DETERMINANTS FOR DISEASE PROGRESSION IN AIDS PATIENTS RECEIVING TREATMENT IN THE UNIVERSITY OF MALAYA MEDICAL CENTRE

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Abstract

Objectives: To determine predictors of disease progression in HIV-infected patients receiving treatment at the University of Malaya Medical Centre (UMMC).

Methods: HIV-infected patients aged 20 years and above on treatment in the UMMC were followed up with a bidirectional cohort study starting in 2007. Patient records were investigated retrospectively to 1986 and prospectively until 2009. Kaplan Meier and Cox regression analysis were performed using SPSS.

Results: A total of 1314 patients, 73.3 per cent were aged 20-39 years, 81.8 per cent male, 61.2 per cent Chinese, 45.2 per cent single, 73.5 per cent had only primary or secondary education, 43.2 per cent worked as professionals or non-manual workers, 42.5 per cent had a monthly income of RM 1000-3000. The majority had baseline CD4 less than 200 cells/μL (62.9 per cent), viral load more than 100,000 copies/ml (51.1 per cent), hemoglobin more than 12 g/dl (62.5 per cent) and normal liver function test (55.2 per cent), were infected via the heterosexual route (65.8 per cent) and were in WHO clinical stage 4 (54.2 per cent). Most initiated HAART with 2 NRTI+ EFV (57.9 per cent), did not need second line HAART (88.5 per cent), and managed to achieve viral load less than 50 copies/ml (61.5 per cent). The median time to death in all AIDS patients was 65.7 months, and 15.0 months in AIDS patients who did not receive anti-retroviral therapy. The median time to achieve viral load less than 50 copies/ml was 5.1 months. At the end of the study, 63.6 per cent of patients survived. The predictors of death in all AIDS patients were unemployment (HR 1.59; 95% CI 1.26, 2.02), manual employment (HR 1.47; 95% CI 1.15, 1.87), those who have three or more opportunistic infections (HR 1.90; 95% CI 1.39, 2.58) and those who did not receive anti-retroviral

therapy (HR 2.89; 95% CI 2.37, 3.47). The predictors of death in AIDS patients on HAART were unemployment (HR 1.64; 95% CI 1.04, 2.57), CD4 which never recovered to more than 200 cells/μL (HR 4.03; 95% CI 2.21, 7.35), and inability to achieve viral load less than 50 copies/ml (HR 4.39; 95% CI 2.69, 7.16). Independent predictors of death for AIDS patients who did not receive anti-retroviral therapy were Chinese ethnicity (HR 1.57; 95% CI 1.15, 2.15), baseline viral load more than 100,000 copies/ml (HR 1.35; 95% CI 1.02, 1.79) and being in WHO clinical stage 4 (HR 2.25; 95% CI 1.65, 3.06). The predictors to achieve viral load less than 50 copies/ml were starting HAART with 2NRTI+EFV (HR 1.56; 95% CI 1.10, 2.20) and not needing a second line of HAART (HR 2.59; 95% CI 1.59, 4.21) and infection via injecting drug use (HR 0.54; 95% CI 0.35, 0.80)

Conclusion: Every effort needs be made to ensure all HIV-infected patients in Malaysia are able to achieve a CD4 more than 200 cells/μL, viral load less than 50 copies/ml, and have access to triple drug anti-retroviral therapy as these are significant modifiable predictors of death in Malaysian HIV patients.

Abstrak

Objectif: Untuk menentukan peramal perkembangan penyakit dalam pesakit yang dijangkiti HIV dan menerima rawatan di Pusat Perubatan Universiti Malaya (PPUM).

Kaedah: Pesakit yang dijangkiti HIV berumur 20 tahun atau lebih yang dirawat di PPUM telah diikuti dalam kajian kohort dua arah bermula pada tahun 2007. Rekod pesakit telah disiasat secara retrospektif hingga 1986 dan prospektif sehingga tahun 2009. Analisa Kaplan Meier dan regresi Cox telah dijalankan menggunakan SPSS.

Keputusan: Dari sejumlah 1314 pesakit, 73.3 peratus berumur 20-39 tahun, 81.8 peratus lelaki, 61.2 peratus berbangsa Cina, 45.2 peratus bujang, 73.5 peratus ber pendidikan rendah dan menengah, 43.2 peratus pekerja profesional atau bukan manual, 42.5 peratus berpendapatan bulanan RM 1000-3000. Kebanyakan mempunyai CD4 awal kurang daripada 200 sel/μL (62.9 peratus), HIV virus lebih daripada 100,000 salinan/ml (51.1 peratus), hemoglobin lebih daripada 12 g/dl (62.5 peratus), ujian fungsi hati yang normal (55.2 peratus), jangkitan melalui hubungan heteroseksual (65.8 peratus) dan dalam WHO peringkat klinikal 4 (54.2 peratus). Kebanyakan memulakan HAART dengan 2 NRTI + EFV (57.9 peratus), tidak bertukar kepada HAART baris kedua (88.5 peratus), dan berjaya mencapai HIV virus kurang dari 50 salinan/ml (61.5 peratus). Tempoh purata hingga kematian untuk semua pesakit AIDS adalah 65.7 bulan, untuk pesakit AIDS yang tidak menerima rawatan anti-retroviral adalah 15.0 bulan dan tempoh purata untuk mencapai HIV virus kurang dari 50 salinan/ml adalah 5.1 bulan.

Pada akhir kajian, 63.6 peratus pesakit terselamat. Peramalan kematian dalam semua pesakit AIDS adalah pengangguran (HR 1.59; 95% CI 1.26, 2.02), pekerja manual (HR 1.47; 95% CI 1.15, 1.87), yang mempunyai tiga atau lebih jangkitan oportunis (HR 1.90; 95% CI 1.39, 2.58) dan tidak menerima terapi anti-retroviral (HR 2.89; 95% CI 2.37, 3.47). Peramal kematian pesakit AIDS yang menerima HAART adalah pengangguran (HR 1,64; 95% CI 1,04, 2,57), CD4 yang tidak pernah pulih ke tahap lebih dari pada 200 sel/μL (HR 4,03; 95% CI 2.21, 7,35), dan ketidakupayaan untuk mencapai HIV virus kurang daripada 50 salinan/ml (HR 4.39; 95% CI 2.69, 7.16). Peramal kematian untuk pesakit AIDS tidak menerima anti-retroviral adalah bangsa Cina (HR 1.57; 95% CI 1.15, 2.15), mempunyai HIV virus lebih dari pada 100,000 salinan/ml (HR 1.35; 95% CI 1.02, 1.79) dan WHO peringkat klinikal 4 (HR 2.25; 95% CI 1.65, 3.06). Peramal untuk mencapai HIV virus kurang dari 50 salinan/ml adalah yang memulakan HAART dengan 2NRTI + EFV (HR 1.56; 95% CI 1.10, 2.20) dan yang tidak perlu HAART baris kedua (HR 2.59; 95% CI 1.59, 4.21) dan jangkitan disebabkan suntikan dadah (HR 0,54; 95% CI 0,35, 0,80)

Kesimpulan: Segala usaha perlu dilakukan untuk memastikan semua pesakit yang berjangkit HIV di Malaysia mampu untuk mencapai CD4 lebih daripada 200 sel/μL, HIV virus kurang dari 50 salinan/ml, mempunyai akses kepada HAART kerana ini adalah peramal kematian yang bermakna boleh diubah di kalangan pesakit HIV Malaysia.

Publications

The following papers have been published or submitted from this thesis:

Conferences:

a. **Oral** presentation title" A 21-Year Review Of HIV/AIDS Patients Seen In The University Of Malaya Medical Centre" in the 40th APACPH Annual Conference "Global Public Health Challenges" (7th-9th November 2008, Kuala Lumpur, Malaysia)

b. **Oral** presentation title " Determinants of Progression to Death after AIDS Diagnosis in University Malaya Medical Centre, Kuala Lumpur" in the 42nd APACPH Conference "Strengthening Public Health Institution to Address Non Communicable Disease and Emerging Health Challenges"(November 24 – 27, 2010, Bali, Indonesia)

c. **Oral** presentation title " Progression to AIDS in HIV patients seen in University Malaya Medical Centre, Kuala Lumpur" in the Asia-link International Conference "Clinical Epidemiology and Evidence Based Medicine in Global Perspective"(November 27 – 28, 2010, Bali, Indonesia

d. **Oral** presentation title " Predictors of survival in Malaysian HIV patients on anti-retroviral therapy" in the 1st Asia Pacific Clinical Epidemiology and Evidence Based Medicine (APCEEBM) International Conference (July 07 – 08, 2012, Kuala Lumpur, Malaysia)

e. **Poster** presentation title " Characteristics of Patients Diagnosed with HIV/AIDS in University Malaya Medical Centre from 1986 – 2008" in the 41st APACPH Conference "Celebration of the 25th Anniversary of APACPH"(December 3 – 6, 2009, Taipei, Taiwan)

Publications:

a. Rahayu Lubis, Awang M Bulgiba, Adeeba Kamarulzaman, M Dahlui, Noran N Hairi, Devi Peramalah. Predictors of survival in Malaysian AIDS patients on antiretroviral therapy.
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b. Rahayu Lubis, Awang M Bulgiba, Adeeba Kamarulzaman, M Dahlui, Noran N Hairi, Devi Peramalah. Progression and 23 years review of HIV-infected patients seen in the University of Malaya Medical Centre. Send to Singapore Medical Journal (under review)

Dedication

This thesis is dedicated to the loving memory of my parent
H. Adenan Lubis and Hj. Rujiah Saleh

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Contents

Tables

Figures

Abbreviations

ADE	AIDS Defining Events
aCRR	Adjusted Cumulative Relative Risk
AIDS	Acquired Immune Deficiency Syndrome
ANOVA	Analysis of Variance
APCPH	Asia Pacific Consortium Public Health
APCEEBM	Asia Pacific Clinical Epidemiology and Evidence Based Medicine
ART	Anti Retroviral Therapy
AZT	Zidovudine
BMI	Body Mass Index
CASCADE	Concerted Action on Sero Conversion to AIDS and Death in Europe
CD	Compact Disk
CD4	Cluster of Different 4
CDC	Centres for Disease Control and Prevention
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central Nervous System
COHERE	Collaboration of Observational HIV Epidemiological Research in Europe
CPG	Clinical Practice Guidelines
CRFs	Circulating Recombinant Forms
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acids
ddC	Zalcitabine
ddI	Didanosine
d4T	Stavudine
DOTS	Directly Observed Treatment Short Course
EDTA	Ethylene Diamine Tetra-acetic Acid
EFV	Efavirenz
EIA	Enzyme Immuno Assay
ELISA	Enzyme Linked Immunosorbent Assay
FDA	Food and Drug Administration
GBV-C	GB virus C similar with hepatitis G virus

GRADE	Grading of Recommendation Assessment Development and Evaluation
HAART	Highly Active Anti Retroviral Therapy
Hb	Haemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGV	Hepatitis G Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSCs	Haematopoetic Stem Cells
IAS	International AIDS Society
ID	Infectious Disease
IDU	Injecting Drug User
IDV	Indinavir
IQR	Inter Quartile Range
IRB	Independent Review Board
IRIS	Immune Reconstitution Infammatory Syndrome
KM	Kaplan Meier
LFT	Liver Function Test
LTR	Long Terminal Repeat
MAC	Mycobacterium Avium intracellulare Complex
MACS	Multicentre AIDS Cohort Study
MARPS	Most At Risk Populations
MBPJ	Majlis Bandaraya Petaling Jaya
MDG	Millennium Development Goals
MMT	Methadone Maintenance Therapy
MOH	Ministry of Health
MSM	Male who have Sex with Men
MTC	Mother To Child
NHL	Non Hodgkin Lymphoma
NK	Natural Killer
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitors
NPV	Nevirapine
NRIC	National Registered Identification Card
NRTI	Nucleoside Reverse Transcriptase Inhibitors

OI	Opportunistic Infection
OR	Odds Ratio
PA	Particle Agglutination
PCP	Pneumocyctic Carinii Pneumonia
PI	Protease Inhibitors
PLWH	People Living with HIV
PS	Power and Sample Size
PTB	Pulmonary Tuberculosis
RBC	Red Blood Cell
RCT	Randomized Controlled Trial
RM	Ringgit Malaysia
RN	Registration Number
RNA	Ribonucleic Acids
ROC	Receiver Operating Characteristic
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RTV	Ritonavir
SD	Standard Deviation
SES	Socio Economic Status
SI	Syncytium Inducing
SIVgor	Simian Immunodeficiency Virus Gorillas
SPSS	Statistical Package for the Social Sciences
SQV	Saquinavir
SRA	Self Reported Adherence
STD	Sexually Transmitted Diseases
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
TLC	Total Lymphocyte Count
UK	United Kingdom
UMMC	University of Malaya Medical Centre
UN	United Nation
UNAIDS	United Nation Acquired Immune Deficiency Syndrome
USA	United States of America
USB	Universal Serial Bus
VL	Viral Load
VCT	Voluntary Counselling and Testing

WBC	White Blood Cell
WHO	World Health Organization
WP	Wad Perubatan

CHAPTER 1

INTRODUCTION

This chapter introduces the whole thesis. Section 1.1 is on the global burden of HIV epidemic and describes the HIV infection worldwide, in the Asian region and in Malaysia. Section 1.2 introduces the anti-retroviral therapy for HIV-infected patients. Section 1.3 looks at the progression of HIV-infected patients. The rationale of this study is discussed in Section 1.4 the problem statement and research question are spelled out in Section 1.5 and 1.6 this is carried into Section 1.7 which looks at the objectives. General and specific objectives are documented in Section 1.7.1 and 1.7.2 while the contribution of the study is stated in Section 1.8. The conceptual framework of the research topic, which is the core issue of this research project is displayed in Section 1.9 Section 1.10 describes the structure of the thesis followed by Section 1.12 which is a summary of this chapter

1.1 Global burden of HIV epidemic

The global burden of HIV epidemic is influenced by many factors including the number of HIV patients, new HIV infection, the number of deaths with AIDS related disease, HIV transmission route and expansion of anti-retroviral therapy. More than 34.0 (95% CI 31.4 –35.9) million people of the world population were living with HIV by the end of 2012 (UNAIDS, 2012). The percentage of adults aged 15-49 years living with HIV was 0.8 per cent. New HIV cases in 2012 numbered 2.5 (95% CI 2.2-2.8) million, which is 20 per cent less than in 2001. The number of deaths due to AIDS related diseases was 1.7 (95% CI 1.5–1.9) million, which is 24 per cent lower than with AIDS-related mortality rate in 2005 (UNAIDS, 2012).

The epidemic burden of HIV infection varies considerably between countries and regions. The rate of infection in Sub-Sahara of Africa is the most severe with about 69 per cent of all-HIV infected persons worldwide from in this region and where the ratio of people living with HIV and healthy people is 1 in 20. When compared to Asia, the prevalence of HIV infection in Sub-Sahara Africa is 25 times higher. One point eight million newly HIV infections are reported in this region but this is a 25 per cent decline in comparison with 2001. Although the death rate from AIDS-related diseases declined by 32 per cent from 2005 to 2011, this region still has the highest death rate, accounting for about 70 per cent of world deaths due to AIDS in 2011 (UNAIDS, 2012).

The Caribbean, Eastern Europe and Central Asia were the regions most highly affected by the HIV epidemic after Sub-Saharan Africa. About 1.0 per cent of adults were living with HIV in all of the regions in 2011 but even in the Caribbean the rate of new HIV infection has declined by 42 per cent since 2001 and the number of AIDS-related deaths

has declined by 48 per cent. In Eastern Europe and Central Asia, the new HIV infection began increasing in the late 2000s with an accompanying 21 per cent increase in mortality from AIDS (UNAIDS, 2012)

The HIV epidemic in Asia is variable and 60 per cent of the total world's HIV epidemics are in Asia. Half of the HIV prevalence of Asia is in India. In Asia almost 5 million people are living with HIV in different parts of South, South-East and East Asia (UNAIDS, 2012).

The one peak of the Asia epidemic was in the mid-1990s and since 2000 the number of new HIV cases per year has declined more than half, but some regional epidemic remained stable. In South and South East Asia, there are 4.0 (95% CI 3.1-4.6) million people living with HIV and 280 000 (95% CI 170 000 - 370 000) new HIV cases in 2011. In East Asia, 830 000 (95% CI590 000 - 1 200 000) people living with HIV and 89 000 (95% CI 44 000 - 170 000) new HIV cases were reported in 2011 (UNAIDS, 2012). In 2011, number of AIDS related deaths in South East Asia were 250 000 (95% CI 1900 000 – 330 000), which is 13.7 per cent less than the peak of mortality in 2005. In East Asia, the rate of HIV related mortality is still increasing; in 2011, total number of deaths due to HIV was 51 per cent higher than the mortality rate in 2005 (UNAIDS, 2012).

In many Asian countries, national epidemics are concentrated in a few provinces. For example, more than half (53 per cent) of people living with HIV of China are in five provinces. Indonesia's HIV infection is in Papua and West Papua provinces (WHO, 2011). In China, the number of people living with HIV decreased from 840 000 in 2003 to 650 000 in 2005, then increased to 700 000 in 2007 and 740 000 in 2009 (Wang et

al., 2010). The number of AIDS cases decreased from 80 000 in 2003 to 75 000 in 2005, then in 2007 it is increased to 85 000 and further increased to 105 000 in 2009 in China. The number of new HIV infections decreased from 70 000 in 2005 to 50 000 in 2007 and again reduced to 48 000 in 2009 (Wang, et al., 2010).

In China, the proportion of cases associated with sexual transmission was 43.6 per cent in 2005 and it is increased to 51.6 per cent and 59 per cent in 2007 and 2009 respectively. The proportion of cases associated with injecting drug use transmission was 48.6 per cent in 2005 and which is decreased to 42.0 per cent in 2007 and further reduced to 24.3 per cent in 2009. Dramatic increases in HIV transmission among homosexual from 12.2 per cent in 2007 to 32.5 per cent in 2009 has been observed (Wang, et al., 2010). Total HIV surveillance sites increased by 20 per cent between 2005 to 2007. Fifty-three point four per cent of prevalence come from the 5 highest prevalence provinces and less than 1 per cent of total infections from the 5 lowest prevalence provinces (Wang et al., 2009). The major route of exposure in China was heterosexual intercourse. There were a total of 37 million male commercial sex workers in China and 1 out of 3 of them were diagnosed with HIV (Wang, et al., 2009).

In South East Asia, all countries except Thailand have an adult HIV prevalence lower than 1 per cent. Thailand is showing increased HIV prevalence among male sex workers, which is almost double when compared to female sex workers (WHO, 2011). The prevalence among homosexual men increased from 17 per cent in 2003 to 31 per cent in 2007 and then reduced to 25 per cent in 2009 in Bangkok (WHO, 2011)

The first HIV case detected in Malaysia was more than 25 years ago in 1986 (Goh, 1987). In December 2012, the number of people living with HIV is estimated to be

more than 81,000. The cumulative figure showed the number of HIV, AIDS and death was 94,841, 17,686 and 14,986 respectively, thus 79,855 people living with HIV was reported in Malaysia in 2011 (MOH, 2012).

The annual report of new HIV cases by the Ministry of Health has been on a steady decline from a peak of 6,978 in 2002. In 2011, there were only 3,479 new cases reported to the Ministry of Health, which is approximately halved of what was reported in 2002 and with an average of 9 new cases each day. The rate of HIV also shows a decrease from 28.4 in 2002 to 23.4 in 2005 and to 12.2 cases per 100,000 populations in 2011 (MOH, 2012) .

Overall, the country is showing a decrease in HIV rate among young people aged 13-29 years while it is increasing among adults of 30-39 years. About 26 per cent of reported infections are amongst young people aged between 13-29 years old and around 1 per cent amongst people of less than 13 years old in 2011 (MOH, 2012).

Males represent the majority (90 per cent) of cumulative HIV cases in Malaysia. Males have been showing a reduction in the rate of infection from 2003, but the rate of infection in females is increasing (MOH, 2012). The main reason for the Malaysian HIV epidemic is injecting drug use and new HIV case distribution reported that injecting drug user (IDU) increased from 60.4 per cent in 1990 to 74.7 per cent in 2000 and decreased 55.2 per cent in 2009 (UNGASS, 2010). While heterosexual route reported from 4.8 per cent in 1990, 17.6 per cent in 2000 and increased 26.7 per cent in 2009 (UNGASS, 2010). Homosexual route in Malaysia is still a stigma, reported to be 0.4 per cent in 1990, 1.2 per cent in 2000 and 5.3 per cent in 2009 (Prime Minister's Department Malaysia & United Nations Country Team, 2010). Among males, 48 per

cent acquired HIV infection through IDU and 47 per cent by sexual mode. Most HIV infections among females occurred through heterosexual transmission (87 per cent). Females are increasingly getting infected with HIV, constituting around 21 percent of newly infected persons nationwide in 2011 compared to being barely 5 percent ten years ago (MOH, 2012)

With respect to geographical distribution, there is quite a distinct trend in transmission mode over a period of 10 years in the states of Malaysia. It appears that HIV infections in eastern region states (Pahang, Terengganu and Kelantan) of Peninsular Malaysia are still driven by IDU whereas infections in the northern states (Perlis, Kedah, Penang and Perak) and southern region (Negeri Sembilan, Melaka and Johor) are mainly sexually driven (MOH, 2010). The infections in the central region (Selangor and Kuala Lumpur) are mainly IDU driven whereas East Malaysia (Sarawak, Sabah and Labuan) have always been predominantly sexually driven from the beginning of the epidemic (MOH, 2012).

There was a decrease in the number of AIDS-related deaths reported in 2011 (UNGASS, 2012). The reduction in death rate has been achieved by the introduction of more affordable and accessible first and second line anti-retroviral therapy. As per 2011 report, there were 14,002 people living with HIV on treatment, which is 37.5 per cent of the estimated number of people living with HIV eligible for anti-retroviral therapy (37,306). It has been estimated that by the end of 2015, Malaysia will have an estimated 81,317 people living with HIV (Prime Minister's Department Malaysia & United Nations Country Team, 2010).

1.2 Anti-retroviral therapy

Anti-retroviral therapy can help people living with HIV to live longer, increase quality of life and reduce AIDS-related deaths. Sixty six per cent of HIV-infected patients survived as a result of anti-retroviral therapy (Djauzi, 2007). According to the 2011 world report, anti-retroviral therapy is enjoyed by 8 million people, which is 20 times the number in 2003. Since 1995, anti-retroviral therapy has added 14 million life-years in low and middle income countries, including 9 million in sub-Saharan Africa (UNAIDS, 2012). The guidelines of when to begin anti-retroviral therapy has been changed frequently (WHO, 2010a).

Highly Active Anti-Retroviral Therapy (HAART) has been available world-wide since 1996. It is a combination of 3 drugs which include 2 NRTI (Nucleoside Analogue Reverse Transcriptase Inhibitors) or NNRTI (Non-Nucleoside Analogue Reverse Transcriptase Inhibitor) and PI (Protease Inhibitor) and has substantially improved the prognosis of HIV-infected patients (WHO, 2010a). The clinical progression in HIV patients receiving treatment is estimated in different levels of viral load and CD4 count. The information about the prognosis of HIV infection is very important to monitor the progress of the HIV/AIDS epidemic, to develop treatment guidelines, to gain a better understanding of the prior treatment of HIV infection and to plan health services in the HAART period. These data are also important for the comparisons of treatment outcomes in resource poor settings once HAART becomes more widely available in less developed countries (Egger et al., 2002). Access to HIV care and anti-retroviral therapy still remain a challenge to control the HIV epidemic in developing countries due to the financial burdens for people living with HIV in accessing and receiving HIV care (Riyarto et al., 2010).

1 Introduction

WHO guidelines currently recommend initiating HAART at CD4 counts less than 350 cells/μL (WHO, 2010a). If CD4 measurement is unavailable, simple tools such as haemoglobin level and total lymphocyte count can be used as laboratory markers to initiate HAART in resource-poor settings (WHO, 2004). The question about when to initiate treatment should take into account that anti-retroviral therapy is a lifelong treatment, with significant adherence issues, potential side effects and high cost. To measure the HAART adherence, self-reported adherence (SRA) is an accurate instrument compared to therapeutic drug monitoring (TDM) and can be reliably used in practice in resource-poor settings (Bulgiba, Mohammed, Chik, Lee, & Peramalah, 2013).

There are six classes of anti-retroviral drugs available namely NRTI, NNRTI, PI (widely used worldwide), the Fusion inhibitor (FIs), Integration Inhibitor (IIs) and Maturation Inhibitors (still in limited used). Each class targets a different step in the HIV life cycle (Volberding & Deeks, 2010).

The standard HAART Regimens (MOH, 2001a, 2001b; WHO, 2010a) comprise one of three possible regimens:

- NRTI + NRTI + PI
- NRTI + NRTI + NNRTI
- NRTI + NRTI + PI + PI

There are 3 classes of anti-retroviral agents in Malaysia: - NRTI: such as AZT (Zidovudine), d4T (Stavudine), 3TC (Lamivudine), ddI (Didanosine), ddC (Zalcitabine)

- NNRTI: Such as EFV (Efavirenz), NVP (Nevirapine)

- PI: Such as IDV (Indinavir), RTV (Ritonavir), SQV (Saquinavir), Kaletra (Lopinavir/ ritonavir)

All the drugs except Saquinavir are available in the Ministry of Health's formulary. Anti-retroviral therapy was introduced in stages in Malaysia. In 1989, AZT was available, in the early 1990's ddI and ddC was also available and in mid-1990's d4T and 3TC became available. In Malaysia, Highly Active Anti-Retroviral Therapy (HAART) was available from February 1997 with the entry of IDV but the cost of these drugs was high. In the late 1990's, a standard regimen of AZT + 3TC + IDV, would cost close to RM 2000 per month. In 2003, the MOH took the initiative to access cheaper generic anti-retroviral drugs from India. This led to the introduction of generic d4T, RTV and NVP into Malaysia. Generic drugs such as AZT, ddI and the fixed drug combination of AZT + 3TC, followed subsequently in early 2004. This led to the second big jump in anti-retroviral therapy uptake locally (MOH, 2001a, 2001b).

In Malaysia, anti-retroviral treatment is available at all general hospitals and some district hospitals where there are specialist physicians managing medical clinics. Anti-retroviral treatment is also provided in some local university hospitals. All HIV clinics are run by physicians, who have had some training in HIV medicine. The infectious disease clinic at University of Malaya Medical Centre is the reference centre for patients with HIV and AIDS in Selangor state and is one of the major sites for anti-retroviral treatment in Malaysia.

One of the three targets of Malaysia millennium development goals (MDG) is to achieve treatment for all HIV/AIDS patients by 2010. The Ministry of Health Malaysia reported that 9,962 people living with HIV had received anti-retroviral therapy by the

end of 2009 (Prime Minister's Department Malaysia & United Nations Country Team, 2010). The Government of Malaysia provides first line anti-retroviral access for all HIV-infected patients without charging money at all government hospitals and clinics. From 2006, the Government of Malaysia provided anti-retroviral therapy to all HIV patients in prisons and drug rehabilitation centres. The second line anti-retroviral therapy is partly subsidized by the government (Prime Minister's Department Malaysia & United Nations Country Team, 2010). Malaysia will continue providing affordable access to clinical care for HIV patients through the public health system (MOH, 2012).

1.3 Progression of HIV-infected patients

There are many factors that may influence progression of HIV-infected patients to AIDS and death. This study is more concerned about AIDS progression to death. Based on the literature, the predictors of death in AIDS patients included socio-demographic characteristic, laboratory, clinical and anti-retroviral therapy. Predictors of disease progression in HIV-infected patients in developed and developing countries included low CD4, high viral load, opportunistic infection, older age and lifestyle such as injection drugs user (Bonnet et al., 2005; COHERE, 2012; Fregonese et al., 2012; Ghate et al., 2011; Osmand, 1998; Schwarcz, Hsu, Vittinghoff, & Katz, 2000). The predictors of death in AIDS patients are described in detail below.

1.3.1 Socio-demographic characteristic

a. Age

Earlier studies showed that faster overall AIDS progression with increasing age in the absence of HAART (Langford, Ananworanich, & Cooper, 2007). A study with 4,252 AIDS patients from the Asia Pacific region showed that people who are more than 50 years old has an increased death rate (HR 4.29, 95% CI 2.10-8.79) (Falster et al., 2009).

The rate of disease progression among younger children, especially newborn HIV positive babies is also higher than adult patients. Between 1987 to 1996, a study involving persons diagnosed with AIDS showed higher mortality for participants aged 40 years and above with a relative hazard of 1.43 (95% CI 1.30, 1.60) in San Francisco (Schwarcz, et al., 2000). Meanwhile, in another study using the Australian national surveillance for AIDS diagnosis, age of more than 45 years was independently associated with disease progression with HR of 1.54 (95% CI 1.29, 1.85) (Li, McDonald, Dore, & Kaldor, 2000). Similarly, in the Aquitaine Cohort, France, a study was conducted in 1996-2002 among patients with older age. This study revealed that participants aged 50 years or above has higher chance to develop AIDS or die, with HR of 2.4 (95% CI 1.4, 4.1) when compared to people with less than 50 years (Bonnet, et al., 2005)

b. Gender

The HIV disease progression rate was found to be influenced by gender. The study in AIDS males and females of 2,862 patients registered at the AIDS Surveillance System in Italy (1993 to 1998), showed different hazards of dying during the first and the second 6 month period of 1997 compared with 1993. In particular, the increase in survival appeared stronger in males than in females with HR of 0.51 (95% CI 0.39, 0.66) in the first 6 month period of 1997 and HR of 0.22 (95% CI 0.16, 0.31) in the second 6 month period of 1997 for males, HR of 0.80 (95% CI 0.51, 1.27) and HR of 0.32 (95% CI 0.18, 0.57) for females (Porta et al., 1999). A study in Malawi to investigate the effect of sex on mortality of HIV-infected patients receiving anti-retroviral therapy from 2004 to 2006, has shown an increased mortality rate in males with HR of 1.70 (95% CI 1.35, 2.15) (Chen et al., 2008). Another study of the

Aquitaine cohort showed that gender was not associated with a significantly higher risk of progression to AIDS or death (Bonnet, et al., 2005).

c. Socioeconomic Status

A study in Canada showed that HIV-infected patients with low income (HR 1.29, 95% CI 1.17, 142) and unemployment status (HR 2.2, 95% 1.67, 2.89) are at increased risk of mortality (Druyts et al., 2009). A group of researchers carried out a study to estimate the AIDS survival by socioeconomic status neighbourhood, comparison between group before HAART (1993 to1995) and after HAART introduction (1996 to 1997) in Rome, Italy. In a retrospective cohort of persons with AIDS (diagnosed in 1993 to 1997) followed through July 31, 1998, socioeconomic status (SES) of the neighborhood was categorized into 4 levels (Level 4 is lowest SES). There was a small difference in the risk of death by SES for patients with AIDS diagnosed in 1993 to 1995. The death risk was higher in patients with lower SES, especially for levels III and IV with HR of 2.81 (95% CI 1.38, 5.76) and HR of 2.55 (95% CI 1.27, 5.14) compared with the level I for 1996 to 1997 (Rapiti et al., 2000).

1.3.2 Laboratory results

a. Lymphocyte T or CD4 cell count

CD4 is the primary target of HIV. Their depletion severely limits the host response capacity. HIV infection can cause a great risk to T-cells directed immune response (Stebbing, Gazzard, & Douek, 2004). The CD4 count is a significant predictor of survival and disease progression. The study in Asia Pacific region showed that among patients with CD4 less than 100 cells/μL had HR of 34.97 (95% CI 18.01, 67.90) for

AIDS mortality risk and had HR of 8.59 (95% CI 5.66, 13.03) for non AIDS mortality risk (Falster, et al., 2009). An assessment of 1,188 AIDS patients from 19 clinical centres across the United States showed that CD4 less than 200 cells/ml is the strongest risk factor for mortality with HR of 2.7 (95% CI 1.9-3.9) (Puhan, Van Natta, Palella, Addessi, & Meinert, 2010). The Multicenter AIDS Cohort Study with 679 HIV infected males, on the clinical progression of disease following initiation of HAART found that CD4 cell count prior to HAART initiation in less than 200 cells/μL had a relative hazard of 2.25 (95% CI 1.13, 4.49) and 2.29 (95% CI 0.83, 6.33) for AIDS and death respectively (Jacobson et al., 2002). Similarly, the study conducted in the Aquitaine Cohort, France in 1996-2002 showed that patients with CD4 counts less than 50 cells/μL had an increased risk of progression with HR of 13.0 (95% CI 3.8, 44.3) while patients with CD4 count 50-199 cells/μL with HR of 5.1 (95% CI 1.6, 16.3) had increased risk of disease progression compared patients with CD4 count more than 350 cells/μL (Bonnet, et al., 2005). The Women's Interagency HIV Study showed that after HAART initiation, those with CD4 counts less than 200 cells/μL had an increased risk of death compared to those with more than 350 cells/μL (HR 2.66; 95% CI 1.42, 4.99), from AIDS with HR 47.61 (95% CI 5.69, 398.40) (Anastos et al., 2004).

b. Viral load

The importance of laboratory marker as CD4 count and in the peripheral blood is based on the quantity of viral load (Anastos, et al., 2004; Osmond, 1998). The association of quantity viral load and risk of HIV has been studied by many researches. From a study of 1,578 adult patients who received HAART for more than 6 months in Thailand showed that, the predictor of AIDS was viral load more than 1,000 copies/ml with HR of 2.8 (95% CI 1.3, 6.1) (Fregonese, et al., 2012). A study cohort of 165 hemophiliac patients revealed that the CD4 count and viral load level were independently associated

with developing AIDS with an HR of 6.4 for viral load more than 10,000 copies/ml (Osmand, 1998). Additionally, in a study involving 679 HIV infected men, one of the significant determinants of developing AIDS was viral load more than 100,000 copies/ml at HAART initiation with HR of 1.63 (95% CI 0.79, 3.36) (Jacobson, et al., 2002) while, the study among 1,132 women patients has shown all cause deaths were higher (HR 3.44; 95% CI 1.67, 7.09) in patients with viral load more than 10,000 compared to those with viral load of less than 80 copies/ml (Anastos, et al., 2004). The strongest prognostic markers in PLWH were viral load and CD4 count and where there is widespread HAART use, the effect of demographic factors is not clear (Anastos, et al., 2004). The effectiveness of anti-retroviral therapy is measured by the ability to achieve viral load less than 50 copies/ml. When an individual first starts HAART, it is desirable that virologic suppression is achieved as quickly as possible (as demonstrated by a reduction in the viral load to 50 copies/ml), preferably within the first 6 months of HAART (Smith et al., 2004).

1.3.3 Clinical condition

a. Exposure Risk

The Concerted Action on Sero Conversion to AIDS and Death in Europe (CASCADE) collaboration study showed strong evidence that the effect of transmission category on AIDS prognosis has changed over time (Porter et al., 2003). Before 1997, IDU had less risk of AIDS progression than men who have sex with men (MSM) with HR of 0.74 (95% CI 0.64, 0.86). However, this trend was reversed in 1999-2001 with HR of 2.76 (95% CI 1.87, 406). Similarly, in the Spanish multicenter study of seroconverters (GEMES) cohort study, IDU had a faster AIDS progression than MSM with HR of 2.28 (95% CI 1.47, 3.54). IDU also had a faster progression to death with HR of 2.17 (95%

CI 1.22, 3.87) (Pérez-Hoyos et al., 2006). After the introduction of HAART, there was continued reduction in AIDS and death. The differences detected in IDU patients could be explained by poorer access to anti-retroviral therapy, undesirable delays in initiating HAART, poorer adherence, and non AIDS related competing mortality such as drug related deaths and hepatitis C virus co-infection (Pérez-Hoyos, et al., 2006).

b. Opportunistic infection

The presence of opportunistic infections (OI) affects the quality of life in HIV-infected patients with OR of 5.29 (95% CI 1.97,14.21) (Astoro, Djauzi, Djoerban, & Prodjosudjadi, 2007). An opportunistic infection that occurs in the course of increasing HIV immune suppression are mainly caused by infectious agents like PCP (*Pneumocystis carinii pneumonia),* CMV (*Cytomegalovirus*) and *Varicella zoster* virus. HIV mediated immune suppression changes host control of the infectious agent resulting in disease and the disease process in turn activates HIV, hastening the rate of immune suppression (Osmand, 1998). However, in Western industrialized countries, many opportunistic infections are now rare (Hoffmann, Rockstroh, & Kamps, 2007). This is particularly true for those infections that are associated with severe immunodeficiency, such as CMV and MAC (*Mycobacterium Avium Intracellulare Complex*). Now, the opportunistic infection incidence has been reduced to less than one tenth of their frequency in the pre HAART era. Moreover, survival times after initial diagnosis of opportunistic infections has also improved. A study with 150 participants with Toxoplasmosis demonstrated 5-year survival of 8 percent after the diagnosis from 1990 to 1993. It increased to 30 per cent in 1994 to 1996 and it rose to approximately 80 per cent in 1997 (Hoffman, 2006).

In developing countries such as in China and India, there are many cases of tuberculosis infection in HIV-infected patients. A study in Indonesia aimed to establish HIV prevalence and uptake of unlinked anonymous testing and voluntary counselling and testing (VCT) among tuberculosis patients in Jogjakarta (Mahendradhata et al., 2008). A total of 1,269 tuberculosis patients, 77.9 per cent agreed to be tested and the study demonstrated HIV prevalence of 1.9 per cent. Unlinked anonymous HIV testing is well accepted and can be implemented with modest additional efforts (Mahendradhata, et al., 2008). Tuberculosis was the primary cause of death in 9.0 per cent of all AIDS-related deaths, while PCP accounted for 4.7 per cent in Brazil (Saraceni et al., 2008). In Malaysia, unsuccessful treatment in TB/HIV patients was associated with intravenous drug use with OR of 2.72 (95% CI 1.44, 5.16) (Ismail & Bulgiba, 2013)

1.5 Problem Statement

Advances in anti-retroviral therapy have changed a fatal disease into a chronic disease and influenced the survival of HIV-infected patients. (Volberding & Deeks, 2010). The evidence from literature review in developed and developing countries suggests that many factors can influence the mortality of HIV-infected patients and the effectiveness of anti-retroviral therapy. However, the picture is not very clear in Malaysia as there are few studies to fall back on. Therefore, the researcher would like to explore the predictors of death and predictors to achieve viral load less than 50 copies/ml in AIDS patients because different patients from different regions may respond differently to HIV infection. The time of death may vary among the patients with some patients taking longer to die while others do so quickly. The progression of disease among Malaysian HIV-infected patients is not well studied and the researcher do not know very much what influences this progression

1.4 Rationale of Study

Anti-retroviral therapy has been helping to increase the survival of HIV patients. Most of the studies have been conducted in developed countries and only a few articles have been published regarding AIDS progression to death in other countries (Wong, Chan, & Lee, 2004). In Malaysia there is a lack of scientific research focusing on AIDS progression and anti-retroviral therapy (Kamarulzaman, 2005). There are few articles on AIDS progression to death in Malaysia. A study was been conducted in Sungai Buloh Hospital, Malaysia on the effect of HAART on AIDS mortality and AIDS defining events among AIDS patients based on a retrospective cohort from 1997 until 2008 (Mat Shah, Bulgiba, Lee, Haniff, & Mohamad Ali, 2012). This study started in 2007, following patients retrospectively to 1986 (20 years) and prospectively until 2009 (3 years). The previous study in Sungai Buloh was on AIDS patients with HAART while our study included all AIDS patients whether they were on HAART or not. The purpose of the Sungai Buloh Hospital study was to determine associated factors in AIDS mortality while this study is to determine the predictors of AIDS death and the predictors of the ability to achieve viral load less than 50 copies/ml.

Based on the research problem statement, there is a need to do a study focused on determining factors associated with progression from AIDS to death and to achieving viral load less than 50 copies/ml. Predictors of death and predictors of ability to achieve viral load less than 50 copies/ml are unknown in Malaysian HIV-infected patients. This is the first study on AIDS progression conducted at the University of Malaya Medical Centre (UMMC). The University of Malaya Medical Centre was chosen because it is a major referral centre in Malaysia and the HIV patients from other government hospitals, private hospitals, and general practitioners are referred to University of Malaya Medical

Centre. The factors that influence progression of the disease and to achieve viral load less than 50 copies among HIV-infected patients attending at the Infectious Disease clinic at University of Malaya Medical Centre not unravel clearly.

1.6 Research Question

What are the determinants of progression to death and to achieve viral load less than 50 copies/ml in HIV-infected patients in the University of Malaya Medical Centre?

1.7 Objectives

1.7.1 General Objective

To determine predictors of progression and survival of HIV-infected patients being followed up in the University of Malaya Medical Centre

1.7.2 Specific Objectives

a. To describe the characteristics of HIV-infected patients in the UMMC
b. To determine the survival time of HIV-infected patients in the UMMC
c. To determine the 5 and 10-year survival of HIV-infected patients in the UMMC
d. To determine the predictors of death in all AIDS patients, AIDS patients on HAART and AIDS patients not on anti-retroviral therapy
e. To determine predictors to achieve viral load less than 50 copies/ml in AIDS patients on HAART

1.8 Contribution of study

1.8.1 Public health significance

The outcome of this study provides meaningful information that can be used to create a better treatment setting in the University of Malaya Medical Centre, which is potentially useful to nurses and clinicians. It will also help to guide health care providers in Malaysia by providing awareness for routine examination of CD4, viral load and anti-retroviral adherence which may help to achieve better survival for AIDS patients. It will also help to determine the predictors of progression in AIDS patients and its accompanying complications which could have an impact on Malaysian Clinical Practice Guidelines (CPG) in AIDS treatment.

1.8.2 Building the knowledge

The major findings of this study are the predictors of death in AIDS patients and time of death in Malaysia. It also has helped to measure time to achieve the effectiveness of anti-retroviral therapy and the predictors to achieve viral load less than 50 copies/ml in Malaysia. This study could help with progression of death in HIV-infected patients mainly in Malaysia and other developing countries.

1.9 Conceptual Framework

This study AIDS progression to death has been conducted based on four components such as socio-demographic characteristic, laboratory, clinical and anti-retroviral therapy. Each component consists of different variables, and twenty two variables and eight outcomes were included in this study. The conceptual framework of the determinants in AIDS progression to death is summarized in Figure 1.1

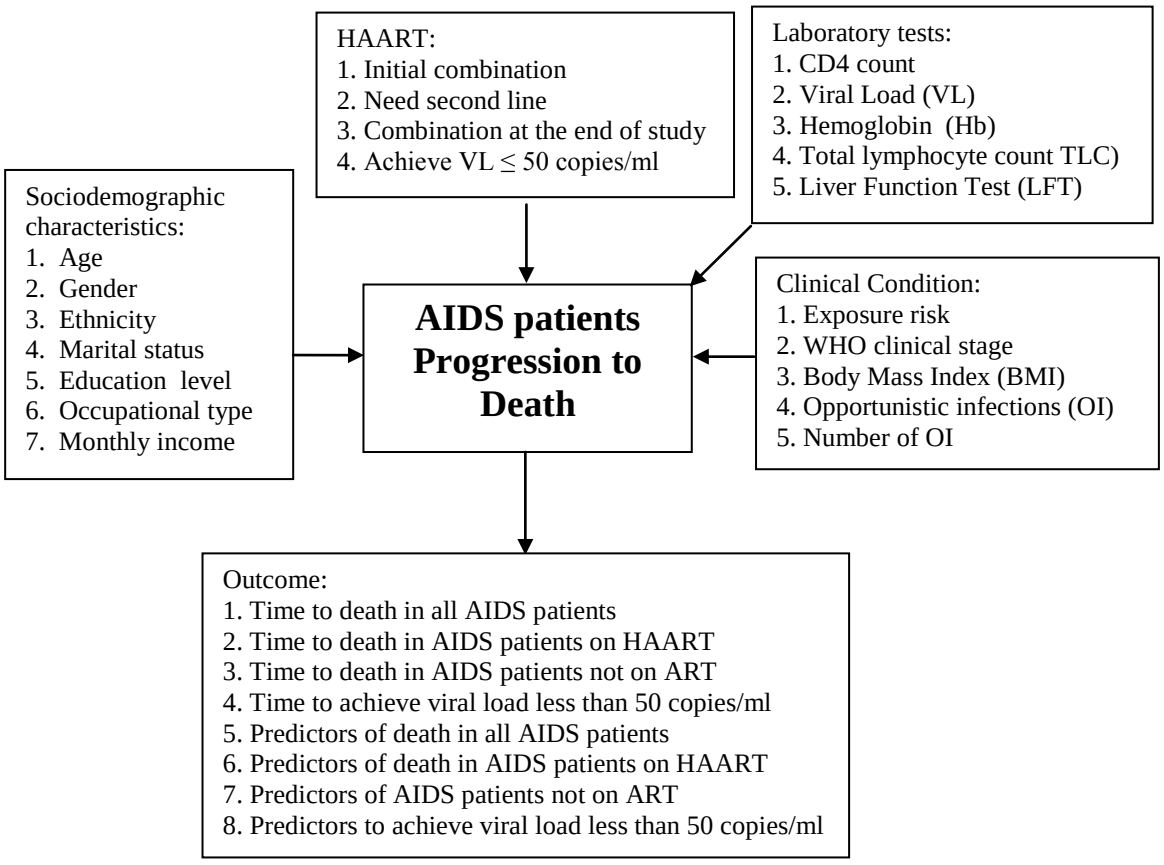


Figure 1.1 Conceptual framework of determinants AIDS progression to death

1.10 Structure of the thesis

This thesis is divided into 6 chapters. Chapter 1 is the introduction of the thesis i.e. the background of study, problem statement, rationale of this study, research questions, objectives and contribution of the study

Chapter 2 discusses the systematic review of the literature. This begins with the biology of HIV, continues with the natural history of HIV infection and pathogenesis of AIDS, detection of HIV antibody and clinical stages of HIV/AIDS and covers the epidemiology, treatment and factors associated with disease progression

Chapter 3 details the materials and methods used for this study, including study design, study area, duration of study, study population, study setting, ethical approval, sampling and sample size calculation, data collection, data management and statistical analysis.

Chapter 4 shows the results of a comprehensive statistical analysis and is divided into the descriptive analysis, survival analysis and Cox regression analysis.

Chapter 5 discusses the findings of this study. This starts with the profile of study subjects continues with a discussion about time to death in all AIDS patients, AIDS patients on HAART and AIDS patients not on anti-retroviral therapy. This includes the required time and major predictors to achieve viral load less than 50 copies/ml in AIDS patients on HAART and a comparison with other studies in developed and developing countries.

Chapter 6 is the concluding chapter with recommendations and further studies.

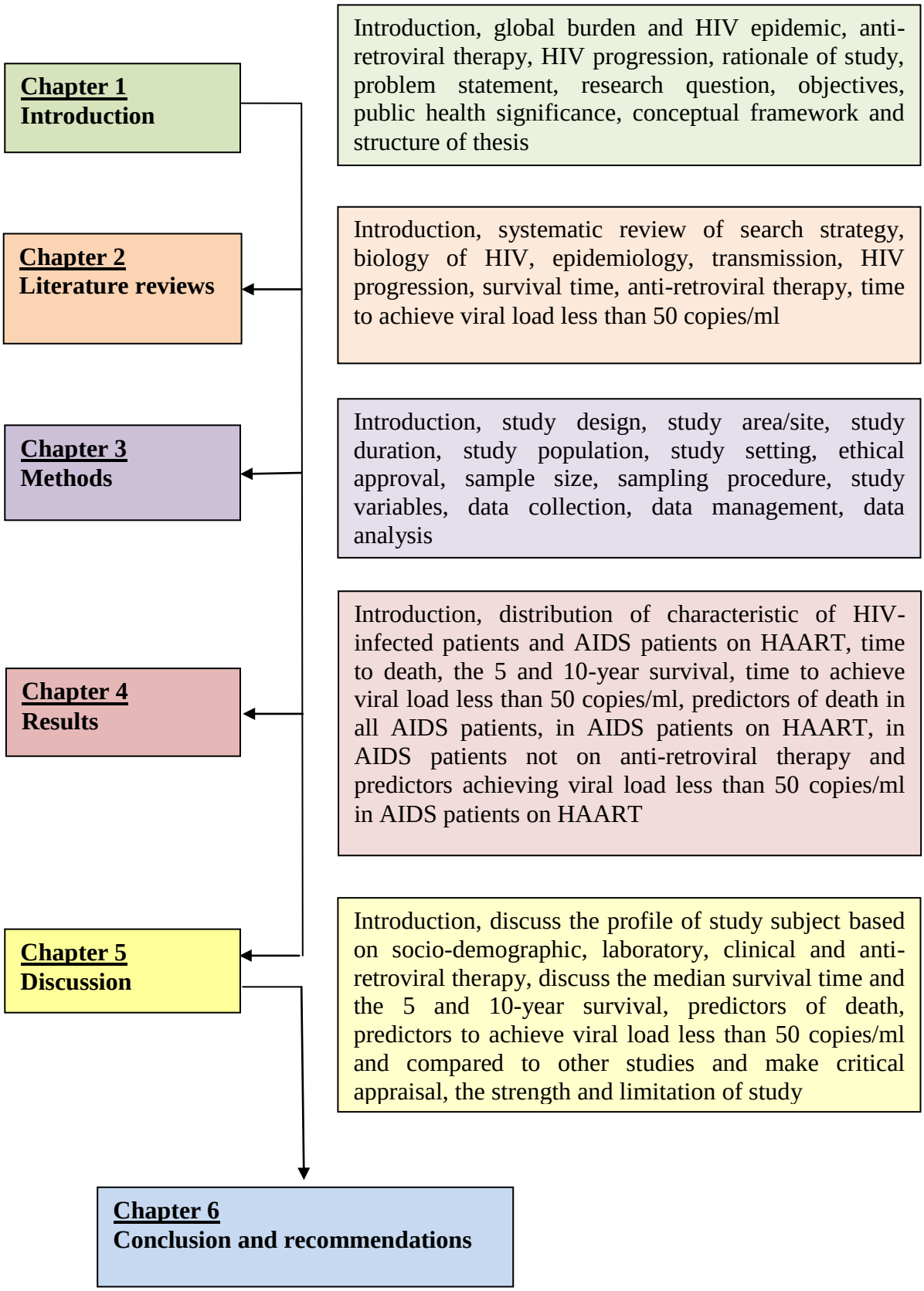


Figure 1.2 Structure of the thesis

1.11 Summary

In this chapter, the global burden of HIV infection in the world, Asia region and Malaysia were reviewed including the transmission mode of HIV-infected patients. From the literature review, it is well documented that the anti-retroviral therapy can reduce the morbidity and mortality of HIV-infected patients, prolong the survival and quality of life. There are many studies regarding progression of HIV-infected patients conducted in developed countries and only a few studies in developing countries including Malaysia. It is still unclear what the predictors of death and predictors to achieve viral load less than 50 copies are in Malaysian HIV-infected patients. This study represents the first known attempt by a researcher to determine the predictors of disease progression in AIDS patients receiving treatment in the University Malaya Medical Centre Kuala Lumpur.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

The detailed literature search on a full topic of research is presented in this chapter. Section 2.1 introduction. Section 2.2 systematic review search strategy. Section 2.3 biology of HIV, discussion on structure of HIV, viral genome, HIV types, blood differentiation and CD4, HIV co-receptors, life cycle of HIV, natural history of HIV infection and pathogenesis of AIDS, detection of HIV antibody and clinical stages of HIV/AIDS. Section 2.4 epidemiology of HIV/AIDS, this is continued in section 2.5 with the transmission of HIV. Section 2.6 progression of HIV infection, this is carried into section 2.7 which looked at the survival time of HIV-infected patients. Section 2.8 explained about anti-retroviral treatment for HIV/AIDS, included classes of drugs, anti-retroviral initiation, switch second line of anti-retroviral therapy, pre HAART era and HAART era and section 2.9 discussed about time and other factors to reach viral load less than 50 copies/ml and section 2.10 summary of the chapter

2.2 Systematic review search strategy

The search strategy techniques applied in this study include extensive querying database, index searches of scientific proceeding, journal supplements and review material, cross referencing of bibliographies and backtracking of references from articles. The following searched were done using full terminology and Boolean keywords. They were entered into electronic bibliography databases, such as Pub Med Central, Science Direct and Scopus. The search as of 25th October 2012 at Pub Med data base, were run through a etiology study filter, limiting the items in human, adult, English language and full text. A total of 5,345 articles containing keyword "HIV progression" were identified. The next search was conducted with a narrow filter and total numbers of articles were shortlisted in 2,107. An advanced search using AND determinants terms managed to generate 514 articles. Finally 66 articles were chosen as potential studies. While the search in Science Direct database in 20th November 2012 using "HIV progression" term resulted in a total of 7,490 articles. The second search which was limited to selected journals and 15 years of publication, showed a total hit of 2,370 articles. This was continued with advance search using AND determinants which resulted in 882 articles and 88 articles were identified as potential studies. In Scopus database, search in 6th December 2012 with "HIV progression" term and limited to 15 years of publication extracted 5,300 articles were obtained after excluding non-medical journals, which is a total of 3,834 articles. Advanced search with AND determinants terms achieved a total of hit of 323 articles of which and 61 articles were shortlisted. Flow chart of search strategy is as shown in Figure 1.1

