV pills / tablets are you taken per day?
□--2 □--3 □--4 □--5 □--6 □--7
□--8 □--9 □--10 □--11 □--12

16- Answer the question by Circling **1or 2** in the space below

	Question	**Yes**	
□--	Do you sometimes find it difficult to remember to take your medicine?	1	2
□--	When you feel better, do you sometimes stop taking your medicine?	1	2
□--	Thinking back over the past few days, have you missed any of your doses?	1	2
□--	Sometimes if you fell worse when you take the medicine, do you stop taking it?	1	2

17- What is the number of doses [specific quantity of a medicine taken at one time] you missed in the LAST 2 [TWO] weeks? ----------

18- What is the number of doses [specific quantity of a medicine taken at one time] you missed in the LAST 4 [FOUR] weeks? ----------

19- What is the number of doses [specific quantity of a medicine taken at one time] you missed in the LAST 6 [SIX] weeks? ----------

Part 3: Factors which facilitate or constrain adherence to HAART

20 -The following reasons facilitate or help you to adhere to your HIV medication. Please circle **1** or **2** for **as many reasons as** possible in the space bellow.

Reasons	**Yes**	**No**
□ Acceptance of one's HIV status	1	2
□ Disclosure (Revealing disease status to people/ friends)	1	2
□ use of alarm / clock for remembering drug time	1	2
□ Belief in the efficacy of pills in the treatment	1	2
□ The needs to care for others	1	2
□ Social support	1	2
□ Afraid of my health condition getting worse	1	2
□ Afraid of developing resistance to drugs and the drug ay stop working	1	2

□	To avoid paying for new drugs	1	
□	Self-efficacy and the ability to take and adhere to ART	1	2

21-The following are reasons for missing medications. If you have ever missed your HIV medication in the last **one Month**, please circle **1** or **2** for **as many reasons as** possible in the space below.

	Reasons	**Yes**	**No**
□--	Was away from home	1	2
□--	Was busy with other things	1	2
□--	Simply forget	1	2
□--	Had simply too many pills to take	1	2
□--	Wanted to avoid side effects	1	2
□--	Did not want other to notice you taking medications	1	2
□--	Had a change in daily routine.	1	2
□--	Felt like the drug was toxic / harmful.	1	2
□--	Fell asleep/ slept through dose time.	1	2
□--	Felt sick or ill	1	2
□--	Felt depressed /overwhelmed.	1	2
□--	Felt well.	1	2
□--	Ran out of pills	1	2
□--	Had problem taking pills at specified times [with meals on empty stomach, etc].	1	2
□--	Religious belief.	1	2
□--	Treatment and drug collection time in the hospital is too long	1	2
□--	Distance to travel to hospital too long and costly	1	2
□--	Poor relationship with health provider [Dr, Nurse].	1	2
□--	Cost of treatment too high.	1	2
□--	Beliefs and preference for traditional medicine.	1	2

Appendix B

SOAL SELIDIK LAPORAN PEMATUHAN SENDIRI

No. instrumen: ……..

No. SB Pesakit: ..... Tarikh penilaian [DD/MM/YYYY]: .....

Pentadbir: .....

Pengenalan:

Saya yang bernama Dr Umar Yagoub Mohammed adalah pelajar pascasiswazah di dalam Kesihatan Awam di Jabatan Perubatan Kemasyarakatan dan Pencegahan, Fakulti Perubatan,Universiti Malaya, di bawah penyeliaan Profesor Awang Bulgiba Awang Mahmud.

Saya sedang melakukan penyelidikan mengenai faktor-faktor pematuhan bagi rawatan antiretroviral pada pesakit Positif HIV di Hospital Sungai Buloh, Malaysia.

Saya amatlah menghargai kesudian anda melengkapkan soalan-soalan ringkas ini, yang mana hanya mengambil masa lima hingga 10 minit sahaja untuk melengkapkannya. Penglibatan anda dalam projek ini adalah secara sukarela sepenuhnya. Segala maklumat yang diperolehi daripada penglibatan anda dalam kajian ini adalah di rahsiakan. Untuk makluman, identiti anda tidak akan didedahkan dalam tesis ini atau dalam mana-mana laporan mahupun penerbitan yg berasaskan kajian ini.

Saya juga ingin meyakinkan bahawa kajian ini telah pun dinilai dan menerima pelepasan dari segi etika. Penglibatan anda akan memberi sumbangan besar kepada kajian perubatan dan kami mendahului dengan ucapan ribuan terima kasih

Arahan

Sila jawab soalan berikut iaitu bahagian I dan II dengan menanda "√" pada kotak yang disediakan

Tandakan pada satu kotak yang anda anggap betul sahaja

Bahagian I: Ciri-ciri sosio-demografik

1. Jantina :

   □--Lelaki □--Perempuan

2. Agama:

   □--Islam □--Budha □--Hindu □--Kristian □--Taoism

   □-- Lain-lain: [Nyatakan]……

3. Kumpulan Etnik:

   □--Melayu □--Cina □--India □-- Lain-lain: [Nyatakan]

4. Status Perkahwinan:

   □-- Bujang □-- Berkawin □--Berpisah[berkahwin tetapi tidak hidup bersama]

   □--Bercerai □-- Janda/Duda

5. Adakah anda mempunyai anak?

□--Ya □--Tidak

Jika ada, berapa ramai anak anda? ----------

Berapa ramai yang masih tinggal dengan anda? ----------

6. Pendidikan tertinggi anda?

□-- Tiada pendidikan formal □-- Sekolah rendah

□-- Sekolah menengah sehingga Tingkatan 3 [PMR/SRP/LCE]

□-- Sekolah menengah sehingga tingkatan 5 [SPM/MCE/O-Levels]

□-- Sekolah menengah Atas [Tingkatan 6/A-Levels/Matrikulasi]

□--Diploma □-- Ijazah Sarjana Muda □--Lain-lain: [Nyatakan]…….....

7. Status pekerjaan sekarang:

□-- Menganggur □--Bekerja □—Bekerja sendiri □—Bersara

□-- Bersara dan bekerja semula

8. Berapa keseluruhan purata pendapatan bulanan anda? Ini termasuk kerja bergaji, bantuan awam/kebajikan

□-- Kurang dari RM 1500 sebulan □--RM 1501--- 2500 □--RM 2501--- 3500

□--RM 3501--- 4500 □--RM 4501--- 5500 □--RM 5501--- 6500

□--RM 6501 atau lebih

9. Pernahkah anda mengalami kesan sampingan (sebarang kesan yang tidak dijangka, rasa tidak selesa atau tindakbalas berbahaya terhadap ubat tersebut seperti rasa gatal-gatal) akibat daripada rawatan HIV anda sepanjang 3 bulan yang lepas? Sila bulatkan 1 atau 2 di dalam ruang yang diberikan di bawah

	Kesan sampingan	**Ya**	**Tidak**
□--	Muntah-muntah	1	2
□--	Cirit-birit	1	2
□--	Hilang selera makan	1	2
□--	Mulut kering	1	2
□--	Merasa gatal-gatal	1	2
□--	Keletihan	1	2
□--	Ruam	1	2
□--	Demam	1	2
□--	Sakit kepala	1	2

Appendix B

Bahagian II: Gred Pematuhan dan faktor-faktor yang mempengaruhi pematuhan

10. Adakah anda menggunakan ubat-ubatan yang tidak dipreskipsikan oleh doktor anda

□--Ya □-- Tidak

11. Adakah di kebelakangan ini anda mengambil alkohol berlebihan yg menyebabkan anda tidak boleh mengambil ubat-ubatan ?

Ubat-ubat HIV ? □--Ya □--Tidak

12. Pernahkah anda mengambil mana-mana ubat-ubatan Tradisional/Alternative berikut. Bagi tujuan rawatan HIV/AIDS? Sila bulatkan 1 atau 2 pada ruang yang diberikan di bawah

	Ya	**Tidak**
□-- Ubat-ubatan herba (Penggunaan tumbuh-tumbuhan)	1	2
□-- Yoga (iaitu mempraktikan latihan pernafasan, kedudukan badan, latihan regangan badan)	1	2
□-- Akupunktur (Jarum halus yang dicucuk pada tempat tertentu pada kulit tetapi tidak menyakitkan)	1	2
□-- Diet tambahan (vitamin , mineral)	1	2
□-- Terapi Minda (Meditasi yang melibatkan pernafasan dalam atau lain lain teknik penumpuan fikiran)	1	2
□-- Menggunakan mana-mana kaedah rawatan keagamaan (meminum air yang telah disembahyangkan, mengambil bahagian di dalam acara sembahyang untuk sembuh)	1	2