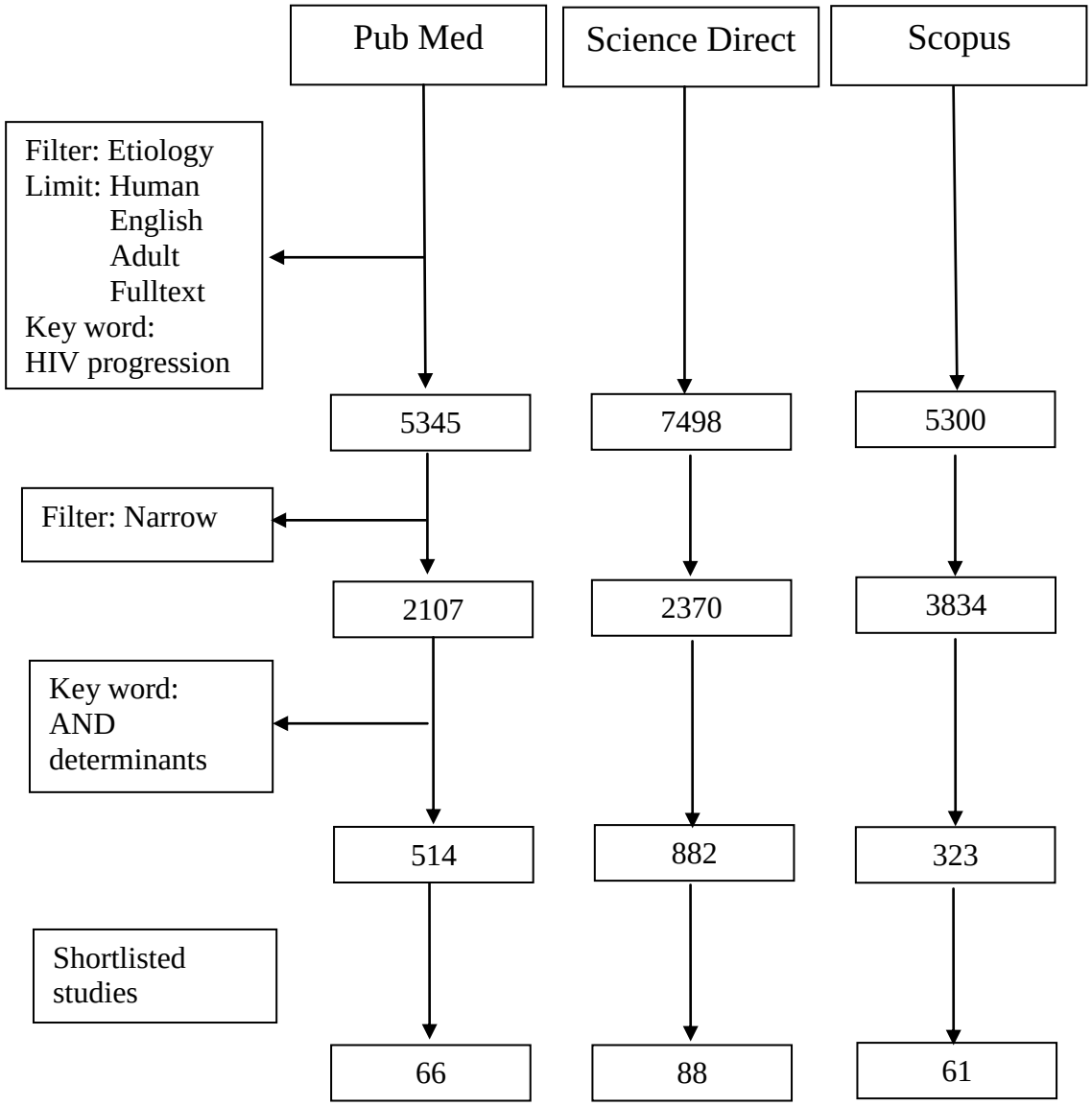


Figure 2.1 Flow chart of search strategy

2.3 Biology of HIV

Human immunodeficiency virus (HIV) is classified as retrovirus, which contains double strands of ribonucleic acid (RNA) as it is a genetic material. It is associated with immune suppression diseases where patients observe symptoms of diseases much later after infection due to long viral incubation. HIV causes Acquired Immune Deficiency Syndrome (AIDS) (Barre-Sinoussi et al., 1983)

2.3.1 Structure of HIV

HIV has a cylindrical eccentric nucleoid or core. The nucleoid surrounds two identical single strands of ribonucleic acids (RNA) which encode the virus genes (Figure 2.2). This genetic code for structural proteins and the regulatory protein control the viral activity. The viral protein p24 is found within the viral envelope in capsid shape. Antigen p17 lies between the virus envelope and the core. External knob-like structure is formed by the envelope glycoprotein gp120 which can be noticed on the surface of HIV. The transmembrane protein, gp41 anchors gp120 to the viral envelope, creating both external and internal domains. The membrane lipid layer is originated from the host cell (Ratner et al., 1985)

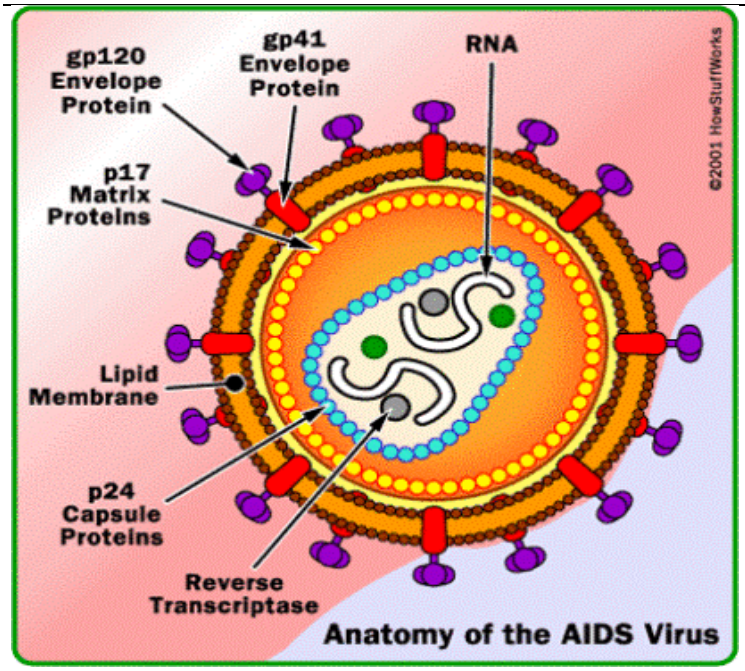


Figure 2.2 Structure of HIV

Source: (http://www.sexuallytransmitteddisease.info/aids/aids-pictures)

2.3.2 Viral genome

Transcription prepares sites for the formation of viral deoxyribonucleic acid (DNA). The viral genome as a transactivator is *tat* (encodes transactivator protein), *rev* (encodes a regulator of expression of viral protein) and *vpr* (encode viral protein R). The viral genome as a protein regulator is *vif* (associated with viral infectivity), *nef* (encodes a 'so-call' negative regulator protein) and *vpu* (encodes viral protein U) to manage the rate of viral replication and termination. For example, *tat* protein p16 and p14 activate the viral transcription. The p14 *rev* protein is responsible for the transport and stability of viral RNA. The p27/p25 *nef* protein is active in the down regulation of CD4 cells (Watts et al., 2009). The viral genome consists of three structural genes termed as *env, gag* and *pol* (Watts, et al., 2009):

a. *env* gene (envelope gene): envelope precursor gp160 (glycosylated polypeptide precursor) which is processed to form gp120 (the exterior glycoprotein) and gp41 (the trans membrane glycoprotein), protein is embedded in the viral envelope which sustains the virus to join the target cells.

b. *gag* gene (specific antigen group): gag precursor (p53), coding of viral core, cleaved into smaller products : p18, p24 (nucleocapsid protein) and p15

c. *pol* gene: (polymerase gene), encodes the viral enzyme: protease (p10). reverse transcriptase (p66/p55) and integrase (p32)

The function of protease is particularly to split *pol* and *gag* precursor polypeptides into functionally active proteins. The replicating of RNA genome is proceeding through reverse transcriptase in the presence of DNA polymerase. Endonuclease is important in proviral integration, *tev* is present in some HIV-1 isolates with the partial incorporation of *env* and with no or little *rev* properties (Watts, et al., 2009)

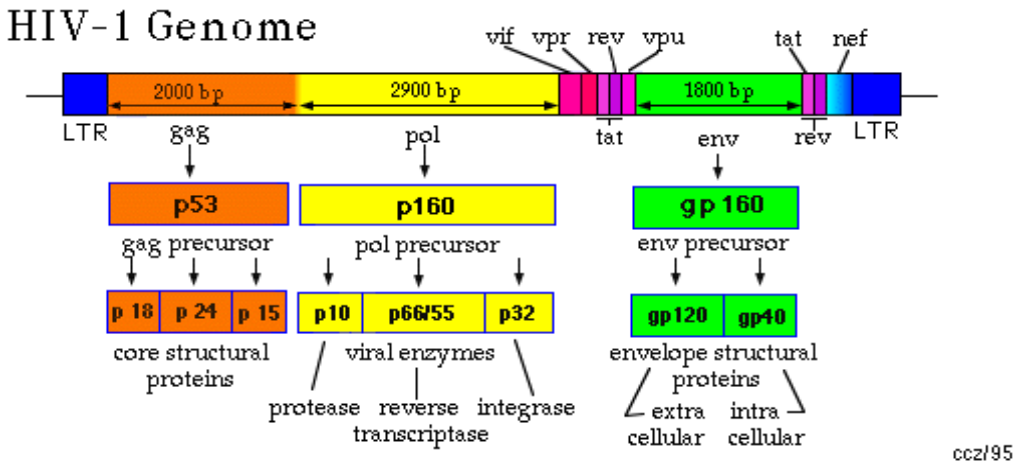


Figure 2.3 HIV genome

Source: (Huckaby, 1998)

2.3.3 HIV types

There are 2 types of HIV infections, HIV-1 and HIV-2. Generally HIV-1 infections are more virulent than HIV-2 (Reeves & Doms, 2002). The type of HIV is defined by the genomic organization, *vpu* is a unique gene found in HIV-1 while *vpx* is found in HIV-2. The HIV-2 crossed reacted with the *gag* core protein p24 of HIV-1. The percentage of amino acid homology between *env* and *pol* is low (Watts, et al., 2009). Genetically, HIV-1 can be classified into four groups, specifically M group (major), O group (outlier) and N and P the two new groups (Figure 2.4). Genetic changes in HIV recombinant viruses could result in altered biologic properties that affect the pathologic features and consequences of HIV infection. Recombinant strains of HIV spread in new regions and new host are identified throughout the world as different subtypes (Hemelaar, Gouws, Ghys, & Osmanov, 2006). The HIV-1 group P is a new strain discovered in August 2009 closely related to the gorilla simian immunodeficiency virus (Plantier et al., 2009). The majority of HIV-1 infection belongs to group M, which have been divided into nine genetically different subtypes; A, B, C, D, F, G, H, J and K (Hemelaar, et al., 2006). The distribution of HIV-1 subtypes in various countries can be seen in Table 2.1. Different subtypes of two viruses can join into a cell of infected human and assimilate with its genetic material. Most of the new strain can be transmitted to more than one person but they cannot remain in the same form for long. This form is called circulating recombinant form (CRFs), the combination of subtypes A and B were called CRF A/B (Hemelaar, et al., 2006).

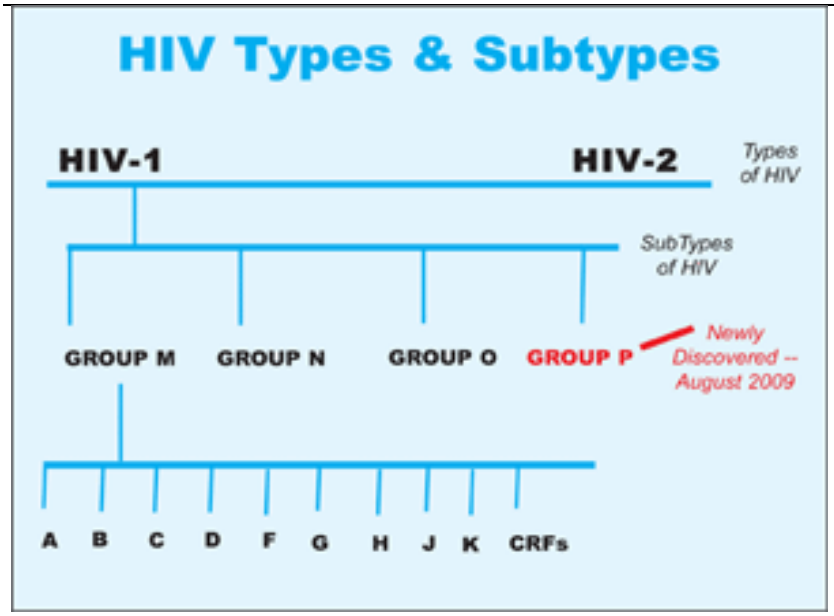


Figure 2.4 HIV type and subtypes

Source: (http://www.Avert.org/hiv-types.htm)

Table 2.1 The relationship between HIV-1 subtype and distribution location

Subtype	Country
A	West Africa
B	Europe, America, Japan, Thailand, Australia
C	Southern Africa, India, Nepal
D	Eastern and Central Asia
F	Central Africa, South America, Eastern Europe
G	Central Europe and Africa
H	Limited to central Africa
J	Central, North Africa, West Africa, Caribbean
K	Limited to Cameroon and Congo

Source: (Hemelaar, et al., 2006)

A study in 1997 showed that group O was formed out of 2 per cent of HIV positive samples where it is usually spotted in Cameroon and not common outside of west central Africa (Peeters et al., 1997). From early versions of HIV-1 test kits, group O could not be detected. Now more advanced HIV test have evolved to detect group O and N. In 1998, group N was discovered in Cameroon. In 2006, only 10 N groups were

identified while group M and group O were not detected at all (Yamaguchi et al., 2006). A new report on analyzed HIV sequence similar to a simian immunodeficiency virus found in gorillas (SIVgor) was released in 2009. This virus was isolated from a Cameroonian woman and believed to belong to group P (Plantier, et al., 2009).

2.3.4 Blood differentiation and CD4

Blood volume consists of 45 per cent blood cells and 55 per cent of blood plasma. Blood plasma is the liquid component of blood with yellow colour as the medium of blood cells. The volume of blood plasma consists of 90 per cent water and 10 per cent in the form of a solution in the form of protein, glucose, coagulation factors, mineral ions, hormones and carbon dioxide emissions. Blood plasma is also as the medium in the process of excretion (Anthea et al., 1993).

All blood cells are generated at the site where haematopoietic stem cells (HSCs) reside, during the foetal period, HSCs resides in the liver and in the bone marrow after birth, except for T-cells, which are formed in the thymus from progenitors derived from these hematopoietic sites. Haematopoietic stem cells have the ability to give rise to all of the different mature blood cell types and have an average lifetime about 3 to 4 days in the human body. A blood cell (a haematocyte) is a cell produced by haematopoiesis and normally found in blood. In children, haematopoiesis occurs in the marrow of the long bones such as the femur and tibia. In adults, it occurs mainly in the pelvis, cranium, vertebrae, and sternum (Kawamoto, Wada, & Katsura, 2010). The process of hematopoiesis in human displayed in Figure 2.5

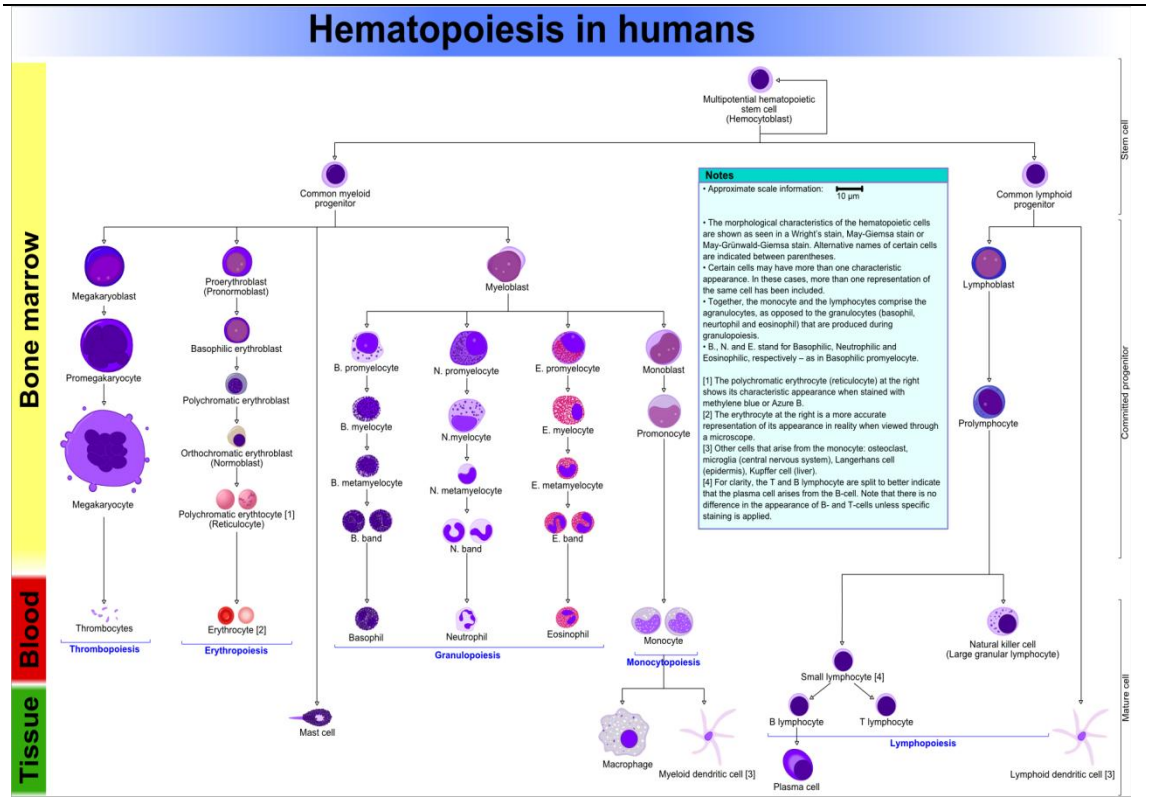


Figure 2.5 The process of hematopoiesis in humans
Source: (Anthea, et al., 1993)

Blood cells are divided into three categories, namely erythrocytes, leukocytes and platelets. Firstly, platelet or thrombocyte is a very small cell with diameter 2–3 µm, irregularly shaped, do not have a nucleus containing DNA and have average lifespan just 5 to 9 days. They circulate in the blood are involved in haemostasis, leading to the formation of blood clots. Platelets form the clots by releasing thread-like fibres. Secondly, red blood cells (RBC) have the main component called hemoglobin. Hemoglobin is an iron-containing protein that facilitates the transportation of oxygen and other respiratory gases to tissues (carries oxygen and collect carbon dioxide) and has a lifetime of about 120 days. Thirdly, white blood cells (WBC) or leukocytes have an average lifespan about 3 to 4 days in the human body and is used for defending the body against both infectious diseases and foreign materials. The WBC divided into five

differentiation are basophils, neutrophils, eosinophils, monocytes and lymphocyte (Anthea, et al., 1993).

The Lymphocytes divided into large lymphocytes and small lymphocytes. Large granular lymphocytes include natural killer (NK) cells. Small lymphocytes consist of T-cells and B-cells. The T-lymphocyte cell or called cluster of differentiation 4 (CD4) is a primary cellular receptor for HIV entry. The CD4 cell or helper T-cells are special cells in the immune system which react when the HIV enters and infects the human body. The CD4 cell count plays an important role in the human immune system as it helps the body to attack the infection and diseases. When the CD4 cell count does not work properly, then the person will easily fall sick. A healthy individual usually has CD4 cell counts in the range of 500-1,800 cells/μL. The schematic of blood differentiation and CD4 are displayed in Figure 2.6.

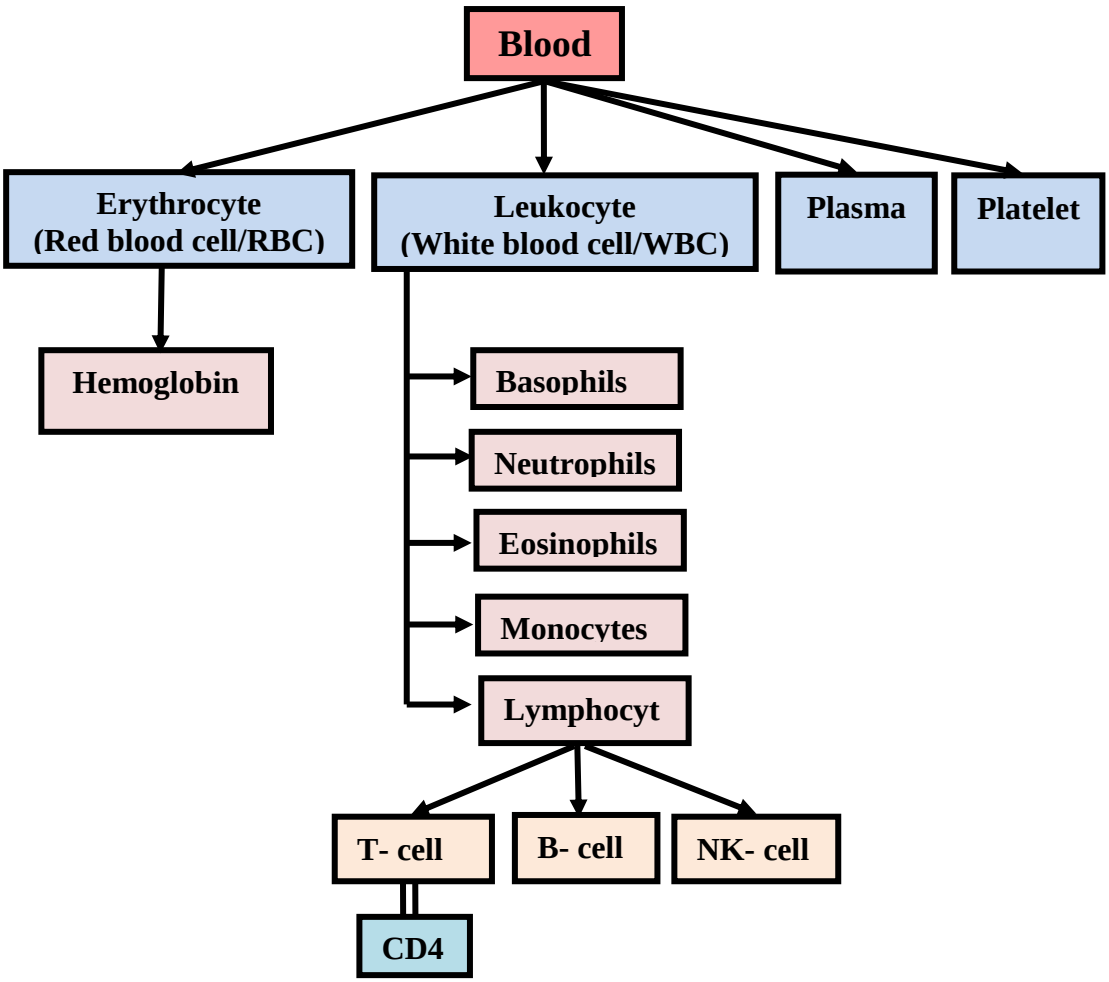


Figure 2.6 Blood differentiation and CD4

2.3.5 HIV co-receptors

The CD4 is a primary cellular receptor for HIV entry. The HIV attaches CD4 cell by the interplay among viral envelope, gp120 and a specific part of the CD4 molecule and it is present in abundance on CD4 cell count, both mature and immature T-lymphocytes. The chemokine receptors function as cofactors and allow HIV entry here:

a. C-X-C chemokine receptor CXCR-4 (fusin)

CXCR4 was expressed by T-lymphocytes (Doranz, Berson, Rucker, & Doms, 1997). CD4 and CXCR4 were co-expresses on cell allowing T-tropic HIV isolates to fuse and infect cells. The gp120 of HIV interacts with CXCR4 and CD4 to the cell and to cause conformational changes in gp120/gp41 complex allowing membrane fusion with gp41. CXCR4 is normally expressed on T cells and not on macrophages and cannot be united with M tropical HIV isolates (Doranz, et al., 1997). Stimulation with bacterial cell wall products can promote CXCR4 expression on macrophages and allow infection by HIV T tropic strain, mediating entry of SI (syncytium inducing). CXCR4 infect lymphocytes and cause a rapid progression of disease (Moriuchi, Moriuchi, Turner, & Fauci, 1998).

b. C-C Chemokine receptor CCR-5

Co-receptor CCR5 was found after the identification of CXCR4. CCR5 is expressed by monocytes, CCR5 with the presence of CD4 to allow fusion to HIV membrane (Deng et al., 1996). HIV gp120 depends on CD4 to bind to CCR5. As antibody inhibition, CD4 can decrease 87 per cent of CCR5 binding (Trkola et al., 1996). M tropic HIV isolates using co-receptor CCR5 for infection of macrophages and T-cells. Individuals with specific mutations in CCR5 co-receptor appear to be resistant to HIV infection. CCR5 strains are transmitted and usually predominate early in infection (Liu et al., 1996).

c. Additional chemokine receptors (CCR-2 and CCR-3)

Can also serve as a co-receptor for HIV under certain circumstances in vitro but are not believed to function as co-receptors in primary isolates. A chemokine CCR3 is

expressed on eosinophils and microglia. It is used for some HIV infection at microglia and resulting CNS pathology (He et al., 1997). It is likely that other chemokine receptors may also bind gp120 and allow HIV entry (Trkola, et al., 1996).

2.3.6 Life cycle of HIV

There are 10 steps of replication in the HIV life cycle (AIDSinfonet.org, 2012):

Step 1: HIV-1 surface glycoprotein gp120 interacts with the high affinity receptor, CD4 leads to a conformational change in gp120, permitting interaction with cellular receptors, CXCR4 or CCR5

Step 2: Interaction of gp120 with CD4 and receptor, the virus then fuses with the host cell allowing RNA release into host cells.

Step 3: Reverse transcription of genomic RNA into DNA

Step 4: Viral DNA enters the host cell's nucleus

Step 5: The integration of DNA is called provirus

Step 6: Transcription

Step 7: RNA processing and nuclear export of processed viral RNA

- HIV-1 *rev* protein controls the expression of different types of viral mRNA
- Once a sufficient level of *rev* accumulates, the single spliced and un-spliced HIV-1 RNA meet up in the cytoplasm and fuse with viral structural proteins

Step 8: Translation of viral mRNA into proteins

Step 9: Assembly of viral proteins and genomic RNA

Step 10: Budding of immature viral particles, viral env proteins are utilized to bud through the host cell membrane. The viral *gag* and *gag* poly-proteins are cleaved by the viral protease during or shortly after budding, generating mature infectious virions.

Primary HIV infection is related to extensive virus replication and widespread dissemination of the virus (AIDSinfonet.org, 2012)

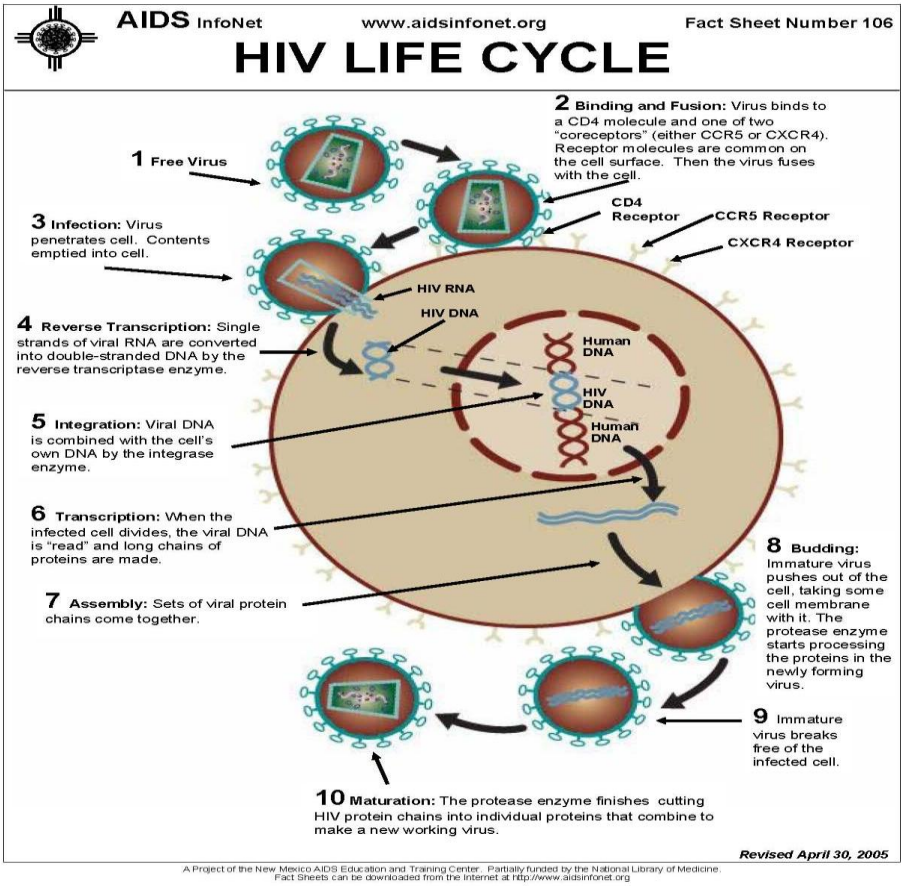


Figure 2.7. Life cycle of HIV

Source: (AIDSinfonet.org, 2012)

2.3.7 Natural History of HIV infection and pathogenesis of AIDS

HIV infection may occur by sexual contact or parenteral exposure to blood and blood products. HIV virus in the blood will appear and the viral can be detected within 7 to 10 days but majority of HIV infection in the initial stage will be silent. HIV-infected patients may not realize any symptoms till about 7-21 days later where HIV antibodies may appear in the blood (Barker et al., 1998). Patients in the early stage of infection often develop a seroconversion illness or acute HIV infection syndrome such as flu-like

symptoms, fever, lymphadenopathy, rash, loss of weight due to low appetite, diarrhoea and general lethargy and malaise. During the acute stage (after infection for 2-4 weeks), levels of virus in the bloodstream may be high (viral load can achieve 10,000.000 copies/ml in the blood) (Barker, et al., 1998). This happens because virus duplicate quickly as the immune system has yet to increase an effective repressive response, including the production of antibodies that can stop the virus particles (at this time as impact the total of CD4 count drops to very low levels and this person is very infectious). Subsequently as immune response recovers, appearance of antibody was directed against the virus. At this point, stabilized viral set point for 3 to 4 months and the level of virus in the blood declined (Figure 2.8). In the blood stream the value of virus become much lower, the patient feels well and less infectious. An infected person in this condition may feel well for 9.4 years (Morgan et al., 2002).

When the virus copies its genetic code many mistakes appear. The body's immune system has limited ability to control HIV. Genome with an average of 9,000 bases in total, might display an error in almost every genome copied. These genetic errors cause changes of appearance in the virus, thus making it more difficult for the immune system to identify it. Consequently, through a progressive shift, the virus takes the form that the immune system cannot respond to the infection, the rate of infection begins to accelerate. The total number of CD4 cell count starts dropping. When the CD4 cell count falls lower than 400 cell/μL (critical threshold), the body can no longer support itself (Barker, et al., 1998). At this point of time HIV infected person starts experiencing AIDS conditions and common opportunistic infections start to occur. Various possible infections that can occur are *mycobacterium tuberculosis* infections, *pneumocystis carinii* pneumonia (PCP), oral/pharyngeal candidiasis, cytomegalovirus (CMV), chronic diarrhoea, meningitis, toxoplasmosis cerebri, etc. Generally doctors will prescribe

prophylactic drug such as cotrimoxazole which helps in preventing infections and slowing down the progression of PCP.

The median survival time for AIDS patients that did not receive treatment is 9 months. Clinical progression among HIV-infected patients varies widely, from 2 weeks to 20 years (Barker, et al., 1998). There are many factors influencing this progression, such as age, the presence of co-existing infections and quality of health care. Genetic factor plays an important role as individuals resistant to special strains of HIV will show symptoms at a later stage of infection. There are even individuals that are totally immune to the viral infection. They carry the CCR5-delta-32 (a mutated cell surface marker), which prevents HIV from locking onto and invading their cells. This process may hold the key to future therapies which can be used to block infection in susceptible individuals. Scientists of today are hoping to understand this mechanism which can increase the resistance towards the virus (Hummel, Schmidt, Kremeyer, Herrmann, & Oppermann, 2005) .

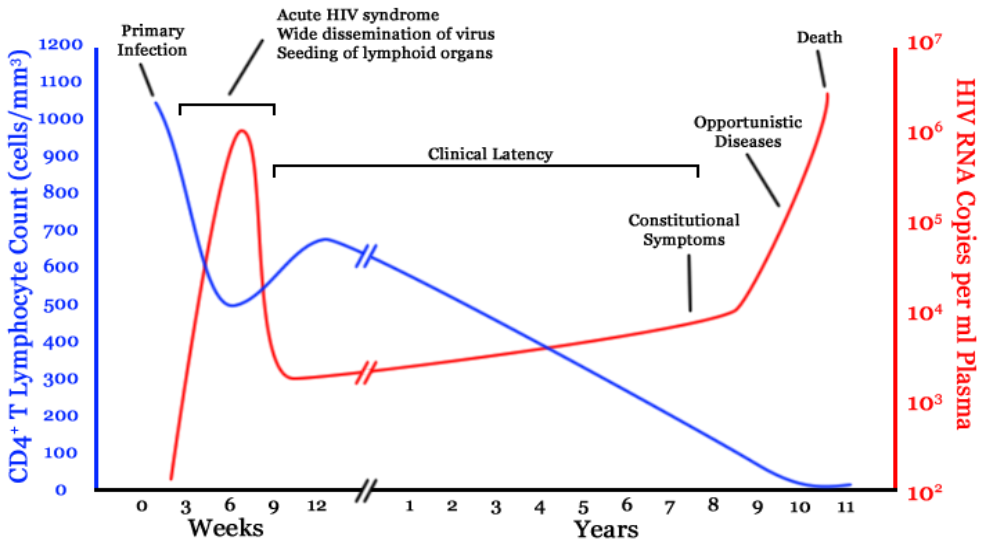


Figure 2.8. Natural history of HIV infection and pathogenesis of AIDS
Source: (http://www.microbiologybytes.com/virology/AIDSI.html, 2009)

2.3.8 Detection of HIV antibodies

Ethically, to conduct a blood test for an HIV infected person, a series of practice should be carried out such as signing informed consent, maintain confidentiality and accompanied by counselling (called 3Cs) (UNAIDS & WHO, 2004). Test to diagnose HIV has to be specific and sensitive. The percentage of positive result when HIV is present is called sensitivity and the percentage of the negative result when HIV not present is called specificity. Diagnosis of HIV by using an algorithm that combines two tests for HIV antibodies is carried out in the United States. The first diagnostic test for HIV an *enzyme immunoassay* (EIA) or *enzyme linked immunosorbent assay* (ELISA) was approved by the Food and Drug Administration (FDA) in 1985 to screen transfusion donors to keep the blood supply safe. This method is used to detect positive antibodies. Second test comes in the form of test kit used to determine antigens binding to antibodies. The test applies procedure like Western blot. The combination of both methods is important to achieve a highly accurate HIV detection. Antibody test was specifically intended for routine diagnostic HIV testing for adult. During the *window period* (3 weeks to 6 months of HIV infection) this test may give false negative. After infection, antibodies can be detectable in a majority of people around 30 days and 97 per cent the of people after 3 months HIV infection antibodies were detectable, it is rare with modern antibody testing of the 6 month window (CDC, 2006). For screening purpose, 2 blood samples will be taken on different occasions. These tests involve virus lysate antigens, recombinant protein antigens and chemically synthesized antigens, but EIA or ELISA testing alone is not sufficient for HIV diagnosis. The Supplemental test is Rapid Particle Agglutination (PA) had 99 per cent sensitivity and 98.9 per cent specificity compared with ELISA (Ramalingam, Kannangai, Raj A, Jesudason, & Sridharan, 2002). The Western Blot was used as a confirmatory test which detects HIV

antibody in human serum sample. It is also an analytical technique to detect specific protein from extract or tissue homogenate sample. Protein from HIV infected cells was obtained and dried on membrane. The serum was subjected to antibody incubation, free antibody was washed away and secondary anti human antibody associated with signal enzyme was added. The stained bands showed that patient's protein serum contains antibody (CDC, 2006).

In most health care settings in the United States of America (USA) an EIA or ELISA is used, followed by Western blot for confirmation. In many global setting two to three rapid HIV test is used for screening and confirmation. Many people are not getting tested for HIV with varied reasons, such as poor access to HIV testing, unaware of their risk, many remain afraid to find out their test result or they avoid testing due to stigma. Either avoids testing because of a dislike of counselling or because of the anxiety associated with waiting for their test result. Some are unaware that they would have access to effective treatment for HIV and so see no point in testing (Holmes et al., 2008). The screening procedure of HIV is as shown in Figure 2.9

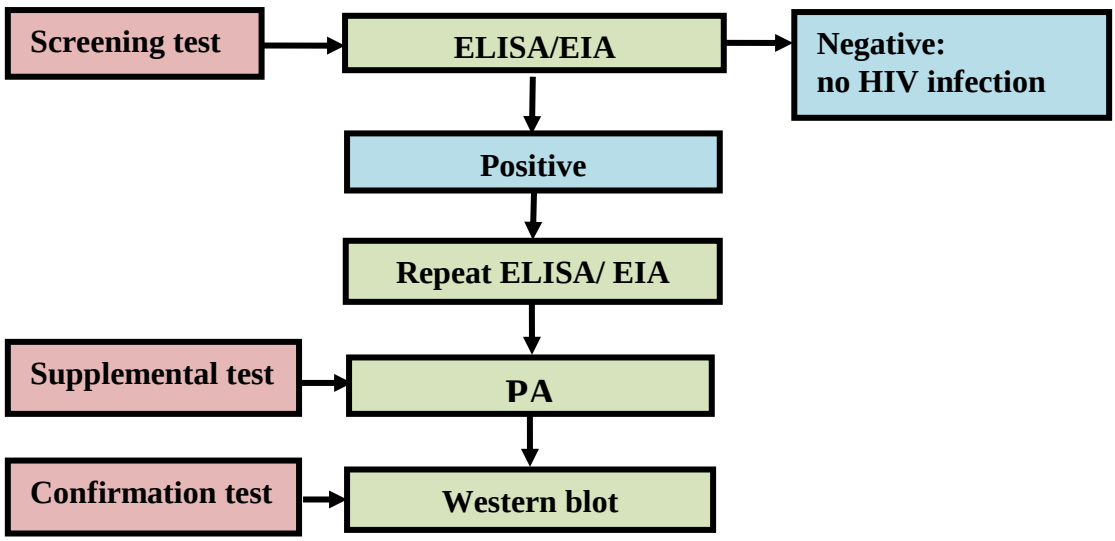


Figure 2.9. Screening procedure of HIV

Source: (CDC, 2006)

2.3.9 Clinical Staging of HIV/AIDS

HIV disease classification systems and staging are tools for monitoring and tracking the HIV epidemic. They provide patients and clinicians with important information about clinical management and staging of the HIV disease. Currently, two classification systems used in the world are Centres for Disease Control and Prevention (CDC) US and World Health Organization (WHO) Disease Classification System.

a. CDC Classification System

In 1986, CDC US published the majority accepted HIV infection classification system. This classification is primarily intended for use in public health practice and is based on certain conditions associated with HIV cases (CDC, 1992). This classification system has been revised by CDC in 1993 to emphasize the clinical importance of the CD4 count in the categorization of HIV related clinical conditions. There were 3 clinical categories (A, B, C) and 3 ranges of CD4 counts represented by a matrix of nine mutually exclusive categories. There are three categories of CD4 count as follows (CDC, 1992):

Category 1: CD4 $\geq$ 500 cells/μL

Category 2: CD4 200- 499 cells/μL

Category 3: CD4 < 200 cells/μL

Meanwhile HIV infection clinical categories are as follows:

Category A, which consists of one or more of the listed below, with documented HIV infection. The conditions listed in categories B and C must not have occurred

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute HIV infection with accompanying illness or history of acute HIV infection

Category B, consists of symptomatic conditions in HIV-infected individuals, which do not include conditions listed in clinical Category C, and minimal one of these criteria: a) the condition attributed to HIV infection or defect in cell mediated immunity, b) conditions considered by physicians to have a clinical course or that require management due to complication of HIV infection. Meanwhile, Category C, includes the clinical conditions listed in the AIDS surveillance case definition. Based on the 1993's revised classification system, CDC has also expanded the AIDS surveillance case definition to include all HIV infected individuals that have CD4 count less than 200/μL. The expansion includes the addition of 3 clinical conditions, PTB (pulmonary tuberculosis), invasive cervical cancer and recurrent pneumonia (CDC, 1992)

b. WHO Clinical Staging

In 1990, WHO developed a case definition and HIV clinical staging. It has been revised in 2007. It is based on clinical findings that guide the HIV/AIDS patients to make a diagnosis, to manage, to evaluate HIV patients and does not require a CD4 count. Many countries are using this staging to determine those eligible for anti-retroviral therapy. There are four categories of clinical stages that are stage 1, 2, 3 and 4, progressing from HIV infection till AIDS infection. These stages are defined by symptoms or specific clinical conditions and according to the WHO staging system, adolescents and adults are defined as individuals aged 15 years (WHO, 2007c). WHO clinical staging detail are found in Appendix F.

2.4 Epidemiology of HIV/AIDS

AIDS was first identified in 1980s. Now, the disease is widespread all over the world. AIDS has become a global pandemic receiving extraordinary attention. HIV infection causes relentless destruction to the immune system thus leading to the onset of the AIDS. AIDS has led half of its victims to death (UNAIDS, 2010). All HIV-infected patients have the risk of illness and death from complications of opportunistic infection and neoplasm that cannot be avoided (Moss & Bacchetti, 1989).

There are 4 stages of evolution of the AIDS pandemic. In the first stage, the spread of HIV increased from endemic rural to urban population. The second stage showed the spread of HIV in certain risk groups. The third stage is the continuation of second stage. It showed the spread depends on the behaviour of the risk group, such as sexual promiscuity and IDU. The fourth stage is development of stabilization in places such as Australia, North America and Western Europe, where control measures have a positive effect. However, some places like central Asia and Africa experienced increasing HIV epidemic since 1990 (CDC, 2001; Quinn, 1996). Even though HIV infection increased dramatically in the USA in 1980's and peaked in the early 1990's. Eventually it declined but the development of a reservoir of people infected with HIV requiring therapy has risen steadily since 1990's and continued into the 21st century (CDC, 2001; Fauci, 1999). More than 21 million people in the world had died from AIDS, over 34 million people living with HIV (PLWH) and over 95 per cent of HIV infected people stayed in developing countries at the end of the 20th century (Gayle & Hill, 2001; Sepkowitz, 2001)

2 Literature Review

The reach of the AIDS pandemic has already caused serious problems in many sectors. For example health care system in many countries cannot cope with increasing AIDS patients, the loss of young to middle aged individuals gave a big impact to national economies as they are most productive economically. In the early 21st century, about 95 per cent of HIV (incidence and deaths) occurred in developing countries and two thirds of people living with HIV in the world were founded in sub Saharan Africa. Forty per cent of HIV incidence affected young people aged from 15 to 24 years old (Merson, 2006). Half of the AIDS cases filed in the world are woman. Consequently, vertical infection from mother to child increased and this caused significant number of children born with HIV infection (Quinn, 1996). The cost effective therapies for individuals with HIV infection and complications are administered to prolong survival. In 1990's, the amount spent for medical care of an HIV infected individual in United States was twice the amount earned (Bozzette et al., 1998). Although treatment using various drugs increases the survival of HIV infected individuals but the price of drugs are still high and it was difficult to reach majority people in the world. The years of useful life lost by the predominantly younger people infected by HIV gave an important economic impact (Whiteside, 2001).

The epidemic had left behind 16 million AIDS orphans by the end of 2009 (WHO, 2010b). These orphans are defined as those aged less than 18 years old and have lost both or one parent to AIDS. These victims have a tendency of getting HIV infection, being exploited and live in poverty. Usually, they were forced to find work and leave their education. Sometimes they also carry responsibility over their younger siblings and family. About 2.5 million children aged less than fourteen years old were infected with HIV in 2009 (WHO, 2010b). More than 90 per cent of children with HIV got the infection from their mother through birth or via mother's breast milk. Almost nine

tenths of such transmissions developed in sub Saharan Africa. This region leads in mother to child transmission (MTC) of HIV. It still stays in first place despite the proof that HIV ultimately impairs women's fertility. Which means once infected, a woman can be expected to bear 20 per cent lower children than she otherwise would. Anti-retroviral treatment is able to decrease the risk of mother to child, but these are still out of reach in remote places where they are most needed. Ninety percent of PLWH stay in the developing countries. The proportion is set to rise even further as infection rate continue to grow in countries where low health care systems, poverty and limited resources for prevention and care fuel the transmission of the virus. Sub Saharan Africa (the area in South Africa of the Sahara desert) is the badly affected country in the world by the AIDS epidemic (WHO, 2010b).

In 2009, there were 1.8 million people newly infected with HIV, 2.3 million children were HIV infected. This amount brought the total of PLWH in this region to 22.5 million by the end of 2009. In 2009 AIDS killed around 1.3 million individuals in sub Saharan Africa only (WHO, 2010b). Anti-retroviral drugs can dramatically improve survival allowing years of healthy life, but still they are not available to most Africans (WHO, 2007a).

These were around 32.8 (95% CI 30.9 - 34.7) million of PLWH, about 2.7 (95% CI 2.4 - 3.0) million of new HIV infections and 2.0 (95% CI 1.7 – 2.4) million deaths due to AIDS related illnesses found worldwide, nearly 16 per cent of all new infections occurred among children below 15 years and 45 per cent of new infections developed in young people aged between 15-24 years at the end of 2008 (WHO, 2009). At the end of 2009, there were 33.3 (95% CI 31.4 – 35.3) million of PLWH and 2.6 (95% CI 2.3 – 2.8) million of new HIV infection (WHO, 2010b)

At the end of 2011, globally there were 34.0 (95% CI 31.4–35.9) million of PLWH, 0.8 per cent of adults aged 15-49 years worldwide are living with HIV and 1.7 (95% CI 1.5–1.9) million people died from AIDS-related causes (UNAIDS, 2012). The burden of the epidemic continues to vary considerably between countries and regions. In sub-Saharan Africa reported that 71 per cent of the adults and children newly infected in 2011(UNAIDS, 2012). The global HIV incidence and number of new infections by year are as shown in Figure 2.10 and Figure 2.11. The Malaysian HIV epidemic (1986-2009) is shown in Figure 2.12

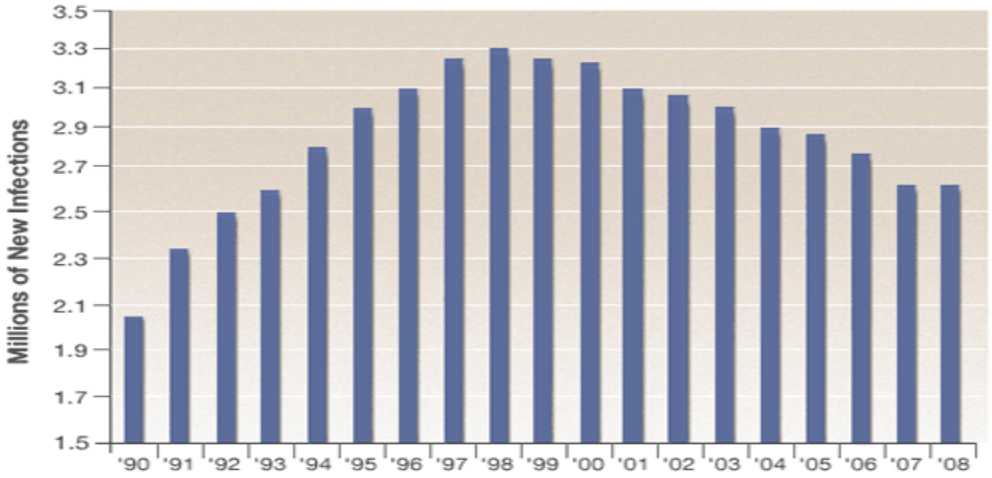


Figure 2.10. Estimation of HIV global incidence and number of new infection by year

Source: (http://www.globalhealth.org/hiv_aids/global_view/)

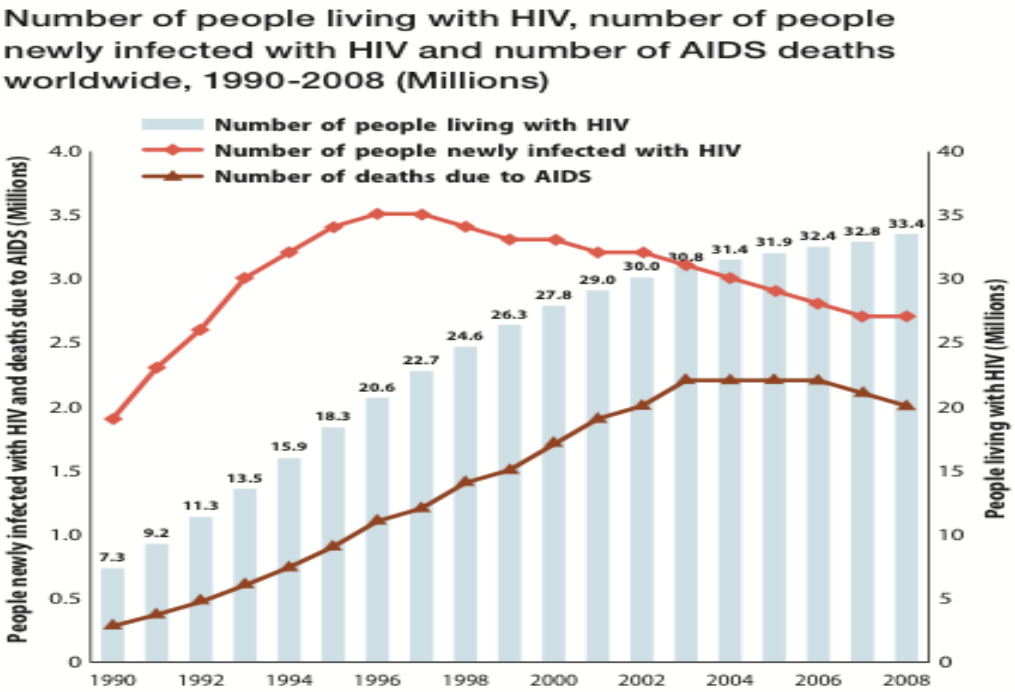


Figure 2.11. Number of people living with HIV, number of new infection and number of AIDS death worldwide, 1990-2008 (in million)

Source: (http://www.globalhealth.org/hiv_aids/global_view/)

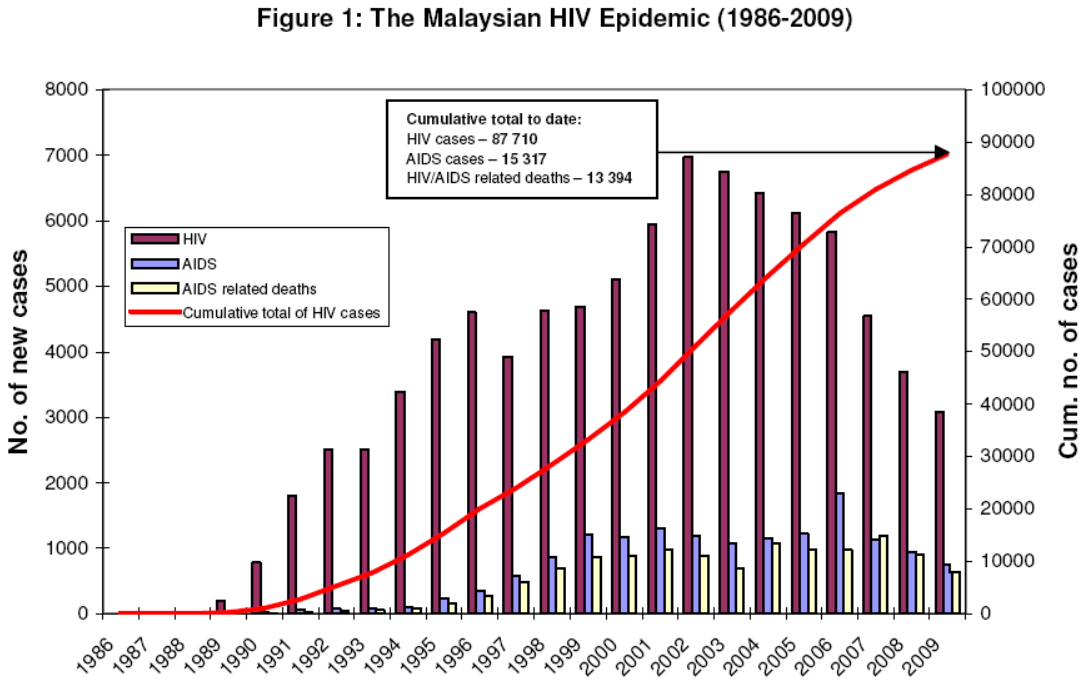


Figure 2.12. The Malaysian HIV epidemic (1986-2009)

Source: (UNGASS, 2010)

In Asia, there were 4.7 (95% CI 3.8-5.5) million of PLWH in 2008, including 350 000 (95% CI 270 000 - 410 000) new HIV cases last year (WHO, 2009). In 2008, there were 330 000 (95% CI 260 000-400 000) death from AIDS in Asia. While the yearly total deaths from AIDS in South and South East Asia in 2008 was around 12 per cent, which is lesser than the mortality statistic in 2004. The rate of death from HIV or AIDS in East Asia showed a continued rise. In 2008, the total was three times higher compared to total death in 2000 (WHO, 2009). The total of PLWH in whole of Asia is 4.9 (95% CI 4.5 – 5.5) million in 2009. Adult HIV prevalence is still less than 1 per cent in most countries in the Asia region, except Thailand the prevalence is close to 1 per cent (WHO, 2010b).

In 2010, about 4.8 (95% CI 4.3–5.3) million PLWH in Asia, 11 per cent more than the 4.2 (95% CI 3.8–4.6) million in 2001. HIV transmission rates have slowed in the larger epidemics, but expanded access to anti-retroviral therapy has increased the survival rates of PLWH. An estimated 3 100 (95% CI 2 600 – 3 400) people died from AIDS-related causes in 2010, the largest death toll outside sub-Saharan Africa. That death toll has stayed relatively stable during the past decade in Asia overall, but in East Asia it doubled from 24 000 (95% CI 16 000 – 45 000) in 2001 to 56 000 (40 000 – 76 000) in 2010 (WHO, 2011). In 2011, there were 4.0 (95% CI 3.1–4.6) million of adults and children living with HIV and 2.8 (95% CI 1.7–3.7) million adults and children newly infected with HIV In South and South-East Asia (UNAIDS, 2012)

Seven countries reported 100,000 or more PLWH in 2009: India, China, and Thailand, Indonesia, Viet Nam, Myanmar and Malaysia (ranked by the number of PLWH in each). More than 90 per cent of the people with HIV in Asia live in these countries, with India alone accounting for 49 per cent of the PLWH in the entire region (WHO, 2011).

Malaysia already has HIV cases for the past 25 years. At the end of 2011, there were 81,000 PLWH cases. The cumulative figure for the first HIV case in 1986 was 94,841, out of which 17,686 were AIDS cases and 14,986 were deaths, thus giving reported PLHIV of 79,855 (UNGASS, 2012). The Ministry of Health reported the annual number of new HIV cases has been on a steady decline from a peak of 6,978 in 2002. In 2011, there were 3,479 new cases reported to the Ministry of Health, approximately half of what was reported in 2002 with an average of 9 new cases each day. The notification rate of HIV also continues to experience a decrease from 28.4 in 2002 to 23.4 in 2005 and to 12.2 cases per 100,000 populations in 2011(UNGASS, 2012). The epidemic in this country is concentrated within most-at-risk populations (MARPS) especially among IDU, sex workers and transgender population (UNGASS, 2012).

2.5 Transmission of HIV

HIV infection can spread via various body fluids and secretion. Generally HIV appears in high concentration in the blood, genital secretions and breast milk. These are significant HIV transmission route to other individuals. The low concentration of HIV in urine, sweat, saliva and tears, has low chances of spreading HIV to other individuals (Lifson, 1988). The main transmission source of HIV is unprotected sexual intercourse. Sexual transmission occurs when HIV secretion of infected individual gets in contact with genital mucous, rectal mucous or oral contact with another individual (Boily et al., 2009). Primarily HIV was a sexually transmitted disease that affected a certain risk group in the population. It is different from the other infectious diseases where the whole population is at risk. The spread of HIV can develop from a man who has sex with woman, man who have sex with men (MSM) and a woman who have sex with men. HIV infections can be transmitted through sexual relationships with multiple

sexual partners, with men with sexually transmitted diseases (STD's), with men who are not circumcised and without protection.