13. Bilakah anda mula iaitu pertama kali mengambil ubat-ubatan HIV? (Bagi Moden/ubat-ubatan Barat sahaja)
    Bulan: ……. Tahun:……..
14. Berapa jenis ubat-ubatan HIV yang anda ambil setiap hari?
    □--2 □--3 □--4 □--5 □--6 □--7 □--8
15. Berapa banyak pil/tablet anda ambil sehari?
    □--2 □--3 □--4 □--5 □--6 □--7
    □--8 □--9 □--10 □--11 □--12
16. Sila jawab soalan dengan menandakan 1 atau 2 pada ruang yang diberikan

	Soalan	**Ya**	**Tidak**
□--	Pernahkah anda mengalami masalah kesukaran untuk mengingat bila sehar snya mengambil ubat-ubatan anda?	1	2
□--	Apabila anda merasa lebih sihat, adakah anda kadang kala berhenti mengambil ubat-ubatan anda?	1	2
□--	Dalam hari yang lepas, adakah anda tertingal mengambil mana-mana dos ubat-ubatan anda?	1	2
□--	Apabila anda merasa semakin teruk apabila mengambil ubat-ubatan anda, adakah anda berhenti mengambilnya?	1	2

17. Yang mana satukah bilangan dos [Nyatakan kuantiti ubat-ubatan yang diambil pada satu-satu masa] anda terlepas pada 2 minggu yang lepas? ……..
18. Yang mana satukah bilangan dos [Spesifikan kuantiti ubat-ubatan yang diambil pada satu-satu masa] anda terlepas pada 4 minggu yang lepas? ……..

Appendix B

19. Yang mana satukah bilangan dos [Nyatakankan kuantiti ubat-ubatan yang diambil pada satu-satu masa] anda terlepas pada 6 minggu yang lepas?.....

20. **Bahagian 3: Faktor-faktor yang mungkin mengekang pematuhan kepada HAART**
Berikut adalah sebab-sebab yang membantu anda mengikuti arahan kepada ubat-ubatan HIV anda. Sila bulatkan 1 atau 2 untuk sebanyak mana penyebab yang mungkin pada ruang yg diberikan dibawah

	Penyebab :	**Ya**	**Tidak**
□--	Penerimaan status HIV anda	1	2
□--	Mengakui (mendedah status penyakit kepada masyarakat/kawan-kawan)	1	2
□--	Menggunakan loceng / Jam untuk mengingatkan masa mengambil ubat-ubatan	1	2
□--	Percaya kepada kesan pil yang diambil semasa rawatan	1	2
□--	Keperluan untuk memberi perhatian kepada orang lain	1	2
□--	Sokongan Sosial	1	2
□--	Risau akan keadaan kesihatan saya bertambah teruk	1	2
□--	Risau akan berlaku rintangan kepada ubat-ubatan dan kemungkinan ianya tidak berkesan lagi	1	2
□--	Bagi meng lakan membayar ubat-ubatan yang baru.	1	2
□--	Kesedaran dan kemampuan diri untuk mengambil patuh pada ART	1	2

21. Berikut adalah sebab-sebab mengapa terlepas daripada mengambil ubat-ubatan. Sekiranya anda pernah terlepas dalam pengambilan ubat-ubatan HIV pada 1 bulan yang lepas. Sila bulatkan 1 atau 2 atau sebanyak mana sebab yang mungkin dalam ruang yang diberikan dibawah:

	Penyebab	**Ya**	**Tidak**
□--	Tidak berada di rumah (Keluar rumah/berada jauh dari rumah)	1	2
□--	Sibuk dengan perkara-perkara lain	1	2
□--	Terlupa	1	2
□--	Terlalu banyak pil yang perlu diambil	1	2
□--	Mengelakan kesan sampingan	1	2
□--	Tidak mahu orang lain mengetahui yang anda mengambil ubat-ubatan	1	2
□--	Perubahan kepada rutin seharian	1	2
□--	Merasa bahawa ubat-ubatan tersebut meracun/memudaratkan	1	2
□--	Mengantuk/tertidur ketika masa dos	1	2
□--	Merasa tidak sihat atau sakit	1	2
□--	Merasa tertekan/teruja	1	2
□--	Merasa sihat	1	2
□--	Kehabisan pil	1	2
□--	Mempunyai masalah mengambil pil pada masa-masa tertentu [masa makan dengan perut kosong, dan lain-lain]	1	2
□--	Kepercayaan agama	1	2
□--	Rawatan dan masa mengambil ubat hospital terlalu lama menunggu	1	2
□--	Tempat kediaman terlalu jauh dan memerlukan kos yng tinggi	1	2
□--	Hubungan yang tidak baik dengan pengamal perubatan [Doktor, Jururawat]	1	2
□--	Kos rawatan terlalu tinggi	1	2
□-	Kepercayaan dan keutamaan kepada ubat-ubatan tradisional	1	2

Appendix C

自我药物遵守评估问卷

仪表编号: ----------

病人双溪毛糯编号: .....
评估日期[日/月/年]: .....
执行者: .....

简介:

我是Umar Yagoub Mohammed博士。我是马来亚大学公共卫生部社会和预防医学系Awang Bulgiba Awang Mahmud教授的研究生。我正于马来西亚双溪毛糯医院进行一项关于影响爱滋病阳性患者正确遵守服用抗逆转录病毒治疗药物的因素之研究。问卷填写大约需要您5至10分钟的时间，您若能协助完成此简短问卷，本人不胜感激。另外，参与此研究与否，完全出自个人意愿。您所提供的所有信息将会获得保密。此外，您的身份将不会在任何以此研究为基础的论文或在报告中被发表。我愿向您保证，这项研究已通过伦理审查和批准。您的参与将为广大的医学研究作出贡献，在此，我们对您的参与再次表达万分谢意。

说明:

请回答第一部分和第二部分的所有问题，并在相关选项或您认为正确的一项打勾“✔”。答案不得复选。

第一部分: 社会人口特征。

1。性别:

□ -男性 □ -女性

2。宗教:

□ -伊斯兰教 □ -佛教 □ -印度教 □ -基督教 □ -道教
□ -其他: [请列明] ... ...

3。民族:

□ –巫裔 □ –华裔 □ -印裔 □ -其他:
[请列明] ... .

4。婚姻状况:

□ -单身 □ -已婚 □ –分居 [已婚但没有生活在一起]
□ -离婚 □ –寡妇(丧夫)/鳏夫(丧妻)

5。您有没有孩子?

□ -有 □ -无

如果有, 多少位? ....
其中有多少位是与您同住? ....

6。您的最高学历?

□ -没受过正规的学校教育 □ -小学
□ -中学, 最高到Form 3 - [PMR/SRP/LCE]
□ -中学, 最高到Form 5 [SPM/MCE/O-Levels]

□ -高中[Form 6 / A--levels/Matriculation]
□ -文凭 □ -学位
□ -其他: [请列明] ... ...

7 。目前的工作状况:
□ -没被雇用 □ -就业 □ -自雇 □ -退休
□ –已退休，再就业

8 。您每月的总收入（包括工作、公共援助或福利金）平均为多少?

□--每月少于RM1500） □--RM 1501--- 2500 □--RM 2501--- 3500
□--RM 3501--- 4500 □--RM 4501--- 5500 □--RM 5501--- 6500
□--RM 6501或以上

9 。 您是否（面对）任何不良反应（药性副作用）?[在过去3个月因为您的爱滋病治疗，是否引起任何意料之外，不利或危险的药物反应如: 发痒] 请在以下选择中圈出1或2。

药性副作用	有	无
□-- 呕吐	1	2
□-- 肚泻	1	2
□-- 没胃口	1	2
□-- 口干	1	2
□-- 发痒	1	2
□-- 疲倦	1	2
□-- 红疹	1	2
□-- 发烧	1	2
□-- 头痛	1	2

第二部分: 药量遵守分级及其影响因素。

10 。 您目前有没有服用不是由您的医生所开的药物?