Randomized controlled trials (RCT) have been conducted with uncircumcised men who were randomly chosen for circumcision with sterile condition and later given counselling. They were then compared with uncircumcised men. Analysis of data showed that sexually transmitted diseases percentage of men to women decreased 60 per cent in South Africa (Williams et al., 2006), 53 per cent in Kenya (Bailey et al., 2007) and 51 per cent in Uganda (Gray et al., 2007). Finally a recommendation was issued by a panel of experts from WHO and the UNAIDS secretariat that circumcision (on man) is an important intervention to decrease the risk of HIV infection in men through sexual relations (WHO, 2007d). Among MSM there is enough evidence that circumcised men may prevent transmission of HIV infection and sexually transmitted diseases (Millett, Flores, Marks, Reed, & Herbst, 2008). The unstable economic and political situation is many countries is becoming the barrier to HIV testing programs, treatment of sexually transmitted diseases, promotion of condom use and behaviour modification treatment. Antiviral drugs can decrease the viral amount and the risk of transmission to others.

There are 3 variables that explain HIV transmission by sexual intercourse transmission efficiency, total number of sexual partners and total of infected individuals in a population. In developed countries, the exposure risk of women who have sex with men is 0.04 per cent per act and the exposure risk for men who have sex with women is 0.08 per cent per act. These rates are 4 to 10 times higher in developing countries with various reasons such as condom use not controlled, higher of sexual transmitted infection, higher antenatal care HIV prevalence (Boily, et al., 2009).

In general HIV transmission can occur when the blood of HIV infected individuals gets contact with another person's wound. For example, different modes of infection transmission are by IDU, blood transfusion, hemophiliacs and blood product recipients. It is also an important concern for those who received medical treatment using injection equipment in the region with low hygiene standards, for example, syringes are reused in third world countries due to lack of resources. Although the chances of accident occurrence are rare but health care workers such as nurses, laboratory workers, and doctors also face the risk of being infected with HIV. Necessary precautions have to be taken to protect themselves from getting contact with HIV infected individual's blood (Lifson, 1988).

2.6 Progression of HIV Infection

HIV-infected patients will progress from AIDS to death. CD4 cell counts have been used as indicators of disease staging in HIV-infected patients for over 20 years. CD4 cell counts are predictors of disease progression, independent of disease duration of clinical symptom and can be used in conjunction with clinical symptoms to provide staging for an individual patient or a population of patients and to a comparison group of patients across different studies. The likelihood of specific opportunistic infections is related to the CD4 cell counts. In the context of HIV disease progression or response to therapy, the CD4 count or a change in the CD4 cell counts explains only a fraction of the clinical progression rates or clinical responses to anti-retroviral therapy. Including clinical symptoms in the algorithms improves the prognostic value of the observations from CD4 less than 200 cells/µL to CD4 more than 200 cells/µL (Holmes, et al., 2008).

AIDS will be diagnosed, when CD4 cells count fall lower than 200 cells/µL (Phillips et al., 1996). Even though CD4 cells count achieved show more than 200 cells/µL, one or more opportunistic infection diseases such as Pulmonary tuberculosis (PTB), PCP, toxoplasmosis, candidiasis and others infections, may be present, thus AIDS can be diagnosed (CDC, 1992). Decreased of CD4 less than 500 cells/µL omen the development of clinical AIDS and CD4 less than 200 cells/µL defines as AIDS and also indicates for AIDS with opportunistic infections or neoplasm. The CD4 more than 200 cells/µL showed a lower risk of death from AIDS (Phillips, et al., 1996; Sterling et al., 2001). Regarding the immunological factors as predictor of HIV progression, when compared to patients with CD4 more than 350 cells/µL, CD4 less than 50 had HR of 13.0 (95% CI 3.8, 44.3), CD4 of 50-199 had HR of 5.1 (95% CI 1.6, 16.3) (Bonnet, et al., 2005). CD4 of 200-350 had HR of 1.72 (95% CI 0.92, 3.21), CD4 less than 200 had HR of 3.79 (95% CI 2.18, 6.57) (Jaén et al., 2008)

There is a positive correlation between level of CD4 and hemoglobin level (Obirikorang & Yeboah, 2009). Rates of hemoglobin decrease also correlate with falling CD4 counts. Hemoglobin is the most widely used screening measures of anemia as a proxy for iron deficiency, because it is simple, quick and inexpensive. Hemoglobin is a marker of nutritionally significant iron deficiency, it captures the more advanced stage and not detect in early stages of iron deficiency (O'Brien et al., 2005). Hemoglobin thresholds are used to define anemia which is based on WHO guideline for women with age more than 15 years and not pregnant (Hb 12 g/dl), pregnant women (Hb 11 g/dl) and men with age more than 15 years (Hb 13 g/dl) (WHO, 2008). Anemia has been associated with progression to AIDS and shorter survival time for HIV-infected patients. A study of EuroSIDA multicenter cohort showed that mild anemia (Hb 8-14 g/dl for men, and Hb 8 – 12 g/dl for women) and severe anemia (Hb < 8 g/dl) were associated with

clinical disease progression, with a relative hazard of disease progression of 2.2 (95% CI, 1.6–2.9) and 7.1 (95% CI, 2.5–20.1), respectively, compared with patients with no anemia (Hb > 14 g/dl for men and Hb > 12 g/dl for women) (Jens D. Lundgren & Amanda Mocroft, 2003).

Total lymphocyte count (TLC) has a correlation with CD4 cell count (Spacek, Griswold, Quinn, & Moore, 2003). Based on WHO guidelines TLC can used as a surrogate marker for CD4 level, the cut-off value TLC less than 1,200 cells/μL is similar with CD4 less than 200 cells/ μL (WHO, 2006b). In asymptomatic HIV-infected patients TLC correlates relatively poorly with the CD4 cell count but in combination with clinical staging it has been reported as a useful marker of prognosis and survival (WHO, 2006b). The finding of a United Kingdom (UK) study showed that a significant linear correlation between the CD4 count and TLC (Pearson's correlation coefficient = 0.70, *p- value* < 0.001). The cut-off value at which the error rate for TLC is at its lowest and the sensitivity maximal was 1,500 cells/μL, with further analysis identifying 1,700 cells/μL being a more precise cut-off (Stebbing et al., 2005). Patients with TLC 1,000–1,500 cells/μL were estimated to be at 40 per cent increased risk of developing an opportunistic infection but the area under the ROC curve for TLC was 10 per cent lower than CD4 count (Stebbing, et al., 2005). As a predictor of opportunistic infection, TLC is less reliable than CD4 count but in a resource limited setting or absence of expensive equipment for CD4 tes,t then the TLC test is useful.

The number of viral load in peripheral blood is the best indication for laboratory examination as a sign of HIV progression to AIDS. CD4 cell count and adult's age do not affect the predictive value of viral load levels. At this level, viral load would have generally decreased and continue to fluctuate from 6 to 9 months. The latent phase of

HIV infection contains relatively stable viral load. This condition depends on factors such as the strain of HIV, host immune response, total of CD4 cell count and macrophages that exist in the process of infection. In the cases of congenital HIV infection, the amount of virus in the blood may be higher at first but it could not be determined until the birth of the baby (Sterling, et al., 2001).

Viral load is typically reported as copies of HIV in a millilitre (ml) of blood. Viral load can predict how long an individual will remain healthy or how quickly the disease will progress. The total number of viral load in the blood is associated with the progression of AIDS, they ranged from less than 50 to 1,000,000 copies/ml. The number of viral load can stay stable for months to years. Every HIV infected person may have a different viral load in the blood where it changes rapidly. The higher number of viral load will mark the progress to more definite AIDS. The HIV infected patient tested with a viral load of more than 100,000 copies/ml will be more prone to attain AIDS or death (Smurzynski et al., 2010). The presence of neoplasm and opportunistic infections can increase the risk of AIDS progression to death (Falster, et al., 2009; Mugavero et al., 2007). Although the rates of progression to AIDS are similar among women and men but the initial viral load is different (Sterling, et al., 2001). The CD4 cell count and viral load test are the gold standard markers for disease progression in monitoring HIV-infected patients, measurement of these parameters is not possible in resource-limited settings, surrogate markers become important for use as markers for disease progression such as total lymphocyte count, hemoglobin and body mass index (BMI) (Zhou & Kumarasamy, 2005)

HIV patients can be categorized into 3 groups which are typical progression, rapid progression and non-progression towards AIDS. Clinical appearance of AIDS can be

detected between 8 to 10 years after HIV infection (Beral et al., 2000). After an acute infection number, the viral load amount will fall and this is seen in HIV patients. Initially, HIV variants replicate slowly over time and replication becomes faster towards progression to AIDS. On the average, 10 per cent of HIV infected people experience rapid progress to AIDS within 2 to 3 years after the first infection (Haynes, Pantaleo, & Fauci, 1996). This occurrence is due to high viral load in the acute phase of infection which do not decline after that or probably the individual was infected with more than one type of HIV virulent (Haynes, et al., 1996). Meanwhile, there are individuals with clinical symptoms of AIDS will certainly stand a chance to live for many years. Development of AIDS by HIV-infected patients is not caused by race, gender or pregnancy but it is the determinant of infection (Bessinger, Clark, Kissinger, Rice, & Coughlin, 1998; Chaisson, Keruly, & Moore, 1995).

Hepatitis G virus (HGV) also known as GB virus C (GBV-C) is a single stranded RNA virus belonging to the Flaviviridae family. It is often found in co-infections with other viruses, such as hepatitis C virus (HCV), hepatitis B virus (HBV) and HIV. About 40 per cent of the prevalence of GBV-C in HIV infected individuals and about 1.8 per cent in blood donors (Xiang et al., 2001). Co-infection HCV was determinant of HIV progression to AIDS or death who started HAART (HR 2.4, 95% CI 1.65 to 3.49) (Jaén, et al., 2008)

Approximately 10 per cent of HIV infected individuals live longer and did not show significant decrease in immune system in the past ten years (Pantaleo et al., 1995). This is opposite to the majority of HIV infected individuals that progressed to AIDS. The group displays stable CD4 cells count, negative plasma cultures for HIV viral load, a strong virus inhibitory CD8 cells count response and fewer HIV infected cells. The viral

subtype is not associated with the increasing number of viral load, presence of neutralizing antibodies or viral growth kinetics (Pantaleo, et al., 1995). Although peripheral mononuclear blood cells containing HIV-1 replicates were detected and virus continued to live longer, the viral load remained low (Rosenberg et al., 1997). Some specific responses of CD4 cells count in HIV patients can help in controlling viral load (Rosenberg, et al., 1997)

There was evidence that there were sexual differences in survival and HIV progression and it depends on time calendar (Jarrin et al., 2008). Before 1997, there were no significant differences between men and women towards its progression to AIDS and death. But since 1997 onwards, women has lower risk of AIDS as compared to men with adjusted cumulative relative risk (aCRR) which is 0.76 (95% CI 0.63, 0.90) and death with adjusted hazard ratio (aHR) was 0.68 (95% CI 0.56, 0.82) (Jarrin, et al., 2008). Progression to death in pre-1997, woman as compared to men aHR, was 0.89 (95% CI 0.76, 1.05), in the 1997 onwards aHR was 0.68 (95% CI 0.56, 0.82) (Jarrin, et al., 2008). After 1997, women also experience low risks of AIDS mortality and non AIDS mortality. This is of benefits even though women have a smaller proportion in the use of HAART in every kind of HIV exposure risk compared with men (Jarrin, et al., 2008). One study showed that women have a tendency of lower risk of mortality than men with a HR of 0.55 (95 % CI 0.28-1.07) (Alibhai et al., 2010).

Gender differences play a role in HIV progression. Three years after HIV diagnosis showed that 45.9 per cent of IDU men did not progress to AIDS as compared with 54.9 per cent of IDU women. Progression to death between IDU men and IDU women when compared to MSM, had RR 1.16 and RR 1.57 respectively (Hall, McDavid, Ling, & Sloggett, 2006). Survival rate among IDU is worse as compared with MSM. It may be

related to their high-risk lifestyle or co-morbidity, such as hepatitis C virus infection (Hall, et al., 2006; Porter, et al., 2003). After adjustment to anti-retroviral therapy, predictor of death included women (*p- value* = 0.02), age at HIV diagnosis (*p- value* = 0.005), CD4 less than 200 cell/µL (*p- value* < 0.001), viral load more than 100,000 copies/ml (*p- value* = 0.007) and opportunistic infections before admission or during follow up (*p- value* < 0.001) (Braga, Cardoso, & Segurado, 2007). The study done from 1996–2004 in 33 US states which compared the survival of IDU to other transmission categories showed 42.2 per cent (11,635) of 27,572 IDU were diagnosed late. For IDU, after three years HIV diagnosis, the risk of progression to AIDS was higher for non-whites, males and older individuals. Three-year survival after HIV diagnosis was lower for IDU men (87.3%, 95% CI 87.1–87.4) as compared with MSM (91.6%, 95% CI, 91.6 - 91.7) and men exposed to heterosexual contact (91.9%, 95% CI, 91.8 - 91.9). Survival was also lower for IDU women (89.5%, 95% CI, 89.4 - 89.6) as compared to women expose to heterosexual contact (93.3%, 95% CI, 93.3 - 93.4) (Grigoryan, Hall, Durant, & Wei, 2009). The exposure risk as predictors of disease progression from several previous findings, IDU has faster progression to death with HR of 2.17 (95% CI 1.22, 3.87) (Pérez-Hoyos, et al., 2006), homosexual after CD4 less than 200 cells/µL with HR 2.12 (95% CI 1.44, 3.11) (Wong, et al., 2004) and homosexual IDU with HR 1.33 (95% CI 1.2, 1.5) (Schwarcz, et al., 2000)

The incidence of opportunistic infection (OI) is significantly associated with morbidity and mortality of HIV-infected patients (Ghate, et al., 2011). Previous studies showed that progression to death with a history of OI had HR of 1.97 (95% CI 1.8, 2.2) (Schwarcz, et al., 2000). The risk ratio for mortality in patients receiving HAART as compared with those who did not, RR 0.41 (95% CI 0.25, 0.67) and five leading OI are Oesophageal Candidiasis, PCP, TB, Herpes simplex and Cytomegalovirus (Hung, Chen,

Hsieh, Sheng, & Chang, 2000). Tuberculosis was the most common OI with an incidence of 15.4 (95% CI 12.2-19.2) per 100 person-years in India (Ghate, et al., 2011). Tuberculosis is also the most common diagnosis of hospital admission as well as the leading cause of death in Nigeria HIV-infected patients (Agaba et al., 2011). The factor worsening the prognosis of HIV-infected patients in Spain is presented with opportunistic infection (tuberculosis or malignancy) (Batalla et al., 1989). *Pneumocystis carinii* pneumonia as a leading cause of death in HIV-infected patients in San Francisco, USA (Fei et al., 2009). Around 66 per cent of AIDS patients attending a large Indian health centre had more than one opportunistic infections (Kumarasamy, Solomon, Jayaker Paul, Venilla, & Amalraj, 1995)

Another factor associated with increased risk of disease progression is advanced age. The findings of study done in developed countries showed that progression to death related to increase of age with, HR of 1.21 by 10 years (95% CI 1.01, 1.51) (Bonnet, et al., 2005). Progression to death of HIV-infected patients aged more than 40 years had HR of 1.43 (95% CI 1.31, 1.61) (Schwarcz, et al., 2000) and age more than 45 years with HR of 1.54 (95% CI 1.29, 1.85) (Li, et al., 2000), age 50-59 years had HR 3.66 (95% CI 3.13, 4.27) compared to age under 20 years old (Hall, et al., 2006). In HIV-infected patients who started anti-retroviral therapy in the Asia Pacific region, older age more than 50 years associated with an increased risk of non AIDS mortality (HR 4.29; 95% CI 2.10, 8.79) (Falster, et al., 2009)

Social economic status (SES) also has influence on disease progression. The risk of death greater for persons with lower SES with HR of 2.81 (95% CI 1.38, 5.76) in SES level III and HR of 2.55 (95% CI 1.27, 5.14) in SES level IV (lowest SES) as compared to the level I (highest SES), Females: in the level IV SES had a high risk of dying HR

4.85 (95% CI 1.05, 22.3), IDU: had a higher risk of dying in level III with HR 4.54 (95% CI 1.08, 19.1) and in level IV with HR of 4.68 (95% CI 1.14, 19.2) (Rapiti, et al., 2000). Prior study in San Francisco wants to examine the association AIDS patients between survival and neighbourhood socioeconomic such as income, housing, demographics, employment and education using census data. HIV-infected patients in the lowest socioeconomic neighbourhoods had a significant HR 1.4 greater mortality compared to higher socioeconomic neighbourhoods (Arnold, Hsu, Pipkin, McFarland, & Rutherford, 2009). In Spain, AIDS patients who are infected by IDU with university education level had a lower risk of death (RR 0.52; 95% CI 0.36, 0.77) as compared to those without education. Independent of HIV status, lower education predicts a higher risk of death in IDU and its impact is stronger after 1997 (HAART era). Education has a protective effect on most causes of death and it cannot be entirely attributable to the access or use of HAART (Jarrin et al., 2007). Prior study in Nigeria showed that AIDS patients with primary education (HR 2.064; 95% CI 1.043, 4.085) and unemployment (HR 1.79; 95% CI 1.21, 2.66) were significantly associated with increased risk of death (DeSilva et al., 2009)

2.7 Survival time of HIV-infected patients

Time taken for progression of HIV to AIDS or death may vary in each patient. Scientists have estimated that 50 per cent of HIV-infected patients would develop AIDS within the average of 8 to 10 years without any anti-retroviral therapy. About 10 per cent of HIV-infected patients would experience rapid progression to AIDS in less than 2 to 3 years and 10 per cent do no progress to AIDS (CDC, 1997; Haynes, et al., 1996). From 1996 onwards, many new drugs have been developed to prevent or cure some of

the illnesses related to AIDS and HIV-infected patients are likely to develop illness and end with death (Li, et al., 2000)

A study in Australia used the national surveillance to describe the survival of HIV progression to AIDS from 1991 to 1996. The median survival of AIDS progression to death was 17.7 months (Li, et al., 2000). The survival time achieved 16.0 months in 1991 and increased to 27.7 months in 1996 (Li, et al., 2000) and other study in Amsterdam had 12.1 years. A 5-year prospective study was done in Taiwan and an estimation of survival after the introduction of Highly Active Antiretroviral Therapy (HAART) in the Asia Pacific region gave median duration of 497 days (mean 609 days range: 1-1825 days) (Hung, et al., 2000) and person had died after a median observation duration of 985 days (range 2-4.025 days) (Hung et al., 2006). Patients with HAART have a median survival duration of 720 days and patients without HAART achieved 205 days (Hung, et al., 2000; Hung, et al., 2006). In a study done in Hong Kong showed in the pre-HAART era (1984-1996), median survival after AIDS was 29.8 months and in the HAART era (1997- 2003) was more than 70 months (Pezzotti et al., 1999). A cohort study in China showed median survival time from HIV to AIDS was 9.2 years (Zhang, Shang, Wang, Cui, & Hu, 2010) and between 8.5 to 8.9 years (Li et al., 2010). Median survival time of HIV progression to death was from 8.8 to 10.7 years (Li, et al., 2010). Studies in Africa and China showed the median survival from developing AIDS to death was 9.2 months (Morgan, et al., 2002), 9.9 months (Zhang, et al., 2010), 1.2-2.0 years (Li, et al., 2010) and 104.4 weeks (Alemu & Sebastian, 2010). Many factors may potentially result in shorter survival of HIV-infected patients in resource poor setting, including more frequent exposure to primary pathogens such as *Mycobacterium tuberculosis*, salmonella, and others, limited access to health care service, under

resourced medical services, poor nutritional status and others (Holmes, et al., 2008). Summarised median survival time is shown in Table 2.2

Table 2.2 Median time to AIDS and death

Authors	Place	Years	Time to AIDS (months)	Time to death (months)
Mary	Ireland	1997		19.2
Maria	Europe	1999	124.8	
Pezzotti	Italy	1999		2.9 (before 1987) 12.3(1987 - 1990) 13.4 (1991 - 1993) 11.4 (1994) 17.6 (1995)
Schwarcz	San Fransisco	2000		19.0 (monotherapy) 17.0 (dual therapy) 15.0 (ART without PI) 31.0 (ART with PI)
Li Y	Australia	2000		27.7
Morgan	Uganda	2000	9.4	9.2
Cautinho	Amsterdam	2000	145.2	
Wong	Hongkong	2004		29.8 (pre-HAART) > 70 (HAART)
Hung	Taiwan	2006		6.8 (non HAART) 24.0 (HAART)
Isidore	Cameroon	2009		58.0
Alemu	Ethiopia	2010		26.1
Zhang	China	2010	110.5	9.91
Li DM	China	2010	102.0 - 106.8	14.4 - 24.0
Dou	China	2010	141.6	19.2 (non-ART)

2.8 Anti-retroviral treatment of HIV/AIDS

All AIDS patients were recommended anti-retroviral treatment by The American National Institutes of Health and other organizations. The HAART is a therapy that consists of three or four drugs (WHO, 2006a). Patients receiving this treatment have to consume several medications for the rest of his life. The anti-retroviral treatment is given to decrease the viral load in the blood. This helps to repair the damage caused by HIV. It is recommended to carry out a basic clinical assessment before starting the anti-retroviral treatment. Existing medical conditions such as tuberculosis, hepatitis, IDU, major psychiatric illness, pregnancy and body weight are identified to determine patient's readiness for treatment. A person's CD4 cells count too is used to determine when to start the treatment. Presence of opportunistic infections also had to be considered prior to starting treatment. CD4 cell count is also a major clue in asymptomatic patients. Treatment should be started when the CD4 cell count is 200 to 350 cells/μL (OARAC, 2011). Several other factors such as symptoms, possible adherence, potential toxicity and patient's concern should be considered in this matter (MOH, 2001b). Now generally CD4 less than 350 cells/μL should be offered therapy to HIV-infected patients. All patients with CD4 cell count less than 200 cells/μL and symptomatic HIV or late disease or severe recurrent HIV illnesses or patients with AIDS or tumor at any CD4 count, should start therapy (OARAC, 2011). The recommendation to start anti-retroviral therapy based on WHO guidelines 2006 is summarized in Table 2.3

Table 2.3 Recommendation an anti-retroviral therapy initiation

Clinical Category	CD4 count	Recommendation
Symptomatic AIDS defining illness Severe symptoms*	Any value	Treat
Asymptomatic	< 200 cells/mm^3	Treat
Asymptomatic	> 200 but < 350 cells/mm^3	Treat Recommended

Source: (WHO, 2006a)

Severe symptom* such as: Candidiasis oropharyngeal or Candidiasis vulvovaginal persistent more than 1 month, poorly responsive of treatment, more than 1 episode or involving more than 1 dermatome of Herpes Zoster: Cervical dysplasia, severe or Carcinoma in situ, Constitutional symptoms, example fever (> 38.5˚C) or diarrhea more than one month.

Table 2.4 Anti-retroviral therapy initiation between WHO guidelines in 2006 and 2010

Target population	2010 ART guidelines	2006 ART guidelines
HIV + asymptomatic	< 350 cell/mm^3	< 200 cells/mm^3
HIV + symptomatic	WHO clinical stage 2 if CD4 < 350 cells/µL WHO clinical stage 3 or 4 irrespective of CD4 cell	WHO clinical stage 2 if CD4 < 200 cells/µL WHO clinical stage 3 if CD4 not available WHO clinical stage 4 if CD4 irrespective of CD4 cell Consider treatment for WHO clinical stage 3 and CD4 cell between 200 and 350 cells/µL
HIV + pregnant	CD4 < 350 cell/µL irrespective of CD4 cell or WHO clinical stage 3 or 4 irrespective of CD4 cell	WHO clinical stage 1 or 2 if CD4 < 200 cells/µL WHO clinical stage 3 or 4 if CD4 < 350 cells/µL WHO clinical stage 4 irrespective of CD4 cell
HIV/TB co-infection	Presence of active TB disease, irrespective of CD4 cell	Presence of active TB disease and CD4 ≤ 350 cells/µL ART Initiation can be delayed if CD4 ≥ 200 cells/µL
HIV/HBV co-infection	Individuals who require treatment for their HBV infection*, irrespective of CD4 cell count	No specific recommendation

* The current diagnosis of chronic active hepatitis in well-resourced settings is based on histological parameters obtained by liver biopsy and/or the availability of HBV DNA testing, neither of which is usually available in resource-limited settings. A global definition of chronic active hepatitis in the context of resource-limited settings based on clinical signs and simpler laboratory parameters is under discussion.

2.8.1 Classes of drugs

There are different classes of antiretroviral drugs classified based on different phases of the retroviral life cycle and inhibitors. Anti HIV medications are grouped into six classes and each class of medication blocks the virus in a different way (WHO, 2006a).

1. NRTI (Nucleoside and nucleotide reverse transcriptase inhibitors) inhibit the transcription back in a way incorporated into newly synthesized viral DNA and prevent further elongation
2. NNRTI (Non nucleoside reverse transcriptase inhibitors) inhibit the reverse transcriptase directly by binding to the enzyme and disrupting its function.
3. PI (Protease inhibitors) targets viral assembly by inhibiting the activity of protease, an enzyme used by HIV to bypass nascent proteins for final assembly of new virions.
4. Integrase inhibitors: inhibit the integration of the enzyme, it is responsible for integration of viral DNA into the DNA of infected cells.
5. Entry inhibitors (or fusion inhibitors): disrupt binding, fusion and entry of HIV-1 into host cells by blocking one of several targets.
6. Maturation inhibitors: inhibit the final step in the processing of *gag* in which the virus capsid poly-protein cleaved, thereby blocking the conversion of the poly-protein to the mature capsid protein (p24), because the virus particle has a core defect, which virions released consist mainly of non-infectious particles (WHO, 2006a)

Using a combination of medications from different classes may increase the treatment's effectiveness while decreasing the risk of drug resistance. The approved medication to treat HIV infection fact sheet, lists the food and drug administration (FDA) approved anti HIV medication by class, brand names, generic and date. Some are available as a combination pill of two or more different anti HIV medications from one or more classes (WHO, 2006a)

Guidelines on anti-retroviral treatment have changed from time to time. Anti-retroviral drug were not available before 1987 and only HIV complications were treated then. After the introduction of anti-retroviral drugs, many clinicians agreed that HIV patients with lower CD4 cell counts should be treated (Levine, Dubler, & Levine, 1991). There were a lot of demand for new antiretroviral drugs and the process of drugs transfer from the laboratory to the pharmacy was conducted with strict supervision. Patients demanding anti-retroviral treatment aimed at labeled experiments and in some trials, subjects analyzed their treatment to know whether the drugs given to them were placebos or active ones. Later patients from the study shared active drugs with other patients causing consumption of additional or unapproved drugs. This violates the provisions of the protocol and compromised data validity. Furthermore, some HIV affected groups view the representation in the trials as discrimination rather than protection from risk or exploitation (Ho, 1995). In 1995, several studies added his voice to those who have been demanding "hit hard, hit early" approach with aggressive treatment with multiple drugs early in the course of infection (Harrington & Carpenter, 2000). A small group of vocal doctors (none who virologists) claimed the Concord study provides evidence that early intervention does not improve survival (Kitahata et al., 2009). Contrary to that, current studies have confirmed that mortality rates are almost two times higher when treatment is started until the CD4 count less than 500

compared to more than 500 (Rachlis & Zarowny, 1998). Experts have a consensus that once an antiretroviral therapy is started then it should not be discontinued (OARAC, 2011). This is because incomplete suppression of viral replication in the presence of drug therapy may lead to selective inhibition of more sensitive drugs. This allows the drug resistant strains to become dominant. Consequently, makes it more difficult to treat the infected patients. Finally, now anti-retroviral therapy is offered to all HIV-infected patients who are ready to commit to take medication for the rest of his life (OARAC, 2011)

2.8.2 Initiation of anti-retroviral therapy

The most important issue in HIV treatment is the determination of the optimal time to initiate anti-retroviral. Anti-retroviral treatment can be initiated after an appropriate time of commencement and combination of drugs to be used are decided. It will be influenced by many factors such as prior anti-retroviral history, stage of disease, concomitant therapies and illnesses, ability to tolerate and comply/adhere to certain combinations of drugs, adverse effects of the anti-retroviral agents, affordability and the cost of the regimen. It is very important that we ensure the patient is able to adhere to the anti-retroviral regimen that he is started on. The importance of reducing the development of resistant viral strains and good drug adherence in maintaining viral suppression was highlighted in current studies. Thus antiretroviral therapy should only begin when the patient is committed to long term treatment (WHO, 2006a). The guideline recommends that in developing countries, HIV infected adults and adolescents should start anti-retroviral therapy when one of the following conditions is present and HIV infection has been confirmed.

The WHO guidelines use new criteria to start HAART as below are (Hammer et al., 2008):

- Clinically advanced HIV disease
- Irrespective of the CD4 cell count and WHO stage IV HIV disease
- Consideration of using CD4 cell counts less than 350 cells/µl to assist decision making and WHO stage III disease
- CD4 cell counts less than 200 cells/µl and WHO stage I or II HIV disease

The majority of the current HAART regimens consisting of 3 drugs (2 NRTI + a NNRTI/PI). The first line drug which is used in initial regimens must have low side effects and high efficacy. Treatment guidelines for adult HIV-1 infected patients in the developed countries have been provided by the International AIDS Society (IAS) USA since 1996. The IAS-USA anti-retroviral guidelines therapy was developed by a panel of volunteer experts. The update was published in the Journal of American Medical Association in August 2008 (Hirsch et al., 2008).

The panel recommended initiating treatment before CD4 cell count drop below 350 cells/µl and treatments to be individualized according to the patient's particular situation. It recommends 2 NRTI with an NRTI for initial therapy and a boosted PI or an integration inhibitor. For further treatment, suppression of HIV-1 RNA to below detection level was targeted (Cane et al., 2005). Resistance tests are recommended prior to initiation of treatment. This is important for urgent treatment needs and to handle high rates of baseline resistance in certain countries. Later the chosen treatment regimen can be started and adjusted further based on resistance test. In Britain, there are 11.8 per cent of moderate to high level of resistance at baseline to a combination of Efavirenz +

Zidovudine + Lamivudine and 6.4 per cent for medium to high level resistance to Stavudine + Lamivudine + Nevirapine (Althoff et al., 2010)

The major guideline panels have raised the CD4 count threshold for recommended initiation of anti-retroviral therapy. In December 2009, the panel of the Department of Health and Human Services (DHHS) gave the strongest recommendation possible for initiation anti-retroviral therapy at less than 350 cells/µL. It is recommended for persons with CD4 level between 350 and 500 cells/µL. Opinion was divided on the strength of the recommendation, where 55 percent of the members gave strong recommendation and 45 percent gave a moderate one. For patients with CD4 more than 500 cells/µL, half of the panel gave a moderate recommendation and half thought it was optional (DHHS, 2009).

In early 2010, the European AIDS Clinical Society (EACS) guidelines issued HIV-infected patients with CD4 count 350 to 500 cells/µL concluded treatment should be considered if there is a viral load of more than 100,000 copies/ml, if CD4 declines to more than 50-100 cells/µL per year, age more than 50 years, high cardiovascular risk and malignancy. For patients with CD4 having more than 500 cells/µL, deferred anti-retroviral therapy. Treatment can be offered if presence of co-morbid condition or patients seeking and ready for anti-retroviral therapy (European AIDS Clinical Society, 2010)

In July 2010, the panel of the International AIDS Society (IAS) in USA, issued a DHHS recommended anti-retroviral for all HIV-infected patients with CD4 count up to 500 cells/µL. For those above 500 cells/µL recommended for those losing CD4 more than

100 cells/µL per year, viral load more than 100,000 and age more than 60 years (Thompson et al., 2010)

WHO in July 2010, updated the WHO 2006 guidelines and used new Grading of Recommendation Assessment Development and Evaluation (GRADE) to classify the quality of evidence for the recommendation. WHO gave a strong recommendation based on moderate evidence to treat all HIV-infected patients with CD4 less than 350 cells/µL. This implication is difficult in poor countries for those previously anti-retroviral therapy initiation with CD4 less than 200 cells/µL. For those with CD4 more than 350 cells/µL, WHO guidelines no have recommendations (WHO, 2010a)

2.8.3 Switch second line anti-retroviral therapy

Second line HAART regimes are indicated for patients who are forced to discontinue their initial treatment regime as consequence of treatment failure or severe toxicity.

The recommendation of WHO (2010) when to switch ART is based on:

1. Where available, use viral load to confirm treatment failure;
2. Where routinely available, use viral load every 6 months to detect viral replication;
3. A persistent viral load more than 5000 copies/ml confirms treatment failure;
4. When VL is not available, use immunological criteria to confirm clinical failure;

Anti-retroviral therapy switching criteria (WHO, 2010a):

1. Clinical failure : new or recurrent stage 4 condition (condition must be differentiated from an immune reconstitution inflammatory syndrome/IRIS; certain WHO clinical stage 3 conditions (PTB, severe bacterial infection) may be an indication of treatment failure;
2. Immunological failure: - Fall or immunological to baseline or below;
   - 50 per cent fall from on treatment peak value;
   - Persistent CD4 level below 100 cells/µL;
3. Virological failure: viral load of more than 5000 copies/ml, the optimal viral load threshold for defining viral load failure has not been determined. Values of viral load which are more than 5000 copies/ml are associated with clinical progression and a decline in the CD4 cell count.

The targeted viral load strategy for failure and switching anti-retroviral therapy is displayed in Figure 2.13

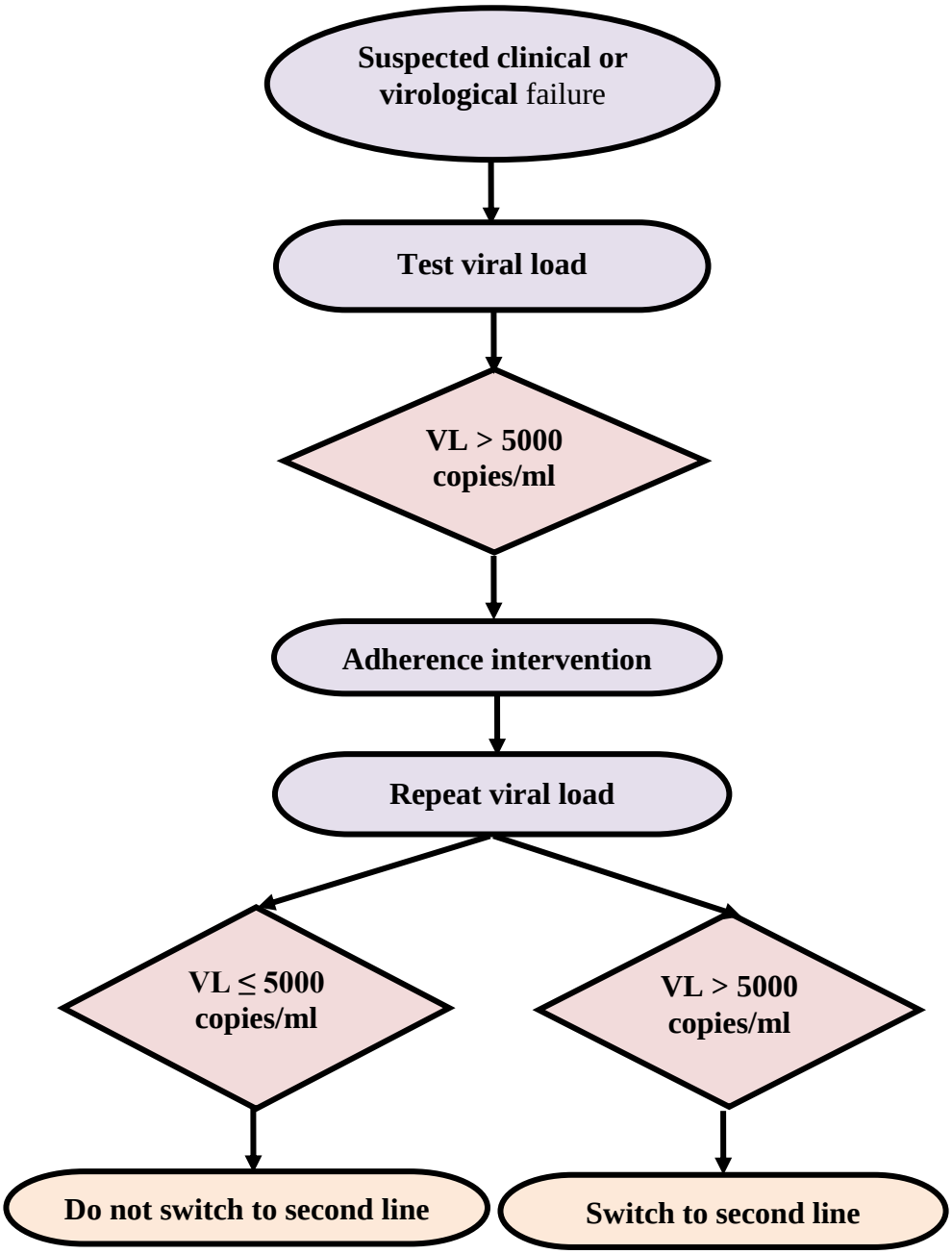


Figure 2.13 Targeted viral load strategy for failure switching

2.8.4 Pre HAART and HAART era

Pre HAART era started in early 1997 where there was limited usage of anti-retroviral drug on HIV-infected patients. Consequently, during the HAART era (1997 onwards), a combination of anti-retroviral drugs (triple therapy) have been introduced (Egger et al., 1997). Anti-retroviral therapy has reduced morbidity and mortality rate of patients with HIV infection (Palella et al., 1998). HIV-infected patients who received the combination therapy for 1 year in short-term randomized controlled trials showed that the rate of AIDS or death were halved as compared to patients who used only one class of antiretroviral drugs (Egger, et al., 1997). In the long term trial the clinical effect of combination therapy has not been studied but observational data showed that this treatment reduces the AIDS or death rate for many years. This applies to patient both with low or high CD4 cell count (Egger, et al., 1997; Palella, et al., 1998). The risk of death after AIDS HR of 1.54 (95% CI 1.17, 2.04) for mono therapy, HR of 0.61 (95% CI 0.46, 0.80) for double therapy and HR of 0.36 (95% CI 0.21, 0.62) for triple therapy as compared with no therapy (Pezzotti, et al., 1999). Injecting drug user had a lower risk of progression to AIDS than MSM with HR of 0.74 (95% CI 0.64, 0.86) in the pre HAART (1997-1998) as compared to HR of 4.28 (95% CI 2.86, 6.41) in the HAART era (1999-2001) (Porter, et al., 2003).

The crude mortality rate declined from 117 deaths in 1,000 people in pre HAART (1984-1996) to 24 deaths of 1,000 people in HAART period (1997- 2003). AIDS related death reduced from 90 per cent in a pre HAART era to 67 per cent in the HAART era. Cause of death related AIDS, such as PCP, Non Hodgkin Lymphoma (NHL) and MAC. Cause of death in non-related AIDS increased from 10 per cent in a pre HAART era to 33 per cent in HAART era such cardiovascular disease, hepatic

disease and drug overdose (Krentz, Kliewer, & Gill, 2005). The crude mortality rate also dropped from level of 10.8-30.4 per 100 midyear patient population in pre HAART to level of 0.8-6.9 per 100 midyear population in the HAART era and death rate in pre HAART 9.2 events/ 1000 person-months compare in HAART era 2.4 events/ 1000 person-months (Chan, Wong, & Lee, 2006). Incidence of AIDS defining event (ADE) in period pre HAART era (1990-1995) compared to period HAART era (1996-2004) with CD4 level less than 50 cells/µL 39.3 events/ 100 person years in period HAART era and 76.4 events/ 100 person years in period pre HAART era, CD4 level less than100 cells/µL 18 events/ 100 person years in period HAART and 65.2 events/ 100 person years in period pre HAART era, CD4 of 100- 200 cells/µL 7.8 events/ 100 person years in period HAART era and 34.5 events/ 100 person years in period pre HAART era (Gandhi, Wei, Amin, & Kazanjian, 2006). The incidence of opportunistic infections in pre HAART era period higher than the HAART era period in all levels of CD4 count, it is summarized in Table 2.5. Risk opportunistic infection with CD4 less than 200 cells/µL prior to HAART initiation HR of 4.45 (95% CI 1.80, 10.90) for 1-12 month, HR of 3.95 (95%t CI 1.62, 9.63) for 13-24 month, HR 5.19 (95% CI 1.99, 13.5) for 25-36 month, HR 3.21 (95% CI 1.61, 10.8) for 37-48 month HAART. Viral load more than 50000 copies/ml prior to HAART initiation HR of 3.77 (95% CI 1.68, 8.43) for 1-12 month, HR of 2.78 (95% CI 1.04, 7.39) for 13-24 month, HR of 2.89 (95% CI 1.80, 5.51) for 25-36 month HAART (Kazanjian, Wei, Brown, Gandhi, & Amin, 2005)

Table 2.5 The incidence of AIDS defining events in the pre HAART era and HAART era

CD4 count (cells/µL)	Pre HAART era (1990-1995)	HAART era (1996-2004)
< 50	74.4/100 person years	39.3/100 person years
< 100	65.2/100 person years	18/100 person years
100 – 200	34.5/100 person years	7.8/100 person years

Source : (Gandhi, et al., 2006)

Proportion of patients receiving combination antiretroviral with Protease Inhibitor (PI) to progressed AIDS or death was 6 per cent in PI contained regimen. In the regimen without PI progression was 11 per cent with HR of 0.50 (95% CI 0.33, 0.76). The mortality in the two groups was 1.4 per cent and 3.1 per cent respectively, with HR of 0.43 (95% CI 0.19, 0.99). Thirty one AIDS defining event occurred among patients with Indinavir and 60 events among those without Indinavir (Hammer et al., 1997). Initiation of boosted PI had 21 per cent of decrease in the likelihood of viral suppression compared to initiation of NNRTI with HR of 0.79 (95% CI 0.75, 0.83) (Althoff, et al., 2010)

Increased risk of disease progression associated with gender factor showed lower survival among women as compared to men. Hazard Ratio of males in early 1997 was 0.51 (95% CI 0.39, 0.66) and females HR of 0.80 (95% CI 0.51, 1.27) (Porta, et al., 1999). Women with CD4 less than 200 cells/µL as compared to women with CD4 more than 350 cells/µL, risk of all causes of death was HR of 2.66 (95% CI 1.42, 4.99) and risk of AIDS death was HR of 47.61 (95% CI 5.69, 398.40) (Anastos, et al., 2004). Prior to HAART initiation, HIV-infected patients with CD4 less than 200 cells/µL have AIDS progression with HR of 2.25 (95% CI 1.13, 4.49) and death with HR of 2.29 (95% CI 0.83, 6.33) (Jacobson, et al., 2002).

2.9 Viral load less than 50 copies/ml

The goal of anti-retroviral treatment in HIV patients is to limit viral replication, slow the progression of HIV disease and increase the level of CD4 cell count. Viral replication is measured by the level of HIV viral load and the effectiveness of ART in reducing HIV viral load. Quantification of viral load is a sensitive indicator of the effectiveness of HAART. Successful HAART is generally defined as suppression of viral load to below 50 copies/ml (Jevtović et al., 2010). The median time taken from initiation of HAART to achieving viral load less than 50 copies/ml was 0.99 years (Taiwo et al., 2009a) and 6.4 months (Resino et al., 2003). After the initiation of HAART, the decrease of viral load (less than 50 copies/ml) was observed in varying periods of time in all 118 subjects studied, time to reach it was between 2 to 24 weeks (Rizzardi et al., 2000). In the UK study which reported the median time from start of HAART to first achieved viral load than 50 copies/ml stratified by regimen of 2 NRTI + 1 NNRTI was 0.3 years (3.6 months) (Geretti et al., 2008). After the implementation of HAART the risk of AIDS and death in HIV-infected patients with low CD4 cells count showed that patients with CD4 count less than 200 cells/μL as compared to more than 350 cells/μL, have a higher risk of attaining AIDS with HR of 5.96 (95% CI 0.40, 87.8) and CD4 cells of 201-350 cells/μL with HR of 5.44 (95% CI 0.47, 63.4). The risk of death at CD4 cells count was less than 200 cells/μL attained HR of 22.8 (95% CI 1.89, 275) and the range of CD4 cells 201-350 cells/μL, HR of 10.8 (95% CI 0.92, 127) (Taiwo, et al., 2009a). The study showed that after 24 weeks of HAART initiation, 482 (73 per cent) of HIV-infected patients achieved viral load less than 50 copies/ml. Use of viral load measured after 4 Weeks of HAART to predict virology outcome at 24 weeks for HIV-infected patients in univariate analysis showed that baseline viral load with HR of 0.76 (95% CI 0.60, 0.96) and in multivariate analysis was viral load at 4 weeks with HR of 0.35 (95% CI 0.27, 0.45) (Smith, et al., 2004). A cohort study on risk factors of poor virological conditions in a workplace was

conducted for 12 months in South Africa. An anti-retroviral therapy program showed that a viral load in a range of 10,000-100,000 copies/ml was attained with HR of 3.63 (95% CI 1.88, 7.00), and when it exceeds 100,000 copies/ml the HR of 3.54 (95% CI 1.79, 7.00) (Fielding et al., 2008). An observational cohort study showed that there is an extensive virological failure to three original antiretroviral drug classes over long term follow up from the initiation of HIV therapy. A result of cohort study, 167 of 27,441 patients that follow up developed extensive triple class failure, 129 (77 per cent) of those who developed extensive triple class failure had a viral load of less than 50 copies/ml, previously (Phillips et al., 2007).

2.10 Summary

In this chapter, it is all about HIV infection such as its natural history, epidemiology, transmission, progression, survival and anti-retroviral therapy were reviewed and many evidences of research that have been done in various places in both developed countries and developing countries. The evidence from literature review showed that varies median survival time of HIV-infected patients and there are many predictors influenced the progression of HIV infected to AIDS and death, for example CD4 level, viral load, hemoglobin, total lymphocyte count, opportunistic infection, transmission route, gender differences, advanced age and socioeconomic status. HIV infected individual receiving anti-retroviral therapy based on WHO guidelines with recommendations for initiation of HAART and switch to second line criteria. Many evidences of antiretroviral therapy in HIV-infected patients can decrease morbidity, mortality, prolong survival in both developed and developing countries.

CHAPTER 3

MATERIALS AND METHODS

3.1 Introduction

The materials and methods used in this study are described in this chapter. Section 3.1 is the introduction. Section 3.2 describes the design utilized in this study. The descriptions are continued in Section 3.3 the study area/site and the duration of this study are described in Section 3.4. The study population is stated in Section 3.5 and the following Section 3.6 describes the setting of this study, while Section 3.7 is on the ethical approval was from the Medical Ethics Committee University of Malaya Medical Centre. The calculation of sample size is explained in Section 3.8. In Section 3.9 the sampling procedures are discussed. Section 3.10 describes the study variables, namely the independent and dependent variables. Section 3.11 explains the operational definition of variables. Section 3.12 and 3.13 presents the data collection method and data management, followed by Section 3.14 which is the summary of this chapter.

3.2 Study Design

This is a cohort study (retrospective and prospective). The study commenced in 2007, with records of patients being investigated retrospectively in 1986 and followed prospectively until 2009. Data from medical records of HIV patients (alive and deceased) was seen at the Infectious Disease (ID) Clinic, University of Malaya Medical Centre (UMMC) starting from January 1986 to December 2006 and were recorded. New HIV/AIDS cases from January 2007 to December 2009 were also included in this study and followed up to December 2009 (see Figure 3.1)

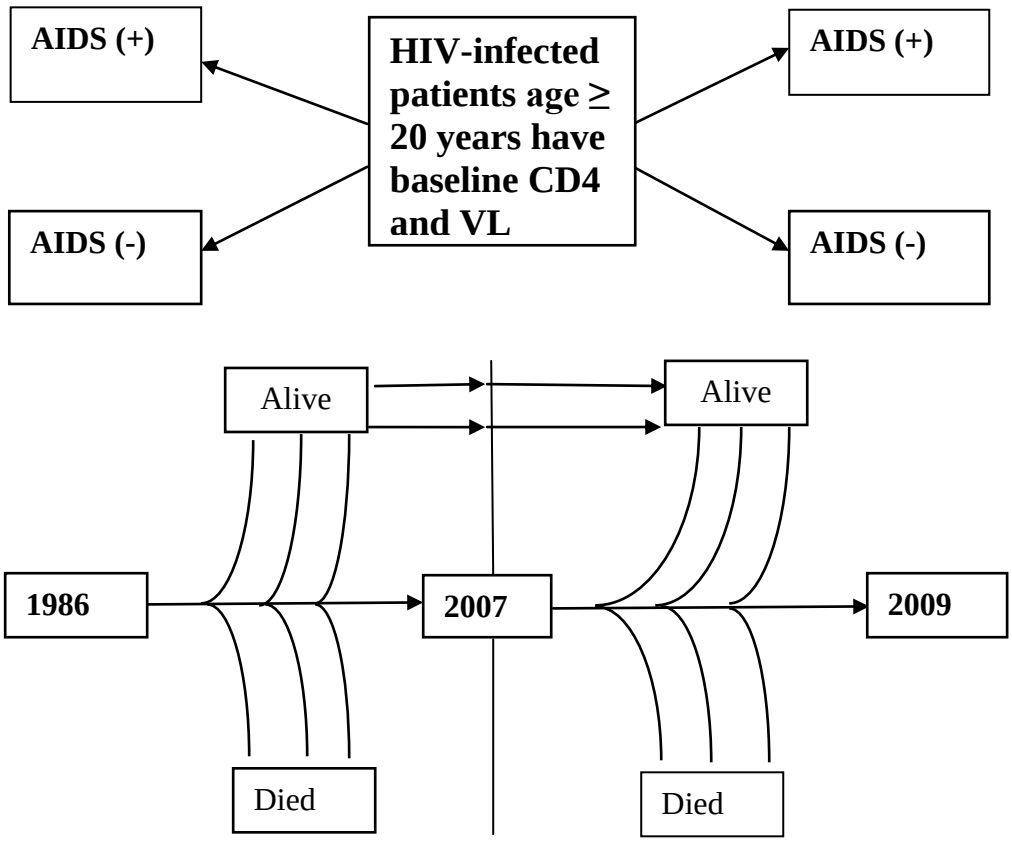


Figure 3.1 Study design cohort retrospective and prospective

The cohort study design is the second best method of measuring the anti-retroviral treatment effectiveness on disease progression (Evans, 2003). The cohort study assesses associations between multiple exposures and outcomes over time while the randomized controlled trial demonstrates efficacy of an intervention (Carlson & Morrison, 2009). The hierarchy of study design in clinical research is summarized in Figure 3.2

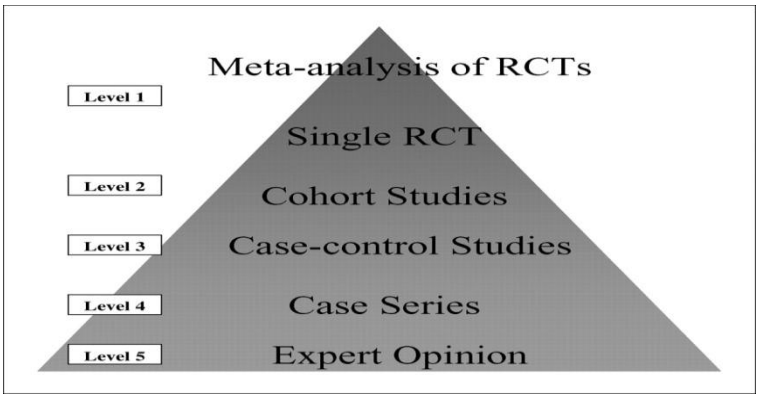


Figure 3.2 Hierarchy of study design in clinical research
Source: (Evans, 2003)

3.3 Study Area/Site

This research was conducted at the Infectious Disease clinic (ID clinic), Department of Medicine in the University of Malaya Medical Centre in Petaling Jaya, which is an industrial area and a satellite township of Kuala Lumpur, located in the Petaling district of Selangor. It comprises mostly residential areas. It has an area of 97.2 km^2 with a population of 480,000 in 2012 (MBPJ, 2012).

University of Malaya Medical Centre is part of the University of Malaya and comprises two major components. One part is the medical centre, which comprises the main hospital building, the east wing and the trauma centre. The other part is the Faculty of Medicine, which is a building of its own in the south part of the medical centre. It is the

premier teaching hospital in Malaysia. It is the major training centre for various medical specialties and subspecialties**.** It is a modern medical facility with over 1,200 inpatient beds and function as a tertiary referral hospital in the Klang Valley and Malaysia. The Klang Valley stretches from Klang to Seremban. It is also the centre of industry and commerce in Malaysia and is also known as Greater Kuala Lumpur or Kuala Lumpur metropolitan area (MBPJ, 2012). It is geographically delineated on the north and east of the Titiwangsa Mountain Range and in the west by the Straits of Malacca. It covers an area of 2,793.27 km^2. The conurbation has a total population of 6.8 million in 2012 (MBPJ, 2012).