□ -有 □ -无

11 。 您目前有没有饮用过量的酒导致您无法服用抗爱滋病药品?
□ -有 □ -无

12 。您可否曾使用以下任何传统药物以治疗爱滋病?请在以下选择中圈出1或2。

	有	无
□—药草(使用植物)	1	2
□—瑜伽 （操练呼吸，姿势与伸展运动）	1	2
□—针灸（无痛地将针刺入人体特定穴位）	1	2
□—营养补助品(维他命，矿物质)	1	2
□—身心治疗(深思；深呼吸或其他帮助聚焦的方法)	1	2
□—任何的宗教治疗法(饮符水；祷告医治)	1	2

13。 **您是什么时候开始服用抗爱滋病药物？** [以现代西药为准] 。

... ... 年.. ... ... 月

14。 **您每天服用多少种不同种类的抗爱滋病药物？**

□--2 □--3 □--4 □--5 □--6 □--7 □--8

15。 **您一天服用多少颗抗爱滋病治疗的药丸？**

□--2 □--3 □--4 □--5 □--6 □--7
□--8 □--9 □--10 □--11 □--12

16。 请回答以下问题，并在相关选项圈出“1”或“2”。

	问题	是	否
□--	**您是否偶尔会觉得很难记得服药？**	1	2
□--	**当您觉得好转时，是否会偶尔停止服药？**	1	
□--	**回想过去的四天，您是否有错过任何的药物剂量？**	1	2
□--	**若偶尔当您服用药物后觉得不适，是否会停止服用？**	1	2

17。 **在过去的两（2）周，您错过了多少的药物剂量（次数）？[根据单一时间内医生所建议服用的药物剂量]** ----------

18。 **在过去四（4）周，您错过了多少的药物剂量（次数）？[根据单一时间内医生所建议服用的药物剂量]** ----------

19。 **在（过去）的六（6）周，您错过了多少的药物剂量（次数）？[根据单一时间内医生所建议服用的药物剂量]** ----------

第三部分：提升或减少抗逆转录病毒治疗（HAART）依从性的因素

20。 **以下的理由能帮助您遵守服用抗爱滋病药品。请尽量在所有相关的理由圈出“1”或“2”。**

	理由	是	否
□--	对爱滋病患的接纳度	1	2
□--	**公开透露（将自己的感染状况告知他人/朋友）**	1	2
□--	**以闹钟/时钟记住服药时间**	1	2
□--	**相信治疗中药物的功效**	1	2
□--	**需要照顾他人**	1	2
□--	**社会支持**	1	2
□--	**担心病情恶化**	1	2
□--	**担心对药物产生抗药性，导致无法让药物达到功效**	1	2
□--	**避免为新药支付药费**	1	2

□-- **自我效能感：抗爱滋病治疗** 1 2

21
。以下所列是错过药物治疗的理由。如果您在过去一个月内曾错过任何药物治疗，请尽量在所有相关的理由圈出"1"**或**"2"**。**

	理由	**是**	**否**
□--	不在家。	1	2
□--	忙于其他事情。	1	2
□--	忘了。	1	2
□--	太多药物需要服食。	1	2
.			
□--	为了避免药物的副作用	1	2
□--	不想让别人知道您接受药物治疗	1	2
□--	日常生活习惯起了改变	1	2
□--	觉得药物是有毒/有害的。	1	2
□--	睡着了/睡过了服药的时间。	1	2
□--	生病或感到不适。	1	2
□--	感到忧郁，沮丧/不知所措。	1	2
□--	感觉病好了。	1	2
□--	药丸服食完了。	1	2
.			
□--	在特定时间内服药面对困难 [比如，需要饭后服食 或空腹服食 等等] 。	1	2
□--	宗教信仰。	1	2
.			
□--	在医院治疗和领取药物的时间太长。	1	2
□--	距离医院太远，交通费用高昂。	1	2
□--	**与医**务人员（医生、护士）的关系不好，无法取得良性交流。	1	2
□--	治疗费用太高。	1	2
□--	相信或优先选择传统疗法	1	2
.			

Appendix D

Adherence to HAART in HIV positive patients
Data collection form from online records
At Sungai Buloh Hospital

Instrument No: ---------- Patients S B NO.....

Date..... Part 1

1- Patients Age in Years.....
2- Date of Birth...../...../...../
3- Address.....
.....
.....
.....
.....
4- Employments Status (e.g. Labour or professional).....
5- Method of exposure to the HIV virus.....
6- CDC HIV STAGE.....