The Infectious Disease Clinic at the University of Malaya Medical Centre provides treatment and follow-up for HIV/AIDS patients who are referred from all private clinics, government hospitals, infectious disease consultants, specialists and medical officers in the Klang Valley and other parts of Malaysia. The Clinic is open on Monday, Tuesday and Friday from 8.00 am to 12.00 pm. At the infectious disease clinic the patients are treated and consulted by four doctors who are Infectious Disease Specialists and Consultants. An average of 25-30 patients were attended in the clinic in a day. The clinic facilitated with more than 20 beds for admitting HIV/AIDS patients. These beds are located in the rooms of *Wad Perubatan 1* (WP1) and *Wad Perubatan 2* (WP2) at level 2 of the University of Malaya Medical Centre building. The location map of Petaling Jaya and the University of Malaya Medical Centre is shown in Figure 3.3

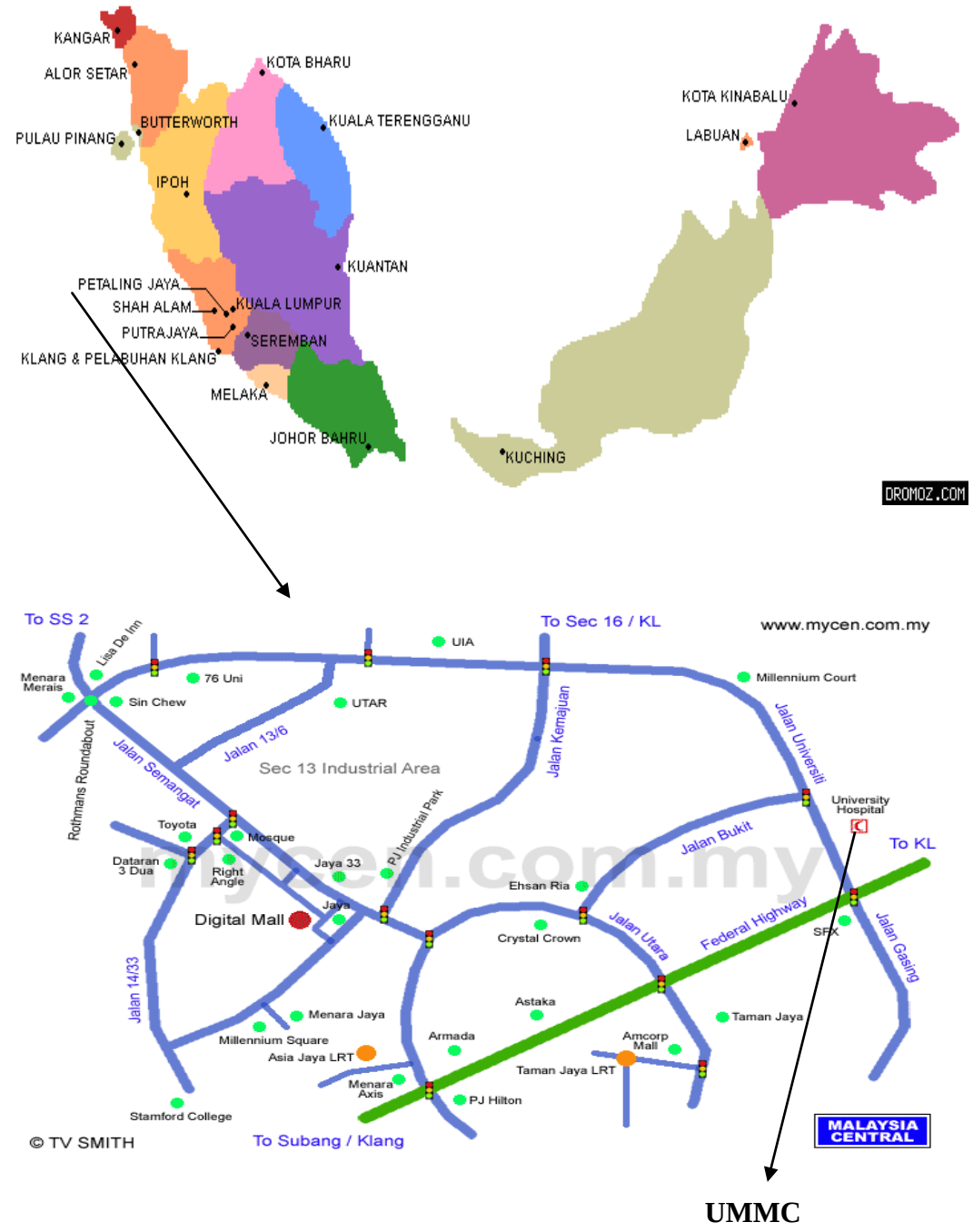


Figure 3.3. Map of Malaysia with location of Petaling Jaya and UMMC

Source: **www.dromoz.com (map of Malaysia)**

www.tvsmith.com (map of Petaling Jaya)

3.4 Study Duration

The data collection began on January 2007 until December 2009 (3 years prospective). Records of patients treated or consulted from December 2006 until January 1986 (20 year retrospective) were also extracted.

3.5 Study Population

The study population was HIV-infected patients who visited the infectious disease clinic at the University of Malaya Medical Centre from 1986 to 2009 for the first time, walk in, follow up cases or those HIV cases referred from other clinics

Inclusion criteria

i) Patients diagnosed as HIV positive using ELISA (enzyme-linked immunosorbent assay) methods and PA (particle agglutination) test,

ii) Adults aged twenty years old and above

Exclusion criteria

The exclusion criteria were HIV infected patients who had missing baseline CD4 count and viral load data

3.6 Study Setting

This cohort study focused on predictors of death and to achieve viral load less than 50 copies/ml. Data of HIV-infected patients consisted of the socio-demographic characteristic at baseline and laboratory and clinical condition of patients at baseline and at start of anti-retroviral therapy. The anti-retroviral therapy efficacy was based on the ability to achieve viral load less than 50 copies/ml.

3.7 Ethical Approval

Ethical approval was obtained from the hospital Medical Ethics Committee University of Malaya Medical Centre, which is an Independent Review Board (IRB), detail are found in Appendix B.

3.8 Sample size

The sample size was calculated by using the formula below (Rosner, 2000):

$$n = \frac{[z_\alpha \sqrt{2P(1-P_1)} + z_\beta \sqrt{P_1(1-P_1) + P_0(1-P_0)}]^2}{(P_1 - P_0)^2}$$

n = required sample size

z_α = value of the standard normal distribution cutting off probability α in one tail for a one sided alternative or α/2 in each tail for a two sided alternative

z_β = value of the standard normal distribution cutting of probability β

P_0 = estimated proportion of study outcome in the unexposed group

P_1 = estimated proportion of study outcome in the exposed group, based on literature review (Cole, 2003) risk of death after AIDS with HR 0.81 for HAART as compared with no HAART (Pezzotti, et al., 1999). In this study used values are:

z_α = 1.96 for α = 0.05; z_β = 0.80 to 80% power; P_0 = 0.19; P_1 = 0.81

$$P = \frac{P_1 + P_0}{2} = 0.5$$

n1 = n2 = 438. Assuming 20 per cent missing data due to death or loss of follow-up with an alpha of 0.05 and power of 0.80, the minimum sample size = n1 + n2 + 20% = 876 + 175 = 1050

Other approaches of calculating sample size based on survival time are (Rosner, 2000):

1. Two median survival time option
2. Median survival time on control patients and hazard ratio of the control group to experimental group option

The sample size was calculated by the Power and Sample size calculations software (PS) version 3.0.43 (Dupont & Plummer, 2009). In this study approaches of calculating sample size based on median survival time on control patients and hazard ratio of the control group in the experimental group option was used

n = sample size; Power (1- β) = 0.8; Significance level (α) = 0.05

R = the hazard ratio of control relative to experimental treatment was determined by clinical expert opinion as obtained from the literature (Cole et al., 2003); R = 0.81

m_1 = median survival time of patients in control group relative to patients with HAART have median survival was 27.7 months (Li, et al., 2000); m_1 = 27.7 months

m = ratio of control to experimental patients (comparing one case and one control), m = 1:1.

A = the accrual time during which patients were recruited, A = 36 months

F= additional follow-up time after end of recruitment, F = 3 months

Table 3.1 Sample size calculation

Hazard ratio / **Median survival**	**0.6**	**0.68**	**0.79**	**0.81**	**0.85**
24 months	121	219	610	769	1312
26.1 months	128	231	645	814	1389
27.7 months	133	240	672	**848**	1447
31 months	143	260	728	918	1569
70 months	270	495	1398	1767	3027

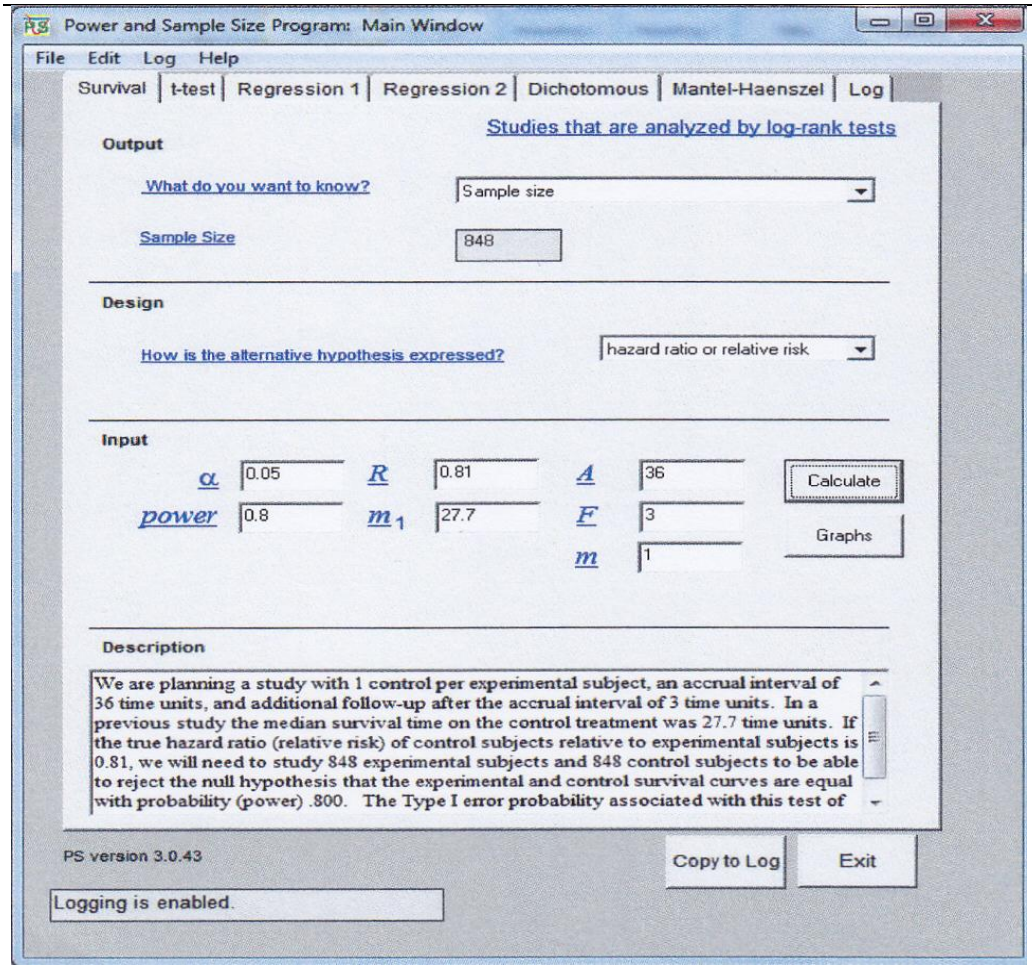


Figure 3.4 Sample size by software of Power and Sample size calculation

Considering an estimated 20 per cent of missing data/loss to follow up an additional 20 per cent was added. The computed sample size was 848 (Figure 3.4), total sample size is n + 20% n = 848 + 170 = 1018. The sample size for this study was 1314 patients, which is more than the minimum required sample size.

3.9 Sampling procedure

In this study, the study population is divided into three groups:

- All AIDS patients

- AIDS patients receiving HAART

- AIDS patients not receiving anti-retroviral therapy

This information was obtained from the patient's case notes available in the medical record folder. Follow up data of AIDS patients regarding the laboratory result such as CD4, viral load, hemoglobin, total lymphocyte count and liver function test, the incidence of opportunistic infection and a combination of anti-retroviral drugs were done every three months. Informed consent of participant was not required because this study used secondary data from University of Malaya Medical Centre and ethical approval also stated that the researcher would not be required to obtain the participant's informed consent when secondary data is collected. This rule is similar to those used elsewhere developed country (University of South Florida, 2008). All data from this hospital is available for the research. The ethical approval included approval to check the mortality status of the patients using mortality data from the National Registration Department.

3.10 Study Variables

3.10.1 Independent Variables are

A. Socio-demographic characteristics which include:

- Age at first diagnosis of HIV: categorized into five age groups with 10 years interval: 20-29, 30-39, 40-49, 50-59 and ≥ 60 years
- Gender : male or female
- Ethnic group : Malay, Chinese, Indians, Others
- Marital status : single, married, others
- Educational level : ≤ secondary, ≥ tertiary
- Occupational type: unemployed, manual workers, professional and non manual workers
- Monthly personal income : < RM 1000, RM 1000 – RM 3000, > RM 3000

B. Baseline laboratory which includes:

- Baseline CD4 count (cells/µL): categorized into 2 groups: < 200 and ≥ 200 cell/µL
- Baseline Viral load (copies/ml): categorized into 2 groups: < 100000 and ≥ 100000 copies/ml
- Baseline Hemoglobin (Hb g/dl): categorized into 2 groups: < 12 and ≥ 12 g/dl
- Baseline total lymphocyte count (TLC cells/µL): categorized into 2 groups: normal (≥ 1200 cell/µL) and abnormal (< 1200 cells/µL)Baseline liver function test (LFT): categorized into 2 groups: normal and abnormal; LFT based on 5 tests such as aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP), transaminase bilirubin (Tbil) and gamma globulin

  Liver function is considered normal if all the five liver enzymes examined falls within normal range. Liver function is said to be abnormal if at least two of the enzymes appears to have twice the normal value
- CD4 at the start of HAART: categorized into 2 groups: < 200 and ≥ 200 cell/µL
- Viral load at start of HAART: categorized into 2 groups: < 100,000 and ≥ 100,000 copies/ml
- Hemoglobin at the start of HAART: categorized into 2 groups: < 12 and ≥ 12 g/dl
- Total lymphocyte count (TLC) at the start of HAART: categorized into 2 groups: normal (≥ 1,200 cells/µL) and abnormal (< 1,200 cells/µL)
- Liver function test (LFT) at the start of HAART: categorized into 2 groups: normal and abnormal
- CD4 recovers: CD4 recovers from less than 200 more than 200 cells/µL; categorized into 3 groups: yes, stable, no
- Hemoglobin recovers: Hemoglobin recovers from less than 12 and more than 12 g/dl; categorized into 3 groups: yes, stable, no

- Total lymphocyte count recovers: Total lymphocyte recovers from (less than 1,200 to more than 1,200 cells/μL; categorized into 3 groups: yes, stable, no

C. Clinical condition variables which include:

- Exposure risk: heterosexual, homosexual, injection drug user (IDU) and others
- WHO Clinical stage: stage 1, stage 2, stage 3 and stage 4 (WHO, 2007c)
- Initial presentation: already diagnosed with HIV or AIDS on presentation to the clinic
- Baseline Body Mass Index (BMI): categorized into 2 groups: < 18.5 and ≥ 18.5
- Clinical presentation at the end of the study: categorized into 2 status: HIV or AIDS
- Opportunistic infection (OI): negative or positive
- Number of opportunistic infections: how many OI occurred in HIV-infected patients, categorized into 4 groups, 0, 1, 2 and ≥ 3
- Living status: categorized into 2 groups: alive or died

D. Anti-retroviral treatment variables which include:

- ART era: categorized into 2 groups: Pre HAART era and HAART era
- Initial HAART: categorized into 3 groups: 2 NRTI + EFV, 2 NRTI +NPV and 2 NRTI + PI
- Need a second line of HAART: categorized into 2 groups: yes or no
- Combination of HAART at the end of study: categorized into 2 groups: ART without PI and ART with PI
- Achieved viral load less than 50 copies/ml: categorized into 2 groups: yes or no

3.10.2 The dependent variables

The dependent variables are the outcomes that will be measured which included:

- Survival time of HIV-infected patients

- Time to death in all AIDS patients

- Time to death in AIDS patients on HAART

- Time to death in AIDS patients not on ART

- Time to achieve viral load less than 50 copies/ml in AIDS patients on HAART

3.11 Operational definition of variables

No	Variable	Definition	Scale of Measurement
1	Age at HIV diagnosis	Patient's age (calculated from the date of HIV diagnosis minus the date of birth) in year	Continuous: mean, median Categorical: 1 = 20 - 29 years 2 = 30 - 39 years 3 = 40 - 49 years 4 = 50 - 59 years 5 = ≥ 60 years
2	Gender	Sex as stated by patients	Categorical: 1 = Male 2 = Female
3	Ethnicity	Ethnic group as stated by patients	Categorical: 1 = Malay 2 = Chinese 3 = Indian 4 = Others
4	Marital status	Status of marital as stated by patients	Categorical: 1 = Single 2 = Married 3 = Others (Divorced, Separated, Widowed)
5	Educational level	The complete highest level of formal education of the respondent according to Malaysian education system(Mohe, 2010) Primary: Standard 1 to Standard 6 Secondary: Awarded SRP/PMR/LCE and SPM/ MCE/O Level (Form 1 – 5). Tertiary: University, institute and college (Awarded, Diploma or Bachelor degree or Post Graduate Degree).	Categorical: 1 = ≤ Secondary 2 = ≥ Tertiary
6	Occupational type at the time of diagnosis	As written in the record and it was created into 3 groups: Group 1: Housewife, student, retired and person not having an earning income job	Categorical: 1 = Unemployed 2 = Manual workers 3 = Professional and non-manual workers

		Group 2: Manual skilled workers, intermediate and unskilled workers (Labour, maid, technician, etc) Group3: Upper and middle intermediate high, Doctor, accountant, supervisor, etc	
7	Monthly income	Total income of patients per month	Categorical: 1 = < RM 1 000 2 = RM 1 000 to 3 000 3 = > RM 3000
8	Baseline CD4 count	The first CD4 count of patients after HIV diagnosis	Continuous: Mean, Median Categorical: 0 = < 200 cells/µL 1 = ≥ 200 cells/µL
9	Baseline Viral Load (VL)	The first plasma HIV viral load of patients after HIV diagnosis	Continuous: Mean, Median Categorical: 0 = < 100,000 copies/ml 1 = ≥ 100,000 copies/ml
10	Baseline Haemoglobin (Hb)	The first Haemoglobin level of patients after HIV diagnosis	Continuous: Mean, Median Categorical: 0 = < 12 g/dl 1 = ≥ 12 g/dl
11	Baseline total lymphocyte count (TLC)	The first total lymphocyte count of patients after HIV diagnosis	Continuous: Mean, Median Categorical: 0 = normal (≥ 1,200 cells/µL) 1 = Abnormal (< 1,200 cells/µL)
12	Baseline liver function test (LFT)	The first liver function test of patients after HIV diagnosis. LFT based on tests(Collier & Bassendine, 2002): Aspartate transaminase (AST), Alanine transaminase (ALT), Alkali phosphatase (AP), transaminase bilirubin (Tbil) and Gamma globulin. LFT normal if all tests in normal value range. LFT abnormal if at least 2 of the test have twice the normal value	Categorical: 0 = Normal 1 = Abnormal

13	CD4 count at start HAART	The CD4 count of patients when start HAART	Continuous: Mean, Median Categorical: 0 = < 200 cell/µL 1 = ≥ 200 cell/µL
14	VL at start HAART	The plasma HIV viral load of patients when start HAART	Continuous: Mean, Median Categorical: 0 = < 100,000 copies/ml 1 = ≥ 100,000 copies/ml
15	Hb at start HAART	The haemoglobin level of patients when start HAART	Continuous: Mean, Median Categorical: 0 = < 12 g/dl 1 = ≥ 12 g/dl
16	TLC at start HAART	The total lymphocyte count of patients when start HAART	Continuous: Mean, Median Categorical: 0 = normal (≥ 1,200 cells/µL) 1 = Abnormal (< 1,200 cells/µL)
17	LFT at start HAART	The liver function test of patients when start HAART	Categorical: 0 = Normal 1 = Abnormal
18	CD4 recovers	CD4 count recovers from < 200 to ≥ 200 cell/µL	Categorical: 0 = No 1 = Stable 2 = Yes
19	Hb recovers	Hb level recovers from < 12 to ≥ 12 g/dl	Categorical: 0 = No 1 = Stable 2 = Yes
20	TLC recovers	Total lymphocyte count recovers from abnormal to normal (< 1,200 to ≥ 1200 cells/µL)	Categorical: 0 = No 1 = Stable 2 = Yes
11	Initial Presentation	The status of patients when first coming to ID Clinic in UMMC	Categorical : 0 = HIV 1 = AIDS
22	Exposure risk	The transmission route of HIV infection	Categorical: 1 = Heterosexual 2 = Homosexual 3 = IDU 4 = Others

23	WHO Clinical Staging	The WHO clinical staging and case definition of HIV for resourced constrained settings in 1990 and revised in 2006 (WHO, 2007c)	Categorical: 1 = Stage 1 2 = Stage 2 3 = Stage 3 4 = Stage 4
24	Baseline Body Mass Index (BMI)	The first measure of patient's weight in relation to height after HIV diagnosis	Continous: Mean, Median Categorical: 0 = < 18.5 1 = ≥ 18.5
25	BMI at start HAART	The Body Mass Index of patients when start HAART	Continous: Mean, Median Categorical: 0 = < 18.5 1 = ≥ 18.5
26	Opportunistic Infection (OI)	Infections caused by a microorganism that does not normally in humans, such as TB, PCP, Candidiasis, and other infections, occurs in AIDS patients	Categorical: 0 = Negative 1 = Positive
27	Number of OI	How many OI occurs in AIDS patients	Categorical: 0 = 0 1 = 1 2 = 2 3 = ≥ 3
28	ART era	The time period of receiving ART, who received ART before 1997 is called Pre HAART era and from 1997 and above is HAART era	Categorical: 0 = Pre HAART era 1 = HAART era
29	Initial HAART	Initial combination of HAART (Highly Active Anti-Retroviral Therapy)	Categorical: 1 = 2 NRTI + EFV 2 = 2 NRTI + PI 3 = 2 NRTI+ NPV
30	Need second line of HAART	Need or no need to switch second line of HAART	Categorical: 0 = No 1 = Yes
31	HAART at the end of study	Combination of HAART at the end of study	Categorical: 0 = HAART without PI 1 = HAART with PI
32	Achieve VL ≤ 50 copies/ml	AIDS patients undergoing HAART and achieve VL ≤ 50 copies/ml	Categorical: 0 = No 1 = Yes

3.12 Data collection

3.12.1 Medical record

The first step of the data collection was to trace the registration numbers (RN) and names of the patients in the registration book of HIV patients at the Medical Records Department. After identifying the HIV patients the names and the respective registration numbers were listed in a special form and passed to the staff of medical records. After 3 to 5 days the medical records staff would provide the patients' folders and compact disk (CD). The folder's cover is coloured red pink for deceased patients and yellow for patients who are still alive. Data is also stored on CD especially for patients registered before 2007. The data stored on the CD can be retrieved using a special personal computer located at the Medical Records Department. All information about deceased patients is stored on the CD. Copying the CD was not permitted. A maximum of 20 patient folders can be retrieved and examined per day. The patient folders were not allowed to be taken out from the medical record room. The Medical Records office is open from 8.00 am to 5.00 pm. During public holidays and weekends, the time to collect data is from 8.00 am until 4.00 pm. In the patients' folder the blue form indicates that the patient has been notified as a case of notifiable disease. Patient's information pertaining to socio-demographic variables such as identification number, name, address, date of birth, age, sex, ethnicity, occupational type, date of HIV diagnosis, AIDS date, partner notification and date of death were retrieved from the blue form.

3.12.2 Laboratory data

The laboratory data such as baseline CD4 and viral load were also obtained from the patients' folders. The blood test was done twice. First time, the blood sample was obtained to calculate the viral load using Amplicor reverse transcription polymerase chain reaction (RT-PCR). Simultaneously, the particle agglutination (PA) test was done for detecting HIV Ag/Ab Combo (Architect) and anti HIV ½ antibody (Axsym), reactive HIV ½ rapid test and reactive HIV ½ particle Agglutination reactive are used. The second time, the blood sample was sent in 2 ethylenediamine tetra-acetic acid (EDTA) tubes to calculate the viral load using Cobas Taqman HIV-1 tests for confirmation. All these tests were done in the Microbiology laboratory in the University of Malaya Medical Centre. During follow up, if the blood test results were not in the patient records folder, the blood samples were taken 3 months later to obtain the viral load and CD4 count.

3.12.3 Pharmacy data

Information pertaining to anti-retroviral drugs administered to the patients was retrieved from the patients' medical record folders. The data was cross-checked with the University of Malaya Medical Centre Pharmacy to verify their anti-retroviral treatment for the patients that were undergoing follow-up. An approval letter from the Supervisor/ Head of Department were addressed to the Head of Pharmacy University of Malaya Medical Centre and included the list of the patient's name and their registration numbers that recruited in this study. After 1-2 weeks processing period, the data from the University of Malaya Medical Centre Pharmacy could be accessed, complete with anti-retroviral drug combination and its date. The data was cross-checked and verified with the patients' medical record.

3.12.4 National Registration Department records

The pink covered folder indicates the death of the patient. The date of death and cause of death was traced from the death certificate in the folder. Living status of the HIV-infected patients who have been treated in the University of Malaya Medical Centre but not doing their follow-up was traced, by sending the name list of patients and National Registered Identification Card Number (NRIC) to the National Registration Department of Malaysia in Putrajaya. After three weeks, National Registration Department delivered the data in a compact disk and this data was cross-checked with the patients' medical records. The steps for data collection are shown in figure 3.5

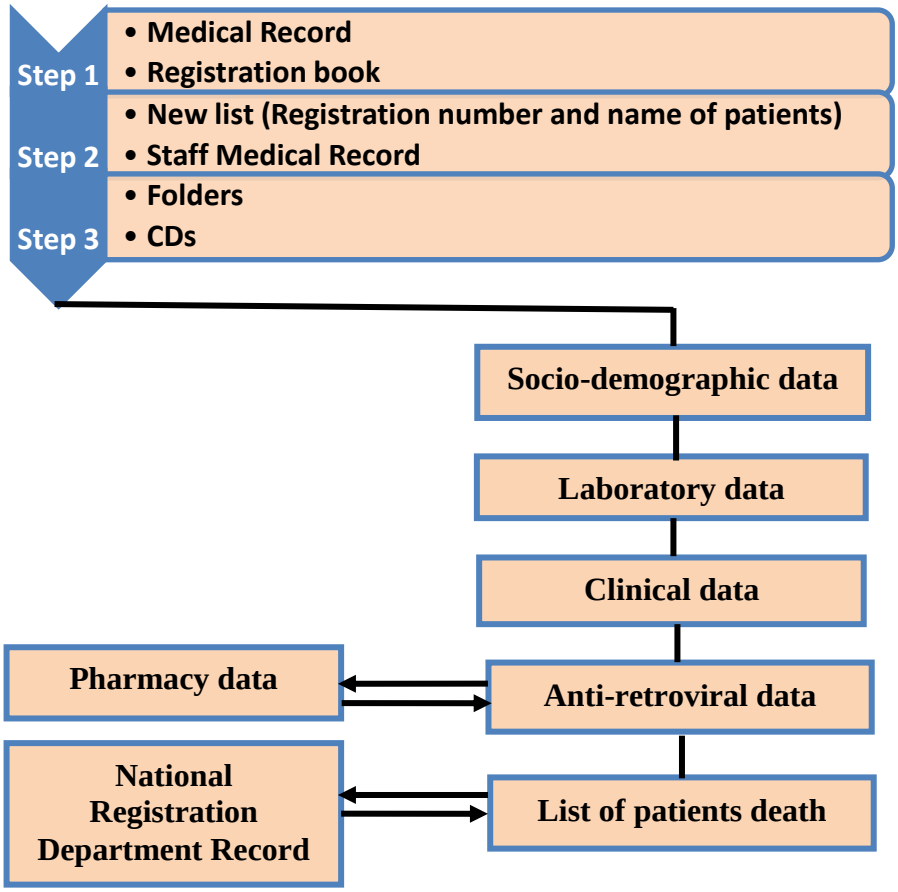


Figure 3.5 The process of data collection

3.13 Data Management

The operational definition of all variables was entered in the Statistical Package for the Social Sciences (SPSS) software. This included the name, description type, labels, values, and maximum field width for each variable. Coding of the information collected was done to make the data more consistent. All data sheets of HIV-infected patients were reviewed and relevant information was extracted and recorded in the data collection sheets. Each record was assigned a study identification number in place of patient initials and identity card number to ensure confidentiality. For the purpose of safekeeping, all files were backed up regularly. Files were also copied and stored on compact disc and universal serial bus (USB) flash drive.

3.13.1 Data Entry

Data was coded prior to entry into the computer except for the continuous variables. Complete data consisting of socio-demographic, laboratory, clinical and anti-retroviral information were checked. These data were entered into a personal computer using the SPSS software version 20.0. Later cross checking, cleaning and transformation were done. The data were validated and edited before it was analyzed. Initial data entry was done by using Microsoft Excel spreadsheet and subsequently imported into SPSS. Double data entry methods were used to ensure the quality of data. The data were compared using Epi Info software to identify dissimilarity between two datasets. Mismatched data was cross-checked with original data set. Duplicate entries were identified and eliminated.

3.13.2 Data Cleaning

Data cleaning involves steps to produce a clean dataset by removing typographical errors, correcting values against the original data set and removing duplicates. The aim of data cleaning is to make sure that the data is free from errors before analysis is carried out. The data were checked for accuracy during the data processing. The process of data cleaning consist of three stages, involving repeated cycles of screening, diagnosing and editing of suspected data abnormalities (Van den Broeck, Cunningham, Eeckels, & Herbst, 2005). This process is summarized in Figure 3.6

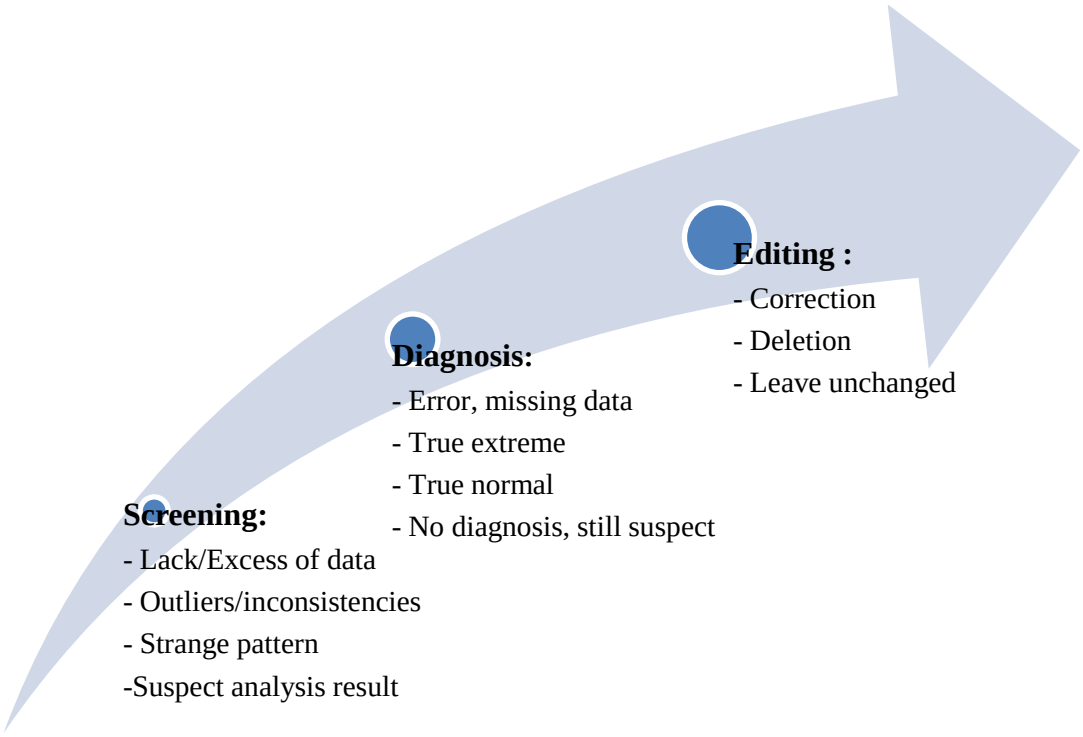


Figure 3.6 The process of cleaning data
Source: (Van den Broeck, et al., 2005)

3.13.3 Data analysis

The first step of data analysis involved calculating the frequency distribution of the variables, mean with standard deviation (SD) and median with inter-quartile range (IQR). Only complete data were included in the analysis in relation to the objectives of this study. Normality tests of relevant variables were conducted before analyzing the dataset.

A. Descriptive analysis

Variable distribution can be described using tables, histogram, box plots and stem-and-leaf plots but in this study most variables were described by using tables. Values of variance, range, standard deviation, and inter-quartile range (IQR) were included in the measures of dispersion. Various assumptions of statistical tests were taken into consideration. One of the most common assumptions is the normal distribution of random variables. The ANOVA (Analysis of Variance) allows statistical analysis of whether the means of several groups are equal or not and hence, generalizes for more than two groups. The t-test assumes that the variable of interest follows a normal probability distribution. Normality assumptions were assessed using the Kolmogorov-Smirnov test, Shapiro-Wilk tests, PP and QQ plots, box & whiskers plot, histograms (Park, 2008). The Levene's test was used to test the homogeneity of variances. Normality testing has two ways, the first by graphical methods and second by numerical method. The differences between an empirical distribution and standard normal distribution or random variables distribution were visualized by graphical methods. The presentation of skewness and kurtosis was statistical tests of normality by numerical methods. Graphical methods were easy to interpret and numerical methods provide objective ways of examining normality (Park, 2008). If the distribution is skewed and

there are many outliers in the box plot so non parametric methods are more appropriate. The types of non-parametric methods depend on the data to be analysed. In investigations there is interested in evaluating the relationship between two variables. This depends on the type of data, different statistics are used to measure the relationship between two variables. The correlation coefficient is a summary statistic that describes the linear relationship between two numerical variables. Person's correlation is often used to explore the relationship between two numerical data. It is an effective method to eliminate or reduce the effect of outliers (Rosner, 2000).

Inferential analysis was performed after descriptive analysis to examine the relationship between each independent variable with the outcome. All the variables were tested for their relationships with the dependent variable using univariate and multiple logistic regression (Kleinbaum, Kupper, & Muller, 1998).

In this study, the socio-demographic characteristic of the samples were described in descriptive analysis section. The continuous variables such as age, baseline CD4 count and baseline viral load were summarized by using the mean with standard deviation and median with inter-quartile range. Categorical variables like age group, gender, ethnicity, marital status, exposure risk, education level, personal income and occupational type were summarized by using proportion and percentage. Pearson's correlation was used to illustrate the correlation between two variables. Percentage and proportion were used for comparison between two variables.

B. Survival analysis

This analysis was used to examine the distribution of time between two events. Survival analysis is a collection of analytical procedures, for which the outcome of interest is the time until an event of interest occurs.

The goals of survival analysis are (Kleinbaum & Klein, 1996):

1. Estimate and interpret survival and/or hazard functions (Kaplan Meier)
2. Compare survival and/or hazard functions (Kaplan Meier)
3. Assess the relationship of explanatory variables to survival time (Cox Regression)

Time: Years, month's weeks or day from the beginning of follow up an individual until an event occurs. In this study, time (month) was used. The median survival time was first to observed with the percentage of cumulative survival is 50 per cent or less. This is preferred measurement as the S (t) value is not normally distributed. S (t) = proportion of individuals surviving until time t. It gives the probabilities of survival up to time t for each $t \geq 0$

Generally, time is equated as the survival time and event equates to failure of survival

Event: death, disease incidence or relapse from remission, recovery or any designated experience of interest that may happen to an individual. In this study, two events are studied - viral load less than 50 copies/ml and death.

Censoring

What particularly distinguishes survival analysis from other statistical methods is to deals with issues involving censoring. Most longitudinal studies occur over a finite period of time; some patients may still be alive at the time of analysis. Those who do not achieve event, they were censored. There are many situations and types of data that may have been censored (cases which are not accounted for the second event) (Kleinbaum & Klein, 1996). This is based on the estimation of conditional probabilities at each time point when an event occurs and taking the product limit to estimate the probability of survival at some point in time. Censoring occurs when we have some information about the individual, but we do not know the exact survival time. There are reasons for censoring (Kleinbaum & Klein, 1996):

1. The study ends, but the subject has no event yet
2. Subject lost to follow up
3. Subject withdraws from study

Standard statistical techniques for analyzing

Continuous data can be used if all survival times were known (i.e. no censored observations). It is right censoring, if the survival time is larger than the censored time. This is most common type of censoring. Left censoring occurs if, age is the time scale and subjects began to follow-up at a specific age. Interval censored data occur only when the subjects fail within an interval, but not when the exact time of failure.

Assumptions for censoring

- Assume censoring is independent of the true (unobserved) survival time
- Assume that survival experience does not change during the course of the study

- Assumptions that censoring is non informative patients who are censored have the same underlying survival curve after their censoring as patients who are not censored.

This may be valid when the study is terminated at a fixed date, when a patient moves to a new city or when a patient dies due to totally unrelated causes. Censoring is independent of exposure and event. It is very difficult to make correct inferences when this assumption is not true.

Kaplan Meier Procedure (KM)

The formula of Kaplan Meier estimation (Kleinbaum & Klein, 1996):

$$S(t) = \pi_{ti<t} \frac{ni - di}{ni}$$

S(t) = proportion of individuals surviving until time t.

ni = the number of survivors just prior to time t_i or the number of survivors less the number of losses/censored cases

di = the number of deaths at time t_i

The Kaplan-Meier method is a nonparametric method, and it assumes there is no parametric form for the survival functions or hazard rate. The Kaplan-Meier estimate of the survival distribution starts with S (0) = 1 and drops off at the distinct failure times. The Kaplan Meier method estimates the time-to-event model in the presence of censored cases (Kleinbaum & Klein, 1996). The model estimates conditional probabilities at each time point when an event occurs and taking the product limit of

those probabilities to estimate the survival rate at each point in time. The variable of time should be continuous data, and the variable of status can be continuous or categorical data but the variable of factors or strata should be categorical data. The probabilities for the event of interest should depend only on time after the initial event and they are assumed to be stable with respect to absolute time. This means, cases that enter the study at different times (for example, patients who begin treatment at different times) should behave similarly. There should also be no systematic differences between censored and uncensored cases. If for example, many of the censored cases are patients with more serious conditions, the results may be biased. The method of calculating life tables that estimated the survival or hazard function at the time of each event was the procedure used by Kaplan Meier (Kleinbaum & Klein, 1996)

Plotting a Kaplan-Meier curve

It is not really a curve, but a step function. Start at S (0) =1, stay flat until the next failure, and then drop down at the failure time. Repeat until last failure, after last failure, either stops, if no more observations or stay flat to last (censored) observation. Then the K-M estimate is undefined past the last censored observation.

Basic specification

- The basic specification prints one survival table followed by the mean and median survival time with standard errors and 95% confidence interval.
- Three statistics test for two or more independent samples of survival data are the log rank (Mantel Cox), Breslow (Generalized Wilcoxon) and Tarone Ware test. The main difference between these 3 tests is the weight given to the survival time
- The Log-Rank test gives equal weight to deaths throughout the survival times

- Breslow test (Generalized Wilcoxon test) gives more weight to earlier deaths than later deaths
- Tarone –Ware test use weights which fall in between the Log rank and Breslow tests

In this study, all the independent variables are skewed to the right after calculating the normality, allowing them to be analyzed using non parametric tests. Overall survival time HIV-infected patients to death, survival time HIV progression to AIDS and survival time AIDS progression to death were assessed by use of Kaplan Meier analysis and compared with log rank test (Kleinbaum & Klein, 1996). The log rank test is a very powerful method for analyzing data where the time to event is important rather than simply whether or not the event occurs. The associated factors of overall survival HIV progression to death, HIV progression to AIDS and death were obtained from Cox proportional hazard models, using both univariate and multivariate analysis. The results were presented as Hazard ratios (HR) and 95% confidence interval (CI).

Hazard function

Hazard function also known as hazard rate or the failure rate, mortality rate, or the force of mortality. The hazard rate at time t, h(t) is proportional to the instantaneous probability of failing at time t (per unit time) given that one has survived up to time t. The hazard function is a measure of the potential for the event to occur at a particular time t, given that the event did not occur yet. Larger values of the hazard function indicate greater potential for the event to occur. The proportional hazard regression model assumes that the time to event and the covariates are related through the following equation below (Kleinbaum & Klein, 1996):

$$h(t) = [h_0(t)]\,[\exp(\beta_1 X_1 + \beta_2 X_2 + \ldots \beta_n X_n)]$$

$h(t)$ = hazards rate for the case at time t

$h_0(t)$ = baseline hazard at time t

β_1, β_2 = value of regression coefficients

X_1, X_2 = value of the covariate

n = number of covariates

The baseline hazard function measures this potential independently of the covariates. The shape of the hazard function over time is defined by the baseline hazard, for all cases. The covariates simply help to determine the overall magnitude of the function. The value of the hazard is equal to the product of the baseline hazard and a covariate effect. When making comparisons, if the proportional hazard assumption is met, the baseline hazards term in the equation above will cancel each other. Thus, the hazard ratio is simply the ratio between the exponential terms in the above equation.

C. Cox Regression Analysis

The Cox proportional hazards regression or Cox regression analysis was used to study the effects of several risk factors on survival time (Kleinbaum & Klein, 1996). This is a method analogous to multiple logistic regressions where the time when an event occurs is considered rather than simply whether or not an event has occurred. The Cox regression with time dependent covariates used if covariates have different values at different point in time for the same cases. Cox regression provide estimated coefficients for each of the covariate, by handling the censored cases correctly and allowing assessment of the impact of multiple covariates in the same model. It is also used to examine the effect of continuous covariates. The Cox regression procedure is useful for modeling the time to a specified event, based upon the values of giving covariates.

In Cox regression analysis the dependent variable is time and the time variable should be independent and quantitative. Status variable can be continuous or categorical. A continuous status variable should be changed to categorical variable first before running the analysis because it must give the defining event for the status variable. The covariates of independent variables are categorical or continuous variables. The hazard ratio should be constant across time and the observation should be independent that is the proportionality of hazard from one case to another should not vary over time. This is known as the proportional hazard assumption. The Cox proportional hazards regression model assumes that the hazard ratio comparing any two specifications of predictors is constant over time. Equivalently, this means that the hazard for one individual is proportional to the hazard for any other individual, where the proportionality constant is independent of time (Kleinbaum & Klein, 1996). If the proportional hazards assumption does not hold, one may need to use the Cox regression with time dependent covariate procedure.

Cox model building

When the data set is ready, the first step was to perform univariate analysis to identify the association between survival time and all important covariates. For categorical variables, it includes the Kaplan Meier estimation of the group specific survivorship functions, and tabulation of the point and interval estimates of the median and quartiles of survival time. One or more of the significance tests is used to compare survivorship among the groups defined by the variable under investigation. Continuous covariates should be broken into quartiles (or other biologically meaningful group) and the same method applied to these groups. A multivariate model should contain at the outset all covariate significant in the univariate analysis with a *p-value* of 0.25 or lower and any

others that are thought to be of clinical importance. Any covariate that has the potential to be an important confounder must also be included. The *p-value* from Wald tests of the individual coefficients are used to identify covariates that might be deleted from the model. The partial likelihood ratio test with the *p*-value should confirm whether the eliminated covariate is significant. The removal of covariates is verified if it is causes significant changes in the coefficients in the remaining model. This is continued until no covariates can be deleted from the model. Covariates are deleted and added back into the model by working backwards.

There were three different ways of performing multivariate Cox regression, the enter method, forward and backward method (Kleinbaum & Klein, 1996) . The enter method is the most simple technique and involves inserting all the variables in the regression model and testing the significance of all the variables in one go. The process of model building started with full model which included all the variables. Significance test used was the likelihood ratio test (-2LL). The difference between the likelihood ratio for the model developed and the likelihood ratio for a reduced model (Kleinbaum, et al., 1998). To develop the reduced models, the non-significant variables (starting with those with higher *p*-values) were removed. The value differences between the likelihood ratio test (-2LL) of the model developed was computed. To compare the fit of two models the likelihood Ratio Test was used. The subsequent reduced model developed was then checked with the value from the Chi-square table at the respective degree of freedom (df). In the final calculation of a statistic, the number of values free to vary was called degree of freedom (Rosner, 2000). If the *p- value* was not significant, the variables were removed. On the other hand, if the *p-value* was significant, the variables were forced back into the model. This process was done until a satisfactory model was obtained.

Stepwise regression, as the name suggests, requires several steps depending on the complexity of the model. Forward stepwise starts with just one significant variable. If the model is significant, the regression will keep adding variables until there are no more significant variables that can be added which will improve the model. Backward stepwise starts with all the variables in the model and then throws out the ones that are not significant. Then the model is tested to see whether it is still significant and whether there are other variables that are not significant. Non significant variables are then removed progressively until no more can be removed.

In this study there are two parts, the first is concerned with determining factors of AIDS progression to death with the dependent variable being mortality status (alive/dead). The second part is concerned with determining predictors of ability to achieve viral load less than 50 copies/ml. Independent variables included socio-demographic characteristic, laboratory, clinical condition and anti-retroviral therapy variables. This study used the Enter method, when performing multivariate Cox regression as it allows one to select important (even if non-significant in univariate analysis) variables in the analysis while the Forward and Backward method relies solely on the software to select significant variables. The significant association and its precision were determined by 95 per cent confidence interval and the magnitude was determined by the Hazard ratio.

Testing for proportional hazards assumption (PH assumption)

Once a suitable set of covariate has been identified, it is wise to check each covariate to ensure that the proportional hazards assumption is valid.

There are 2 ways of testing (Kleinbaum & Klein, 1996):

1. Can be viewed using the Log –Minus-Log plot - one should get parallel lines

2. Correlating the residuals and the survival time rank (more confirmatory test).

The procedure here involves testing the significant covariate from the Kaplan Meier procedure one by one. This is done by performing Cox regression with one variable (example age alone) as the covariate and saving the partial residuals. The time variable is ranked from 1 to the smallest value and then correlated with the residuals. If the correlation value is very small the proportional hazard assumption is met but if high the proportional hazard assumption is violated. Based on Cohen (1989) criterion, a correlation value of more than 0.3 is considered to be sizeable.

If assumptions are violated, there are three ways of fitting the model

1. Stratify on the variable that violates the PH assumption. The weakness of stratification is that one cannot estimate the total effect.
2. Include a time varying covariate. Treat the violators as a time varying covariate by handling the variable as an interaction with time.
3. Separate analysis for early and late time period

Interaction

An interaction term is a new variable that is the product of two other variables in the model. In etiological studies interaction is important if it involves the main exposure in question, in prognostic studies involving prediction, all interactions gain importance. The problems with interaction are the interpretation or stratify the model by the interacting covariate.

Testing for interaction

It is important to check for interaction in the final stages of modelling. The effect of adding an interaction term should be assessed using the partial likelihood ratio test. All significant interaction should be included in the main effect model. Wald statistic p

values can be used as a guide to select interaction that may be eliminated from the model, with significance checked by the partial likelihood ratio test. A Likelihood Ratio Test should be performed to compare two models, the model without interaction compared with the model with the interactions.

Comparability of Logistic regression and Cox Proportional Hazards Models

- Logistic regression models cumulative incidence whereas proportional hazards regression models hazard rates
- They give similar estimates if: the disease is rare, the risk factor is moderate and censoring rates are similar across covariates
- Both models can accommodate updated covariates by creating new observations at regular intervals

In this study there are four Cox regression analysis:

A. Cox regression analysis for All AIDS patients progression to death

Time: date of patient's death or the end of the study minus date of AIDS diagnosis calculating in month (continuous)

Status: Alive and died (categorical)

Covariate: 18 variables

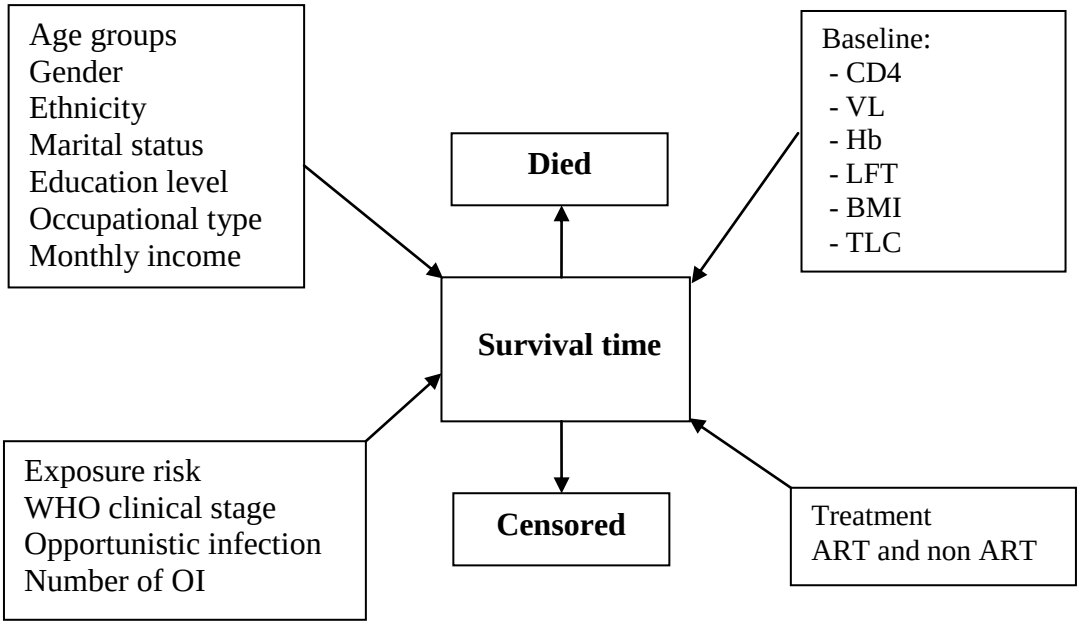


Figure 3.7 Covariate frame of all AIDS patients progression to death

B. Cox regression analysis for AIDS on HAART progression to death

Time: date of patient's death or the end of the study minus date of starting HAART calculating in month (continuous)

Status: Alive and died (categorical)

Covariate: 24 variables

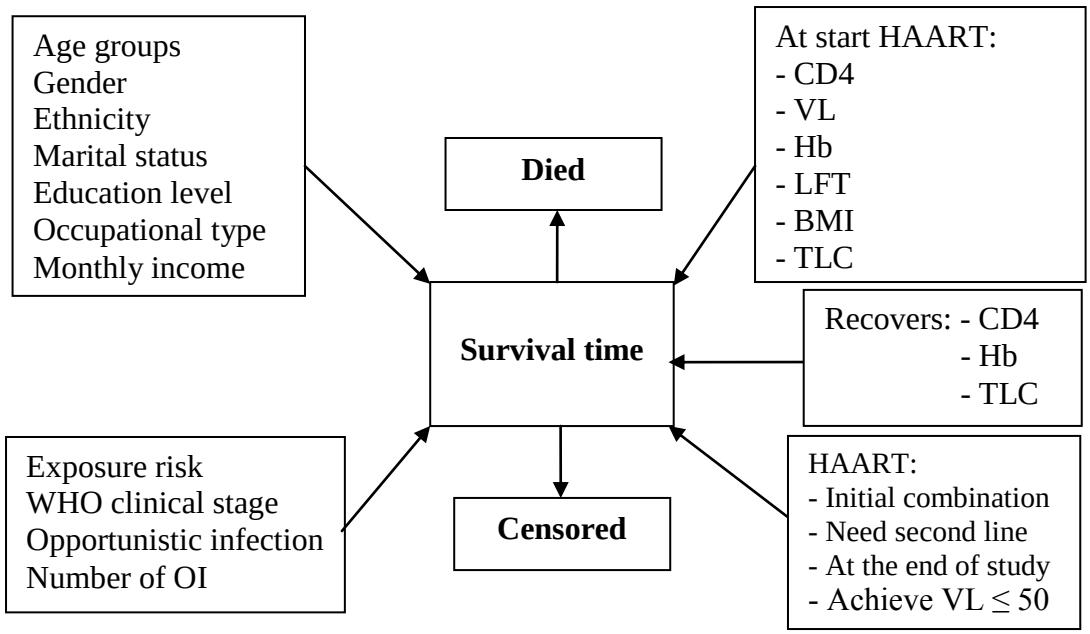


Figure 3.8 Covariate frame of AIDS patients on HAART progression to death

C. Cox regression analysis for AIDS not on ART progression to death

Time: date of patient's death or the end of the study minus date of AIDS diagnosis calculating in month (continuous)

Status: died and alive (categorical)

Covariate: 17 variables

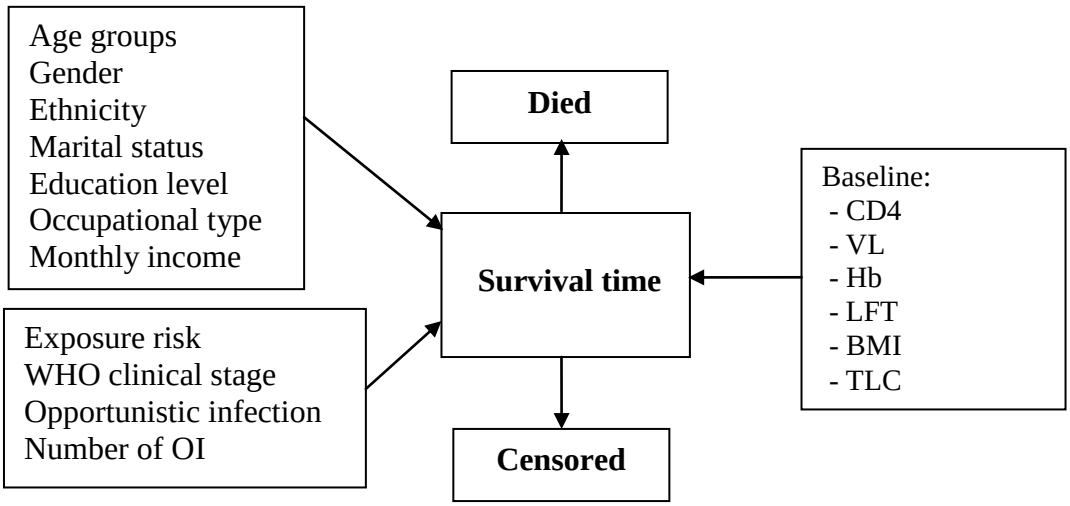


Figure 3.9 Covariate frame of AIDS patients not on anti-retroviral therapy progression to death

D. Cox regression analysis for AIDS on HAART to achieve viral load less than 50 copies/ml

Time: date of achieving viral load less than 50 copies/ml minus date of starting HAART calculating in month (continuous)

Status: Achieve and not achieve viral load less than 50 copies/ml (categorical)

Covariate: 23 variables

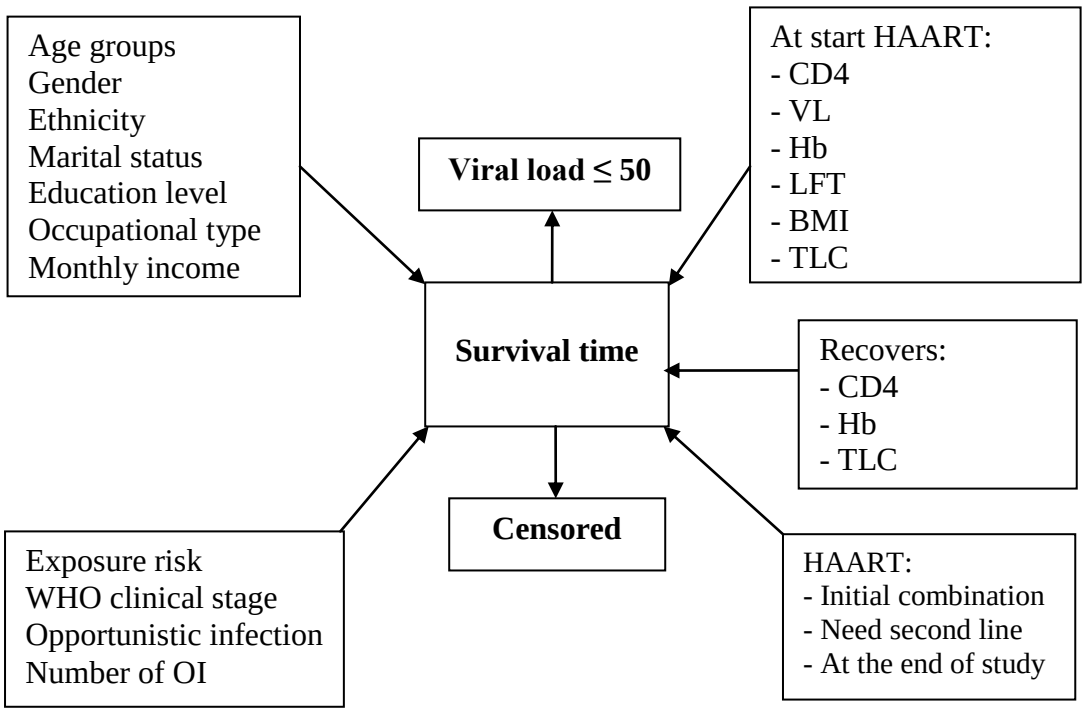


Figure 3.10 Covariate frame AIDS patients on HAART to achieve viral load less than 50 copies/ml

3.14 Summary

This chapter deals with material and methods used in this study. From the literature search known that the cohort study is the next best study design for antiretroviral treatment after Randomized Controlled Trial which was chosen in this study. Data taken from HIV-infected patient's folders from 1986-2009 in the medical record UMMC includes data of socio-demographic, laboratory, clinical condition, pharmacy data regarding anti-retroviral therapy and list of death patients checked the mortality status to the National Registration Department records. A total of 1314 patients were included for analysis using SPSS version 20.0. The total of 32 variables and 9 outcomes in this study. Regarding statistical analysis, firstly, done descriptive analysis of socio-demographic, laboratory, clinical and anti-retroviral data. Secondly, the Kaplan Meier procedure is used in this study to estimating conditional probabilities at each time point when an event occurs and taking the product limit of those probabilities to estimate the survival rate at each point in time. Survival analysis divided into four models, survival analysis of all AIDS patients progression to death, AIDS patients on HAART to death, AIDS patients not on anti-retroviral therapy to death and AIDS patients on HAART to achieve viral load less than 50 copies/ml. Thirdly, to study the effects of several risk factors on survival time used Cox regression analysis. The Cox regression analysis will provide estimated coefficients for each of covariate, it will handle the censored cases correctly and allow assessment of the impact of multiple covariates in the same model. All the variables were tested for univariate and multivariate analysis of Cox regression analysis and log rank *p-value* less than 0.25 was set as cut off point, checking the interactions between the variables and checked and the proportional hazards assumption by Log –Minus-Log plot before achieved the final Cox regression model.

CHAPTER 4

RESULTS

4.1 Introduction

This chapter presents the results of statistical analysis and divided into the descriptive analysis, survival analysis and Cox regression analysis. Section 4.1 is the introduction to this chapter. Section 4.2 comparison of socio-demographic characteristic between HIV-infected patients included and excluded from analysis. This continues in Section 4.3 covers the distribution of characteristics of HIV-infected patients according to socio-demographic characteristic, laboratory result, clinical condition and anti-retroviral therapy. Section 4.4 illustrates the survival time of HIV-infected patients. While Section 4.4.1 looks at the time of death in all AIDS patients. Section 4.4.2 looks at the time to death in AIDS patients on HAART. The time of death in AIDS patients not on ART is spelled out in Section 4.4.3. The time for AIDS patients on HAART to achieve viral load less than 50 copies/ml is in Section 4.4.4 Progression to death in all AIDS patients is described in Section 4.5. Progression to death in AIDS patients on HAART are shown in Section 4.6. Progression to death in AIDS patients not receiving anti-retroviral therapy is explained in Section 4.7. AIDS patients on HAART achieved viral load less than 50 copies/ml are documented in Section 4.8. While Section 4.9 is a summary of this chapter

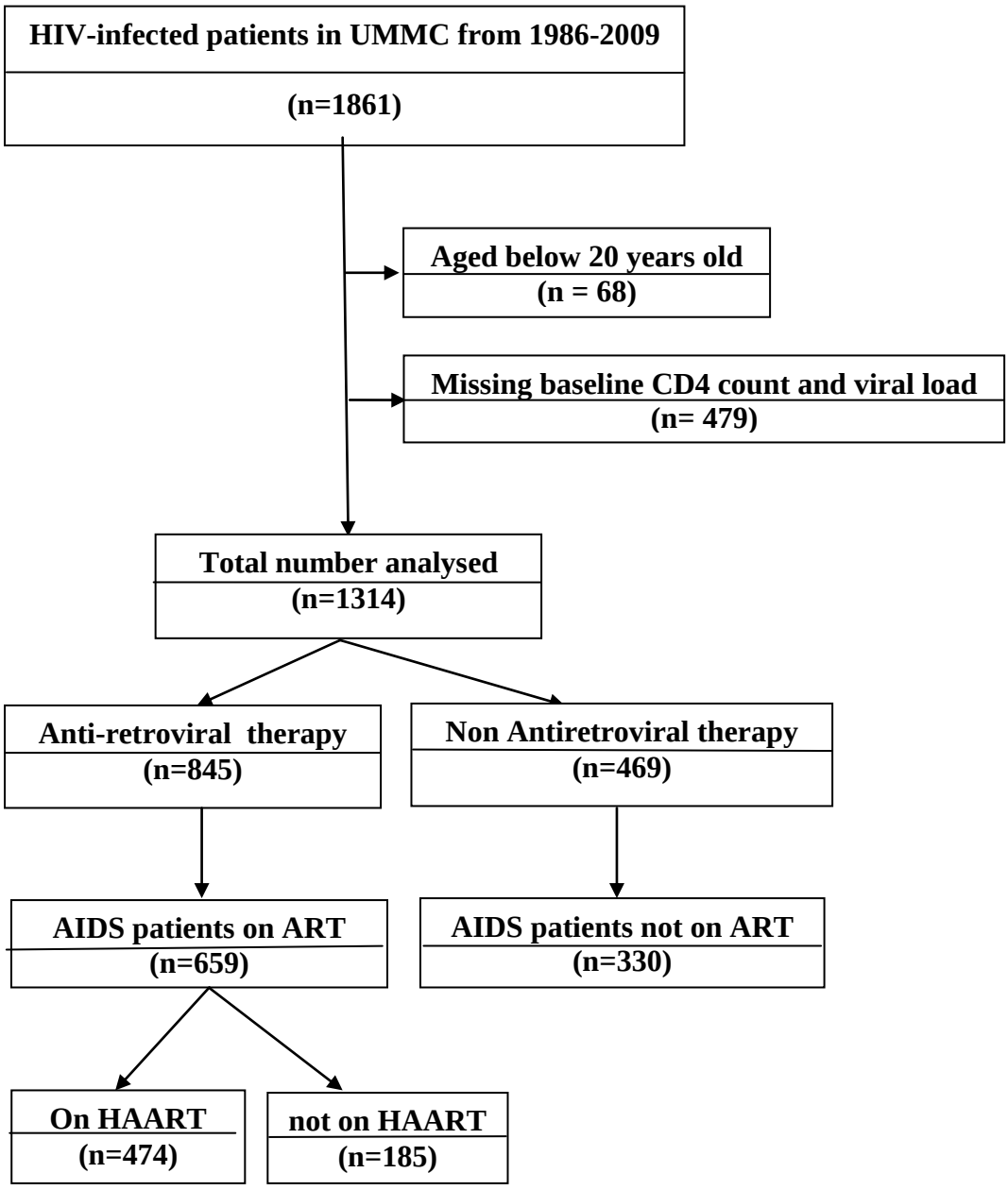


Figure 4.1 The process of selecting HIV-infected patients

4.2 Comparison of socio-demographic characteristic between HIV infected patient included and excluded from analysis

A comparison of socio-demographic characteristics between HIV-infected patients included and excluded from analysis are summarized in Table 4.1. There were no major differences between these two groups and the characteristics were generally similar.

Table 4.1 Comparison of socio-demographic characteristic between HIV-infected patient included and excluded from analysis

Variables	Total included (n = 1314) n (%)	Total excluded (n = 479) n (%)
Age Groups (years)		
20 – 29	420 (32.0)	172 (35.9)
30 – 39	543 (41.3)	189 (39.5)
40 – 49	219 (16.7)	64 (13.4)
50 – 59	85 (6.4)	39 (8.1)
≥ 60	47 (3.6)	15 (3.1)
Median (IQR)	33.7 (12.0)	33.1 (12.4)
Gender		
Male	1075 (81.8)	398 (83.1)
Female	239 (18.2)	81 (16.9)
Ratio male : female	4.5 : 1	4.9 : 1
Ethnicity		
Malay	256 (19.5)	97 (20.3)
Chinese	804 (61.2)	290 (60.5)
Indian	167 (12.7)	65 (13.6)
Others	87 (6.6)	27 (5.6)
Marital status		
Single	594 (45.2)	218 (45.5)
Married	575 (43.8)	210 (43.8)
Others	145 (11.0)	51 (10.7)
Educational level		
≤ Secondary	966 (73.5)	361 (75.4)
≥ Tertiary	348 (26.5)	118 (24.6)
Occupational type		
Unemployed	375 (28.5)	159 (33.2)
Manual workers	372 (28.3)	144 (30.1)
Professional and non manual worker	567 (43.2)	176 (36.7)
Monthly income (RM)		
< 1000	451 (34.3)	163 (34.0)
1000 to 3000	558 (42.5)	197 (41.1)
> 3000	305 (23.2)	119 (24.9)

4.3 Distribution of characteristic of HIV-infected patients

The median age of the HIV-infected patients was 33.7 years (IQR 12.0) and AIDS patients was 34.1 (IQR 12.7). Most of them (73.3 per cent) were aged between 20-39 years, male (81.8 per cent) and Chinese (61.2 per cent). Forty five point two per cent were single, 73.5 per cent had primary and secondary education, 43.2 per cent were professional or non-manual workers and 42.5 per cent earned between RM 1000 to 3000 per month. The distribution of socio-demographic characteristic of HIV-infected patients are summarized in Table 4.2

The distribution of laboratory and clinical variables show that 62.9 per cent patients had baseline CD4 count less than 200 cells/μL. Fifty one point one per cent had baseline viral load more than 100,000 copies/ml. Sixty two point five per cent had baseline hemoglobin more than 12 g/dl. Sixty two point seven per cent had normal baseline total lymphocyte count and 55.2 per cent had normal liver function test. The distribution of laboratory test of HIV-infected patients is highlighted in Table 4.3

About 65.8 per cent of patients contracted HIV via the heterosexual route and 61.7 per cent presented with AIDS. Fifty four point two per cent already at the WHO clinical stage 4. Sixty three point nine per cent had opportunistic infection and 30.9 per cent had one opportunistic infection. Seventy four point four per cent had baseline body mass index more than 18.5 and 64.3 per cent patients receiving anti-retroviral therapy. At the end of the study, 36.4 per cent patients had died with majority due to AIDS related illness (79.7 per cent). The distribution of laboratory test and clinical condition of HIV-infected patients is highlighted in Table 4.4

Table 4.2 Distribution of socio-demographic characteristic of HIV-infected patients

Variables	Total (n = 1314) n (%)	Total AIDS (n = 989) n (%)
Age Groups (years)		
20 – 29	420 (32.0)	308 (31.2)
30 – 39	543 (41.3)	399 (40.3)
40 – 49	219 (16.7)	173 (17.5)
50 – 59	85 (6.4)	69 (7.0)
≥ 60	47 (3.6)	40 (4.0)
Median (IQR)	33.7 (12.0)	34.1 (12.7)
Gender		
Male	1075 (81.8)	843 (85.2)
Female	239 (18.2)	146 (14.8)
Ratio male : female	4.5 : 1	5.8 : 1
Ethnicity		
Malay	256 (19.5)	191 (19.3)
Chinese	804 (61.2)	620 (62.7)
Indian	167 (12.7)	123 (12.4)
Others	87 (6.6)	55 (5.6)
Marital status		
Single	594 (45.2)	448 (45.3)
Married	575 (43.8)	425 (43.0)
Others	145 (11.0)	116 (11.7)
Educational level		
≤ Secondary	966 (73.5)	744 (75.2)
≥ Tertiary	348 (26.5)	245 (24.8)
Occupational type		
Unemployed	375 (28.5)	310 (31.3)
Manual workers	372 (28.3)	288 (29.1)
Professional and non manual worker	567 (43.2)	391 (39.5)
Monthly income (RM)		
< 1000	451 (34.3)	337 (34.1)
1000 to 3000	558 (42.5)	420 (42.5)
> 3000	305 (23.2)	232 (23.5)

Table 4.3 Distribution baseline laboratory result of HIV-infected patients

Variables	Total (n = 1314) n (%)	Total AIDS (n = 989) n (%)
Baseline CD4 (cell/µL)		
< 200	826 (62.9)	746 (75.4)
≥ 200	488 (37.1)	243 (24.6)
Median (IQR)	105 (295)	52 (183)
Baseline VL (copies/ml)		
< 100,000	643 (48.9)	392 (39.6)
≥ 100,000	671 (51.1)	597 (60.4)
Median (IQR)	100,000 (124,924)	100,000 (188,025)
Baseline Hb (g/dl)		
< 12	493 (37.5)	420 (42.5)
≥ 12	821 (62.5)	569 (57.5)
Median (IQR)	12.8 (31.0)	12.4 (30.0)
Baseline TLC		
Normal	824 (62.7)	547 (55.3)
Abnormal	490 (37.3)	442 (44.7)
Median (IQR)	1,410 (1,253)	1,280 (1,180)
Baseline LFT		
Normal	725 (55.2)	500 (50.6)
Abnormal	589 (44.8)	489 (49.4)

Note: - VL = Viral load
- Hb = Hemoglobin
- TLC = Total lymphocyte count
- LFT = Liver function test

Table 4.4 Distribution clinical condition of HIV-infected patients

Variables	Total (n = 1314) n (%)	Total AIDS (n = 989) n (%)
Exposure Risk		
Heterosexual	864 (65.8)	665 (67.2)
Homosexual	173 (13.2)	93 (9.4)
IDU	250 (19.0)	211 (21.3)
Others	27 (2.1)	20 (2.0)
WHO Clinical stage		
Stage 1	117 (8.9)	0 (0.0)
Stage 2	123 (9.4)	0 (0.0)
Stage 3	362 (27.5)	304 (30.7)
Stage 4	712 (54.2)	685 (69.3)
Initial Presentation		
HIV	503 (38.3)	0 (0.0)
AIDS	811 (61.7)	989 (100.0)
Baseline BMI		
< 18.5	336 (25.6)	285 (28.8)
≥ 18.5	978 (74.4)	704 (71.2)
Opportunistic Infection (OI)		
Negative	475 (36.1)	259 (26.2)
Positive	839 (63.9)	730 (73.8)
Number of OI		
0	475 (36.1)	259 (26.2)
1	406 (30.9)	364 (36.8)
2	274 (20.9)	242 (24.5)
≥ 3	159 (12.1)	124 (12.5)
Treatment		
Non ART	469 (35.7)	330 (33.4)
ART	845 (64.3)	659 (66.6)
Living status (at the end of the study)		
Alive	836 (63.6)	527 (53.3)
Died	478 (36.4)	462 (46.7)
Cause of death		
AIDS related illness	381 (79.7)	376 (81.4)
Non AIDS related illness	97 (20.3)	86 (18.6)

4.4 Distribution of characteristic of AIDS patients on anti-retroviral therapy

Total of AIDS patients receiving anti-retroviral was 659 patients with median age was 34.2 years (IQR 13.6). AIDS patients receiving anti-retroviral have similar distribution with HIV-infected patients, however it differs from marital status variable, showing that married more than single in AIDS patients receiving anti-retroviral therapy. The distribution of socio-demographic characteristic of AIDS patients receiving anti-retroviral and HAART are summarized in Table 4.5

The laboratory and clinical variables at the start of HAART, 84.2 per cent had CD4 counts less than 200 cells/μL and 64.8 per cent had viral load more than 100,000 copies/ml. Fifty five point five per cent had hemoglobin more than 12 g/dl, 52.1 per cent had a normal total lymphocyte count and 57.4 per cent had normal liver function test. Three new variables added for AIDS patients on HAART were CD4 recovers, hemoglobin recovers and total lymphocyte count recovers. There was no progress of CD4 to achieve more than 200 cells/μL for 42.2 per cent of patients. Forty one point six per cent found no increment in hemoglobin level to achieve more than 12 g/dl and total lymphocyte count of 41.1 per cent patients had no recovers. The median time for CD4 recovers, hemoglobin recovers and total lymphocyte count recovers were 9.7 months (IQR 13.9), 5.4 months (IQR 7.0) and 5.6 months (IQR 7.2).

Body mass index more than 18.5 at HAART initiation was 73.8 per cent, patients with WHO clinical stage 4 was 67.9 per cent. Positive opportunistic infection was 78.3 per cent and with one opportunistic infection was 42.4 per cent, mainly infected with Tuberculosis (142 or 30 per cent).

Around 71.9 percent patients receiving anti-retroviral therapy in HAART era and 80.6 per cent of HAART initiation with combination (2 NRTI + EFV), whereas 84.2 per cent of them did not need to switch second line of HAART. The median follow up measured from the date of starting HAART until the date of death or the end of the study was 37.5 (IQR 55.6) months. At the end of the study, only 9.3 per cent changed to the HAART combination with PI. Seventy point five per cent achieved viral load less than 50 copies/ml and 20 per cent die with cause of death AIDS related illness (PCP and Tuberculosis). From total HAART initiation with 2 NRTI + PI, those still continue until the end of study were 16 (61.5 per cent) and 10 (38.5 per cent) patients have stopped. The distribution of laboratory results and clinical of AIDS patients on anti-retroviral therapy and HAART is highlighted in Table 4.6 and Table 4.7

Table 4.5 Distribution of socio-demographic characteristics of AIDS patients receiving anti-retroviral therapy

Variables	Total ART (n = 659) n (%)	Total HAART (n = 474) n (%)
Age Groups (years)		
20 – 29	194 (29.4)	121 (25.5)
30 – 39	262 (39.8)	200 (42.2)
40 – 49	121 (18.4)	97 (20.5)
50 – 59	49 (7.4)	32 (6.8)
≥ 60	33 (5.0)	24 (5.1)
Median (IQR)	34.2 (13.6)	35.0 (12.9)
Gender		
Male	546 (82.9)	397 (83.8)
Female	113 (17.1)	77 (16.2)
Ratio male : female	4.8 : 1	5.2 : 1
Ethnicity		
Malay	100 (15.2)	83 (19.3)
Chinese	457 (69.3)	309 (62.7)
Indian	70 (10.6)	59 (12.4)
Others	32 (4.9)	23 (5.6)
Marital status		
Single	278 (42.2)	198 (41.8)
Married	305 (46.3)	219 (46.2)
Others	76 (11.5)	57 (12.0)
Educational level		
≤ Secondary	471 (71.5)	330 (69.6)
≥ Tertiary	188 (28.5)	144 (30.4)
Occupational type		
Unemployed	186 (28.2)	122 (25.7)
Manual workers	163 (24.7)	110 (23.2)
Professional and non manual worker	310 (47.0)	242 (51.1)
Monthly income (RM)		
< 1000	203 (30.8)	156 (32.9)
1000 to 3000	287 (43.6)	206 (43.5)
> 3000	169 (25.6)	112 (23.6)

Table 4.6 Distribution laboratory result of AIDS patients receiving anti-retroviral therapy

Variables	Total ART (n = 659) n (%)	Total HAART (n = 474) n (%)
CD4 at the start of ART (cell/µL)		
< 200	545 (82.7)	399 (84.2)
≥ 200	114(17.3)	75 (15.8)
Median (IQR)	46 (138)	46 (125)
VL at start of ART (copies/ml)		
< 100,000	250 (37.9)	167 (35.2)
≥ 100,000	409 (62.1)	307 (64.8)
Median (IQR)	100,000 (197,200)	100,000 (237,800)
Hb at start of ART (g/dl)		
< 12	286 (43.4)	211 (44.5)
≥ 12	373 (56.6)	263 (55.5)
Median (IQR)	12.8 (31.0)	12.5(31.0)
TLC at start ART		
Normal	372 (56.4)	247 (52.1)
Abnormal	287 (43.6)	227 (47.9)
Median (IQR)	1,300 (1,136)	1,200 (1,079)
LFT at start of ART		
Normal	374 (56.8)	272 (57.4)
Abnormal	285 (43.3)	202 (42.6)
CD4 recovers		
No	299 (45.4)	200 (42.2)
Stable	88 (13.4)	56 (11.8)
Yes	272 (41.3)	218 (46.0)
Time CD4 recovers (months)		
Median (IQR)	9.8 (13.9)	9.7 (13.9)
Hemoglobin recovers		
No	296 (44.9)	197 (41.6)
Stable	188 (28.5)	146 (30.8)
Yes	175 (26.6)	131 (27.6)
Time Hb recovers (months)		
Median (IQR)	5.6 (6.9)	5.4 (7.0)
TLC recovers		
No	292 (44.3)	195 (41.1)
Stable	196 (29.7)	153 (32.3)
Yes	171 (25.9)	126 (26.6)
Time TLC recovers (months)		
Median (IQR)	5.8 (7.5)	5.6 (7.2)

Note: - CD4 recovers from < 200 to ≥ 200 cell/µL; Hb recovers from < 12 to ≥ 12 g/dl; TLC recovers from < 1200 to ≥ 1,200

Table 4.7 Distribution clinical condition and anti-retroviral therapy variables of AIDS patients receiving anti-retroviral therapy

Variables	Total ART (n = 659) n (%)	Total HAART (n = 474) n (%)
BMI at start of ART		
< 18.5	163 (24.7)	124 (26.2)
≥ 18.5	496 (75.3)	350 (73.8)
WHO clinical stage		
Stage 3	199 (30.2)	152 (32.1)
Stage 4	460 (69.8)	322 (67.9)
Opportunistic Infection (OI)		
Negative	133 (20.2)	103 (21.7)
Positive	526 (79.8)	371 (78.3)
Number of OI		
0	133 (20.2)	103 (21.7)
1	261 (39.2)	201 (42.4)
2	170 (25.8)	120 (25.3)
≥ 3	95 (14.4)	50 (10.5)
ART era		
Pre-HAART era	185 (28.1)	0 (0.0)
HAART era	474 (71.9)	474 (100.0)
Initial combination of HAART		
2 NRTI+ EFV	382 (57.9)	382 (80.6)
2 NRTI+ NVP	66 (10.0)	66 (13.9)
2 NRTI+ PI	26 (3.9)	26 (5.5)
Single and double drugs	185 (28.1)	
Need second line of HAART		
No	583 (88.5)	399 (84.2)
Yes	76 (11.5)	75 (15.8)
HAART at the end of study		
HAART without PI	567 (86.0)	430 (90.7)
HAART with PI	92 (14.0)	44 (9.3)
Achieve VL ≤ 50 copies/ml		
No	254 (38.5)	140 (29.5)
Yes	405 (61.5)	334 (70.5)
Living status (the end of the study)		
Alive	433 (65.7)	379 (80.0)
Died	226 (34.3)	95 (20.0)
Cause of death		
AIDS related illness	185 (81.9)	77 (81.1)
Non AIDS related illness	41 (18.1)	18 (18.9)

4.5 Survival time of HIV-infected patients

Survival time was measured from date of HIV diagnosis until the date of the patient's death or the end of the study. For the total number of HIV-infected patients (1314), there were 36.4 per cent deaths. About 79.7 per cent of deaths were caused by AIDS-related illnesses (*Pneumocystis carinii pneumonia* 35.4 per cent and *Tuberculosis*r 34.1 per cent). The mean survival time was 159.1 (95% CI 150.6, 167.6) months and the median survival time were 142.4 months (95% CI 121.5, 163.5 months). There were 64.3 per cent of total patients receiving anti-retroviral therapy and 35.7 per cent not receiving anti-retroviral therapy. The mean and median survival time of patients receiving anti-retroviral therapy was 168.6 (95% CI 157.6, 179.6) months and 177.5 (95% CI 147.4, 207.6) months respectively. The mean and median survival time of patients not receiving anti-retroviral therapy was 123.5 (95% CI 111.4, 135.6) months and 73.2 (95% CI 62.0, 84.4) months respectively. The 5 and 10-year survival of the anti-retroviral therapy group (80.7 per cent and 64.5 per cent) was higher than non anti-retroviral therapy group (55.6 per cent and 37.8 per cent). The Kaplan Meier survival curve for anti-retroviral therapy and the non anti-retroviral therapy group is presented in Figure 4.2.

4.5.1 Time to death in all AIDS patients

Survival time was measured from the date of the AIDS diagnosis until the date of patient's death or the end of the study. Total number of AIDS patients were 989 and 46.7 per cent had died at the end of the study. About 81.4 per cent of deaths were caused by AIDS-related illnesses (*Tuberculosis* 45.5 per cent and *Pneumocystis carinii pneumonia* 40.7 per cent). The mean and median survival time was 119.9 (95% CI 110.3, 129.5) months and 65.7 (95% CI 49.9, 81.3) months respectively. The 5 and 10-year survival after being treated as AIDS patients were 51.8 per cent (95% CI 48.3, 55.3) and 41.4 per cent (95% CI 36.9, 45.9).

There were 66.6 per cent of total AIDS patients receiving anti-retroviral therapy and 33.4 per cent did not. The mean survival time of AIDS patients on anti-retroviral therapy was 103.5 (95% CI 97.1, 109.9) months and the median survival time was 121.7 months, those not on anti-retroviral therapy had mean and median survival time was 62.2 (95% CI 50.2, 74.2) months and 15.0 (95% CI 11.7, 18.3). The 5 and 10-year survival of anti-retroviral therapy group (65.6 and 51.5 per cent) was higher than non anti-retroviral therapy group (23.6 and 18.9 per cent). The Kaplan Meier survival curve of anti-retroviral therapy and non anti-retroviral therapy in all AIDS patients are presented in Figure 4.3

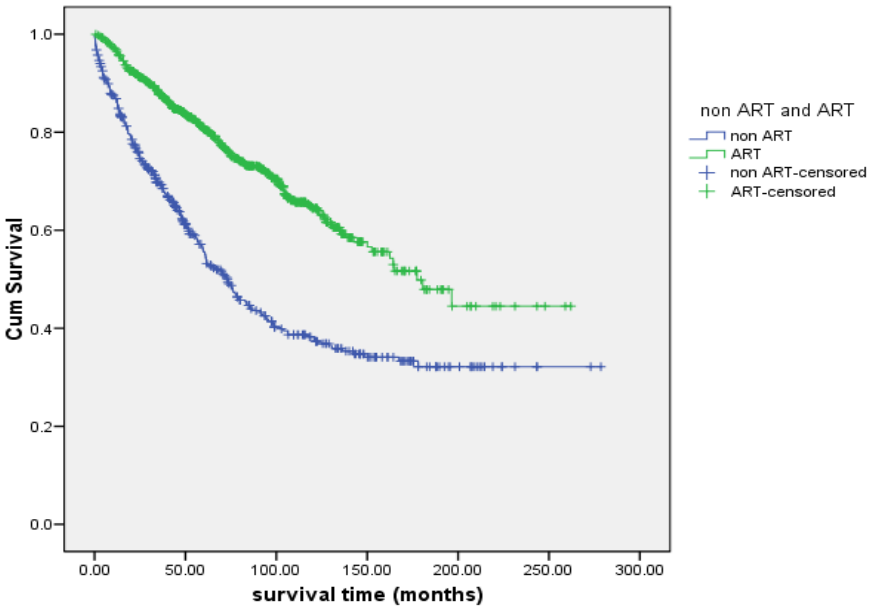


Figure 4.2 The Kaplan Meier survival curve of HIV-infected patients progression to death according to received anti-retroviral therapy and not received

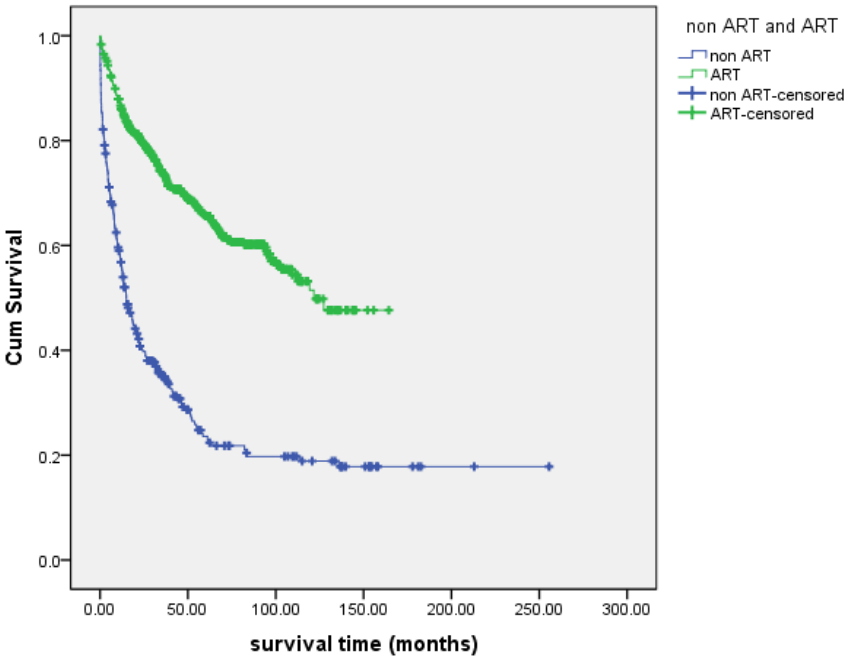


Figure 4.3 The Kaplan Meier survival curve of all AIDS patients progression to death according to received anti-retroviral therapy and not received

4.5.2 Time to death in AIDS patients on HAART

Survival time was measured from the date of starting HAART until the date of patient's death or the end of the study. There were 474 AIDS patients on HAART. Out of these 20.0 per cent had died at the end of the study. The mean survival time was 105.8 (95% CI 100.4, 111.1) months. The median survival time was not calculated because the cumulative proportion of survival was still high (more than 50 per cent). The 5 and 10-year survival were 76.7 per cent (95% CI 72.2, 81.2) and 70.6 per cent (95% CI 63.7, 77.5). The Kaplan Meier survival curve of patients undergoing HAART is presented in Figure 4.4

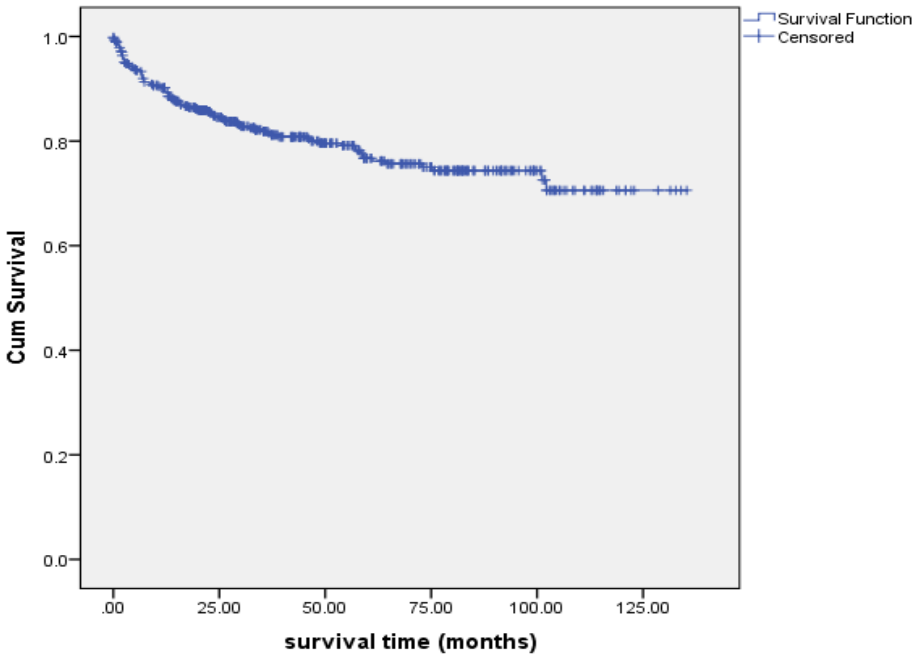


Figure 4.4 The Kaplan Meier survival curve of AIDS patients on HAART progression to death

4.5.3 Time to death in AIDS patients not on anti-retroviral therapy

Survival time was measured from the date of the AIDS diagnosis until the date of patient's death or the end of the study. The AIDS patients not on anti-retroviral therapy were 330, out of these 71.5 per cent died. The mean and median survival time was 62.3 (95% CI 50.3, 74.2) months and 15.0 (95% CI 11.7, 18.3) months respectively. The 5 and 10-year survival were 23.6 per cent (95% CI 18.3, 28.9) and 18.9 per cent (95% CI 13.6, 24.2). The Kaplan Meier survival curve of AIDS patients not on anti-retroviral therapy is presented in Figure 4.5

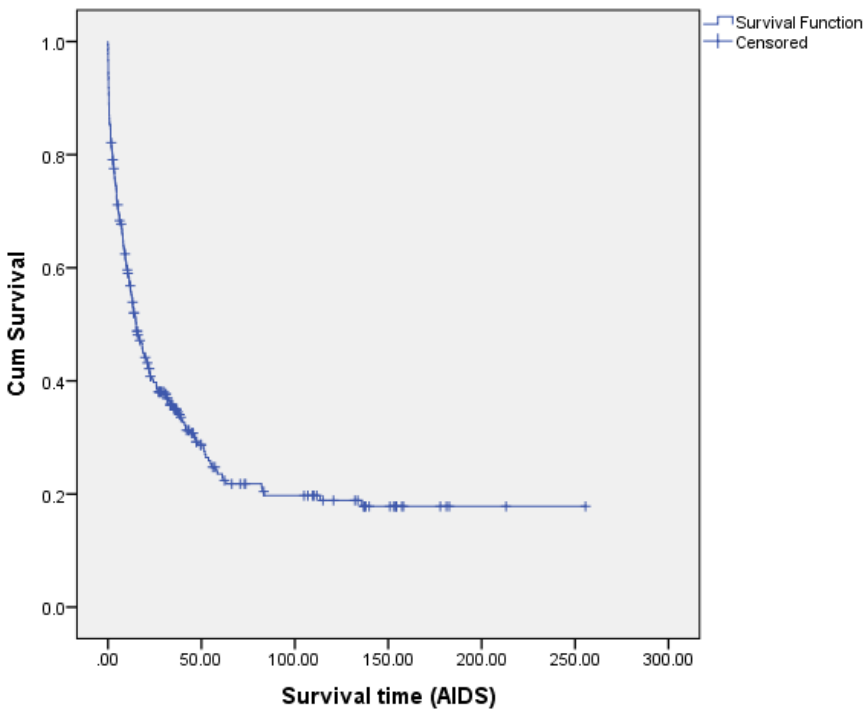


Figure 4.5 The Kaplan Meier survival curve of AIDS patients not on anti-retroviral therapy progression to death

4.5.4 Time to achieve viral load less than 50 copies/ml in AIDS patients on HAART

Survival time was measured from the date of starting HAART until the date of achieving viral load less than 50 copies/ml. There were 474 AIDS patients on HAART, of these 70.5 per cent achieved viral load less than 50 copies/ml. The mean time was 9.2 (95% CI 7.9, 10.6) months and median time was 5.1 (95% CI 4.7, 5.6) months. The Kaplan Meier survival curve for patients on HAART to achieve viral load less than 50 copies/ml is presented in Figure 4.6

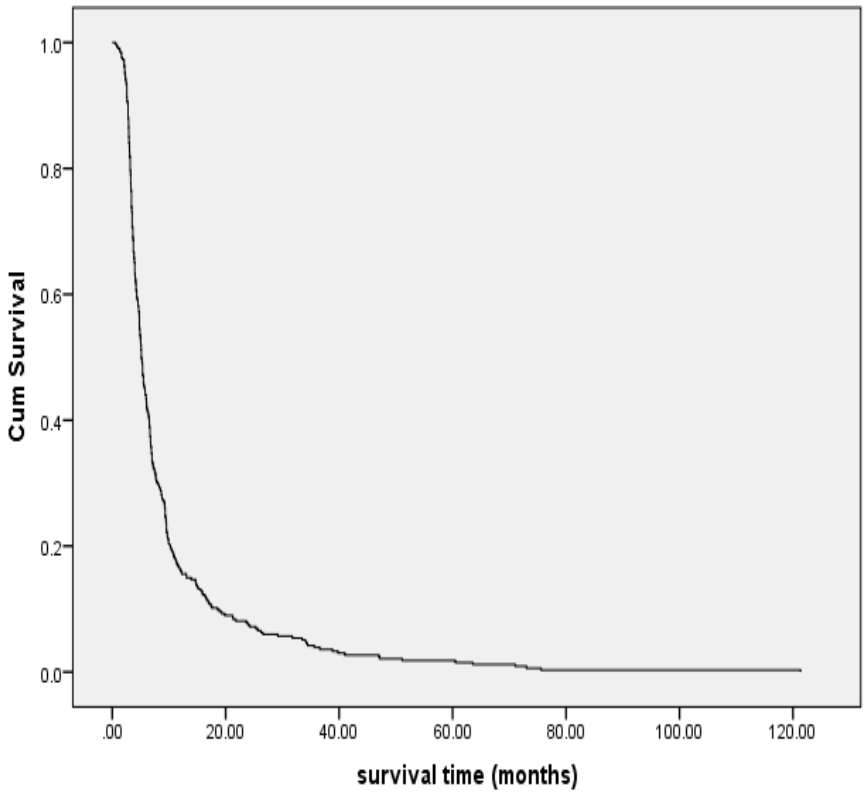


Figure 4.6 The Kaplan Meier survival curve of AIDS patients on HAART to achieve viral load less than 50 copies/ml

4.6 Progression to death in all AIDS patients

Survival probabilities of all AIDS patient progression to death stratified by significant socio-demographic, laboratory and clinical variables

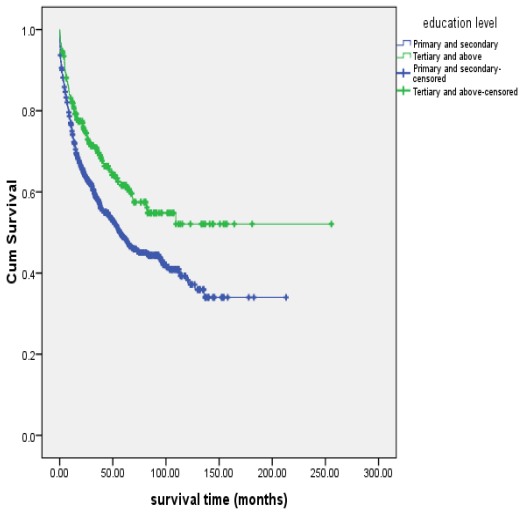
Kaplan Meier was used to assess the impact of the various factors on the time progression to death according to socio-demographic, laboratory and clinical condition. The significant variables of socio-demographic characteristic and laboratory result were; education level (*p-value* < 0.001), occupational type (*p-value* < 0.001), monthly income (*p-value* = 0.002) and baseline hemoglobin (*p-value* = 0.020). Table 4.8 shows the 5 and 10-year survival from Kaplan Meier estimates of all AIDS patients progression to death stratified by significant socio-demographic characteristic and laboratory result. The Kaplan Meier curve for AIDS to death stratified by significant socio-demographic and laboratory variables is presented in Figure 4.7

The significant variables of clinical condition were; exposure risk (*p-value* < 0.001), baseline body mass index (*p-value* = 0.013), opportunistic infection (*p-value* = 0.010), number of opportunistic infections (*p-value* < 0.001) and treatment (*p-value* < 0.001). Table 4.9 shows the 5 and 10-year survival from Kaplan Meier estimates of all AIDS patients progression to death stratified by significant clinical variables. The Kaplan Meier curve of all AIDS patients progression to death stratified by significant of clinical variables is presented in Figure 4.8

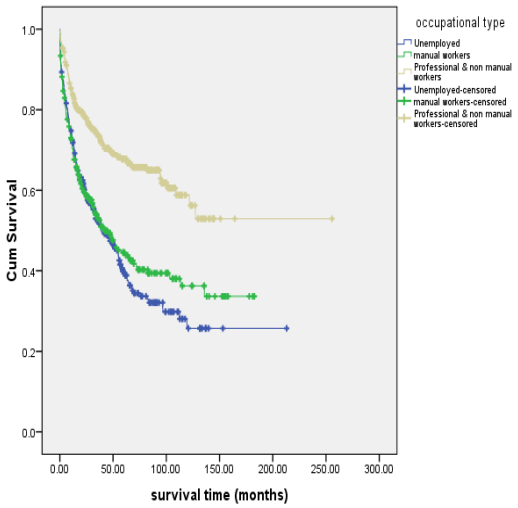
Table 4.8. The 5 and 10-year survival from Kaplan Meier estimates of all AIDS patients progression to death stratified by significant socio-demographic and laboratory variables

Variable	n	Survival (years)	% Survival (95% CI)	Median Survival (95% CI) in months	Log rank *P*-value
Educational level					< 0.001
≤ Secondary	744	5	48.8 (44.9, 52.7)	56.3 (40.9, 71.6)	
		10	38.3 (33.2, 43.4)		
≥ Tertiary	245	5	61.6 (54.6, 68.6)	65.7 (49.9, 81.3)	
		10	52.1 (42.7, 61.5)		
Occupational type					< 0.001
Unemployed	310	5	39.5 (33.4, 45.6)	39.1 (26.9, 51.3)	
		10	25.7 (17.9, 33.5)		
Manual workers	288	5	43.9 (37.4, 50.4)	41.8 (26.9, 56.6)	
		10	33.7 (26.7, 40.7)		
Professional/ non manual worker	391	5	67.3 (62.2, 72.4)	(not calculated)*	
		10	56.2 (47.8, 64.6)		
Monthly income (RM)					0.002
< 1000	337	5	43.9 (37.8, 50.0)	46.3 (35.1, 57.5)	
		10	33.2 (23.8, 42.6)		
1000 to 3000	420	5	58.3 (53.2, 63.4)	96.6 (not calculated)	
		10	46.8 (40.3, 53.3)		
> 3000	232	5	49.2 (41.6, 56.8)	58.8 (42.9, 74.7)	
		10	38.1 (28.2, 48.0)		
Baseline Hb (g/dl)					0.020
<12	420	5	49.2 (43.9, 54.5)	58.8 (28.2, 89.4)	
		10	38.8 (29.4, 48.2)		
≥12	569	5	53.6 (49.1, 58.1)	26.4 (19.6, 33.2)	
		10	41.3 (35.2, 47.4)		

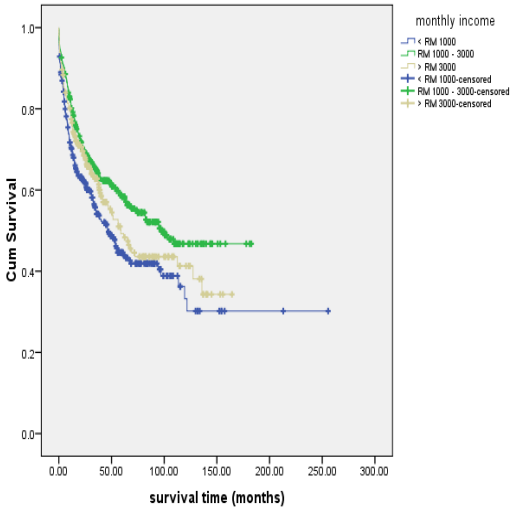
* The median survival was not calculated because the cumulative proportion surviving was still high (> 50%)



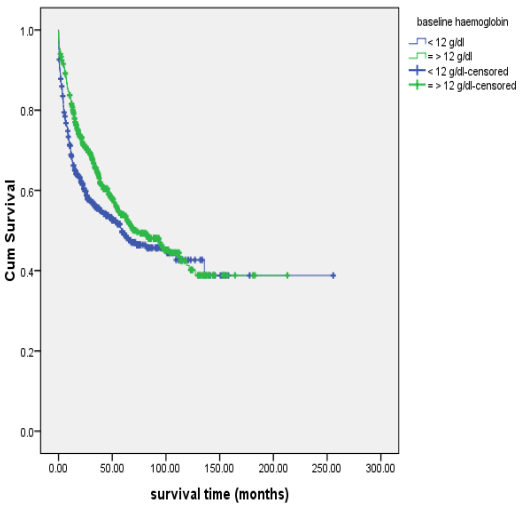
a. Education level



b. Occupational type



c. Monthly income



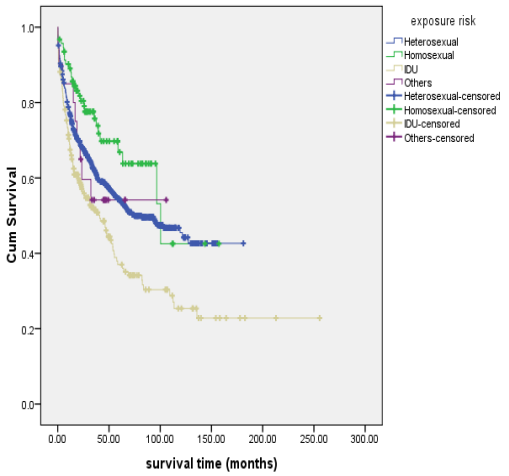
d. Baseline Hb

Figure 4.7 The Kaplan Meier curve of all AIDS patients progression to death stratified by significant socio-demographic and laboratory variables

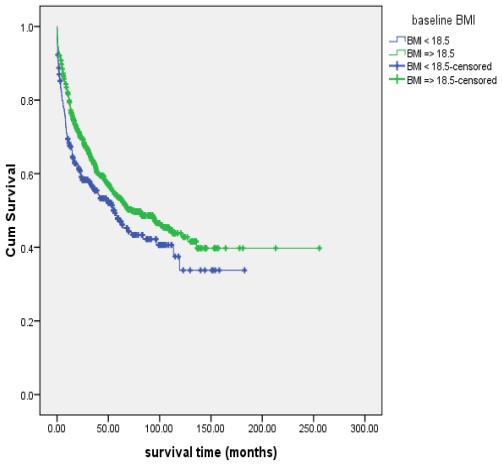
Table 4.9 The 5 and 10-year survival from Kaplan Meier estimates of all AIDS patients progression to death stratified by significant clinical variables

Variable	n	Survival (years)	% Survival (95% CI)	Median Survival (95% CI) in months	Log rank *P*-value
Exposure risk					< 0.001
Heterosexual	665	5	59.2 (55.1, 63.3)	74.5 (48.7, 100.3)	
		10	45.5 (40.2, 50.8)		
Homosexual	93	5	66.9 (55.1, 78.7)	100.4 (55.9, 144.7)	
		10	42.5 (17.0, 68.0)		
IDU	211	5	37.0 (29.2, 44.8)	40.9 (26.4, 55.5)	
		10	25.4 (17.0, 33.8)		
Others	20	5	**	(not calculated)*	
		10	**		
Baseline BMI					0.013
< 18.5	285	5	47.0 (40.3, 53.7)	56.2 (37.4, 75.0)	
		10	33.8 (23.0, 44.6)		
≥ 18.5	704	5	53.4 (49.3, 57.5)	71.9 (49.9, 93.9)	
		10	42.8 (37.5, 48.1)		
OI					0.010
Negative	178	5	58.0 (50.0, 66.0)	(not calculated)*	
		10	50.4 (39.0, 61.8)		
Positive	811	5	50.2 (46.3, 54.1)	61.1 (47.4, 74.8)	
		10	39.5 (34.6, 44.4)		
Number of OI					< 0.001
0	178	5	58.0 (50.0, 66.0)	(not calculated)*	
		10	50.4 (39.0, 61.8)		
1	385	5	58.3 (52.8, 63.8)	112.5(not calculated)	
		10	49.4 (42.3, 56.5)		
2	268	5	47.5 (40.4, 54.6)	54.9 (36.7, 73.0)	
		10	36.4 (27.2, 45.6)		
≥ 3	158	5	33.0 (24.4, 41.6)	20.6 (12.8, 28.5)	
		10	18.4 (9.6, 27.2)		
Treatment					< 0.001
Non ART	330	5	23.6 (18.3, 28.9)	15.0 (11.7, 18.3)	
		10	18.9 (13.6, 24.2)		
ART	659	5	65.6 (61.5, 69.7)	121.7(not calculated)	
		10	51.5 (44.8, 58.2)		

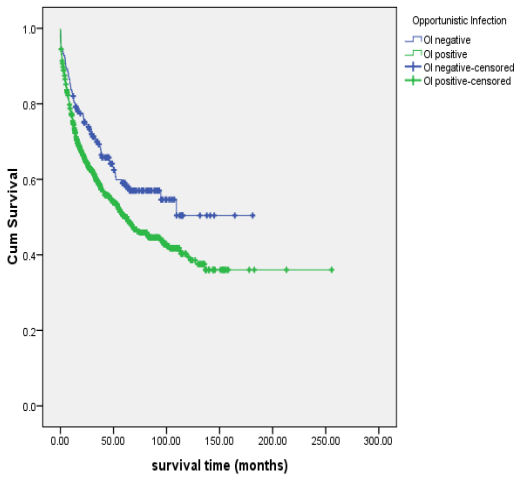
* The median survival was not calculated because the cumulative proportion surviving was still high (> 50%)
** Probability of survival cannot calculate from the survival table because no patients survived 10 years



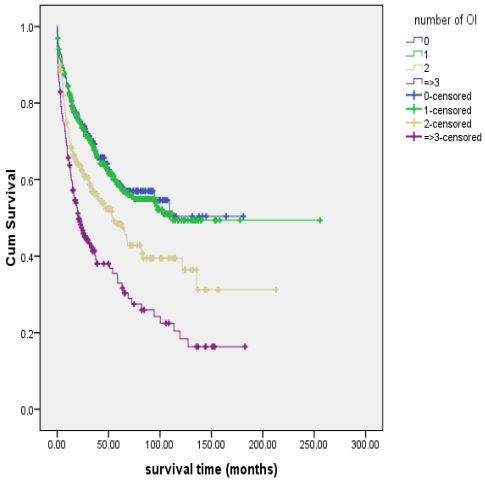
a. Exposure risk



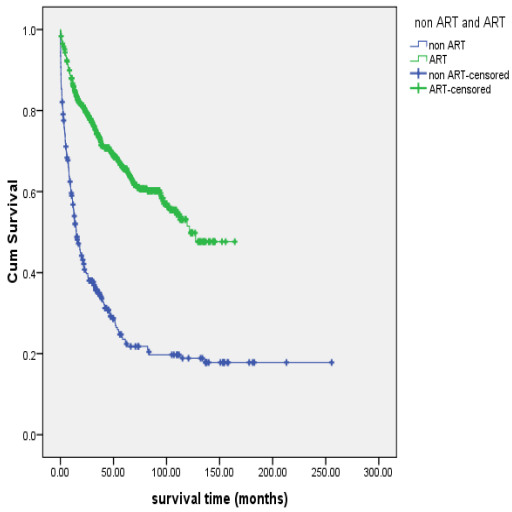
b. Baseline BMI



c. Opportunistic infection (OI)



d. Number of OI

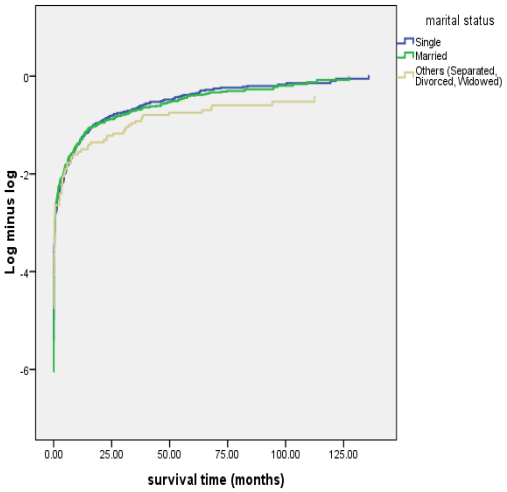


e. Treatment ART and non ART

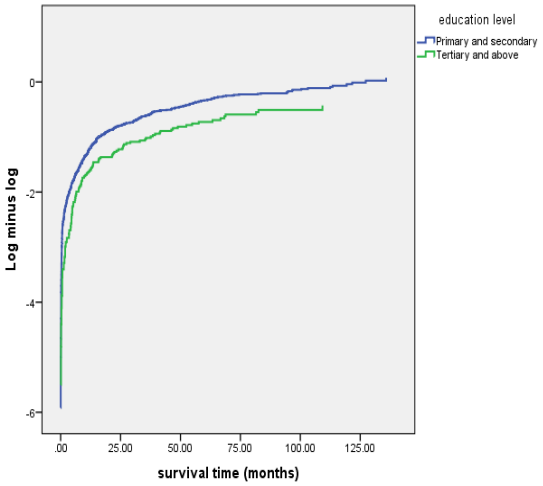
Figure 4.8 The Kaplan Meier curve of all AIDS patients progression to death stratified by significant clinical variables

The Cox regression analysis was used to look for independent predictors of death. The log rank *p-value* less than 0.25 was set as cut off values to choose variables for univariate analysis. Fifteen variables have a log rank *p-value* of less than 0.25. That included are age groups, gender, marital status, education level, occupational type, monthly income, baseline CD4, viral load, hemoglobin, total lymphocyte count, body mass index, exposure risk, opportunistic infection, number of opportunistic infection and anti-retroviral therapy. These variables included in the univariate Cox regression analysis. All possible two way interactions between the variables in the main effect model were checked. No significant interaction term was identified. There were three variables not significant in the univariate Cox regression analysis (age groups, gender and monthly income).