Pharmacy records of current treatment:

Treatment was initiated on...../...../..... Duration of current treatment.....Months

No	Drug Name	Dose	Pills No per Dose	Date dispensed	Date Refilled
1					
2					
3					
4					
4					
5					
6					

Table 2 Measurements:

No	Date	Weight (KG)	Height (M)	BMI

Appendix D

Table 3 Investigations done:

No	Date	HB	WBC	CD4	CD8	Viral load	Log-viral load
1							
2							
3							
4							

Table 4 Liver function tests

No	Date	Total protein	Albumin	ALP	BIL	ALT	AST	GGT
1								
2								

Additional information

.....
.....
.....
.....
.....
.....
.....
.....

Appendix E

Adherence to HAART in HIV positive patients
Blood sample collection form for TDM

Form No: .....

Patient S B NO:-.....

Instructions:-

1-Blood samples should be obtained if patient is on any of the following three named HIV drugs **Lamivudine, Nevirapine and Efavirenz.**

2- Blood samples should only be collected if patient's last dose has been taken **more than 4 hours ago.**

3-Blood samples should be obtained using **EDTA or lithium** heparin collection tubes.

4-**6mls** of blood should be collected.

5-The blood should be centrifuged within **2 Hours** of collection. After centrifugation, **plasma** should be placed in **a plain tube** and then stored in the fridge.

6-Ensure that the Test Request **form below** is completed fully.

Sample Information:-

First sample ID:-..... Date taken: .....

Time Taken:-..... Time centrifuged: .....

No	Drug name	Dose (MG)	Date of last dose	Time of last dose	No of doses / day
1	Lamivudine				
2	Efavirenz				
3	Nevirapine				

Sample collected by:-..... Sign:-.....

Date:-..... Time:-.....

Appendix F

Adheren kepada HAART pada pesakit positive HIV
Borang pengumpulan sampel darah untuk TDM

No. Borang:……..
No. SB pesakit:……..

Arahan:

1- *Sampel darah patut diambil jika pesakit sedang dalam pengambilan mana-mana tiga daripada nama ubat HIV berikut* ***Lamivudine, Nevirapine and Efavirenz.***
2- *Sampel darah hanya diambil jika dos terakhir pesakit telah diambil lebih dari 4 jam yang lepas*
3- *Sampel darah mesti diambil dengan menggunakan tiub pengumpul EDTA atau Lithium heparin.*
4- *6 ml darah patut diambil*
5-*Darah tersebut patut diemparkan dalam masa 2 jam selepas diambl. Selepas emparan, plasma patut diletakkan didalam tiub kosong dan disimpan di dalam peti sejuk*
6- *Pastikan bahawa borang permintaan ujian dibawa dilengkap dengan betul*

Maklumat sampel:-

ID sample pertama:-..... *Tarikh diambil*: .....
Masa diambil:-..... *Masa diemparkan*: .....

No	***Nama Ubat***	***Dos (MG)***	***Tarikh dos terakhir***	***Masa dos terakhir***	***Tiada (bilangan) dos /hari***
1	Lamivudine				
2	Efavirenz				
3	Nevirapine				

Sampel diambil oleh:-..... *Tandatangan*:-.....
Tarikh :-..... *Masa*:-.....

Appendix G

Adherence to HAART in HIV positive patients
Pharmacy Refill Data from Patients online records

Instrument No: --------- Patients S B NO..... Index visit date ...../...../.....

Instructions:

Please complete the following tables below, starting from the **first fill** as the **most recent pharmacy visit** and going **retrospectively** and **consecutively** until you complete the spaces for all the **6** refills for each table below.

1-Lamivudine (3TC)

Refill inform	Refill status		No of pills prescribed per day	No of pills dispensed	Date dispensed (dd/mm/yyyy)	Days b/w refills
	Yes	No				
1st Fill						
2nd Fill						
3rd Fill						
4th Fill						
5th Fill						
6th Fill						
Total						

2-Efavirenz(Stocrin)

Refill inform	Refill status		No of pills prescribed per day	No of pills dispensed	Date dispensed (dd/mm/yyyy)	Days b/w refills
	Yes	No				
1st Fill						
2nd Fill						
3rd Fill						
4th Fill						
5th Fill						
6th Fill						
Total						

3-Nevirapine (Viramunie)

Appendix G

Refill inform	Refill status		No of pills prescribed per day	No of pills dispensed	Date dispensed (dd/mm/yyyy)	Days b/w refills
	Yes	No				
1st Fill						
2nd Fill						
3rd Fill						
4th Fill						
5th Fill						
6th Fill						
Total						

HAART Treatment was started on

(DD/MM/YYYYY).....