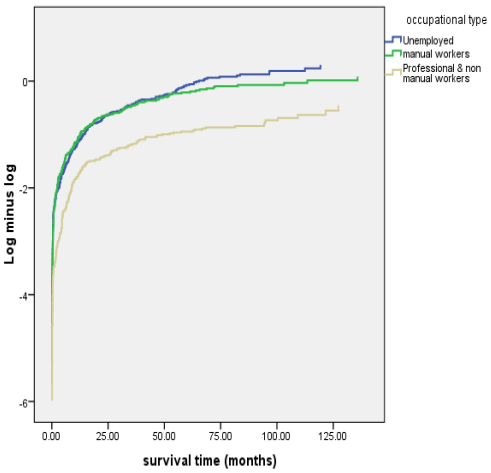
The proportional hazards assumption univariate was tested in two ways. First, by the log minus log estimated survivor function plotted against survival in variables. Twelve variables had parallel lines which indicated that the proportional hazard assumption was fulfilled. Four variables (baseline CD4, viral load, hemoglobin, total lymphocyte count) did not have parallel lines which indicated proportional hazard assumption violation. The viewing Log–Minus-Log plot of variables socio-demographic characteristic and clinical condition can see in Figure 4.9 and Figure 4.10.



a. Marital status

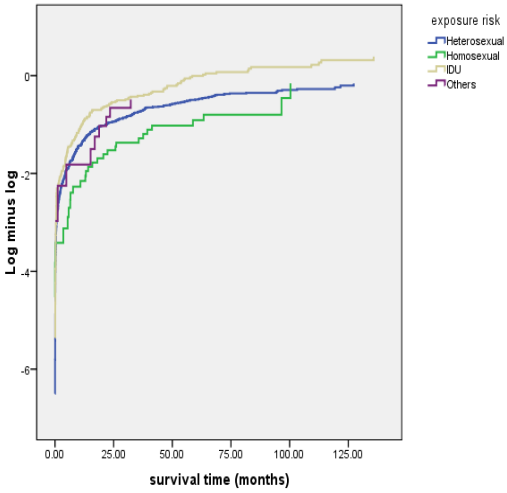


b. Education level

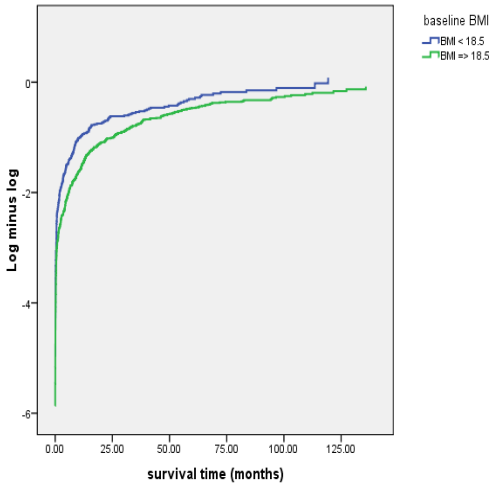


c. Occupational type

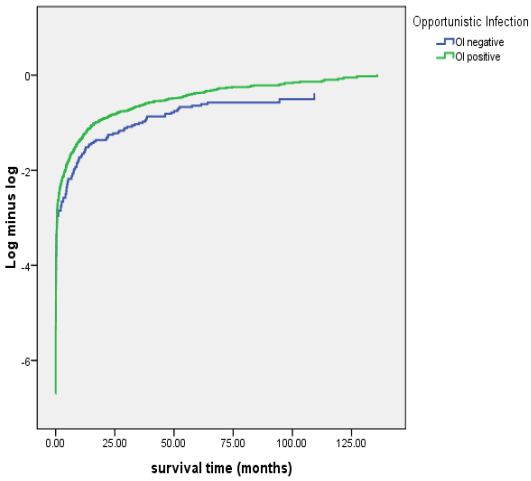
Figure 4.9 The Log-Minus-Log plotted against survival time of all AIDS patients progression to death stratified by socio-demographic variables



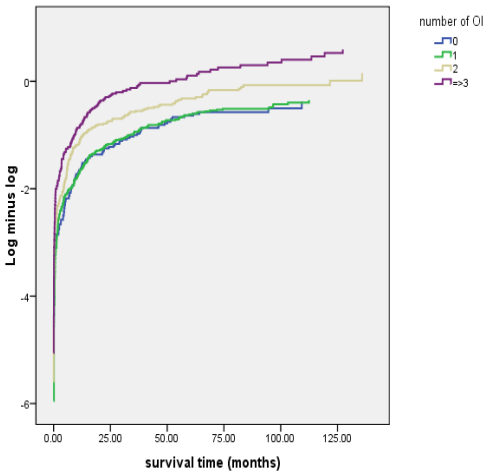
a. Exposure risk



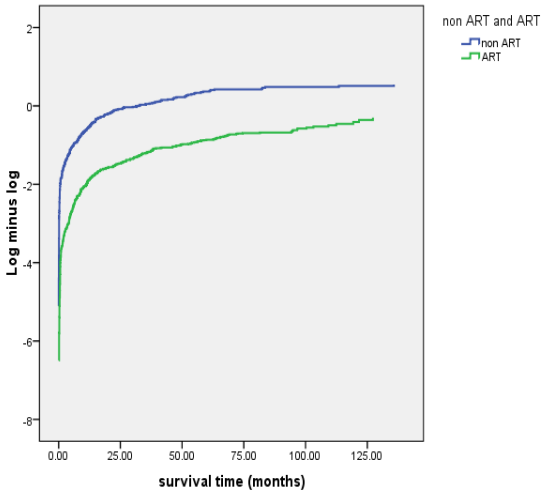
b. Baseline BMI



c. Opportunistic infection



d. Number of OI



e. Treatment non ART and ART

Figure 4.10 The Log-Minus_Log plotted against survival time of all AIDS patients progression to death stratified by clinical variables

There are eight variables fulfilled the proportional hazard assumption and included in multivariate Cox regression analysis. The univariate Cox regression analysis of variables as predictors AIDS patients progression to death is presented in Table 4.10.

Table 4.10 Univariate predictors of death in all AIDS patients

Variable	Crude Hazard Ratio	95% CI
Marital status		
Single	1.0	
Married	0.97	0.79, 1.17
Others	0.72	0.52, 0.99
Educational level		
≥ Tertiary	1.0	
≤ Secondary	1.49	1.18, 1.88
Occupational type		
Professional and non manual workers	1.0	
Manual workers	2.03	1.60, 2.58
Unemployed	2.23	1.78, 2.79
Exposure Risk		
Heterosexual	1.0	
Homosexual	0.64	0.43, 0.95
IDU	1.52	1.23, 1.87
Others	1.08	0.55, 2.09
Baseline BMI		
≥ 18.5	1.0	
< 18.5	1.28	1.05, 1.56
Opportunistic Infection		
Negative	1.0	
Positive	1.39	1.08, 1.80
Number of OI		
0	1.0	
1	1.03	0.78, 1.37
2	1.53	1.15, 2.05
≥ 3	2.37	1.75, 3.21
Treatment		
ART	1.0	
Non ART	3.33	2.77, 4.00

In a multivariate Cox regression analysis only three variables were significant (occupational type, number of opportunistic infection and anti-retroviral therapy). Table 4.11 displays the multivariate Cox regression analysis of predictors of death in AIDS patients. The significant independent predictors of AIDS patients to death were being unemployed, manual workers, those who have three or more opportunistic infections and did not receive anti-retroviral therapy were more likely to die compared to their reference categories.

Table 4.11 Multivariate predictors of death in AIDS patients

Variable	Crude Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Occupational type				
Professional and non manual worker	1.0		1.0	
Manual workers	2.03	1.60, 2.58	1.47	1.15, 1.87
Unemployed	2.23	1.78, 2.79	1.59	1.26, 2.02
Number of OI				
0	1.0		1.0	
1	1.03	0.78, 1.37	0.93	0.70, 1.24
2	1.53	1.15, 2.05	1.30	0.97, 1.74
≥ 3	2.37	1.75, 3.21	1.90	1.39, 2.58
Treatment				
ART	1.0		1.0	
Non ART	3.33	2.77, 4.00	2.89	2.37, 3.47

4.7 Progression to death in AIDS patients on HAART

Survival probabilities of AIDS patients on HAART progression to death stratified by significant socio-demographic, laboratory, clinical and HAART variables

Table 4.12 shows the 5 and 10-year survival according to socio-demographic characteristic variables among AIDS patients on HAART. The significant variables were occupational type (*p-value* = 0.001) and monthly income (*p-value* = 0.029). The Kaplan Meier curve for AIDS to death according to significant variables of socio-demographic characteristic is presented in Figure 4.11.

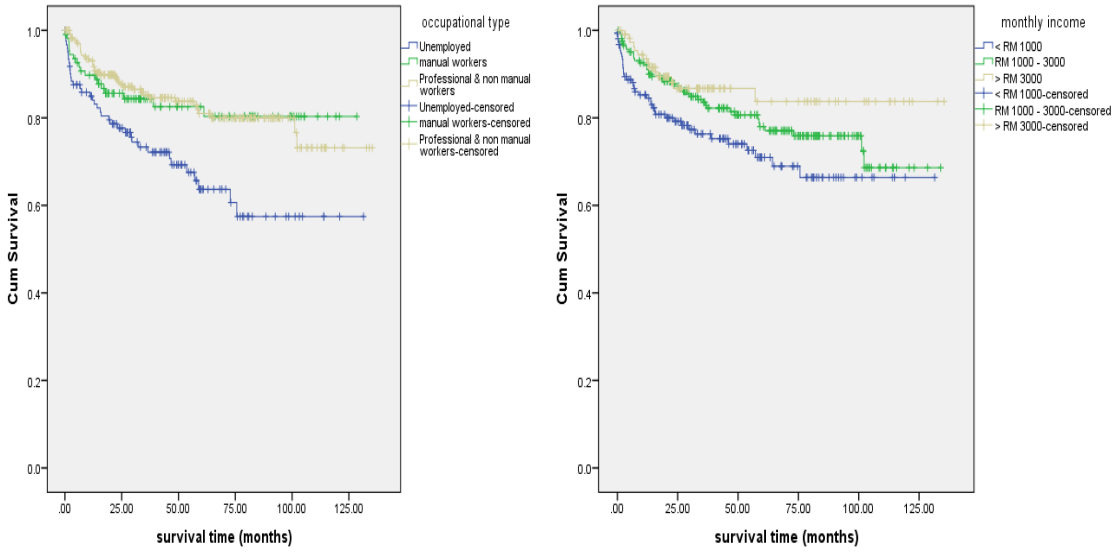
Table 4.13 shows the 5 and 10-year survival of Kaplan Meier estimates AIDS patients on HAART progression to death stratified by significant laboratory variables. The significant variables were hemoglobin at HAART initiation (*p-value* = 0.036), CD4 recovers (*p-value* < 0.001), hemoglobin recovers (*p-value* < 0.001) and total lymphocyte count recovers (*p-value* < 0.001). The Kaplan Meier curve for AIDS to death according to significant variables of laboratory result is presented in Figure 4.12.

Table 4.14 shows the 5 and 10-year survival from Kaplan Meier estimates AIDS patients on HAART progression to death, stratified by significant clinical condition and HAART variables. The significant variables were numbers of opportunistic infection (*p-value* < 0.043) and achieve viral load less than 50 copies/ml (*p-value* < 0.001). The Kaplan Meier curve for AIDS to death according to significant variables of clinical and HAART can be seen in the Figure 4.13.

Table 4.12 The 5 and 10-year survival from Kaplan Meier estimates of AIDS patients on HAART to death stratified by significant socio-demographic variables

Variable	n	Survival (years)	% Survival (95% CI)	Mean Survival (95% CI) in months#	Log rank *P* value
Occupational type					0.001
Unemployed	122	5	48.8 (40.8, 56.8)	87.9 (76.8, 99.2)	
		10	**		
Manual workers	110	5	80.3 (71.7, 88.9)	106.6 (97.4, 115.9)	
		10	**		
Professional and non manual worker	242	5	81.0 (75.1, 86.9)	110.9 (103.9, 117.9)	
		10	73.2 (62.6, 83.8)		
Monthly income (RM)					0.029
< 1000	156	5	56.6 (48.8, 64.4)	95.5 (85.8, 105.1)	
		10	42.5 (26.6, 58.4)		
1000 to 3000	206	5	69.0 (63.1, 74.9)	105.8 (98.3, 113.4)	
		10	57.1 (48.1, 66.1)		
> 3000	112	5	64.0 (55.4, 72.6)	116.6 (107.3, 125.9)	
		10	52.6 (39.9, 65.4)		

#Mean survival because most of the median survival was not calculated
** Probability of survival cannot calculate from the survival table because no patients survived 10 years



a. Occupational type b. Monthly income

Figure 4.11 The Kaplan Meier curve of AIDS patients on HAART to death stratified by significant socio-demographic variables

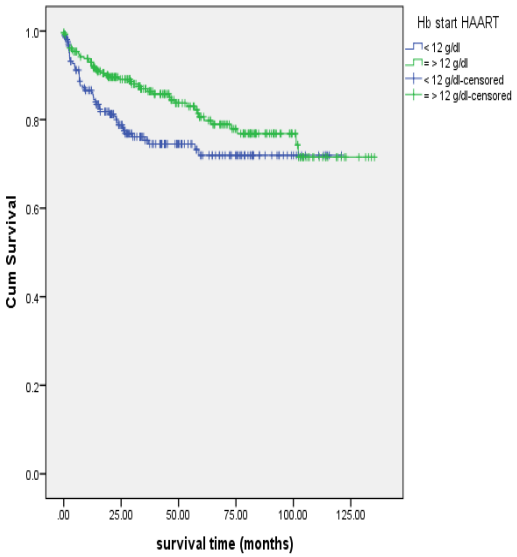
Table 4.13 The 5 and 10-year survival from Kaplan Meier estimates in AIDS patients on HAART to death stratified by laboratory variables

Variable	n	Survival (years)	% Survival (95% CI)	Mean Survival (95% CI) in months#	Log rank *P* value
CD4 at start HAART (cell/µL)					0.753
< 200	399	5	75.9 (71.0, 80.8)	105.7 (99.9, 111.5)	
		10	70.8 (63.2, 78.4)		
≥ 200	75	5	77.5 (65.3, 89.7)	104.4 (91.5, 117.4)	
		10	69.5 (54.4, 84.6)		
Hb at start HAART (g/dl)					0.036
< 12	211	5	71.9 (64.8, 79.0)	91.7 (84.6, 98.8)	
		10	**		
≥ 12	263	5	79.8 (73.7,85.9)	109.6(102.9, 116.2)	
		10	71.5 (62.1, 80.9)		
TLC at start HAART					0.930
Normal	247	5	77.9 (72.0, 83.8)	105.9 (98.8, 113.1)	
		10	69.9 (60.9, 78.9)		
Abnormal	227	5	73.8 (66.5, 81.1)	105.3 (97.8, 112.9)	
		10	**		
CD4 recovers					< 0.001
No	200	5	50.3 (39.7, 60.9)	74.4 (63.5, 85.4)	
		10	**		
Stable	56	5	84.6 (72.3, 96.9)	114.9(102.8, 127.0)	
		10	**		
Yes	218	5	91.1 (86.6, 95.6)	124.4(119.4, 129.4)	
		10	87.2 (79.8, 94.6)		
Hb recovers					< 0.001
No	197	5	52.4 (42.5, 62.3)	73.9 (63.1, 84.9)	
		10	**		
Stable	146	5	93.8 (89.3, 98.3)	126.1(120.5, 131.6)	
		10	**		
Yes	131	5	85.2 (77.8, 92.6)	113.8(106.6, 121.0)	
		10	**		
TLC recovers					< 0.001
No	195	5	52.2 (41.6, 62.8)	76.4 (65.3, 87.4)	
		10	**		
Stable	153	5	89.8 (84.5, 95.1)	121.4(114.9, 127.8)	
		10	**		
Yes	126	5	86.5 (79.1, 93.9)	115.3(108.2, 122.3)	
		10	**		

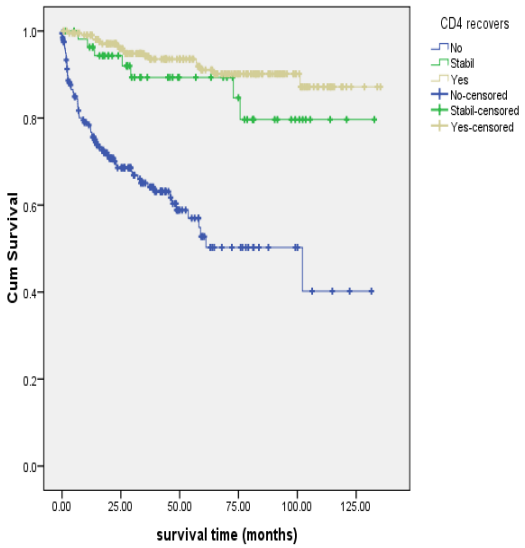
Note: - CD4 recovers from CD4 < 200 cell/µL to CD4 ≥ 200 cells/µL
- Hb = hemoglobin, recovers from Hb < 12 g/dl to Hb ≥ 12 g/dl
- TLC = total lymphocyte count, recovers from TLC < 1,200 cell/µL to TLC ≥ 1,200 cells/µL

#Mean survival because most of the median survival was not calculated

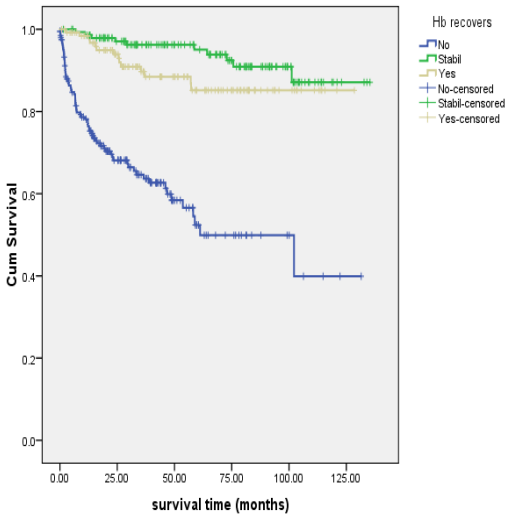
** Probability of survival cannot be calculated from the survival table because no patients survived for 10 years



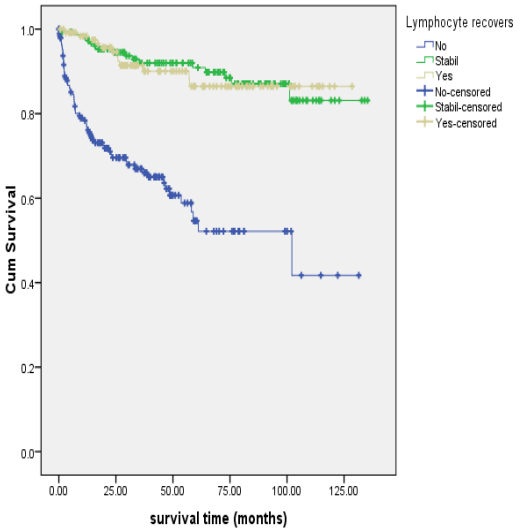
a. Hb at start HAART



b. CD4 recovers



c. Hb recovers



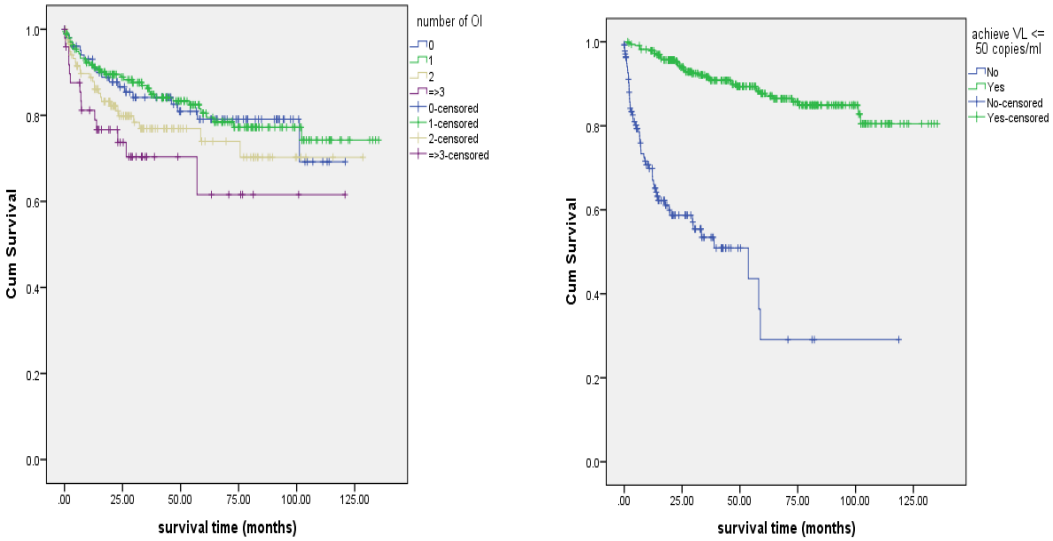
d. TLC recovers

Figure 4.12 The Kaplan Meier curve of AIDS patients on HAART to death stratified by significant laboratory variables

Table 4.14 The 5 and 10-year survival from Kaplan Meier estimates in AIDS patients on HAART stratified by significant clinical and HAART variables

Variable	n	Survival (years)	% Survival (95% CI)	Mean Survival (95% CI) in months#	Log rank *P* value
Number of OI					0.043
0	103	5	79.1 (70.1, 88.1)	98.3 (89.2, 107.4)	
		10	**		
1	201	5	79.5 (73.0, 86.0)	110.2 (102.8, 117.5)	
		10	**		
2	120	5	74.0 (64.2, 83.8)	97.7 (87.1, 108.3)	
		10	**		
≥ 3	50	5	61.6 (41.4, 81.8)	82.2 (64.7, 99.8)	
		10	**		
Achieve VL ≤ 50 copies/ml					< 0.001
No	140	5	29.1 (9.5, 48.7)	52.3 (38.2, 66.5)	
		10	**		
Yes	334	5	87.1 (83.0, 91.2)	118.8 (113.9, 123.7)	
		10	80.5 (73.1, 87.9)		

#Mean survival because most of the median survival was not calculated
** Probability of survival cannot calculate from the survival table because no patients survived 10 years



a. Number of OI

b. Achieve VL ≤ 50 copies/ml

Figure 4.13 The Kaplan Meier curve of AIDS patients on HAART to death stratified by clinical and HAART variables

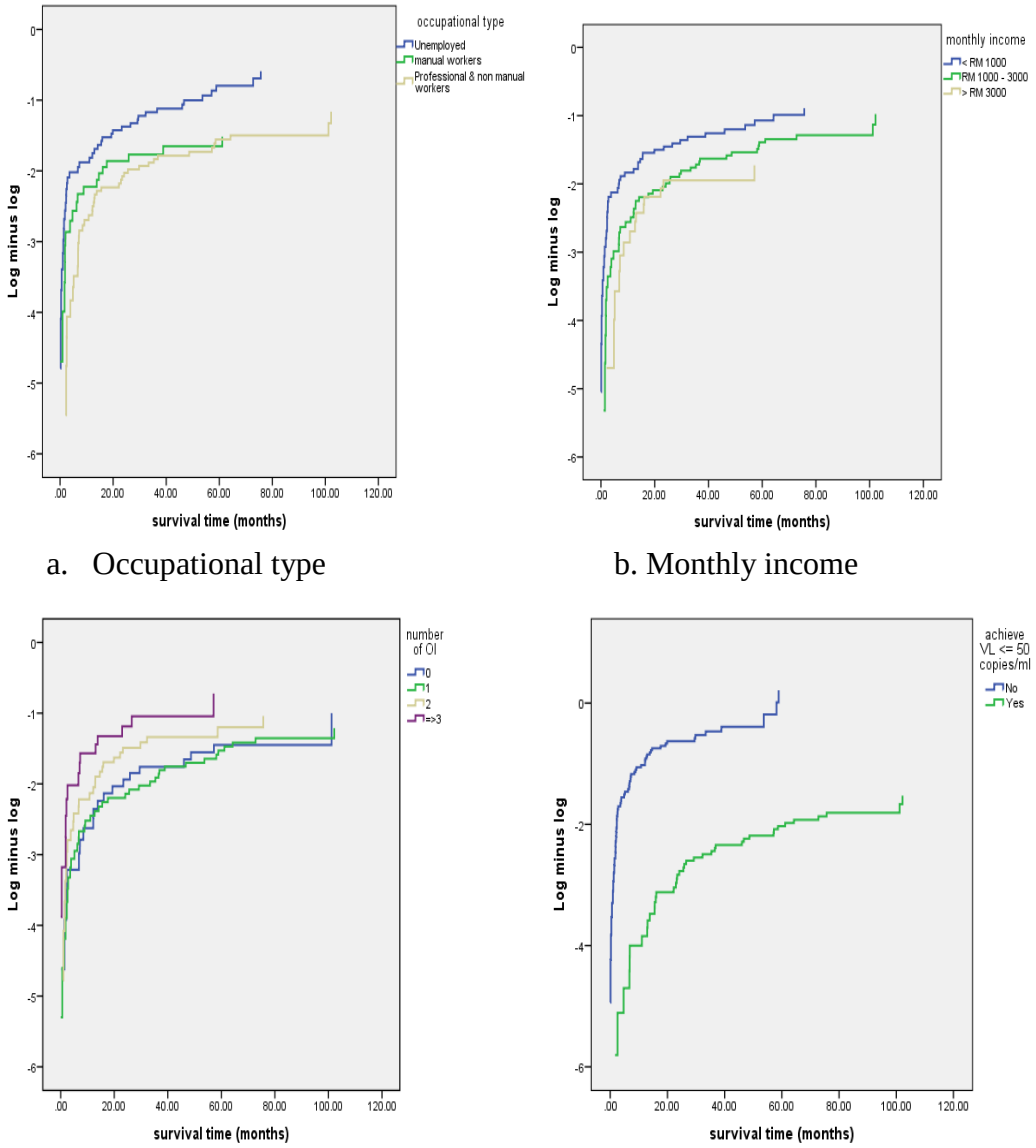
There were nine variables that met the criteria log rank *p-value* less than 0.25. It were occupational type, education level, monthly income, hemoglobin at start HAART, CD4 recovers, hemoglobin recovers, total lymphocyte count recovers, number of opportunistic infections and achieve viral load less than 50 copies/ml. All these variables were included in the univariate Cox regression analysis. All possible two way interactions were checked and no significant interaction was found.

The proportional hazard assumption was checked by two methods. First with the log minus log estimated survivor function plotted against survival showed the parallel line. Second with the correlation test between residuals and survival time showed correlation very small (less than 0.3). The variable education level did not show parallel lines which indicated a proportional hazard assumption violation, other variables had parallel line. The Log –Minus-Log plots of the variables are displayed in Figure 4.14 and Figure 4.15.

There were eight variables which fulfilled the proportional hazard assumption and were included in multivariate Cox regression analysis. The length of time taken to recover CD4 (*p-value* = 0.053), hemoglobin (*p-value* = 0.129) and total lymphocyte count (*p-value* = 0.269) were not significant in this analysis. The univariate Cox regression analysis of significant variables as predictors of death in AIDS patients on HAART is presented in Table 4.15.

Three significant variables in multivariate Cox regression analysis (Occupational type, CD4 recovers and achieve viral load less than 50 copies/ml). Table 4.16 displays the multivariate Cox regression analysis of death predictors in AIDS patients on HAART.

Significant independent predictors of death in AIDS patients on HAART were unemployed patients, those who's CD4 never recovered to more than 200 cells/μL and those who were unable to achieve viral load less than 50 copies/ml. These patients were more likely to die compared to their reference categories.



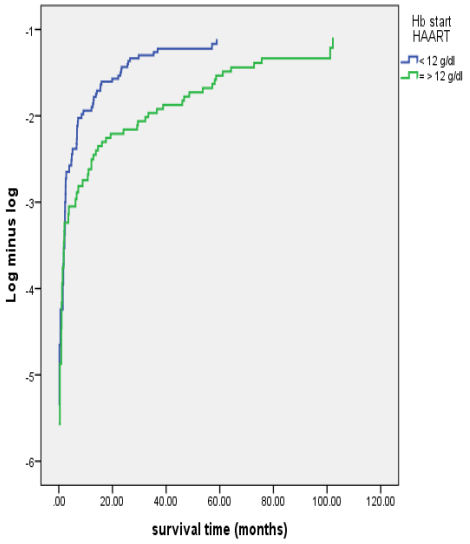
a. Occupational type

b. Monthly income

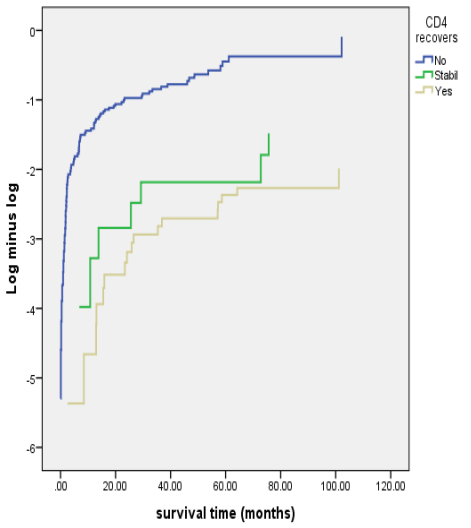
c. Number of OI

d. Achieve VL ≤ 50 copies/ml

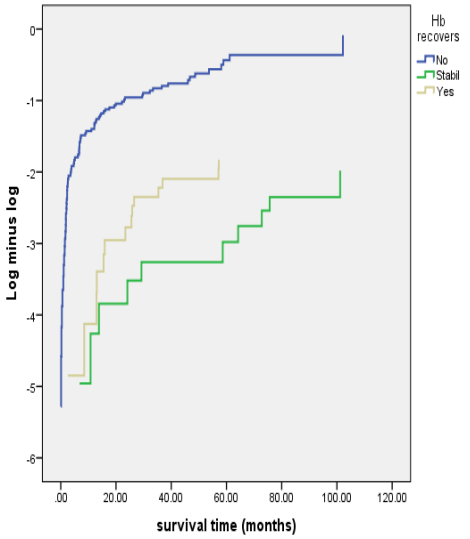
Figure 4.14 The Log-Minus-Log plotted against survival time of AIDS patients on HAART stratified by socio-demographic, clinical and HAART variables



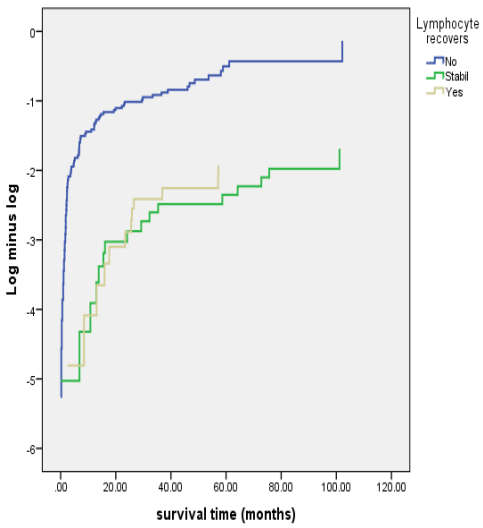
a. Hb at start HAART



b. CD4 recovers



c. Hb recovers



d. TLC recovers

Figure 4.15 The Log-Minus-Log plotted against survival time of AIDS patients on HAART to death stratified by laboratory variables

Table 4.15 Univariate predictors of death in AIDS patients on HAART

Variable	Crude Hazard Ratio	95% CI
Occupational type		
Professional and non manual workers	1.0	
Manual workers	1.06	0.61, 1.86
Unemployed	2.14	1.37, 3.35
Monthly income (RM)		
> 3000	1.0	
1000 to 3000	1.44	0.79, 2.64
< 1000	2.14	1.16, 3.95
Hb at start ART (g/dl)		
≥ 12	1.0	
< 12	1.53	1.02, 2.29
CD4 recovers		
Yes	1.0	
Stable	1.76	0.73, 4.24
No	7.54	4.39, 12.92
Hb recovers		
Yes	1.0	
Stable	0.54	0.24, 1.22
No	4.99	2.79, 8.89
TLC recovers		
Yes	1.0	
Stable	0.95	0.45, 1.99
No	5.14	2.77, 9.54
Number of OI		
0	1.0	
1	0.96	0.55, 1.67
2	1.43	0.79, 2.59
≥ 3	2.15	1.08, 4.31
Achieve VL ≤ 50 copies		
Yes	1.0	
No	8.08	5.21, 12.53

Note: - CD4 recovers from CD4 < 200 cell/µL to CD4 ≥ 200 cell/µL
- Hb = haemoglobin, recovers from Hb < 12 g/dl to Hb ≥ 12 g/dl
- TLC = total lymphocyte count, recovers from TLC < 1,200 cell/µL to ≥ 1,200 cell/µL

Table 4.16 Multivariate predictors of death in AIDS patients on HAART

Variable	Crude Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Occupational type				
Professional and non manual worker	1.0		1.0	
Manual workers	1.06	0.61, 1.86	0.77	0.44, 1.36
Unemployed	2.14	1.16, 3.95	1.64	1.04, 2.57
CD4 recovers				
Yes	1.0		1.0	
Stable	1.76	0.73, 4.24	1.56	0.65, 3.79
No	7.54	4.39, 2.92	4.03	2.21, 7.35
Achieve VL ≤ 50 copies				
Yes	1.0		1.0	
No	8.08	5.21, 2.53	4.39	2.69, 7.16

Note: - CD4 recovers from CD4 < 200 cell/µL to CD4 ≥ 200 cell/µL

4.8 Progression to death in AIDS patients not on anti-retroviral therapy

Survival probabilities of AIDS patients not on ART stratified by significant socio-demographic, laboratory and clinical variables

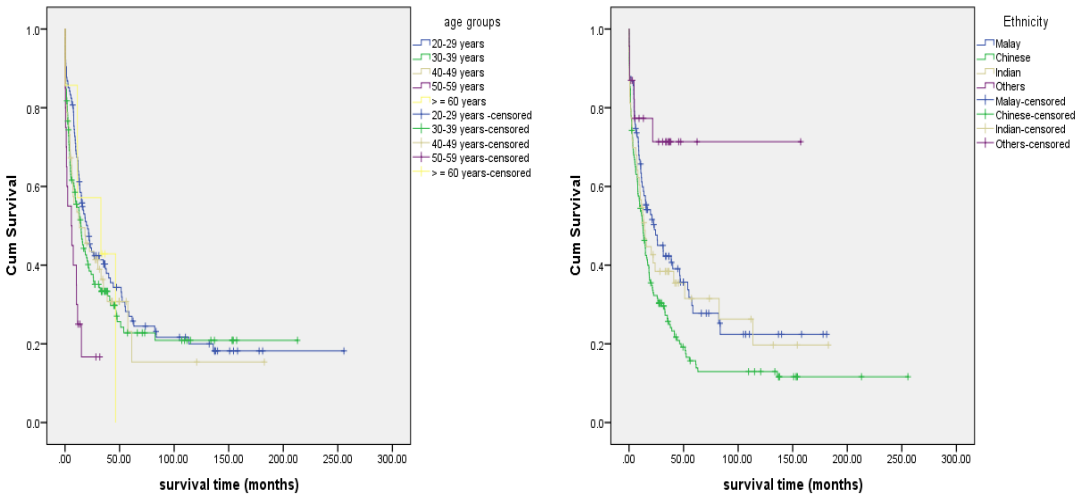
Table 4.17 shows the 5 and 10-year survival for AIDS patients not on anti-retroviral therapy stratified by significant socio-demographic characteristic variables. The significant variables were age groups (*p-value* = 0.030) and ethnicity (*p-value* = 0.003). The Kaplan Meier curves for AIDS patients not receiving anti-retroviral therapy progression to death stratified by significant socio-demographic characteristic variables are displayed in Figure 4.16.

Table 4.18 shows the 5 and 10-year survival for AIDS patients not on anti-retroviral therapy stratified by significant laboratory and clinical variables. The significant variables were baseline CD4 (*p-value* < 0.001), baseline viral load (*p-value* = 0.009), WHO clinical stage (*p-value* < 0.001) and number of opportunistic infections (*p-value* = 0.023). The Kaplan Meier curves for AIDS patients not on anti-retroviral therapy stratified by significant laboratory and clinical variables are displayed in Figure 4.17.

Table 4.17 The 5 and 10-year survival of Kaplan Meier estimates in AIDS patients not on anti-retroviral therapy stratified by significant socio-demographic variables

Variable	N	Survival (years)	% Survival (95% CI)	Median Survival (95% CI) in months	Log rank *P* value
Age Groups (years)					0.030
20 – 29	114	5	27.0 (18.0, 36.0)	20.6 (13.9, 27.3)	
		10	20.0 (11.6, 28.4)		
30 – 39	137	5	22.8 (14.6, 31.0)	14.5 (9.3, 19.8)	
		10	**		
40 – 49	52	5	23.1 (6.6, 39.6)	13.2 (0.1, 29.6)	
		10	**		
50 – 59	20	5	**	5.8 (0.1, 14.1)	
		10	**		
≥ 60	7	5	**	2.9 (0.1, 8.0)	
		10	**		
Ethnicity					0.003
Malay	91	5	27.8 (17.0, 38.6)	23.2 (8.7, 37.7)	
		10	**		
Chinese	163	5	14.8 (8.7, 20.9)	12.8 (9.1, 16.5)	
		10	11.6 (5.9, 17.3)		
Indian	53	5	31.5 (17.4, 45.6)	14.1 (7.9, 20.3)	
		10	19.7 (3.8, 35.6)		
Others	23	5	**	(not calculated)*	
		10	**		

*The median survival was not calculated because the cumulative proportion surviving was still high (> 50%)
** Probability of survival cannot be calculated from the survival table because no patients reached 10-year survival



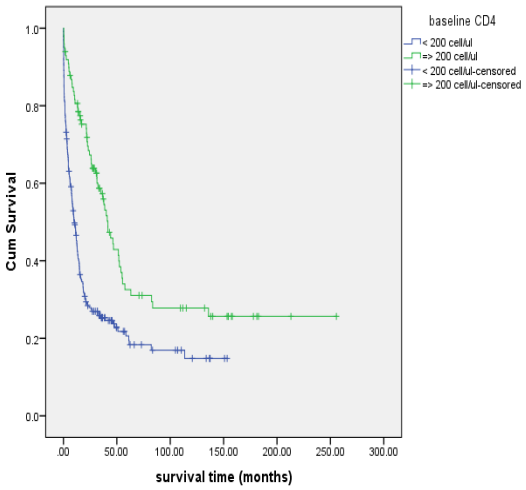
a. Age group b. Ethnicity

Figure 4.16 The Kaplan Meier curve of AIDS patients not on anti-retroviral therapy stratified by significant socio-demographic variables

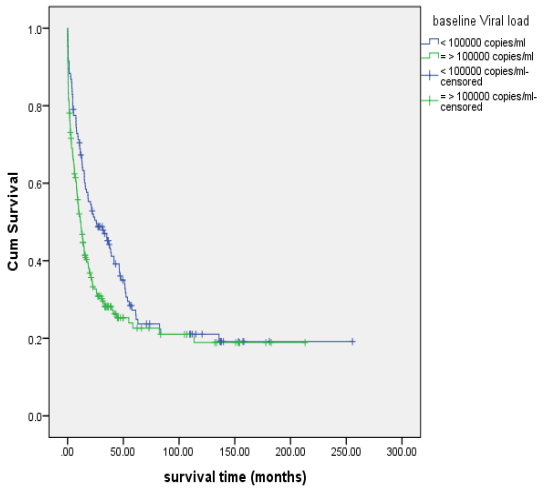
Table 4.18 The 5 and 10-year survival of Kaplan Meier estimates in AIDS patients not on anti-retroviral therapy stratified by significant laboratory and clinical variables

Variable	N	Survival (years)	% Survival (95% CI)	Median Survival (95% CI) in months	Log rank *P* value
Baseline CD4 (cell/µL)					< 0.001
< 200	231	5	19.5 (13.4, 25.6)	10.1 (7.4, 12.8)	
		10	14.8 (8.1, 21.5)		
≥ 200	99	5	32.5 (21.9, 43.1)	41.6 (32.6, 50.5)	
		10	25.7 (15.3, 36.1)		
Baseline VL (copies/ml)					0.009
< 100000	129	5	26.1 (17.7, 34.5)	25.8 (11.4, 40.2)	
		10	19.2 (11.0, 27.4)		
≥ 100000	201	5	22.6 (15.7, 29.5)	11.5 (8.5, 14.5)	
		10	18.9 (11.5, 26.3)		
WHO clinical stage					< 0.001
Stage 3	105	5	34.5 (23.7, 45.3)	41.6 (29.9, 53.4)	
		10	27.5 (16.7, 38.3)		
Stage 4	225	5	19.2 (13.3, 25.1)	9.4 (6.9, 11.8)	
		10	13.6 (7.1, 20.1)		
Number of OI					0.023
0	45	5	**	21.4 (9.2, 33.6)	
		10	**		
1	124	5	29.1 (19.9, 38.3)	21.0 (14.3, 27.7)	
		10	**		
2	98	5	25.5 (14.9, 36.1)	12.5 (4.5, 20.4)	
		10	14.9 (3.3, 26.5)		
≥ 3	63	5	16.4 (5.6, 27.2)	10.1 (5.1, 15.1)	
		10	**		

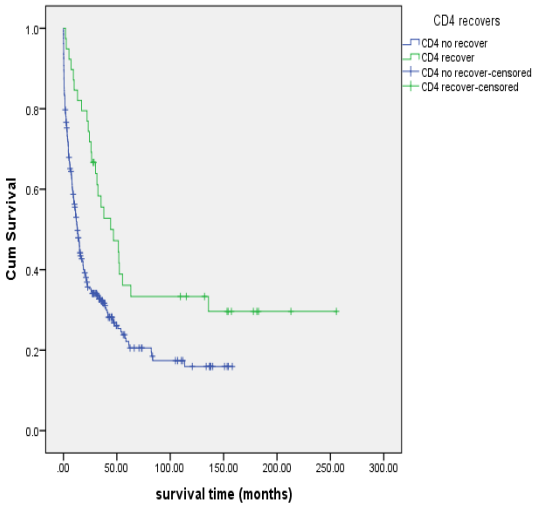
** Probability of survival cannot be calculated from the survival table because no patients attained 10-year survival



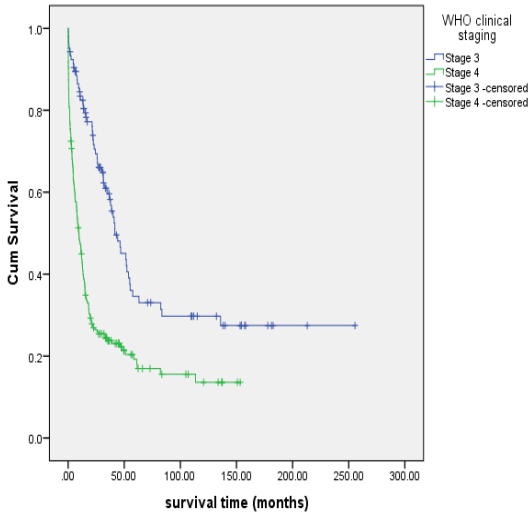
a. Baseline CD4



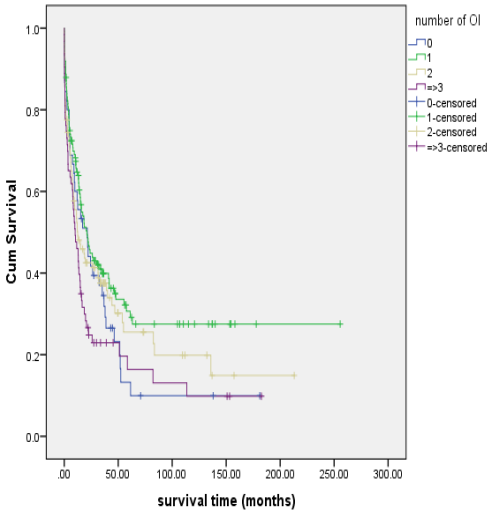
b. Baseline VL



c. Baseline CD4



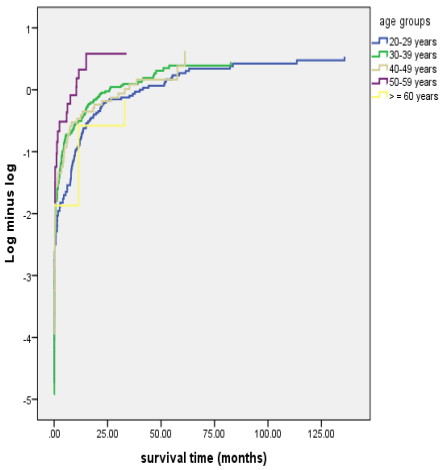
d. Baseline viral load



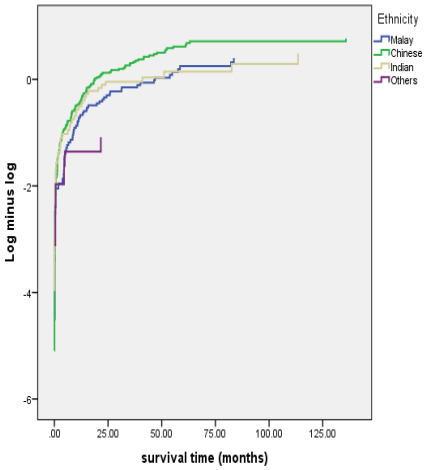
e. Number of OI

Figure 4.17 The Kaplan Meier curve of AIDS patients not on anti-retroviral therapy stratified by significant laboratory and clinical variables

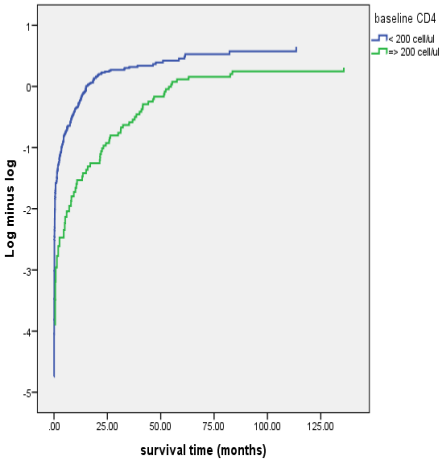
There were eleven variables with log rank *p-value* less than 0.25. There were age groups, gender, ethnicity, marital status, education level, monthly income, baseline CD4, viral load, total lymphocyte count, WHO clinical stage and number of opportunistic infection. These variables included in the univariate Cox regression analysis. All possible interactions between the variables in the main effect model were checked with no significant interaction found. The proportional hazards assumption was checked using the Log –Minus-Log plots which showed parallel lines indicating that the proportional hazard assumption was fulfilled (Figure 4.18). There were six variables (gender, marital status, education level, monthly income, baseline total lymphocyte count and number of opportunistic infection) which did not show parallel lines.



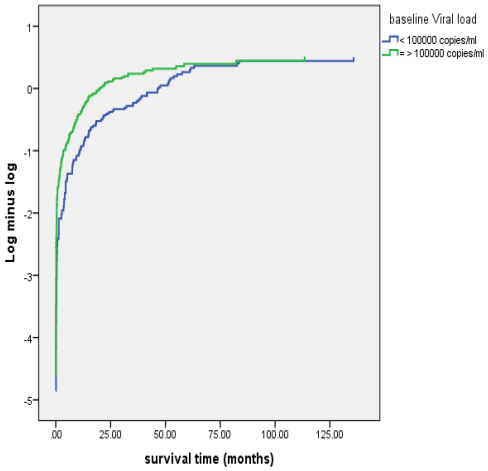
a. Age group



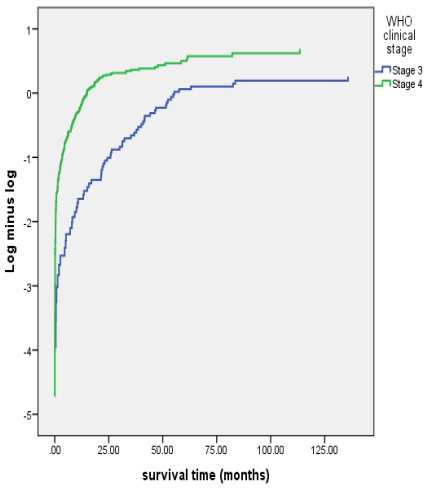
b. Ethnicity



c. Baseline CD4



d. Baseline VL



d. WHO clinical stage

Figure 4.18 The Log-Minus-Log plotted against survival time of AIDS patients not on anti-retroviral therapy stratified by socio-demographic, laboratory and clinical variables

The five variables which fulfilled the proportional hazard assumption were included in the multivariate Cox regression analysis. There were age groups, ethnicity, baseline CD4, baseline viral load and WHO clinical stage. The univariate analysis of predictors AIDS patients not on anti-retroviral therapy progression to death is presented in Table 4.19. In the multivariate Cox regression analysis, only three variables were significant (ethnicity, baseline viral load and WHO clinical stage). Table 4.20 shows the multivariate Cox regression analysis of predictors AIDS patients not on anti-retroviral therapy progression to death. Chinese patients, those with baseline viral load more than 100,000 copies/ml and in WHO clinical stage 4 were more likely to die compared to their reference categories, the others ethnic group had a significantly lower risk of death (HR 0.35; 95% CI 0.15, 0.82) compared to Malays.

Table 4.19 Univariate predictors of death in AIDS patients not on anti-retroviral therapy

Variable	Crude Hazard Ratio	95% CI
Age groups		
20 – 29	1.0	
30 – 39	1.20	0.89, 1.61
40 – 49	1.17	0.79, 1.74
50 – 59	2.41	1.40, 4.16
≥ 60	1.07	0.43, 2.63
Ethnicity		
Malay	1.0	
Chinese	1.50	1.11, 2.04
Indian	1.16	0.77, 1.75
Others	0.42	0.18, 0.96
Baseline CD4 (cell/µL)		
≥ 200	1.0	
< 200	2.13	1.59, 2.87
Baseline VL (copies/ml)		
< 100000	1.0	
≥ 100000	1.42	1.09, 1.85
WHO clinical stage		
Stage 3	1.0	
Stage 4	2.39	1.77, 3.22

Table 4.20 Multivariate predictors of death in AIDS patients not on anti-retroviral therapy

Variable	Crude Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Ethnicity				
Malay	1.0		1.0	
Chinese	1.50	1.11, 2.04	1.57	1.15, 2.15
Indian	1.16	0.77, 1.75	1.12	0.74, 1.69
Others	0.42	0.18, 0.96	0.35	0.15, 0.82
Baseline VL (copies/ml)				
< 100000	1.0		1.0	
≥ 100000	1.42	1.09, 1.85	1.35	1.02, 1.79
WHO clinical stage				
Stage 3	1.0		1.0	
Stage 4	2.39	1.77, 3.22	2.25	1.65, 3.06

4.9 AIDS patients on HAART achieving viral load less than 50 copies/ml

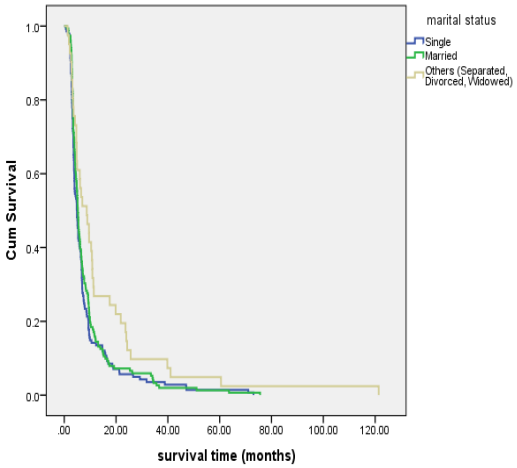
Survival probabilities of AIDS patients on HAART to achieve viral load less than 50 copies/ml stratified by significant socio-demographic characteristic and HAART variables

Table 4.21 displays the Kaplan Meier estimates to achieve viral load less than 50 copies/ml stratified by significant variables of socio-demographic characteristic, laboratory and clinical condition. The significant variables were marital status (*p-value* = 0.018), education level (*p-value* = 0.016), monthly income (*p-value* = 0.012), total lymphocyte count at start HAART (*p-value* = 0.043), exposure risk (*p-value* = 0.007) and WHO clinical stage (*p-value* = 0.017). The Kaplan Meier curves for AIDS patients on HAART to achieve viral load less than 50 copies/ml stratified by significant socio-demographic characteristic, laboratory and clinical variables are presented in Figure 4.19.

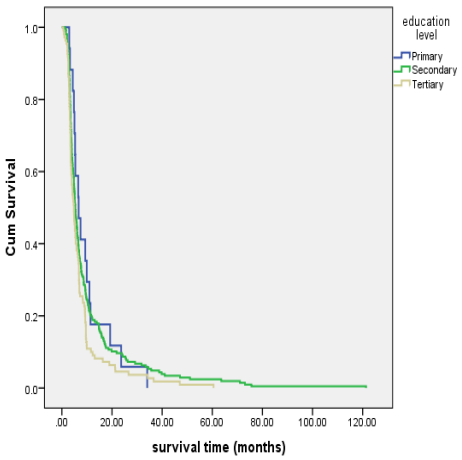
Table 4.22 shows the Kaplan Meier estimates to achieve viral load less than 50 copies/ml stratified by significant variables of HAART. The significant variables were the initial combination of HAART (*p-value* = 0.010), needing second line of HAART (*p-value* < 0.001) and HAART at the end of the study (*p-value* = 0.009). The Kaplan Meier curves for AIDS patients on HAART achieving viral load less than 50 copies/ml stratified by significant HAART variables are presented in Figure 4.20.