Adherence =
(Pills dispensed/ pills prescribed per day)/days between refills) x 100%

Appendix G

Appendix H

STUDY INFORMATION SHEET

Please read the following information carefully, do not hesitate to discuss any questions you may have with the researcher or your own doctor.

STUDY TITLE: Factors affecting adherence to antiretroviral treatment in HIV positive patients a major hospital in Malaysia

Introduction: We are glad to inform you that we are very committed to the health, safety and welfare of HIV positive patients in this hospital undertaking treatment. We recognize that Adherence to antiretroviral treatment in HIV positive patients is a health and safety issue and acknowledge the importance of tacking the factors affecting adherence to antiretroviral treatment.Therefore, we would be most grateful if you could participate in this study. The principal investigator for this study is Prof Dr Awang Bulgiba the Head of Department of Social and Preventive Medicine, Faculty of Medicine, University Malaya.

What is the purpose of the study?

We are asking you to take part in this study now to ensure that we can recommend measures which will be used to improve patient's adherence to antiretroviral treatment in Malaysia and be used as guidelines by Doctors and Pharmacist for treatment of HIV positive in Malaysia.

What are the procedures to be followed?

The first part of this study involves you completing a questionnaire which will take less than 10 minutes of your time. All information obtained from this study will be **STRICTLY** treated as **CONFIDENTIAL**. Only the study investigators will have access to the confidential data which identifies you by your socio-demographic characteristics. Your responses to this questionnaire will remain ANONYMOUS and only group data will be presented. **It WILL NOT** be used as an evaluation of your work capabilities. You'll not be identified in any report resulting from this study.

Please take the time to complete the questionnaire. Once you have completed the questionnaire, please hand over the questionnaire to the study investigators who are at your clinic

The second part of this study involves collecting blood from you which will take only 5 minutes. The investigators will collect 3 mls of blood which will be used for test.

Appendix I

研究信息表

请仔细地阅读以下信息，如有任何疑问，请别迟疑向研究人员或医生讨论。

研究标题：
在马来西亚主要医院的爱滋病呈阳性患者对遵守
Antiretroviral（抗逆转录病毒）药物正确服用（守时守量）的影响因素 简介：我们很荣幸地向您表示，我方非常致力于确保爱滋病患者在这个医院进行治疗的同时，您的健康，安全和福利也会受到高度的兼顾。我们察觉到
抗逆转录病毒治疗
药物药量遵守态度的坚持对患者的健康和安全问题，并认知到必须着手解决影响对遵守 **抗逆转录病毒治疗药物** 正确服用方法的因素。
因此，如果您能参与这项研究，我们将会深深感激。
这项研究是由马来亚大学医学系，社会和预防医学系系主任Prof Dr Awang Bulgiba 教授担任首席研究员

研究目的是什么？
我们要求您参于这项研究，以确保我们可以采取建议措施以改善马来西亚病人对**抗逆转录病毒**
疗法的坚持和正确服用方法以作为马来西亚医生和药剂师治疗爱滋病患者的指导方针。

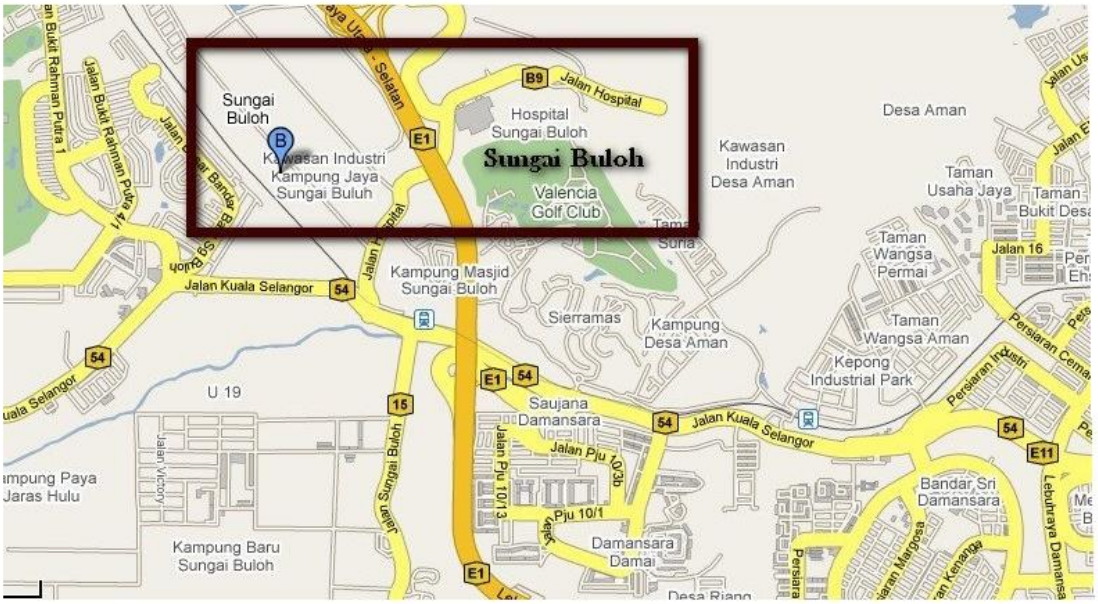
此研究会遵循什么样的程序？
这项研究的第
一部分涉及您填写一份需少于10分钟来完成的调查表。本研究所收集资料将**严格**地视为**机密**。只有调查研究人员才会以您的社
会人口特征来获得机密数据以进行研究。您对这一份调查表的所有回答将保持**匿名**，以及只有**以群**体方式的资料才会被公布。它不会被用来作为评价您工作能力的评论表。您的身份将会保密以及不会在任何以这项研究为中心的报告或出版中曝露。

请花一些时间来完成这份调查问卷。一旦您完成了调查问卷，请将这份调查问卷交还于您诊所的研究人员。

本研究第二部分涉及5分钟的时间来收集您的血液样本。研究人员将收集您3毫升的血液样本以充作研究用途与测试。

Appendix J

Map and Picture of Sungai Buloh Hospital



Appendix G

UNIVERSITI MALAYA
KUALA LUMPUR
PUSAT PERUBATAN UM

JAWATANKUASA ETIKA PERUBATAN
PUSAT PERUBATAN UNIVERSITI MALAYA
ALAMAT: LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEFON: 03-79494422 samb. 3209 FAKSIMILI: 03-79494638

NAME OF ETHICS COMMITTEE/IRB: Medical Ethics Committee, University Malaya Medical Centre **ADDRESS:** LEMBAH PANTAI 59100 KUALA LUMPUR	**ETHICS COMMITTEE/IRB REFERENCE NUMBER:** 714.14
PROTOCOL NO: **TITLE:** Factors Affecting Adherence To Anti-Retroviral Treatment In HIV Patients In Malaysia	
PRINCIPAL INVESTIGATOR: Prof. Awang Bulgiba Bin Awang Mahmud **TELEPHONE:** **KOMTEL:**	**SPONSOR:**

The following item [✓] have been received and reviewed in connection with the above study to be conducted by the above investigator.

[✓] Borang Permohonan Penyelidikan	Ver date: 10 Mac 09
[✓] Study Protocol	Ver date:
[ ] Investigator's Brochure	Ver date:
[ ] Patient Information Sheet	Ver date:
[ ] Consent Form	Ver date:
[ ] Questionnaire	
[✓] Investigator(s) CV's (Prof. Awang Bulgiba Bin Awang Mahmud)	

and have been [✓]

[✓] Approved
[ ] Conditionally approved (identify item and specify modification below or in accompanying letter)
[ ] Rejected (identify item and specify reasons below or in accompanying letter)

Comments:

i. *Investigator is required to follow instructions, guidelines and requirements of the Medical Ethics Committee.*
ii. *Investigator is required to report any protocol deviations/violations through the Clinical Investigation Centre and provide annual/closure reports to the Medical Ethics Committee.*

Date of approval: 22th APRIL 2009

s.k Ketua
Jabatan Perubatan Kemasyarakatan & Pencegahan

Timbalan Dekan (Penyelidikan)
Fakulti Perubatan, Universiti Malaya

Setiausaha
Jawatankuasa Penyelidikan Pusat Perubatan
Fakulti Perubatan, Universiti Malaya

.....
PROF. LOOI LAI MENG
Chairman
Medical Ethics Committee