Table 4.21 Kaplan Meier estimates to achieve viral load less than 50 copies/ml stratified by significant of socio-demographic, laboratory and clinical variables

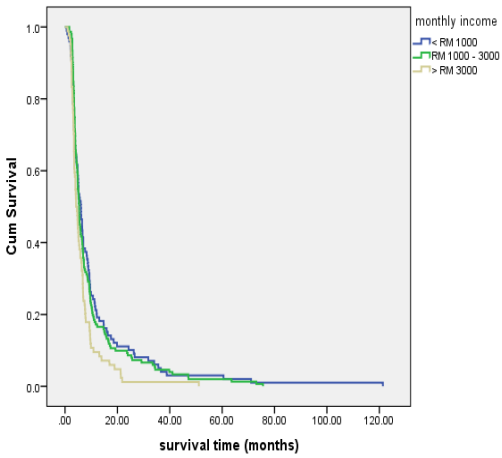
Variable	n	Median Survival time (95% CI) in months	Log rank *P* value
Marital status			0.018
Single	141	4.9 (4.0, 5.8)	
Married	152	5.3 (4.8, 5.7)	
Others	41	8.7 (4.3, 13.0)	
Educational level			0.016
≤ Secondary	224	5.4 (4.8, 5.9)	
≥ Tertiary	110	4.8 (3.9, 5.6)	
Monthly income (RM)			0.012
< 1000	99	6.0 (4.7, 7.3)	
1000 to 3000	151	5.4 (4.8, 5.9)	
> 3000	84	4.2 (3.3, 5.1)	
TLC at start HAART			0.043
Normal	193	4.8 (4.2, 5.4)	
Abnormal	141	6.0 (5.0, 7.0)	
Exposure Risk			0.007
Heterosexual	249	5.4 (4.8, 5.9)	
Homosexual	51	3.9 (2.6, 5.1)	
IDU	29	8.4 (3.7, 13.2)	
Others	5	5.1 (2.6, 7.6)	
WHO clinical stage			0.017
Stage 3	117	4.4 (3.6, 5.2)	
Stage 4	217	5.5 (4.8, 6.2)	



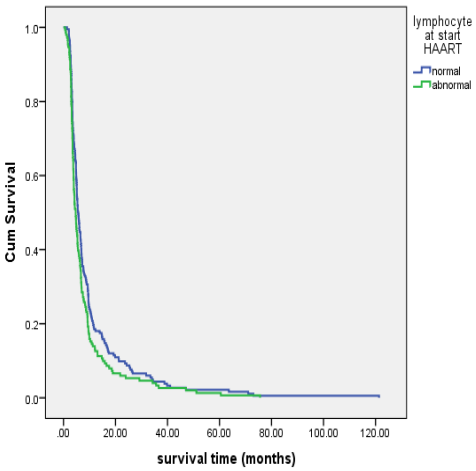
a. Marital status



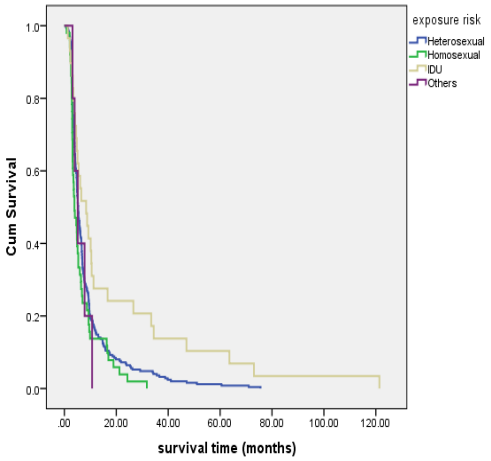
b. Education level



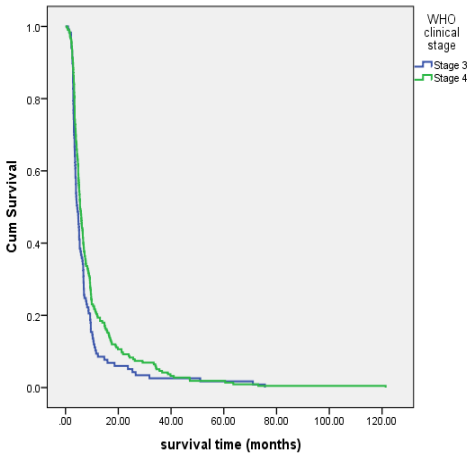
c. Monthly income



d. Lymphocyte at start HAART



e. Exposure risk

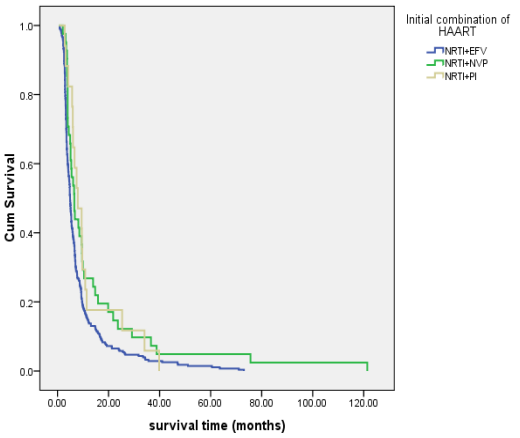


f. WHO clinical stage

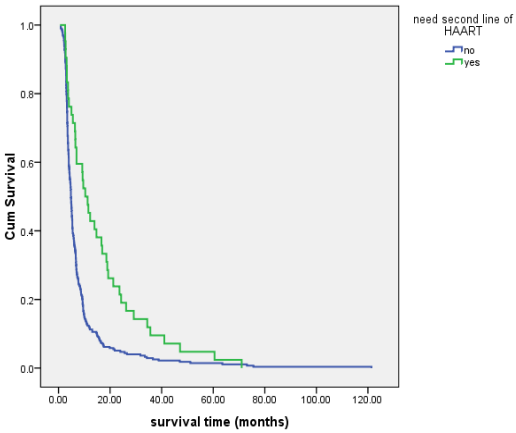
Figure 4.19 The Kaplan Meier curve of AIDS patients on HAART to achieve viral load less than 50 copies/ml stratified by significant socio-demographic, laboratory and clinical variables

Table 4.22 Kaplan Meier to achieve viral load less than 50 copies/ml stratified by significant of HAART variables

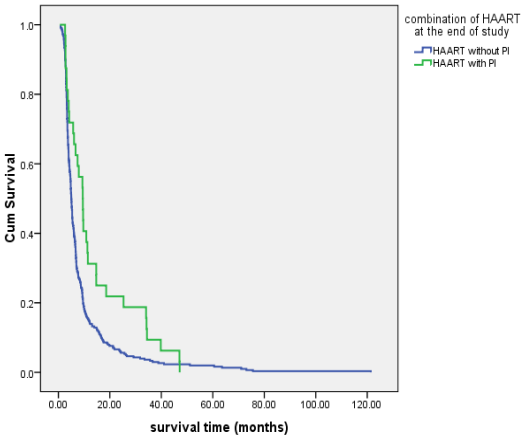
Variable	n	Median Survival time (95% CI) in months	Log rank *P* value
Initial combination of HAART			0.010
2 NRTI+ EFV	276	4.9 (4.5, 5.3)	
2 NRTI+ PI	17	7.9 (4.2, 11.7)	
2 NRTI+ NVP	41	6.6 (4.9, 8.2)	
Need second line of HAART			< 0.001
No	275	4.8 (4.4, 5.2)	
Yes	42	10.4 (7.2, 13.6)	
HAART at the end of study			0.009
HAART without PI	302	5.0 (4.7, 5.4)	
HAART with PI	32	9.5 (7.2, 11.8)	



a. Initial combination of HAART



b. Need second line of HAART



c. HAART at the end of study

Figure 4.20 The Kaplan Meier curve of AIDS patients on HAART to achieve viral load less than 50 copies/ml stratified by significant HAART variables

There were sixteen variables with log rank *p-values* of less than 0.25. It were ethnicity, marital status, education level, occupational type and monthly income, CD4, viral load, liver function test and total lymphocyte count at start HAART, hemoglobin recovers, total lymphocyte count recovers, exposure risk, WHO clinical stage, initial combinations of HAART, need a second line of HAART and HAART at the end of the study also included. These variables were included in the univariate Cox regression analysis. Six variables were not significant in univariate analysis. It was occupational type, (CD4, viral load and liver function test at start HAART), hemoglobin recovers and total lymphocyte count recovers. All possible interactions between the variables in the main effect model were checked and no significant interaction was found.

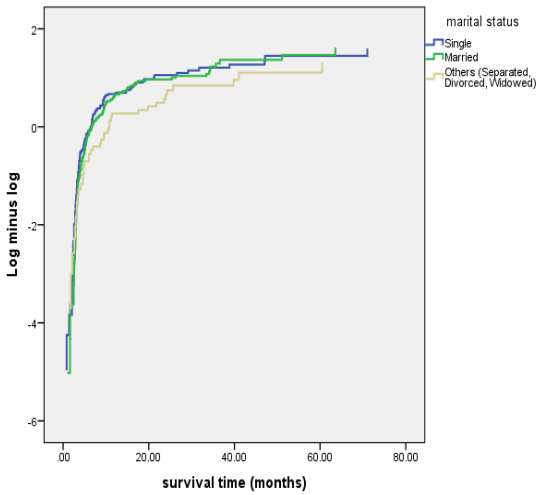
The proportional hazards assumptions were checked. Log minus log plots showed parallel lines which indicated the proportional hazard assumption was fulfilled (Figure 4.21). There were four variables (ethnicity, monthly income, total lymphocyte count at start HAART and WHO clinical stage) which did show parallel lines which indicated a proportional hazard assumption violation. The univariate Cox regression analysis of predictors to achieve viral load less than 50 copies/ml in AIDS patients on HAART are displayed in Table 4.23.

Total six variables included in multivariate Cox regression analysis, but three variables were significant. Table 4.24 displays the multivariate Cox regression analysis of predictors to achieve viral load less than 50 copies/ml in AIDS patients on HAART. In this model, higher hazard ratio is better because achieving viral load less than 50 copies is a measure of the effectiveness of HAART. Patients who started HAART with 2NRTI+NVP and who did not need a second line of HAART were more likely to achieve viral load less than 50 copies/ml compared to their reference categories.

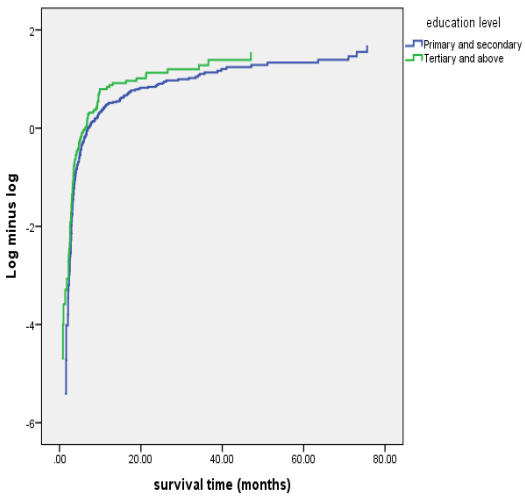
Patients who were infected through the injecting drug user were less likely to achieve viral load less than 50 copies/ml compared to the heterosexual route

Table 4.23 Univariate predictors to achieve viral load less than 50 copies/ml in AIDS patients on HAART

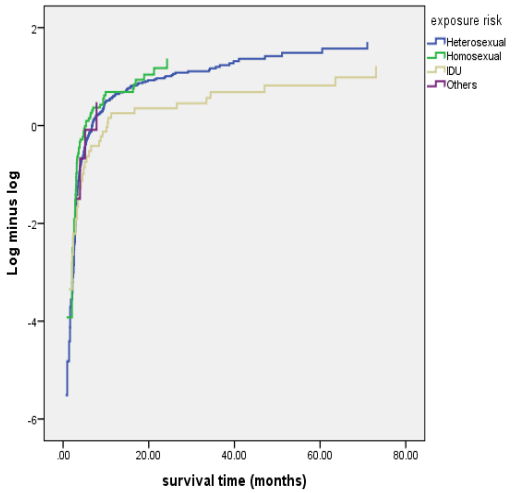
Variable	Crude Hazard Ratio	95% CI
Marital status		
Single	1.0	
Married	0.89	0.71, 1.13
Others	0.60	0.42, 0.86
Education level		
≤ Secondary	1.0	
≥ Tertiary	1.32	1.05, 1.67
Exposure Risk		
Heterosexual	1.0	
Homosexual	1.33	0.98, 1.79
IDU	0.58	0.39, 0.87
Others	1.19	0.49, 2.89
Initial combination of HAART		
2 NRTI+ NVP	1.0	
2NRTI +PI	1.04	0.58, 1.84
2 NRTI+ EFV	1.57	1.12, 2.20
Need second line of HAART		
Yes	1.0	
No	2.29	1.70, 3.09
HAART at the end of study		
HAART with PI	1.0	
HAART without PI	1.62	1.12, 2.34



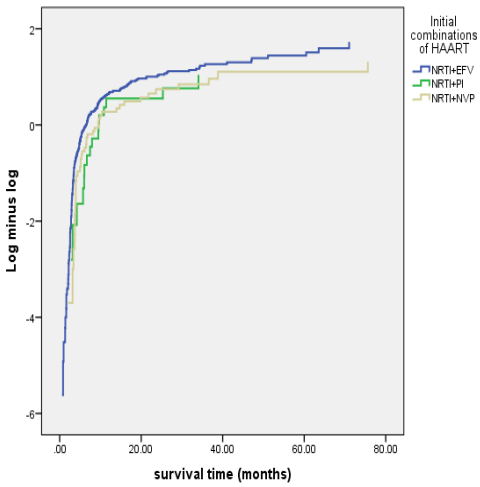
a. Marital status



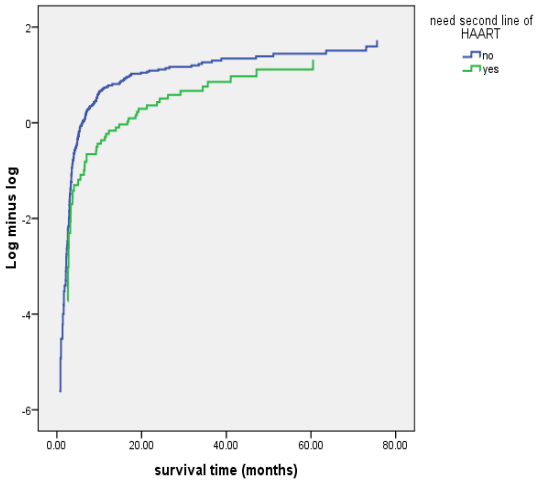
b. Education level



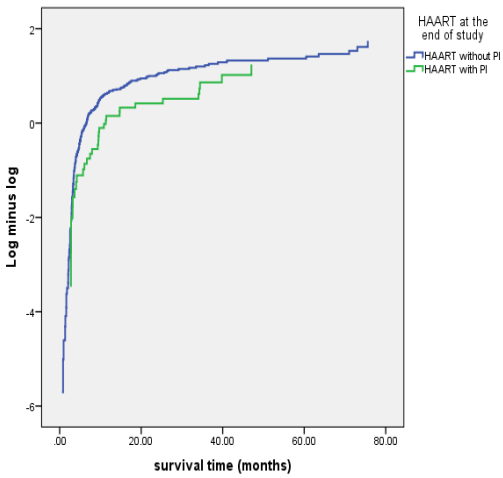
c. Exposure risk



d. Initial combinations of HAART



e. Need second line of HAART



f. HAART at the end of study

Figure 4.21 The Log-Minus-Log plotted against survival time of AIDS patients on HAART to achieve viral load less than 50 copies/ml

Table 4.24 Multivariate predictors to achieve viral load less than 50 copies/ml in AIDS patients on HAART

Variable	Crude Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Initial combination of HAART				
2 NRTI+ NVP	1.0		1.0	
2NRTI +PI	1.04	0.58, 1.84	1.03	0.58, 1.83
2 NRTI+ EFV	1.57	1.12, 2.20	1.56	1.10, 2.20
Need second line of HAART				
Yes	1.0		1.0	
No	2.29	1.70, 3.09	2.59	1.59, 4.21
Exposure Risk				
Heterosexual	1.0		1.0	
Homosexual	1.33	0.98, 1.79	1.29	0.95, 1.76
IDU	0.58	0.39, 0.87	0.54	0.35, 0.80
Others	1.19	0.49, 2.89	0.99	0.41, 2.39

4.10 Summary

Factors identified as predictors of death in all AIDS patients were unemployed patients, manual workers, those who had three or more opportunistic infections and who did not receive anti-retroviral therapy. Predictors of death in AIDS patients on HAART were unemployment, those whose CD4 did not recover to more than 200 cells/μL and those who were unable to achieve viral load less than 50 copies/ml. Predictors of death in AIDS patients not on anti-retroviral therapy were Chinese ethnicity, those with baseline viral load more than 100,000 copies/ml and who stay in WHO clinical stage 4. Finally, predictors to achieve viral load less than 50 copies/ml were patients who started HAART with 2NRTI+EFV and who did not need a second line of HAART, patients who were infected through the injecting drug user were less likely to achieve viral load less than 50 copies/ml compared to the heterosexual route.

CHAPTER 5

DISCUSSION

5.1 Introduction

This chapter presents the results of discussion. Section 5.1 is the introduction. Section 5.2 discusses the profile of study subject based on socio-demographic characteristic, laboratory, clinical and anti-retroviral therapy and comparison to other studies. Section 5.3 discusses the median survival time from AIDS progression to death. This continues in Section 5.4 which discusses the predictors of death in all AIDS patients, AIDS patients on HAART and AIDS patients not on anti-retroviral therapy. Section 5.5 discusses the time and predictors to achieve viral load less than 50 copies/ml in AIDS patients on HAART. Section 5.6 revealed the strengths and limitations of the study and Section 5.7 is a summary of the chapter

5.2 Profile of the study subject

5.2.1 Socio-demographic

Generally, the most productive age is affected by HIV infection. Approximately 76.1 per cent of the reported HIV/AIDS cases in Malaysia occur in the age group of between 20–39 years, the younger and potentially most productive segment of the nation's population (MOH, 2012). This is consistent with the results of this study in which 73.3 per cent of HIV patients are between the age group of 20-39 years and the median age were 33.7 years (IQR 12.0) which is similar to others studes in Asia (Thailand and Taiwan) (Fregonese, et al., 2012; Hung, et al., 2006). However, this study shows a slightly younger age group compared to the developed countries (Fielding, et al., 2008; Hulgan et al., 2007).

This study also shows that the majority of the patients are male, which reflects the fact that HIV-infected patients in Malaysia are predominantly male (MOH, 2012). This is in agreement with other studies in Malaysia and Hong Kong (Lee et al., 2011; Vicknasingam, Narayanan, & Navaratnam, 2009). This study also reveals a higher male to female ratio of 4.5 : 1. This is similar to the HIV population in Malaysia with the ratio of 4 : 1 (MOH, 2012). The HIV infected patient ratio in the whole of Malaysia is, higher than the ratio of India which is 2.6 : 1 (Kumarasamy et al., 2003).

The majority of HIV-infected patients in the University of Malaya Medical Centre are Chinese followed by Malays, Indians and other ethnic groups. However, it is different from the general HIV population in Malaysia, where the Malays predominates other ethnic groups (UNGASS, 2010). This could largely be due to the UMMC's status as a

tertiary hospital where cases are being referred from the private and government clinics from the neighboring cities of Kuala Lumpur and Petaling Jaya where the majority of the population are Chinese (Department of Statistic, 2010). This is consistent with previous reports in Hong Kong (Lee, et al., 2011) and Singapore (Wong, Lye, Lee, & Leo, 2011)

There is not much difference in percentage between single patients and married patients. Among the AIDS patients who receive HAART, there are more married patients than singles. This is similar to a study in South Africa (Shisana et al., 2004) and in India where married patients are more than the singles (Vallabhaneni, Chandy, Heylen, & Ekstrand, 2012). The discrepancy may be caused by married patients receiving more support and care from their spouses or families thus avoiding delays in seeking treatment. AIDS is a chronic disease. Partners, families and friends are an important source of support for AIDS patients and it correlates with a reduction in stress, hopelessness and depression (Shanthi, Damodharan, & Priya, 2007).

Socioeconomic status, whether assessed by income, education, or occupation, is linked to a wide range of health problems, including HIV/AIDS. Lower socioeconomic status is associated with higher mortality. In this study the majority of patients had primary and secondary education. The rest of them work as professional and non manual workers and earned between RM 1000 to 3000 per month. It is similar to studies in India and Africa (Rougemont, Stoll, Elia, & Ngang, 2009; Vallabhaneni, et al., 2012) but Spain and Barcelona report lower education levels than this study (Jarrin, et al., 2007; Lima et al., 2006).

5 Discussion

Unemployment in HIV-infected patients is likely to be the result of a debilitating effect of HIV infection on workforce participation (Dray-Spira, Gueguen, Ravaud, & Lert, 2007). This is reflected as socio-demographic or behavioural disadvantages in the workforce participation (i.e., female gender, advanced age, low educational level, manual occupation, foreign nativity, injection drug use) existing prior to HIV infection (Dray-Spira, et al., 2007). Developed country studies reported the unemployment rate among HIV-infected patients as ranging from 45 to 65 per cent (Dray-Spira, Lert, Marimoutou, Bouhnik, & Obadia, 2003; Rabkin, McElhiney, Ferrando, Van Gorp, & Lin, 2004). In this study, the proportion of unemployed HIV-infected patients were lower than the Nigerian study (28.5 compared to 34.0 per cent) (DeSilva, et al., 2009).

As far as monthly income is concerned, these findings cannot be directly compared with the India and Cameroon studies due to differences in categories used in India (Vallabhaneni, et al., 2012) and in Cameroon (Rougemont, et al., 2009). The profile of socio-demographic of AIDS patients receiving anti-retroviral therapy is similar to the entire sample of HIV-infected patients except marital status as married patients receive more anti-retroviral therapy compared to single patients. This is similar to the India study in that the majority of married patient adhered to anti-retroviral therapy because of better support from family compared to singles (Sarna et al., 2008).

The comparison of socio-demographic characteristic findings and other studies are summarized in Table 5.1

Table 5.1 Comparison findings of this study and other studies

Findings of this study	Findings of other studies
Median age: HIV-infected patients 33.7 years (IQR 12.0) AIDS patients was 34.1 years (IQR 12.7)	Median age: Thailand: 33 years (28-38) Taiwan : 34 years (15-83) North Carolina : 38 years (18-82) South Africa: 41years (35-46)
Gender: HIV-infected patients: male 81.8% AIDS patients: male 85.2 %	Hong Kong : male HIV patients 80.6 % India : male HIV patients 72.9 %
Ethnicity: HIV-infected patients: Chinese 61.2 % AIDS patients : Chinese 62.7 %	Hong Kong : Chinese HIV patients 77.7 % Singapore : Chinese HIV patients 88.0%
Marital status: HIV-infected patients: 45.2 % AIDS patients : 45.3 %	South Africa: Unmarried HIV patients 59.2 % India : married HIV patients 70.0 %
Education level: Primary and secondary education: 73.5%	India : Primary and secondary : 72 % Cameroon : Primary and secondary education: 79% Spain : Primary education : 55.8% Barcelona : Deprived neighborhood and low education: 32.4%
Occupational type: Unemployment : 28.5%	Nigeria : Unemployment : 34%
Monthly income: RM 1000 to 3000 : 42.5%	Cameroon : < USD 50 : 46 % India : < 5000 Rs : 48%

5.2.2 Laboratory results

The level of CD4 cell count is related to the immune status and indicates the stage of HIV infection, guides treatment, and predicts the progression of HIV-infected patients. This study shows more than 60 per cent of HIV-infected patients presented with baseline CD4 of less than 200 cells/μL and more than 82.7 per cent of AIDS patients started anti-retroviral therapy with CD4 less than 200 cells/μL. CD4 less than 200 cells/μL in HIV-infected patients and AIDS patients both are high. It is not difficult to

explain the high proportion of AIDS patients starting anti-retroviral therapy with very low CD4 counts as this is a criteria for starting therapy but the very high proportion of HIV patients presenting with low CD4 counts is probably because HIV infection in the early stages is asymptomatic. People may be seeking care because they had symptoms due to low immunity or opportunistic infection. Elsewhere in Nigeria a similar picture emerges where 81.4 per cent of patients had baseline CD4 less than 200 cells/µL (Agaba, et al., 2011). Another study in the US showed 64 per cent of HAART initiation with CD4 less than 200 cells/µL (Fox et al., 2010). The initial presentation of HIV-infected patients to medical care continues to occur in an advanced stage of immune suppression (Ndiaye et al., 2011). In the medical literature, there are multiple definitions of delayed HIV diagnosis or late presentation. For example the United Kingdom Collaborative HIV Cohort (UK CHIC) Steering Committee defines presentation at a stage when there is a substantial risk of death (CD4 counts less than 200 cells/µL or clinically-defined AIDS) as presenting with advanced HIV disease. The presentation with a CD4 less than 350 cells/µL, resulting in a delay in treatment initiation is defined as a late presentation (The UK Collaborative HIV Cohort Steering Committee, 2010). The consequences of a late presentation are unknown risk of transmission and a poor prognosis or a higher level and cost of use of medical resources (Toure et al., 2012). Future research on this is needed especially in Malaysia.

On the other hand, baseline viral load more than 100,000 copies/ml occur in 51.1 per cent of HIV-infected patients and in 64.8 per cent of AIDS patients when they start HAART. The CASCADE collaboration from 20 cohorts in Europe and Australia has shown this correlation between lower CD4 and a higher viral load (Phillips & Pezzotti, 2004). CD4 count has an inverse relationship with viral load. When CD4 drops, viral load increases (Phillips & Pezzotti, 2004). CD4 and viral load are the two most

commonly used prognostic indicators of the clinical progression of HIV and as a measure of anti-retroviral treatment response (Gilks et al., 2006; Hammer, et al., 2008; Thompson, et al., 2010). The viral load measurement has limitations and is not done routinely in all hospitals because of poor access to viral load facilities. Commonly patients who are initiated with HAART are sent for viral load measurements especially in developing countries. In this study more than 50 per cent of patients come in advanced stages with low CD4 and high viral load.

Based on the Pearson's correlation, there was a significant and positive correlation between the hemoglobin level and their CD4 counts (Obirikorang & Yeboah, 2009). Measurement of hemoglobin levels is simple. It would be difficult to use this simple test as a replacement for CD4 count as the correlation between hemoglobin and CD4 is low but where flow cytometry is not available, this does give a rough indication of the immune status of the patient. Flow cytometry is an expensive technique which is unavailable in many developing countries (Obirikorang & Yeboah, 2009).

Furthermore, in resource limited settings total lymphocyte count appear useful in predicting who would be eligible for anti-retroviral therapy based on CD4 count criteria (Moore et al., 2007). A cut-off total lymphocyte count (TLC) 1,200 cells/µL is considered to be normal value according to the WHO criteria and this is comparable with a CD4 count of 200 cells/µL (WHO, 2004). According to this study, 62.7 per cent of HIV-infected patients and 57.4 per cent of AIDS patients had normal baseline total lymphocyte count and at HAART initiation. The Johns Hopkins HIV observational cohort study in USA found that total lymphocyte count less than 1,200 cells/µL and hemoglobin less than 12 g/dl significantly predicted CD4 less than 200 cells/µL (Spacek, et al., 2003). Several studies revealed reasonably adequate sensitivity and

specificity to consider total lymphocyte count as a surrogate measure for CD4 (Alavi, Ahmadi, & Farhadi, 2009; Bedell et al., 2003; Jacobson et al., 2003). A study in Europe indicated that despite the minimal reliability of total lymphocyte count as a surrogate for CD4, total lymphocyte count is an important tool in the absence of expensive equipment especially in the developing countries to measure CD4 (Stebbing, et al., 2005). The sensitivity and specificity of total lymphocyte count as a surrogate for CD4 in Malaysia not clearly known. Further research needs to be done to evaluate how well the inexpensive total lymphocyte count functions as a surrogate marker to predict CD4 count.

Routine liver function tests (LFT) is important, because in HIV-infected patients there is frequent co-infection with the hepatitis C virus, especially where HIV infection is caused injecting drug use (Macias et al., 2003). Some anti-retroviral drugs are also associated with liver enzyme elevations (Bonacini, 2004) although in this study more than fifty per cent of patients had normal liver function test at baseline and at HAART initiation. HIV-infected patients with poor immune status are at risk of infections and the liver function test is needed to detect any infection (Mata-Marin et al., 2009). In those taking anti-retroviral therapy, liver function tests help to assure that the treatment is working well and make sure that any unwanted side-effects do not develop. The liver plays a key role in breaking down and processing the medicines used to treat HIV and other infections (Jain, 2007; Mata-Marin, et al., 2009)

5.2.3 Clinical condition

The scenario of exposure risk at the University of Malaya Medical Centre is different from the rest of the country. Instead of intravenous drug usage being the main exposure risk as in the whole of Malaysia (70.6 per cent) (MOH, 2010), the majority of patients contracted the infection through the heterosexual route (65.8 per cent). This seems to be congruent with findings worldwide where heterosexual transmission is the most common mode of transmission. The route of transmission as seen in the University of Malaya Medical Centre may be indicative of the future when Malaysia reaches the status of a developed nation where the HIV epidemic in Malaysia may no longer be a concentrated epidemic. This is cause for concern as heterosexual transmission as the most common route of HIV transmission in Malaysia is yet to be acknowledged officially. Furthermore, the comparison between sexual transmission route and injecting drug user has changed over the time in Malaysia among the HIV population. The ratio of sexual transmission compared to injecting drug user was 1 : 9 in 1990, 2 : 8 in 2000, 3 : 6 in 2009, 5 : 5 in 2010 and 6 : 4 in 2011 (MOH, 2012). The implementation of harm reduction programmes since 2005 has been able to reduce the number of HIV infection through sharing needles (MOH, 2012). On the other hand, the ratio of sexual transmission compared to injecting drug use transmission in HIV-infected patients in the University of Malaya Medical Centre is 3 : 1.

In this study, the proportion of AIDS patients in WHO clinical stage 3 and stage 4 was 30.7 per cent and 69.3 per cent respectively. Patients in WHO stage 4 accounted for 67.9 per cent of patients initiated on HAART. The findings from a study in Nigeria found 53.5 per cent of those initiating anti-retroviral therapy in stage 3 and 3.4 per cent in stage 4 (Odafe et al., 2012). In Ethiopia 54 per cent are in stage 3 and 16 per cent in

stage 4 (Alemu & Sebastian, 2010). The proportion of patients with stage 4 in this study was much higher than those reported in both those other studies. The reasons for advanced stage presentation or delay in seeking care is probably because HIV-infected patients with good immunity are asymptomatic, fear of diagnosis as well as treatment and other financial problem. Further studies are required to ascertain specific reasons for the high proportion of patients in WHO stage 4 in Malaysia

HIV-infected patients show a substantial weight loss during the course of infection and thus poor nutritional status is considered an unfavourable prognostic factor of survival (Malvy, Thiebaut, Marimoutou, & Dabis, 2001). Body mass index (BMI) is commonly used to measure the nutritional status and long-term monitoring of this can predict disease progression (Langford, et al., 2007). The findings of this study are that 74.4 per cent of patients had a baseline body mass index more than 18.5 kg/m^2 and 73.8 per cent had this at the start of HAART. There is a significant but low Pearson's correlation between hemoglobin and body mass index. A body mass index of less than 18.5 kg/m2 is strongly associated with increased risk of disease progression consistently and may prove to be a valuable indicator of the need for HAART (Langford, et al., 2007).

From the total of HIV-infected patients, 63.9 per cent patients are positive for opportunistic infection and 30.9 per cent presented with one opportunistic infection. At the start of HAART, 78.3 per cent of AIDS patients had opportunistic infections and 42.4 per cent had one opportunistic infection. Opportunistic infections in AIDS patients are associated with lower CD4 counts. Eighty-six point one percent of patients with CD4 counts less than 200 cells/µL at baseline and 81 percent of patients at HAART initiation had positive opportunistic infections. This was also demonstrated in a study in South Africa where those with CD4 less than 200 cells/µL had a higher incidence of

opportunistic infection compared to those with CD4 more than 200 cells/µL (8 versus 3.1 per cent) (Fox, et al., 2010).

At the end of the study, 36.4 per cent of HIV-infected patients and 20 per cent of AIDS patients on HAART were dying with most causes of death being AIDS related illness. The leading causes of death in HIV-infected patients and in AIDS patients on HAART were AIDS related illness especially PCP and tuberculosis.

5.2.4 Anti-retroviral therapy

Single drug and double drug anti-retroviral therapy were more common in the pre HAART era (before 1997). It has proven less effective than the triple drugs of HAART (1997 and later) in reducing viral load to less than 50 copies/ml (Geretti, et al., 2008; Schwarcz, et al., 2000). In this study, 71.9 per cent of AIDS patients received anti-retroviral therapy in the HAART era and 29.1 per cent in the pre HAART era.

Generally, the decision to start anti-retroviral therapy depends on the clinical or immunological criteria. Clinical criteria are based on the presence of one or more severe opportunistic infections, categorized by the WHO as stage 3 and 4. All developed and developing country guidelines recommend starting anti-retroviral therapy if a patient presented with stage 3 or 4 though decisions based on such clinical criteria alone are generally only used in resource limited settings where laboratory capacity is limited (WHO, 2010a). Commonly, the decision to start anti-retroviral therapy is based on immunological criteria, as defined by the level of CD4 count. According to current WHO guidelines, all HIV-infected patients with a CD4 less than 350 cells/µL must be started on HAART (WHO, 2010a). In this study, 84.2 per cent of patients started HAART with CD4 less than 200 cells/µL.

5 Discussion

A decision about when to initiate anti-retroviral therapy on a public health level must be balanced between any expected population level benefits of initiating treatment at higher CD4 counts with the cost implications of potentially increased demand for treatment. If treatment thresholds are raised, any possible cost savings associated with earlier treatment including reduced hospitalization and treatment of opportunistic infections are lost (Walensky et al., 2009).

Anti-retroviral therapy programs in developing countries follow a public-health approach rather than an individualized approach. Guidelines for developed countries cover individual patient management delivered by specialist doctors prescribing from the full range of anti-retroviral drugs, supported by routine high-technology laboratory monitoring. This approach is not suitable in resource-limited settings where doctors are scarce, laboratory infrastructure is not adequate and the procurement and supply-chain management is frail. This difficulty in translating guidelines from developed to developing nations caused concerns over whether anti-retroviral therapy scale-up in poor countries is feasible, affordable and cost-effective (Gilks, et al., 2006).

WHO began to develop a public-health approach to providing anti-retroviral therapy based on experience of using the Directly Observed Treatment Short-course (DOTS) approach for tuberculosis. This approach took into account country requirements, the realities of weak health systems, and the experiences of pioneering anti-retroviral therapy programs (WHO, 2003). The key tenets were standardization and simplification of regimens to support efficient implementation also ensuring anti-retroviral therapy programs that are based on the most rigorous scientific data and equity aiming to set standards for treatment that should be accessible by all in need. The key conceptual shift was the move from an individual based approach to a population based one,

recognized as the only way to make anti-retroviral therapy rapidly accessible to the millions in need (Beaglehole, Bonita, Horton, Adams, & McKee, 2004).

The most important achievement is to standardize first-line and second-line treatments. Issues of potency, durability of efficacy, ease of administration, tolerability and toxicity need to be balanced with cost and availability (Gilks, et al., 2006). There are three classes of oral anti-retroviral available, nucleoside and non-nucleoside reverse transcriptase (NRTI and NNRTI) inhibitors and protease inhibitors (PI). Public-health therapy readily accommodates the use of two sequential triple drug anti-retroviral therapy regimens. On the basis of available data, the initial consensus was to use one NNRTI in first-line treatment, supported by an NRTI (WHO, 2004), which remained in the year 2006 recommendations (WHO, 2006b). Protease inhibitor is reserved for second line therapy, supported by 2 NRTI to minimize cross-resistance (WHO, 2010a)

In this study, 80.6 per cent of HAART initiation was with 2 NRTI + EFV, 13.9 per cent with 2 NRTI + NVP and 5.5 per cent with 2 NRTI + PI. The NNRTI based HAART regimes especially Efavirenz (EFV) and Nevirapine (NPV) are commonly used as components of first line regimens worldwide (Ananworanich et al., 2005). The choice between EFV and NPV is based on toxicity, interaction with other drugs, and cost (WHO, 2010). Rash, Stevens-Johnson syndrome and hepatic toxicity are adverse drug reactions associated with NVP but it is better for HIV infected women during the first semester of pregnancy (WHO, 2010) while EFV is well tolerated but more costly. Toxicities to the central nervous system (CNS) and mild rash are caused but self-resolving after 2−4 weeks. Efavirenz should be avoided for severe psychiatric patients and women in their first semester of pregnancy. Efavirenz is the choice in individuals

with TB/HIV (WHO, 2010). In this study there are 30 per cent of AIDS patients on HAART with tuberculosis co-infection.

Furthermore the findings showed that most of the patients still continue with the first line regimen and it was not necessary to switch to second line drugs. Only 15.8 per cent need to switch to second line drugs. Unfortunately in this study, we could not determine the reasons for switching to second line drugs because we relied on secondary data from medical records. To determine the reasons it would be necessary for further primary research. The recommendations for changes in treatment differ according to its indication. Based on WHO recommendations, the criteria to switch anti-retroviral therapy include clinical failure, immunological failure and virological failure (WHO, 2010). Persistent viral load more than 5,000 copies/ ml confirms treatment failure and in the absence of viral load measurement, an immunological criteria is used to confirm clinical failure. In these guidelines, protease inhibitors remain reserved as second line therapies, mainly due to cost, higher pill burden, drug interactions and refrigeration requirements (WHO, 2010a)

The end result of the study shows that 90.7 per cent HAART combination were without PI, and only 9.3 per cent of HAART had PI. There were 5.5 per cent patients with first line combination with PI. Of them 61.5 per cent were still on first line drugs until the end of study while 38.5 per cent stopped without any clear reason. The majority of AIDS patients on HAART in the University of Malaya Medical Centre majority still used first line drugs because these are free while the second line drugs are not.

The period of follow up of this study was very long which had the potential to be affected by changes in the management policies of HIV/AIDS patients. This was

however, not likely to affect the outcome of study because most AIDS patients presented at a late stage and HAART was consistently initiated when CD4 was < 200 cell/µL, although WHO guidelines in 2010 recommended for HAART initiation when CD4 was < 350 cell/µL. Tests for proportional hazards did not show any significant change in hazard over time which supports this assertion.

5.3 Median Survival time

The findings of this study show that median survival time from the HIV diagnosis had improved in those receiving anti-retroviral therapy. The median survival of 177.5 months in HIV-infected patients receiving anti-retroviral therapy is far higher than the 73.2 months in those who did not receive anti-retroviral therapy. The median time from AIDS diagnosis to death was 65.7 months. This study shows that median survival in anti-retroviral initiation from HIV diagnosis is better than from AIDS diagnosis. This result is consistent with other Asian studies (Hung, et al., 2006; Wong, et al., 2004) and in developed countries (Li, et al., 2000; Schwarcz, et al., 2000). Before 1997 (pre-HAART era), the median survival duration ranged from 15 months to 31 months in San Francisco (Schwarcz, et al., 2000), 2.9 months to 17.6 months in Italy (P. Pezzotti, et al, 1999), and 17.7 months in Australia (Li, et al., 2000), 29.8 months in Hong Kong (Wong, et al., 2004). After 1997 (HAART era) median survival increased e.g. in a study carried out in Hong Kong where this was more than 70 months (Wong, et al., 2004), 24 months in Taiwan (Hung, et al., 2000), 58 months in Cameroon (Sieleunou, Souleymanou, Schonenberger, Menten, & Boelaert, 2009), 26.1 months in Ethiopia (Alemu & Sebastian, 2010), 9.91 months and 14.4 - 24 months in China (Li, et al., 2010). On the other hand, the median survival for the non anti-retroviral therapy group in Taiwan was only 6.8 months (Hung, et al., 2006) and in China 19.2 months (Dou et

al., 2010). The median survival time from AIDS to death varies among Asia, Africa and developed countries due differences in the inclusion criteria of the sample, study time, study design and sample size. In this study, only adults aged 20 years and above were included while in other studies adult and adolescents were included in the analysis (aged 16 years at HIV diagnosis). This present study followed patients from 1986 to 2006 (retrospective) and from 2007 to 2009 (prospective), a longer follow-up study period when compared to others. In addition, the present study is hospital based while the study in San Francisco was population based (Schwarcz, et al., 2000).

5.4 Predictors of death

5.4.1 Predictors of death in all AIDS patients

Socio-demographic characteristics such as education level, occupational type and marital status are univariate predictors of death in this study. Clinical predictors of death are exposure risk, baseline body mass index, presence of opportunistic infections, number of opportunistic infections and type of treatment.

Univariately speaking, those with primary and secondary education were more likely to die compared to those with tertiary education. The same group also had 5 and 10-year survival rates of 48.8 per cent and 38.3 per cent respectively. However, it is not significant in the multivariate analysis probably because of low power. A retrospective cohort study conducted in Ethiopia showed that 61 per cent of HIV-infected patients on anti-retroviral therapy had less than secondary education and patients with primary education seem to be at higher risk of death (Biadgilign, Reda, & Digaffe, 2012).

According to a previous study report, the lower educational level is associated with a higher risk of mortality (Jarrin, et al., 2007; Wood et al., 2002).

Occupational type was significant in univariate and multivariate analysis. Unemployed patients are more likely to die compared to those working as professional or non-manual worker. A study in Nigeria showed that unemployed HIV-infected patients and patients with primary education were shown to be significantly associated with increased mortality (DeSilva, et al., 2009). Unemployment has a correlation with income and it is a strong predictor of socioeconomic status. A study carried out in Italy showed that the increased risk of death following AIDS was more obvious among patients with lower socioeconomic status (Rapiti, et al., 2000). Occupational types were associated with the duration and severity of HIV infection (Dray-Spira, et al., 2003). It is depending on disease stage, the patients with the highest risk of losing their job were those with physically demanding work, those who had low control over the pace and scheduling of their work activities (Dray-Spira, et al., 2003; Yelin, Greenblatt, Hollander, & McMaster, 1991).

In the pre-HAAR era, developed country studies showed that 28 per cent of patients had stopped working within a year after HIV diagnosis, 48 per cent by two years, 69 per cent from four years and no one was still employed by 10 years of HIV infection (Yelin, et al., 1991). Moreover mental and physical demands of job have a significant impact on employment loss of HIV-infected patients. The loss of earnings will reduce monthly income by 75 per cent (Dray-Spira, et al., 2007; Massagli, Weissman, Seage, & Epstein, 1994).

5 Discussion

Since 1996 with wide scale diffusion of HAART, HIV infection has become a chronic disease and the HIV epidemic has shifted toward more socially vulnerable population (Dray-Spira, et al., 2007). Employment is a major factor in maintaining income levels and living conditions among patients with chronic diseases. Discrimination at work of HIV-infected patients are still reported but not associated with occupational status. In HIV-infected patients, low education level is associated with decreased workforce participation but this does not happen among those with high education level (Dray-Spira, et al., 2007). Further research needed to determine the impact of HIV-infected patients and employment in Malaysia

Previous studies showed inconsistency with regards to exposure risk of HIV infection as a predictor of death in AIDS patients (Langford, et al., 2007). The CASCADE collaboration examined the change in morbidity and mortality between the pre and post HAART periods and showed mortality reduction in the post HAART era among homosexual and heterosexual patients but there was no such change in injecting drug users (Porter, et al., 2003). In this study, patients infected through the injecting drug user route are more likely to die (HR=1.52) and those who are infected by the homosexual route have a lower chance to die (HR=0.64) compared to the heterosexual route. This is an interesting finding but we cannot offer any explanation. It warrants further investigation in future research. This finding is similar to developed country studies (Europe, Australia and Canada), where injecting drug users had increased risk of death (HR= 4.28) (Porter, et al., 2003). Another study carried out in Spain showed injecting drug user had increased risk of death with HR of 2.17 (Pérez-Hoyos, et al., 2006). This variable is only significant in univariate but not in multivariate analysis. Other factors e.g. opportunistic infections play a larger role in clinical deterioration than the mode of transmission (Porter, et al., 2003).

5 Discussion

Not many articles reported opportunistic infection as a predictor of death in AIDS patients. One study in San Francisco showed that AIDS patients with a history of opportunistic infections had increased risk of death with HR of 1.97 (Schwarcz, et al., 2000). In this study, opportunistic infection and number of opportunistic infection were significant in univariate analysis as predictors of death. However, in the multivariate analysis, only the number of opportunistic infection fitted in the final model. AIDS patients with three or more opportunistic infections had increased risk of death (HR=1.90). The 5 and 10-year survival of patients with one opportunistic infection was 58.3 per cent and 49.4 per cent. Those who had two opportunistic infections had 5 and 10-year survival of 47.5 per cent and 36.4 per cent while patients with three or more opportunistic infection had 5 and 10-year survival of 33.0 per cent and 18.4 per cent. That the number of opportunistic infection influences hospitalization and the survival of AIDS patients is a fact that cannot be denied. It is therefore unsurprising that the reduction of survival with the increased number of opportunistic infection is supported by a Brazil study (Candiani et al., 2007).

A study in India showed that the number of opportunistic infection in AIDS patients increased when there is a significant increase in the mean viral load and decrease in the CD4 counts and high viral loads and low CD4 were seen in AIDS patients with multiple opportunistic (Nagalingeswaran et al., 2000).

This study shows that the increased number of opportunistic infection caused AIDS to be exacerbated and increased mortality. Prevention of opportunistic infection is thus very important. Counselling, chemoprophylaxis and active management of opportunistic infection were important in the care of AIDS patients especially in developing countries.

5 Discussion

This study shows that PCP and tuberculosis are the leading causes of AIDS related death in HIV-infected patients. This is consistent with a study in Brazil where tuberculosis is the primary cause of death in 9.0 per cent of all AIDS-related deaths while PCP accounted for 4.7 per cent of a total 8,601 AIDS-related deaths (Saraceni, et al., 2008). Throughout the developing world, the rate of co-infection with tuberculosis and PCP are high, ranging from 25 per cent to 80 per cent (Fisk, Meshnick, & Kazanjian, 2003). In the industrialized nations, viral hepatitis, non-AIDS related malignancies and cardiovascular events are now more common causes of death (Crum et al., 2006; Porter, et al., 2003). Although it is well known that HAART reduces the incidence of opportunistic infection and mortality of AIDS patients. PCP occurs mainly in patients with CD4 count less than 200 cells/μL, while tuberculosis occur in low and high CD4 counts. Future research is needed regarding this discrepancy between PCP and tuberculosis in AIDS patients associated with level CD4

In this study, the risk of death is higher in the non anti-retroviral therapy group as compared to those who in the anti-retroviral therapy group (HR=2.89). This is consistent with another study where the usage of HAART decreased the risk of death by almost 50 per cent (Hung, et al., 2006) and an India study with HR of 5.60 (Ghate, et al., 2011). The India study used a prospective cohort from 2002-2004 and collection of demographic and clinical information. Structured questionnaires were captured at each follow up visit (primary data) consisted of pre-test and post-test counselling and informed consent.

Other studies show that more than 50 per cent patients initiated anti-retroviral therapy when they are in WHO clinical stage 3 and 4 (Auld et al., 2011) Despite the fact that the WHO clinical stage 4 is a strong predictor of death in the first month of treatment

(Jerene, Endale, Hailu, & Lindtjorn, 2006). Thus early diagnosis and anti-retroviral therapy are needed to improve program outcomes (Lawn, Harries, Anglaret, Myer, & Wood, 2008). The campaigns of mass HIV testing needs earlier entry into HIV care, pre anti-retroviral therapy care retention in order to reduce absolute numbers of late starters. It is also appropriate to initiate anti-retroviral therapy at raised CD4 threshold compared to current practice. HAART initiation in adult patients with WHO stage 1 or 2 and CD4 from 200 – 250 cells/μL based on WHO criteria in 2008 and CD4 from 250-350 cells/μL based WHO criteria in 2010 (WHO, 2010a), should reduce the proportion of patients initiating anti-retroviral therapy with end stage disease.

5.4.2 Predictors of death in AIDS patients on HAART

This study shows the CD4 count less than 200 cells/μL, viral load more than 100,000 copies/ml and hemoglobin less than 12 g/dl are significantly associated with increased risk of death. This is consistent with studies in developed countries demonstrating the same outcomes with lower CD4 count and higher viral load (Egger, et al., 1997; Mellors et al., 1997; Smurzynski, et al., 2010; Sterling, et al., 2001) and lower hemoglobin (Jean D Lundgren & Amanda Mocroft, 2003; Obirikorang & Yeboah, 2009). Low hemoglobin level is prognostic of HIV infection. Regular measurements of hemoglobin level could help to determine patients who are at greatest risk of disease progression allowing these patients to be identified for closer monitoring or therapeutic intervention (Obirikorang & Yeboah, 2009). Hemoglobin level, hematocrit and body mass index as parameters which are conventionally thought to be proxies for general nutritional status. Anemia (hemoglobin less than 12 g/dl) is a known predictor of HIV related mortality in resource-limited settings (Harris et al., 2008; Melekhin et al., 2012; Obirikorang & Yeboah, 2009). Recovery from anemia is associated with improved survival (Lifson et al., 2012; Melo, Lacerda, Campelo, Moraes, & Ximenes, 2008).

Unfortunately not many studies have looked into hemoglobin recovery in HIV-infected patients. Further studies are required in Malaysian HIV-infected patients

CD4 levels which never recover to more than 200 cells/μL were significantly associated with death (HR=7.54). This is consistent with studies in Spain (Jaen et al., 2008) with HR of 3.7 and in Kenya (Brown et al., 2009) with HR of 11.5. Patients with CD4 counts less than 200 are more likely to die compared to those with more than 350 cells/μL. The previous study finding in Kenya seems to indicate that the magnitude of risk attributed to this factor is higher than that found in this study. However, in Kenya study, only pregnant women were studied which might affect the underlying immune status of the patients involved. In addition, CD4 was measured 8 months after initiating HAART in the Kenya study. In contrast, the CD4 count was taken at the time the AIDS diagnosis was made before initiating HAART in this study.

In this study, patients with low hemoglobin and who never recover to more than 12 g/dl after the use of HAART are more likely to die. A similar study in Tanzania reported an increased risk (HR=2.21) of AIDS related death for patients with moderate anemia (Hb 8.5-10.9 g/dl) (O'Brien, et al., 2005). Those with severe anemia (Hb < 8.5 g/dl) had even higher risk of death (HR=3.31) compared to normal hemoglobin (O'Brien, et al., 2005). There are possible explanations for the findings of the Tanzania study. Women enrolled in the previous cohort were pregnant, so their hemoglobin levels at the baseline visit may have been lowered as a result of pregnancy. Seventy eight per cent of participants were at least 16 weeks pregnant at the time of enrolment and the mean hemoglobin for these women was significantly lower compared to those less than 16 weeks pregnant. One measurement of hemoglobin taken during pregnancy may not be accurate as a predictor of AIDS progression. For this study, adult HIV-infected

patients (men and women) with at least two repeated measures of hemoglobin level at baseline and at HAART initiation were used. A study in Brazil reported that AIDS patients with an initial presentation of normal hemoglobin showed the highest rate of survival and that AIDS patients with hemoglobin less than 10 mg/dl had lower survival (Melo, et al., 2008). This is supported by a collaborative cohort study using data from 11 sites in Asia Pacific region which reported that lower levels of hemoglobin have been shown to be associated with an 88 to 91 per cent increase in the risk of death (Zhou & Kumarasamy, 2005). AIDS patients who can improve their hemoglobin levels will make it possible to have improved survival (Volberding et al., 2004)

Unemployment and manual employment were predictors of death in AIDS patients on HAART. It is not difficult to explain why unemployed patients with no any source of income have a higher risk of death as similar results have been found elsewhere (DeSilva, et al., 2009). A study in San Francisco demonstrated the effect of household income of neighborhood of residence on survival after AIDS diagnosis (McFarland, Chen, Hsu, Schwarcz, & Katz, 2003). Persons living in poor neighborhoods were less likely to use HAART at any time in the past compared to persons in wealthier neighbourhoods. AIDS survival in the HAART era was worse for people living in poor neighborhoods compared to wealthier neighborhoods as a result of unequal access to the use of HAART (McFarland, et al., 2003; Wood, et al., 2002). Both of these studies have similarities in that data was collected both retrospectively and prospectively and used Kaplan Meier analysis for survival and Cox regression for prediction of survival but there are differences in sources of data. The previous studies used population-based data while this study used hospital-based data.

CD4 counts that never recovers more than 200 cells/µL and an inability to achieve viral load less than 50 copies/ml have high hazard ratios in the progression from AIDS to death (patients on HAART). The CD4 cells play an important role in the human immune system as CD4 less than 200 cells/µL defines a patient as having AIDS and as a predictor of disease progression (Hulgan, et al., 2007). A higher CD4 was associated with a much greater decrease in the risk of progression compared to a patient had a CD4 less than 200 cells/µL (COHERE, 2012) while the current CD4 count was the strongest predictor of the development of opportunistic infection (Podlekareva et al., 2006). Furthermore the inability to achieve viral load less than 50 copies/ml was associated with increased risk of death (Taiwo et al., 2009b). This may explain two main clinical implications. First, they add to the evidence that suggests, to facilitate immune system recovery, combination anti-retroviral therapy should be started when a patient's CD4 count is between 350 and 500 cells/µl, the current recommended range for combination anti-retroviral therapy initiation. Unfortunately, most patients in this study started HAART when their CD4 cell count was less than 200 cells/µl. Secondly, these findings suggest that patients with sustained viral suppression with low CD4 count should be monitored regularly to ensure that any life threatening AIDS defining events are dealt with quickly and effectively. The European cohort study reported that patients on anti-retroviral therapy with a CD4 count more than 200 cells/µL had a lower risk of death (HR= 0.75). Those with CD4 more than 350 cells/µL had a lower risk of death (HR= 0.68) compared to CD4 less than 200 cells/µL (COHERE, 2012). This finding shows that AIDS patients whose CD4 count recovers to more than 200 cells/µL and whose viral load is less than 50 copies/ml will improve their chances of survival.

5.4.3 Predictors of death in AIDS patients not on ART

The median survival of AIDS patients not on anti-retroviral therapy in this study decreased with increased age. The median survival for age groups 20-29, 30-39, 40-49, 50-59 and 60 years and above were 20.6, 14.5, 13.2, 5.8 and 2.9 months respectively. Patients in age groups of 50-59 years had higher risk of progression to death (HR= 2.41). The USA study showed an even higher risk of death than this study (HR= 3.66) for age group 50-59 years (Hall, et al., 2006). Both studies differ in reference group and terms of age of participants. The US study included adult and adolescents while the current study includes only adults. Univariate analysis produced a similar finding where there was a higher risk of progression to death with increased age (Babiker, Peto, Porter, Walker, & Darbyshire, 2001; Schwarcz, et al., 2000). Increased age and AIDS are associated with a diminished immune response. With consequent high viral load and increased probability of opportunistic infections, it is therefore not surprising that these factors increase the risk of death (May et al., 2007).

In the multivariate analysis, Chinese ethnicity, WHO clinical stage 4 and viral load more than 100,000 copies/ml were independent predictors of death in AIDS patients not on anti-retroviral therapy. The Chinese had a shorter median survival (12.8 months) compared to the Malays (23.2 months) and Indian (14.1 months). A study in USA has investigated the differences in the risk death by race/ethnicity and reported no racial/ethnic differences in clinical progression of HIV (Anastos et al., 2005). A California study confirms that in settings with similar access to integrated care for HIV infected persons, there is no difference with respect to clinical outcomes for racial/ethnic minorities (Silverberg, Leyden, Quesenberry, & Horberg, 2009). Other studies indicated that Black and Hispanic patients had higher mortality rates compared

to White patients (McGinnis et al., 2003). Another study indicated higher mortality rates for Hepatitis C co-infected White compared with Black patients (Merriman, Porter, Brensinger, Reddy, & Chang, 2006). It is difficult to explain why Chinese patients are more likely to die compared to Malay or Indian patients. One possible explanation could be that the majority of patients in the University of Malaya Medical Centre are Chinese and who seek medical care or whether the Chinese patients were sicker than other ethnic groups. Further research is needed to evaluate this finding.

The 5 and 10-year survival decrease rapidly with more advanced WHO clinical stage. In this study, 5 and 10-year survival in WHO clinical stage 3 (34.5 per cent and 27.5 per cent respectively) were higher compared to stage 4 (19.2 per cent and 13.6 per cent respectively). Those in WHO clinical stage 4 when compared to stage 3 had an increased risk of death (HR= 2.25). Some studies have provided similar evidence that WHO clinical staging is a factor associated with disease progression (Jerene, et al., 2006; Palombi et al., 2009) so this comes as little surprise.

Those with viral load more than 100,000 copies/ml had a significantly increased risk of dying (HR= 1.35) and a shorter median survival (11.5 months) compared to those with viral load less than 100,000 copies/ml (25.8 months). Studies in Kenya and Spain demonstrated viral load and CD4 as predictors of mortality (Brown, et al., 2009; Jaen, et al., 2008). In addition, an independent effect of viral load on progression to death was also found after adjusting for other covariates, including CD4 count (Phillips & Pezzotti, 2004).

5.5 Time and predictors achieved viral load less than 50 copies/ml

The goal of anti-retroviral therapy in HIV-infected patients is to limit viral replication, slow the progression of HIV disease and increase the level of CD4 count (MOH, 2001c). Viral replication is measured by the level of viral load. The effectiveness of anti-retroviral therapy is reflected by its ability to reduce viral load to less than 50 copies/ml. In this study for a total of 474 patients receiving HAART, 70.5 per cent achieved viral load less than 50 copies/ml. The mean time to achieve this was 9.2 months and the median time was 5.1 months. These findings were not as good as the findings from a study in the United Kingdom where 482 of 656 (73 per cent) patients managed to achieve viral load less than 50 copies/ml within 6 months after the initiation of HAART (Smith, et al., 2004). Similarly, in the European Collaborative study of pregnant women, undetectable viral load were achieved by 73 per cent (175 of 240 pregnant women) at the time of delivery (the median time to achieve undetectable viral load was 9.5 months). It was noted that all pregnant women in the study had received initial HAART based on two combinations; 65 per cent with 2 NRTI + PI (Nelfinavir) and 35 per cent with 2 NRTI + NVP (Nevirapine) (Patel, Cortina-Borja, Thorne, & Newell, 2007). The differences in time taken to achieve viral load less than 50 copies/ml between the patients in this study and the stated two studies could be attributed to the initial status of anti-retroviral therapy used by the patients. In another study from a Multicenter AIDS Cohort, the median time taken from HAART initiation to first achieve viral load less than 50 copies were 11.8 months (Taiwo, et al., 2009b). The median time to achieved viral load less than 50 copies in this study was 5.1 months. This finding is shorter than the multicentre AIDS cohorts study (MACS) due to the different study design and sample size. The MACS study applied a prospective cohort design with a small sample size of men (n= 121) infected among men who have sex

with men route compared to this study. Our study applied both retrospective and prospective cohort design and which included men and women infected via the heterosexual, homosexual, IDU and other routes and a larger sample size. The findings of this study are similar to those from the observational study conducted in Salvador (Resino, et al., 2003). In Italy a study on predicting the duration of anti-retroviral therapy needed to suppress the viral load (Rizzardi, et al., 2000) showed that after HAART initiation with baseline CD4 more than 250 cells/μL and baseline viral load more than 5000 copies/ml, a decreased viral load to less than 50 copies/ml was observed after varying periods of time. All 118 subjects studied took between 2 and 24 weeks to achieve viral load less than 50 copies/ml (Rizzardi, et al., 2000).

Those who received initial HAART with 2 NRTI + EFV had higher chance to achieve viral load less than 50 copies/ml compared to initial HAART with 2 NRTI + PI. Patients who did not need to switch to second line of HAART had higher chance to achieve viral load less than 50 copies/ml compared to those who needed to switch to a second line of HAART. There are similar findings in developed countries on initial HAART (Geretti, et al., 2008). Patients who were infected by injecting drug use had a lower chance of achieving viral load less than 50 copies/ml and increased risk of death. This is supported by a study done using pooled data from the CASCADE Collaboration and European study that demonstrated that injecting drug user had an increased risk of death (Borrell et al., 2006; Schwarcz, et al., 2000).

Most adult HIV-infected patients achieve viral load less than 50 copies/ml within a year of starting anti-retroviral therapy. Patients who start anti-retroviral therapy when they have a high CD4 count tend to do better than people who start treatment when they have a low CD4 count. A Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) study estimated the association between CD4 and progression to

AIDS and death among patients who have achieved viral suppression on anti-retroviral therapy. The finding was that a higher CD4 is associated with a reduced risk of AIDS and death in patients on anti-retroviral therapy with a suppressed viral load (COHERE, 2012).

This finding gives hope to patients with terminal AIDS if their CD4 can recover to more than 200 cells/μL, hemoglobin more than 12 g/dl, normal total lymphocyte count and undetectable viral load (less than 50 copies/ml) as the chances of survival are improved in these patients.

5.6 Strengths and limitations of study

This study has several strengths. Firstly, this is the first study to report survival time of AIDS progression to death and to achieve viral load less than 50 copies in the University of Malaya Medical Centre. Secondly, this is a cohort (combined prospective and retrospective) study of HIV patients which is rare in Malaysia and second in only to randomised control trials to study anti-retroviral therapy effectiveness on disease progression after (Evans, 2003). Thirdly, the relatively large sample size of HIV-infected patients (n = 1314) and AIDS patients (n = 989) for a Malaysian study gives it sample power to test associations. Fourthly, there were four sources of data, socio-demographic characteristic, laboratory, clinical and anti-retroviral therapy and a large number of variables (n = 32). Finally, is the fact that the University of Malaya Medical Centre is a major referral centre and our ability to accurately crosscheck with mortality records of the National Registration Department

There are some limitations in this study. Firstly, this study used secondary data. This limitation led to some gaps in information about the uncertainty of the exact time of HIV infection and history of prior anti-retroviral therapy before having treatment in the University of Malaya Medical Centre. It is difficult to ascertain the route of infection except to rely on the patient's history. The reasons to switch to second line HAART therapy might be clinically relevant which would in itself explain the poorer outcomes in patients who had to switch to second line treatment. Secondly, the scenario at the University of Malaya Medical Centre is different from the rest of Malaysia. In the University of Malaya Medical Centre the main exposure route is by the heterosexual route, most patients are Chinese and come from an urban population whereas in the rest of the country, injecting drug use is the main exposure route and most HIV patients are Malays. The patients in the University of Malaya Medical Centre was relatively affluent, largely due to the catchment area that the hospital is serving and because the University of Malaya Medical Centre caters to a predominantly middle class urban population owing to its location.

5.7 Summary

Inability to achieve viral load less than 50 copies/ml is the most important predictor of death in AIDS patients on anti-retroviral therapy followed by CD4 counts which never recovers to more than 200 cells/μL and unemployment. Unemployment has a strong correlation with income. It is a strong predictor of socioeconomic status but how much income is required for better survival in Malaysia is unknown and requires further research. Patients with terminal AIDS but whose hemoglobin recovers to more than 12 g/dl and those with normal total lymphocyte count (more than 1,200 cells/μL) has a better chance of survival. Further research is required on the role of hemoglobin level

and total lymphocyte count as surrogate markers to predict CD4 counts in resource limited settings. Most findings from this study are consistent with other Asian, African and developed country studies but two things still remain unclear the lower survival of Chinese patients compared to Malays and Indian and the reason why AIDS patients infected via the injecting drug use route in the University of Malaya Medical Centre had a lower chance to achieve viral load less than 50 copies/ml.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 Introduction

This chapter presents conclusions and recommendations of this study. Section 6.1 is the Introduction. Section 6.2 presents major findings of this study, including the characteristics of HIV-infected patients seen at the University of Malaya Medical Centre stratified by socio-demographic, laboratory, clinical and anti-retroviral therapy in section 6.2.1 Section 6.2.2 is a summary of the observation about survival time and the 5 and 10-year survival. Section 6.2.3 is a summary of the predictors of death in all AIDS patients, AIDS patients on HAART and AIDS patients not on anti-retroviral therapy. Section 6.2.4 is about the time and predictors to achieve viral load less than 50 copies/ml. This continues in Section 6.3 where the recommendations and need for further studies are summarized. Contributions of the study are spelled out in Section 6.3.1,implications of study in Section 6.3.2 and conclusion in Section 6.4

6.2 Major findings of this study

The purpose of this study was to determine predictors of progression and survival of HIV-infected patients who received follow up treatments at the University of Malaya Medical Centre.

6.2.1 The characteristics of HIV-infected patients

Socio-demographic studies have shown that 73.3 per cent of HIV-infected patients were 20-39 years old with median age of 33.7 years (IQR 12.0). The majority were male, Chinese, single, had primary and secondary education, work as professionals and non-manual workers and earned between RM 1,000 to 3,000 per month. The socio-demographic profile of AIDS patients receiving anti-retroviral therapy was similar to the HIV-infected patients except for marital status, i.e. most AIDS patients were married with median age of 34.1 years (IQR 12.7).

The majority of HIV-infected patients and AIDS patients on anti-retroviral initiation had CD4 less than 200 cells/μL, viral load more 100,000 copies/ml, meaning they were in at an advanced infection stage, but hemoglobin more 12 g/dl, normal total lymphocyte count and normal liver function test.

The majority of HIV-infected patients and AIDS patients on anti-retroviral therapy initiation contracted infection via the heterosexual route, with WHO clinical stage 4, body mass index more 18.5 kg/m2, positive opportunistic infection and presented with one opportunistic infection.

The majority of HAART started with 2 NRTI + EFV, and there was no need to switch to second line drugs. At the end of the study 90.7 per cent of these patients were on HAART without PI and only 9.3 per cent of HAART needed a PI. There were 5.5 per cent patients with first line combination with PI and out of them 61.5 per cent are on first line drugs until end of the study while the other 38.5 per cent stopped without a clear reason.

The major cause of death in these patients is recognized as an AIDS related illness and among them, PCP and Tuberculosis are the leading cause.

6.2.2 The survival time and the 5 and 10 year survival

The survival time of HIV-infected patients and AIDS patients were greatly improved by anti-retroviral therapy. The median survival time was 177.5 months for receiving anti-retroviral therapy, 73.2 months of not receiving anti-retroviral therapy in HIV-infected patients. In AIDS patients, 121.7 months for those receiving anti-retroviral therapy, 15.0 months of not receiving anti-retroviral therapy.

The 5 and 10-year survival of AIDS patients were 51.8 and 41.4 per cent for those with anti- retroviral, 23.6 and 18.9 per cent for patients non anti-retroviral therapy

6.2.3 Predictors of death

a. Predictors of death in all AIDS patients

Unemployed patients, those with three and above of opportunistic infection and non receiving anti-retroviral therapy are the predictors of death in all AIDS patients. These findings are consistent with previous studies that have found HIV-infected patients with unemployed as predictors of death in Nigeria and San Francisco (DeSilva, et al., 2009; McFarland, et al., 2003). The number of opportunistic infection as predictors of death consistent in developed countries studies (Candiani, et al., 2007; Schwarcz, et al., 2000). Asia studies (China and India) shows that AIDS patients those not receiving anti-retroviral therapy as predictors of death (Ghate, et al., 2011; Hung, et al., 2006)

b. Predictors of death in AIDS patients on HAART

The WHO guidelines in 2010 for anti-retroviral therapy initiation when patients with CD4 less than 350 cells/µL (WHO, 2010a). While the majority of patients in this study start HAART with CD4 less than 200 cells/µL because come in the clinic in late stage. The predictors of death in AIDS patients on HAART are unemployed patients, those with CD4 never recovers to more than 200 cells/µL and inability to achieve viral load less than 50 copies/ml. These findings consistent with previous studies in developed countries (COHERE, 2012; Hulgan, et al., 2007; Taiwo, et al., 2009b)

c. Predictors of death in AIDS patients not on anti-retroviral therapy

Chinese patients in WHO clinical stage 4 with baseline viral load more than 100,000 copies/ml are predictors of death in AIDS patients not on anti-retroviral therapy. Advanced clinical staging and higher viral load as predictors of death on AIDS patients not on anti-retroviral therapy are consistent with previous studies in Africa and developed countries (Brown, et al., 2009; Jaen, et al., 2008; Palombi, et al., 2009), but difficult to explain that Chinese as predictors of death, needed further research

6.2.4 The time and predictors to achieve viral load less than 50 copies/ml

The mean time to achieve viral load less than 50 copies/ml was 9.2 months and the median time was 5.1 months. Initial combination of 2 NRTI + EFV, lack of necessity switch to second line of HAART and infection through injecting drug use are predictors to achieve viral load less than 50 copies/ml. These findings are consistent with previous studies (Smith, et al., 2004; Taiwo, et al., 2009b).

The findings of this study are consistent with studies from other developed and developing countries. However, there are several findings which warrant further research as they seem to be peculiar to Malaysia. Every effort needs be made to ensure all HIV-infected patients in Malaysia are able to achieve a CD4 count of more than 200 cells/µL, viral load less than 50 copies/ml and have access to triple drug anti-retroviral therapy as these are significant modifiable predictors of death in Malaysian HIV patients.

6.3 Recommendations and further studies

6.3.1 Contribution of study

There are two majors contribution of this study. This includes a contribution to building of knowledge in HIV-infected patients and a contribution to public health policy

a. Building knowledge

This study helps in building the knowledge of disease progression and survival of HIV infected patients receiving anti-retroviral therapy in the University of Malaya Medical Centre. It is hoped that findings of this study will provide meaningful information that can be used to create a better treatment setting in the University of Malaya Medical Centre. This is potentially useful to nurses and clinicians who look after HIV-infected patients so that they are able to intervene early with anti-retroviral therapy and closely monitor the treatment regimes of patients. The success of HAART to improve survival and quality of life should be based on an individualized approach, with timely monitoring of laboratory indicators and health education especially with respect to adherence, nutrition and life style factors.

The outcome of this study will help to guide health care providers in Malaysia to have a better understanding of the predictors of AIDS progression to death in the local context by providing awareness for routine examination of CD4, viral load and anti-retroviral adherence. This may help to achieve better survival for AIDS patients. It will also help to determine the predictors of progression in AIDS patients and its accompanying complications which could have an impact on Malaysian Clinical Practice Guidelines (CPG) in AIDS treatment.

b. Public health policy

The Ministry of Health Malaysia had set the target of reducing the notification rate of new HIV infection of 11 cases per 100,000 and later adjusted it to 9 cases per 100,000 population by 2015 (Prime Minister's Department Malaysia & United Nations Country Team, 2010). There needs to be a focus in terms of prevention, care and support to reduce the rate of HIV infection.

The surveillance and screening mechanism has grown extensively in Malaysia. Groups routinely screened for HIV are women receiving antenatal care in government facilities, blood donors, inmates in drug rehabilitation centres, high-risk prison inmates, drug users, sex workers, confirmed tuberculosis cases, sexually transmitted infections cases, patients with suspected clinical symptoms, traced contacts of confirmed persons with HIV, premarital couples, migrant workers, and participants in harm-reduction programmes (Prime Minister's Department Malaysia & United Nations Country Team, 2010). There needs to be increased HIV counselling in the community because HIV infection still a stigma in Malaysia to reduce late presentation and underreporting.

The Ministry of Health conducts a routine HIV surveillance system but intensive surveillance is required in most at risk populations (MARPs) in Malaysia including injecting drug users, female sex workers, men who have sex with men and the transgender population because the trend of the HIV epidemic in Malaysia is slowly changing to that of a sexually transmitted epidemic.

On a practical level, although anti-retroviral therapy is available free of charge by the Malaysian government, monitoring of laboratory testing as prescribed by the WHO guidelines is chargeable and causes the treatment and management of HIV infection to

be costly. The burden of this expense falls largely on the patients. Quality initiatives based on clinical outcomes will continue to be a requirement. While morbidity and mortality have dropped dramatically since the introduction of HAART, these reductions are not uniform across populations. It is imperative that the reasons for these inequities are identified, and strategy for improvement in access and quality be implemented. Collaboration with non-governmental organizations are needed for the program to succeed and to decrease the burden of HIV-infected patients

6.3.2 Implications of the study

The findings of this study highlight several things for further research in AIDS progression such as:

Further research should seek to investigate why patients who were infected by injecting drug use had a lower chance of achieving viral load less than 50 copies/ml.

Further research is recommended to look into why Chinese patients had lower survival compared to Malays and Indian.

Further research is needed to look into the usefulness of hemoglobin recovery in HIV-infected patients as an independent predictor of death especially in resource limited settings.

Further research would be helpful to confirm total lymphocyte count as surrogate markers to predict CD4 counts in resource limited settings. It is still unclear, whether

the cut off value of total lymphocyte counts less than 1,200 cells/μL can predict CD4 less than 200 cells/μL is suitable in developing countries especially in Malaysia.

Further research is needed to look into the impact of HIV infection on employment status and how long the HIV-infected patients can continue to work after being diagnosed with HIV/AIDS.

Further research will be helpful to investigate the influence of unemployment as a predictor of death in AIDS patients. This is necessary to determine how much funding is required by an HIV-infected patient for better survival in Malaysia.

Appendix A: References

Agaba, P. A., Digin, E., Makai, R., Apena, L., Agbaji, O. O., Idoko, J. A., Kanki, P. (2011). Clinical characteristics and predictors of mortality in hospitalized HIV-infected Nigerians. *J Infect Dev Ctries, 5*(5), 377-382.

AIDSinfonet.org. (2012). HIV life cycle. Retrieved from http://www.aidsinfonet.org/fact_sheets/view/106 website: [updated 16 April 2012; cited]

Alavi, S. M., Ahmadi, F., & Farhadi, M. (2009). Correlation between Total Lymphocyte Count, Hemoglobin, Hematocrit and CD4 Count in HIV/AIDS Patients. *Acta Medica Iranica, 47*(1), 1-4.

Alemu, A. W., & Sebastian, M. S. (2010). Determinants of survival in adult HIV patients on antiretroviral therapy in Oromiyaa, Ethiopia. *Glob Health Action, 3*. doi: 10.3402/gha.v3i0.5398

Alibhai, A., Kipp, W., Saunders, L. D., Senthilselvan, A., Kaler, A., Houston, S., Rubaale, T. (2010). Gender-related mortality for HIV-infected patients on highly active antiretroviral therapy (HAART) in rural Uganda. *Int J Womens Health, 2*, 45-52.

Althoff, K. N., Justice, A. C., Gange, S. J., Deeks, S. G., Saag, M. S., Silverberg, M. J., Gebo, K. A. (2010). Virologic and immunologic response to HAART, by age and regimen class. *AIDS, 24*(16), 2469-2479. doi: 10.1097/QAD.0b013e32833e6d14

Anastos, Barron, Cohen, Greenblatt, Minkoff, Levine, Gange. (2004). The prognostic importance of changes in CD4+ cell count and HIV-1 RNA level in women after initiating highly active antiretroviral therapy. *Ann Intern Med, 140*(4), 256-264. doi: 140/4/256 [pii]

Anastos, Schneider, Gange, Minkoff, Greenblatt, Feldman, Cohen. (2005). The association of race, sociodemographic, and behavioral characteristics with response to highly active antiretroviral therapy in women. *J Acquir Immune Defic Syndr, 39*(5), 537-544. doi: 00126334-200508150-00005 [pii]

Anthea, M., Hopkins, J., McLaughlin, C. W., Johnson, S., Warner, M. Q., LaHart, D., & Wright, J. D. (1993). *Human Biology and Health*. New Jersey, USA: Englewood Cliffs.

Arnold, M., Hsu, L., Pipkin, S., McFarland, W., & Rutherford, G. W. (2009). Race, place and AIDS: the role of socioeconomic context on racial disparities in treatment and survival in San Francisco. *Soc Sci Med, 69*(1), 121-128. doi: 10.1016/j.socscimed.2009.04.019 S0277-9536(09)00245-7 [pii]

Astoro, N. W., Djauzi, S., Djoerban, Z., & Prodjosudjadi, W. (2007). Quality of life of HIV patients and influential factors. *Acta Med Indones, 39*(1), 2-7. doi: 040579197 [pii]

Auld, A. F., Mbofana, F., Shiraishi, R. W., Sanchez, M., Alfredo, C., Nelson, L. J., & Ellerbrock, T. (2011). Four-year treatment outcomes of adult patients enrolled in Mozambique's rapidly expanding antiretroviral therapy program. *PLoS One, 6*(4), e18453. doi: 10.1371/journal.pone.0018453

Babiker, Peto, Porter, Walker, & Darbyshire. (2001). Age as a determinant of survival in HIV infection. *J Clin Epidemiol, 54 Suppl 1*, S16-21. doi: S0895435601004565 [pii]

Bailey, R. C., Moses, S., Parker, C. B., Agot, K., Maclean, I., Krieger, J. N., Ndinya-Achola, J. O. (2007). Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet, 369*(9562), 643-656. doi: S0140-6736(07)60312-2 [pii] 10.1016/S0140-6736(07)60312-2

Appendix A References

Barker, E., Mackewicz, C. E., Reyes-Terán, G., Sato, A., Stranford, S. A., Fujimura, S. H., Levy, J. A. (1998). Virological and Immunological Features of Long-Term Human Immunodeficiency Virus–Infected Individuals Who Have Remained Asymptomatic Compared With Those Who Have Progressed to Acquired Immunodeficiency Syndrome. *Blood, 92*(9), 3105-3114.

Barre-Sinoussi, F., Chermann, J., Rey, F., Nugeyre, M., Chamaret, S., Gruest, J., Montagnier, L. (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science, 220*(4599), 868-871. doi: 10.1126/science.6189183

Batalla, J., Gatell, J. M., Cayla, J. A., Plasencia, A., Jansa, J. M., & Parellada, N. (1989). Predictors of the survival of AIDS cases in Barcelona, Spain. *AIDS, 3*(6), 355-359.

Beaglehole, R., Bonita, R., Horton, R., Adams, O., & McKee, M. (2004). Public health in the new era: improving health through collective action. *Lancet, 363*(9426), 2084-2086. doi: 10.1016/S0140-6736(04)16461-1S0140-6736(04)16461-1 [pii]

Bedell, R., Heath, K. V., Hogg, R. S., Wood, E., Press, N., Yip, B., Montaner, J. S. (2003). Total lymphocyte count as a possible surrogate of CD4 cell count to prioritize eligibility for antiretroviral therapy among HIV-infected individuals in resource-limited settings. *Antivir Ther, 8*(5), 379-384.

Beral, V., Babiker, A., Darby, S., Angelis, D. D., Ewart, D., Porter., K., Day, N. (2000). Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. *The Lancet, 355*(9210), 1131-1137.

Bessinger, R., Clark, R., Kissinger, P., Rice, J., & Coughlin, S. (1998). Pregnancy is Not Associated with the Progression of HIV Disease in Women Attending an HIV Outpatient Program. *American Journal of Epidemiology, 147*(5), 434-440.

Biadgilign, S., Reda, A. A., & Digaffe, T. (2012). Predictors of mortality among HIV infected patients taking antiretroviral treatment in Ethiopia: a retrospective cohort study. *AIDS Res Ther, 9*(1), 15. doi: 10.1186/1742-6405-9-15 1742-6405-9-15 [pii]

Boily, M.-C., Baggaley, R. F., Wang, L., Masse, B., White, R. G., Hayes, R. J., & Alary, M. (2009). Heterosexual risk of HIV-1 infection per sexual act: sytematic review and meta-analysis of observational studies. *Lancet, 9*(2), 118-129.

Bonacini, M. (2004). Liver injury during highly active antiretroviral therapy: the effect of hepatitis C coinfection. *Clin Infect Dis, 38 Suppl 2*, S104-108. doi: 10.1086/381453
CID32528 [pii]

Bonnet, Thiebaut, Chene, Neau, Pellegrin, Mercie, Morlat. (2005). Determinants of clinical progression in antiretroviral-naive HIV-infected patients starting highly active antiretroviral therapy. Aquitaine Cohort, France, 1996-2002. *HIV Med, 6*(3), 198-205. doi: HIV290 [pii]10.1111/j.1468-1293.2005.00290.x

Borrell, C., Rodriguez-Sanz, M., Pasarin, M. I., Brugal, M. T., Garcia-de-Olalla, P., Mari-Dell'Olmo, M., & Cayla, J. (2006). AIDS mortality before and after the introduction of highly active antiretroviral therapy: does it vary with socioeconomic group in a country with a National Health System? *Eur J Public Health, 16*(6), 601-608. doi: ckl062 [pii] 10.1093/eurpub/ckl062

Bozzette, S. A., Berry, S. H., Duan, N., Frankel, M. R., Leibowitz, A. A., Lefkowitz, D., Richman, D. (1998). The Care of HIV-Infected Adults in the United States. *New England Journal of Medicine, 339*(26), 1897-1904. doi: doi:10.1056/NEJM199812243392606

Braga, P., Cardoso, M. R., & Segurado, A. C. (2007). Gender differences in survival in an HIV/AIDS cohort from Sao Paulo, Brazil. *AIDS Patient Care STDS, 21*(5), 321-328. doi: 10.1089/apc.2006.0111

Appendix A References

Brown, E. R., Otieno, P., Mbori-Ngacha, D. A., Farquhar, C., Obimbo, E. M., Nduati, R., . . . John-Stewart, G. C. (2009). Comparison of CD4 cell count, viral load, and other markers for the prediction of mortality among HIV-1-infected Kenyan pregnant women. *J Infect Dis, 199*(9), 1292-1300. doi: 10.1086/597617

Bulgiba, A., Mohammed, U. Y., Chik, Z., Lee, C., & Peramalah, D. (2013). How well does self-reported adherence fare compared to therapeutic drug monitoring in HAART? *Preventive Medicine*(0). doi: http://dx.doi.org/10.1016/j.ypmed.2013.01.002

Candiani, T. M., Pinto, J., Cardoso, C. A., Carvalho, I. R., Dias, A. C., Carneiro, M., & Goulart, E. A. (2007). Impact of highly active antiretroviral therapy (HAART) on the incidence of opportunistic infections, hospitalizations and mortality among children and adolescents living with HIV/AIDS in Belo Horizonte, Minas Gerais State, Brazil. *Cad Saude Publica, 23 Suppl 3*, S414-423. doi: S0102-311X2007001500009 [pii]

Cane, P., Chrystie, I., David, Dunn, D. T., Evans, B., Geretti, A. M., Zuckerman, M. (2005). Time trends in primary resistance to HIV drugs in the United Kingdom: multicentre observational study. *BMJ, 331*(7529), 1368. doi: 10.1136/bmj.38665.534595.55

Carlson, M. D., & Morrison, R. S. (2009). Study design, precision, and validity in observational studies. *J Palliat Med, 12*(1), 77-82. doi: 10.1089/jpm.2008.9690

CDC. (1992). 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults

CDC. (1997). Update: Trends in AIDS Incidence -- United States, 1996 *MMWR* (Vol. 46, pp. 165-173).

CDC. (2001). The global HIV and AIDS epidemic. MMWR (Vol. 50, pp. 434-439).

CDC. (2006). Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings (pp. 1-17).

Chaisson, R. E., Keruly, J. C., & Moore, R. D. (1995). Race, Sex, Drug Use, and Progression of Human Immunodeficiency Virus Disease. *New England Journal of Medicine, 333*(12), 751-756. doi: doi:10.1056/NEJM199509213331202

Chan, K. C. W., Wong, K. H., & Lee, S. S. (2006). Universal decline in mortality in patients with advanced HIV-1 disease in various demographic subpopulations after the introduction of HAART in Hong Kong, from 1993 to 2002. *HIV Medicine, 7*(3), 186-192. doi: 10.1111/j.1468-1293.2006.00352.x

Chen, S. C.-C., Yu, J. K.-L., Harries, A. D., Bong, C.-N., Kolola-Dzimadzi, R., Tok, T.-S., . . . Wang, J.-D. (2008). Increased mortality of male adults with AIDS related to poor compliance to antiretroviral therapy in Malawi. *Tropical Medicine & International Health, 13*(4), 513-519. doi: 10.1111/j.1365-3156.2008.02029.x

COHERE. (2012). CD4 Cell Count and the Risk of AIDS or Death in HIV-Infected Adults on Combination Antiretroviral Therapy with a Suppressed Viral Load: A Longitudinal Cohort Study from COHERE. *PLoS Med 9*(3). doi: 10.1371/journal.pmed.1001194

Cole, S. R., Hernán, M. A., Robins, J. M., Anastos, K., Chmiel, J., Detels, R., Muñoz, A. (2003). Effect of Highly Active Antiretroviral Therapy on Time to Acquired Immunodeficiency Syndrome or Death using Marginal Structural Models. *American Journal of Epidemiology, 158*(7), 687-694. doi: 10.1093/aje/kwg206

Collier, J., & Bassendine, M. (2002). How to respond to abnormal liver function tests. *Clin Med, 2*(5), 406-409.

Crum, N. F., Riffenburgh, R. H., Wegner, S., Agan, B. K., Tasker, S. A., Spooner, K. M., . . . Wallace, M. R. (2006). Comparisons of causes of death and mortality rates

among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr, 41*(2), 194-200. doi: 00126334-200602010-00011 [pii]

Deng, H., Liu, R., Ellmeier, W., Choe, S., Unutmaz, D., Burkhart, M., Landau, N. R. (1996). Identification of a major co-receptor for primary isolates of HIV-1. *Nature, 381*(6584), 661-666. doi: 10.1038/381661a0

Department of Statistic. (2010). Population and housing cencus of Malaysia, population distribution and basic demographic characteristics.

DeSilva, Merry, S. P., Fischer, P. R., Rohrer, J. E., Isichei, C. O., & Cha, S. S. (2009). Youth, unemployment, and male gender predict mortality in AIDS patients started on HAART in Nigeria. *AIDS Care, 21*(1), 70-77. doi: 10.1080/09540120802017636
906615711 [pii]

DHHS. (2009). DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents Panel Roster.

Djauzi, S. (2007). Quality of life in people living with HIV/AIDS. *Acta Med Indones, 39*(1), 1.

Doranz, B., Berson, J., Rucker, J., & Doms, R. (1997). Chemokine receptors as fusion cofactors for human immunodeficiency virus type 1 (HIV-1). *Immunologic Research, 16*(1), 15-28. doi: 10.1007/bf02786321

Dou, Z., Chen, R. Y., Wang, Z., Ji, G., Peng, G., Qiao, X., Zhang, F. (2010). HIV-infected former plasma donors in rural Central China: from infection to survival outcomes, 1985-2008. *PLoS One, 5*(10), e13737. doi: 10.1371/journal.pone.0013737

Dray-Spira, R., Gueguen, A., Ravaud, J. F., & Lert, F. (2007). Socioeconomic differences in the impact of HIV infection on workforce participation in France in the era of highly active antiretroviral therapy. *Am J Public Health, 97*(3), 552-558. doi: AJPH.2005.081083 [pii] 10.2105/AJPH.2005.081083

Dray-Spira, R., Lert, F., Marimoutou, C., Bouhnik, A. D., & Obadia, Y. (2003). Socio-economic conditions, health status and employment among persons living with HIV/AIDS in France in 2001. *AIDS Care, 15*(6), 739-748. doi: 10.1080/09540120310001618595

Druyts, E. F., Rachlis, B. S., Lima, V. D., Harvard, S. S., Zhang, W., Brandson, E. K., Hogg, R. S. (2009). Mortality is influenced by locality in a major HIV/AIDS epidemic. *HIV Med, 10*(5), 274-281. doi: 10.1111/j.1468-1293.2008.00684.x
HIV684 [pii]

Dupont, W. D., & Plummer, W. D. (Producer). (2009). Power and Sample Size Calculation Retrieved from http://ps-power-and-sample-size-calculation.software.informer.com/.

Egger, M., Hirschel, B., Francioli, P., Sudre, P., Wirz, M., Flepp, M., Battegay, M. (1997). Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. *BMJ, 315*(7117), 1194-1199.

Egger, M., May, M., Chene, G., Phillips, A. N., Ledergerber, B., Dabis, F., Sterne, J. A. (2002). Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet, 360*(9327), 119-129. doi: S0140673602094114 [pii]

European AIDS Clinical Society. (2010). Guidelines Clinical Management and Treatment of HIV Infected Adult in Europe.

Evans, D. (2003). Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. *Journal of Clinical Nursing, 12*(1), 77-84. doi: 10.1046/j.1365-2702.2003.00662.x

Appendix A References

Falster, K., Choi, J. Y., Donovan, B., Duncombe, C., Mulhall, B., Sowden, D., Law, M. G. (2009). AIDS-related and non-AIDS-related mortality in the Asia-Pacific region in the era of combination antiretroviral treatment. *AIDS, 23*(17), 2323-2336. doi: 10.1097/QAD.0b013e328331910c

Fauci, A. S. (1999). The AIDS Epidemic — Considerations for the 21st Century. *New England Journal of Medicine, 341*(14), 1046-1050. doi: doi:10.1056/NEJM199909303411406

Fei, M. W., Kim, E. J., Sant, C. A., Jarlsberg, L. G., Davis, J. L., Swartzman, A., & Huang, L. (2009). Predicting mortality from HIV-associated Pneumocystis pneumonia at illness presentation: an observational cohort study. *Thorax, 64*(12), 1070-1076. doi: 10.1136/thx.2009.117846

thx.2009.117846 [pii]

Fielding, Charalambous, Stenson, Pemba, Martin, Wood, Grant. (2008). Risk factors for poor virological outcome at 12 months in a workplace-based antiretroviral therapy programme in South Africa: a cohort study. *BMC Infect Dis, 8*, 93. doi: 1471-2334-8-93 [pii]

10.1186/1471-2334-8-93

Fisk, D. T., Meshnick, S., & Kazanjian, P. H. (2003). Pneumocystis carinii pneumonia in patients in the developing world who have acquired immunodeficiency syndrome. *Clin Infect Dis, 36*(1), 70-78. doi: CID020951 [pii]

10.1086/344951

Fox, M. P., Sanne, I. M., Conradie, F., Zeinecker, J., Orrell, C., Ive, P., Wood, R. (2010). Initiating patients on antiretroviral therapy at CD4 cell counts above 200 cells/microl is associated with improved treatment outcomes in South Africa. *AIDS, 24*(13), 2041-2050. doi: 10.1097/QAD.0b013e32833c703e

Fregonese, F., Collins, I. J., Jourdain, G., Lecoeur, S., Cressey, T. R., Ngo-Giang-Houng, N., Lallemant, M. (2012). Predictors of 5-year mortality in HIV-infected adults starting highly active antiretroviral therapy in Thailand. *J Acquir Immune Defic Syndr, 60*(1), 91-98. doi: 10.1097/QAI.0b013e31824bd33f

Gandhi, T., Wei, W., Amin, K., & Kazanjian, P. (2006). Effect of Maintaining Highly Active Antiretroviral Therapy on AIDS Events among Patients with Late-Stage HIV Infection and Inadequate Response to Therapy. *Clinical Infectious Diseases, 42*(6), 878-884. doi: 10.1086/500210

Gayle, H. D., & Hill, G. L. (2001). Global Impact of Human Immunodeficiency Virus and AIDS. *Clin. Microbiol. Rev., 14*(2), 327-335. doi: 10.1128/cmr.14.2.327-335.2001

Geretti, A. M., Smith, C., Haberl, A., Garcia-Diaz, A., Nebbia, G., Johnson, M., Staszewski, S. (2008). Determinants of virological failure after successful viral load suppression in first-line highly active antiretroviral therapy. *Antivir Ther, 13*(7), 927-936.

Ghate, M., Deshpande, S., Tripathy, S., Godbole, S., Nene, M., Thakar, M., Mehendale, S. (2011). Mortality in HIV infected individuals in Pune, India. *Indian J Med Res, 133*, 414-420. doi: IndianJMedRes_2011_133_4_414_80133 [pii]

Gilks, C. F., Crowley, S., Ekpini, R., Gove, S., Perriens, J., Souteyrand, Y., De Cock, K. (2006). The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. *Lancet, 368*(9534), 505-510. doi: S0140-6736(06)69158-7 [pii]

10.1016/S0140-6736(06)69158-7

Goh, K., et al. (1987). The acquired immune deficiency syndrome - report of the first case in Malaysia. *Medical Journal of Malaysia*, 58-60.

Appendix A References

Gray, R. H., Kigozi, G., Serwadda, D., Makumbi, F., Watya, S., Nalugoda, F., Wawer, M. J. (2007). Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *The Lancet, 369*(9562), 657-666.

Grigoryan, A., Hall, H. I., Durant, T., & Wei, X. (2009). Late HIV diagnosis and determinants of progression to AIDS or death after HIV diagnosis among injection drug users, 33 US States, 1996-2004. *PLoS One, 4*(2), e4445. doi: 10.1371/journal.pone.0004445

Hall, H. I., McDavid, K., Ling, Q., & Sloggett, A. (2006). Determinants of Progression to AIDS or Death After HIV Diagnosis, United States, 1996 to 2001. *Annals of epidemiology, 16*(11), 824-833.

Hammer, S. M., Eron, J. J., Reiss, P., Schooley, R. T., Thompson, M. A., Walmsley, S., Volberding, P. A. (2008). Antiretroviral Treatment of Adult HIV Infection. *JAMA: The Journal of the American Medical Association, 300*(5), 555-570. doi: 10.1001/jama.300.5.555

Hammer, S. M., Squires, K. E., Hughes, M. D., Grimes, J. M., Demeter, L. M., Currier, J. S., Cook, J. C. (1997). A Controlled Trial of Two Nucleoside Analogues plus Indinavir in Persons with Human Immunodeficiency Virus Infection and CD4 Cell Counts of 200 per Cubic Millimeter or Less. *New England Journal of Medicine, 337*(11), 725-733. doi: doi:10.1056/NEJM199709113371101

Harrington, M., & Carpenter, C. C. J. (2000). Hit HIV-1 hard, but only when necessary. *The Lancet, 355*(9221), 2147-2152.

Harris, R. J., Sterne, J. A., Abgrall, S., Dabis, F., Reiss, P., Saag, M., Egger, M. (2008). Prognostic importance of anaemia in HIV type-1-infected patients starting antiretroviral therapy: collaborative analysis of prospective cohort studies. *Antivir Ther, 13*(8), 959-967.

Haynes, B. F., Pantaleo, G., & Fauci, A. S. (1996). Toward an Understanding of the Correlates of Protective Immunity to HIV Infection. *Science, 271*(5247), 324-328. doi: 10.1126/science.271.5247.324

He, J., Chen, Y., Farzan, M., Choe, H., Ohagen, A., Gartner, S., Gabuzda, D. (1997). CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. *Nature, 385*(6617), 645-649. doi: 10.1038/385645a0

Hemelaar, J., Gouws, E., Ghys, P. D., & Osmanov, S. (2006). Global and regional distribution of HIV-1 genetic subtypes and recombinants in 2004. *AIDS, 20*(16), W13-W23 10.1097/1001.aids.0000247564.0000273009.bc.

Hirsch, M. S., Günthard, H. F., Schapiro, J. M., Vézinet, F. B., Clotet, B., Hammer, S. M., . . . Richman, D. D. (2008). Antiretroviral Drug Resistance Testing in Adult HIV-1 Infection: 2008 Recommendations of an International AIDS Society-USA Panel. *Clinical Infectious Diseases, 47*(2), 266-285. doi: 10.1086/589297

Ho, D. D. (1995). Time to Hit HIV, Early and Hard. *New England Journal of Medicine, 333*(7), 450-451. doi: doi:10.1056/NEJM199508173330710

Hoffmann, C., Rockstroh, J. K., & Kamps, B. S. (2007). HIV Medicine 2007 *Opportunistic infections (OIs)* (pp. 395-397). Retrieved from http://www.hivmedicine.com [updated 15 June 2012; cited]

Holmes, K. K., Sparling, P. F., Stamm, W. E., Piot, P., Wasserheit, J. N., corey, L., watts, D. H. (2008). *Sexually Transmitted Disease* (Fourth ed.): The Mc Graw Hill Medical companies Inc.

http://www.Avert.org/hiv-types.htm (Producer). [updated 11 July 2012; cited]

http://www.globalhealth.org/hiv_aids/global_view/ (Producer). [updated 10 May 2012; cited]

http://www.microbiologybytes.com/virology/AIDSI.html (Producer). (2009). the pathologenesis of AIDS. [updated 6 April 2012; cited]

http://www.sexuallytransmitteddisease.info/aids/aids-pictures (Producer). [updated 7 March 2012; cited]

Huckaby, J. (1998). HIV Lab: Yale University.

Hulgan, T., Shepherd, B. E., Raffanti, S. P., Fusco, J. S., Beckerman, R., Barkanic, G., & Sterling, T. R. (2007). Absolute count and percentage of CD4+ lymphocytes are independent predictors of disease progression in HIV-infected persons initiating highly active antiretroviral therapy. *J Infect Dis, 195*(3), 425-431. doi: JID36919 [pii] 10.1086/510536

Hummel, S., Schmidt, D., Kremeyer, B., Herrmann, B., & Oppermann, M. (2005). Detection of the CCR5-[Delta]32 HIV resistance gene in Bronze Age skeletons. *Genes Immun, 6*(4), 371-374. doi: http://www.nature.com/gene/journal/v6/n4/suppinfo/6364172s1.html

Hung, Chen, Hsieh, Sheng, & Chang. (2000). Clinical Spectrum, Morbidity, and Mortality of Acquired Immunodeficiency Syndrome in Taiwan: A 5-Year Prospective Study. *JAIDS Journal of Acquired Immune Deficiency Syndromes, 24*(4), 378-385.

Hung, Hsiao, C. F., Chen, M. Y., Hsieh, S. M., Chang, S. Y., Sheng, W. H., Chang, S. C. (2006). Improved survival of persons with human immunodeficiency virus type 1 infection in the era of highly active antiretroviral therapy in Taiwan. *Jpn J Infect Dis, 59*(4), 222-228.

Ismail, I., & Bulgiba, A. (2013). Determinants of unsuccessful tuberculosis treatment outcomes in Malaysian HIV-infected patients. *Preventive Medicine*(0). doi: http://dx.doi.org/10.1016/j.ypmed.2012.12.023

Jacobson, Li, Phair, Margolick, Rinaldo, Detels, & Muñoz. (2002). Evaluation of the Effectiveness of Highly Active Antiretroviral Therapy in Persons with Human Immunodeficiency Virus using Biomarker-based Equivalence of Disease Progression. *American Journal of Epidemiology, 155*(8), 760-770. doi: 10.1093/aje/155.8.760

Jacobson, Liu Leaa, Khayam-Bashi Hassan, Deeks Steven, Hecht Frederick, & Kahn Jamesa. (2003). Absolute or total lymphocyte count as a marker for the CD4 T lymphocyte criterion for initiating antiretroviral therapy. *AIDS, 17*(6), 917-919. doi: 10.1097/01.aids.0000060338.12269.f9

Jaén, Á., Esteve, A., Miró, J. M., Tural, C., Montoliu, A., Ferrer, E., Group, t. P. S. (2008). Determinants of HIV Progression and Assessment of the Optimal Time to Initiate Highly Active Antiretroviral Therapy: PISCIS Cohort (Spain). *JAIDS Journal of Acquired Immune Deficiency Syndromes, 47*(2), 212-220 210.1097/QAI.1090b1013e31815ee31282.

Jaen, A., Esteve, A., Miro, J. M., Tural, C., Montoliu, A., Ferrer, E., Casabona, J. (2008). Determinants of HIV progression and assessment of the optimal time to initiate highly active antiretroviral therapy: PISCIS Cohort (Spain). *J Acquir Immune Defic Syndr, 47*(2), 212-220.

Jain, M. K. (2007). Drug-induced liver injury associated with HIV medications. *Clin Liver Dis, 11*(3), 615-639, vii-viii. doi: S1089-3261(07)00051-7 [pii]
10.1016/j.cld.2007.06.008

Jarrin, Geskus, Bhaskaran, Prins, Perez-Hoyos, Muga, Amo. (2008). Gender Differences in HIV Progression to AIDS and Death in Industrialized Countries: Slower Disease Progression Following HIV Seroconversion in Women. *American Journal of Epidemiology, 168*(5), 532-540. doi: 10.1093/aje/kwn179

Appendix A References

Jarrin, Lumbreras, Ferreros, Perez-Hoyos, Hurtado, & Hernandez-Aguado. (2007). Effect of education on overall and cause-specific mortality in injecting drug users, according to HIV and introduction of HAART. *Int J Epidemiol, 36*(1), 187-194. doi: dyl231 [pii] 10.1093/ije/dyl231

Jerene, D., Endale, A., Hailu, Y., & Lindtjorn, B. (2006). Predictors of early death in a cohort of Ethiopian patients treated with HAART. *BMC Infect Dis, 6*, 136. doi: 1471-2334-6-136 [pii] 10.1186/1471-2334-6-136

Jevtović, D., Salemović, D., Ranin, J., Dulović, O., Ilić, D., & Brmbolić, B. (2010). The prognosis of highly active antiretroviral therapy (HAART) treated HIV infected patients in Serbia, related to the time of treatment initiation. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology, 47*(2), 131-135.

Kamarulzaman, A. (2005). Taking stock of two decades of the HIV/AIDS epidemic in Malaysia. *Med J Malaysia, 60*(1), 1-4.

Kawamoto, H., Wada, H., & Katsura, Y. (2010). A revised scheme for developmental pathways of hematopoietic cells: the myeloid-based model. *International Immunology, 22*(2), 65-70. doi: 10.1093/intimm/dxp125

Kazanjian, P., Wei, W., Brown, M., Gandhi, T., & Amin, K. (2005). Viral load responses to HAART is an independent predictor of a new AIDS event in late stage HIV infected patients: prospective cohort study. *Journal of Translational Medicine, 3*(1), 1-7. doi: 10.1186/1479-5876-3-40

Kitahata, M. M., Gange, S. J., Abraham, A. G., Merriman, B., Saag, M. S., Justice, A. C., . . . Moore, R. D. (2009). Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. *New England Journal of Medicine, 360*(18), 1815-1826. doi: doi:10.1056/NEJMoa0807252

Kleinbaum, D. G., & Klein, M. (1996). *Survival Analysis. A self-Learning Text. Statistics in the Health Sciences*. New York: Springer.

Kleinbaum, D. G., Kupper, L. L., & Muller, K. E. (1998). *Applied Regression Analysis and Other Multivariable Methods* (3 rd ed.): Brooks/Cole Publishing Company.

Krentz, H. B., Kliewer, G., & Gill, M. J. (2005). Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. *HIV Medicine, 6*(2), 99-106. doi: 10.1111/j.1468-1293.2005.00271.x

Kumarasamy, N., Solomon, S., Flanigan, T. P., Hemalatha, R., Thyagarajan, S. P., & Mayer, K. H. (2003). Natural history of human immunodeficiency virus disease in southern India. *Clin Infect Dis, 36*(1), 79-85. doi: CID011589 [pii] 10.1086/344756

Kumarasamy, N., Solomon, S., Jayaker Paul, S. A., Venilla, R., & Amalraj, R. E. (1995). Spectrum of opportunistic infections among AIDS patients in Tamil Nadu, India. *Int J STD AIDS, 6*(6), 447-449.

Langford, S. E., Ananworanich, J., & Cooper, D. A. (2007). Predictors of disease progression in HIV infection: a review. *AIDS Res Ther, 4*, 11. doi: 1742-6405-4-11 [pii] 10.1186/1742-6405-4-11

Lawn, S. D., Harries, A. D., Anglaret, X., Myer, L., & Wood, R. (2008). Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS, 22*(15), 1897-1908. doi: 10.1097/QAD.0b013e32830007cd 00002030-200810010-00001 [pii]

Lee, S. S., Lee, K. C., Lee, M. P., Tse, I. C., Mak, W. L., Li, P. C., Sung, J. J. (2011). Development of an HIV clinical cohort database for enhancing epidemiologic surveillance in Hong Kong. *Asia Pac J Public Health, 23*(3), 408-418. doi: 1010539509346979 [pii] 10.1177/1010539509346979

Levine, C., Dubler, N. N., & Levine, R. J. (1991). Building a new consensus: ethical principles and policies for clinical research on HIV/AIDS. *IRB, 13*(1-2), 1-17.

Li, McDonald, Dore, & Kaldor. (2000). Improving survival following AIDS in Australia, 1991-1996. National HIV Surveillance Committee. *AIDS, 14*(15), 2349-2354.

Li, Wang, Gao, Wang, Cui, Song, Wang. (2010). [Study on the natural history of HIV among former commercial plasma donors caused by contaminated plasma donation in central China.]. *Zhonghua Liu Xing Bing Xue Za Zhi, 31*(6), 633-637.

Lifson. (1988). Do Alternate Modes for Transmission of Human Immunodeficiency Virus Exist? A Review. *JAMA: The Journal of the American Medical Association, 259*(9), 1353-1356. doi: 10.1001/jama.1988.03720090043032

Lifson, Krantz, Grambsch, Macalino, Crum-Cianflone, Ganesan, Agan. (2012). Clinical, demographic and laboratory parameters at HAART initiation associated with decreased post-HAART survival in a U.S. military prospective HIV cohort. *AIDS Res Ther, 9*(1), 4. doi: 10.1186/1742-6405-9-4

1742-6405-9-4 [pii]

Lima, V. D., Kretz, P., Palepu, A., Bonner, S., Kerr, T., Moore, D., Hogg, R. S. (2006). Aboriginal status is a prognostic factor for mortality among antiretroviral naive HIV-positive individuals first initiating HAART. *AIDS Res Ther, 3*, 14. doi: 1742-6405-3-14 [pii]

10.1186/1742-6405-3-14

Liu, R., Paxton, W. A., Choe, S., Ceradini, D., Martin, S. R., Horuk, R., Landau, N. R. (1996). Homozygous Defect in HIV-1 Coreceptor Accounts for Resistance of Some Multiply-Exposed Individuals to HIV-1 Infection. *Cell, 86*(3), 367-377.

Lundgren, J. D., & Mocroft, A. (2003). Anemia and Survival in Human Immunodeficiency Virus. *Clinical Infectious Diseases, 37*(Supplement 4), S297-S303. doi: 10.1086/376909

Lundgren, J. D., & Mocroft, A. (2003). Anemia and Survival in Human Immunodeficiency Virus. *CID, 37*(Suppl 4), 297-303.

Macias, J., Pineda, J. A., Lozano, F., Corzo, J. E., Ramos, A., Leon, E., Gomez-Mateos, J. (2003). Impaired recovery of CD4+ cell counts following highly active antiretroviral therapy in drug-naive patients coinfected with human immunodeficiency virus and hepatitis C virus. *Eur J Clin Microbiol Infect Dis, 22*(11), 675-680. doi: 10.1007/s10096-003-1015-2

Mahendradhata, Y., Ahmad, R. A., Kusuma, T. A., Boelaert, M., Van der Werf, M. J., Kimerling, M. E., & Van der Stuyft, P. (2008). Voluntary counselling and testing uptake and HIV prevalence among tuberculosis patients in Jogjakarta, Indonesia. *Trans R Soc Trop Med Hyg, 102*(10), 1003-1010. doi: 10.1016/j.trstmh.2008.04.042

S0035-9203(08)00213-7 [pii]

Malvy, E., Thiebaut, R., Marimoutou, C., & Dabis, F. (2001). Weight loss and body mass index as predictors of HIV disease progression to AIDS in adults. Aquitaine cohort, France, 1985-1997. *J Am Coll Nutr, 20*(6), 609-615.

Massagli, M. P., Weissman, J. S., Seage, G. R., 3rd, & Epstein, A. M. (1994). Correlates of employment after AIDS diagnosis in the Boston Health Study. *Am J Public Health, 84*(12), 1976-1981.

Mat Shah, R., Bulgiba, A., Lee, C. K. C., Haniff, J., & Mohamad Ali, M. (2012). Highly Active Antiretroviral Therapy Reduces Mortality and Morbidity in Patients with AIDS in Sungai Buloh Hospital. *Journal of Experimental & Clinical Medicine, 4*(4), 239-244.

Mata-Marin, J. A., Gaytan-Martinez, J., Grados-Chavarria, B. H., Fuentes-Allen, J. L., Arroyo-Anduiza, C. I., & Alfaro-Mejia, A. (2009). Correlation between HIV viral

load and aminotransferases as liver damage markers in HIV infected naive patients: a concordance cross-sectional study. *Virol J, 6*, 181. doi: 10.1186/1743-422X-6-181 1743-422X-6-181 [pii]

May, M., Sterne, J. A., Sabin, C., Costagliola, D., Justice, A. C., Thiebaut, R., Egger, M. (2007). Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS, 21*(9), 1185-1197. doi: 10.1097/QAD.0b013e328133f285 00002030-200705310-00012 [pii]

MBPJ. (2012). Background of Petaling Jaya.

McFarland, W., Chen, S., Hsu, L., Schwarcz, S., & Katz, M. (2003). Low Socioeconomic Status Is Associated With a Higher Rate of Death in the Era of Highly Active Antiretroviral Therapy, San Francisco. *JAIDS Journal of Acquired Immune Deficiency Syndromes, 33*(1), 96-103.

McGinnis, K. A., Fine, M. J., Sharma, R. K., Skanderson, M., Wagner, J. H., Rodriguez-Barradas, M. C., Justice, A. C. (2003). Understanding racial disparities in HIV using data from the veterans aging cohort 3-site study and VA administrative data. *Am J Public Health, 93*(10), 1728-1733.

Melekhin, V. V., Shepherd, B. E., Stinnette, S. E., Rebeiro, P. F., Turner, M. M., & Sterling, T. R. (2012). Hemoglobin may contribute to sex differences in mortality among HIV-infected persons in care. *PLoS One, 7*(9), e44999. doi: 10.1371/journal.pone.0044999 PONE-D-12-03680 [pii]

Mellors, J. W., Munoz, A., Giorgi, J. V., Margolick, J. B., Tassoni, C. J., Gupta, P., Rinaldo, C. R., Jr. (1997). Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med, 126*(12), 946-954.

Melo, Lacerda, Campelo, Moraes, & Ximenes. (2008). Survival of AIDS patients and characteristics of those who died over eight years of highly active antiretroviral therapy, at a referral center in northeast Brazil. *Braz J Infect Dis, 12*(4), 269-277. doi: S1413-86702008000400003 [pii]

Merriman, N. A., Porter, S. B., Brensinger, C. M., Reddy, K. R., & Chang, K. M. (2006). Racial difference in mortality among U.S. veterans with HCV/HIV coinfection. *Am J Gastroenterol, 101*(4), 760-767. doi: AJG531 [pii]

10.1111/j.1572-0241.2006.00531.x

Merson, M. H. (2006). The HIV–AIDS Pandemic at 25 — The Global Response. *New England Journal of Medicine, 354*(23), 2414-2417. doi: doi:10.1056/NEJMp068074

Millett, G. A., Flores, S. A., Marks, G., Reed, J. B., & Herbst, J. H. (2008). Circumcision Status and Risk of HIV and Sexually Transmitted Infections Among Men Who Have Sex With Men. *JAMA: The Journal of the American Medical Association, 300*(14), 1674-1684. doi: 10.1001/jama.300.14.1674

MOH. (2001a). Malaysian Society of Infectious Disease and Chemotherapy, Consensus on antiretroviral treatment. 2nd edition. *Ministry of Health, Kuala Lumpur Malaysia*.

MOH. (2001b). Malaysian Society of Infectious Disease and Chemotherapy, Consensus on Antiretroviral Treatment. 2nd edition. Ministry of Health. Kuala Lumpur, Malaysia.

MOH. (2001c). Malaysian Society of Infectious Disease and Chemotherapy: Consensus on antiretroviral treatment. 2nd edition. Kuala Lumpur Malaysia.

MOH. (2010). UNGASS Country Progress Report, Reporting period: January 2008 – December 2009

MOH. (2012). The Global AIDS Response Progress Report, Country Progress Report January 2010 – December 2011.

Mohe. (2010). Education system of Malaysia.

Moore, D. M., Awor, A., Downing, R. S., Were, W., Solberg, P., Tu, D., Mermin, J. (2007). Determining eligibility for antiretroviral therapy in resource-limited settings using total lymphocyte counts, hemoglobin and body mass index. *AIDS Res Ther, 4*, 1. doi: 1742-6405-4-1 [pii] 10.1186/1742-6405-4-1

Morgan, Mahe, Mayanja, Okongo, Lubega, & Whitworth. (2002). HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS, 16*(4), 597-603.

Moriuchi, M., Moriuchi, H., Turner, W., & Fauci, A. S. (1998). Exposure to bacterial products renders macrophages highly susceptible to T-tropic HIV-1. *J Clin Invest, 102*(8), 1540-1550. doi: 10.1172/JCI4151

Moss, A. R., & Bacchetti, P. (1989). Natural history of HIV infection. *AIDS, 3*(2), 55-61.

Mugavero, M. J., Pence, B. W., Whetten, K., Leserman, J., Swartz, M., Stangl, D., & Thielman, N. M. (2007). Predictors of AIDS-related morbidity and mortality in a southern U.S. Cohort. *AIDS Patient Care STDS, 21*(9), 681-690. doi: 10.1089/apc.2006.0167

Nagalingeswaran, Solomon, Madhivanan, Yepthomi, Venkatesan, Amalraj, Mayer. (2000). *Correlation between plasma viral load and CD4+T cell count to opportunistic infections in persons with HIV in South India.* Paper presented at the 13th International AIDS Conference, Durban, South Africa - July 9-July 14, 2000.

Ndiaye, B., Salleron, J., Vincent, A., Bataille, P., Bonnevie, F., Choisy, P., Yazdanpanah, Y. (2011). Factors associated with presentation to care with advanced HIV disease in Brussels and Northern France: 1997-2007. *BMC Infect Dis, 11*, 11. doi: 10.1186/1471-2334-11-11 1471-2334-11-11 [pii]

O'Brien, M. E., Kupka, R., Msamanga, G. I., Saathoff, E., Hunter, D. J., & Fawzi, W. W. (2005). Anemia is an independent predictor of mortality and immunologic progression of disease among women with HIV in Tanzania. *J Acquir Immune Defic Syndr, 40*(2), 219-225. doi: 00126334-200510010-00015 [pii]

OARAC. (2011). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

Obirikorang, C., & Yeboah, F. A. (2009). Blood haemoglobin measurement as a predictive indicator for the progression of HIV/AIDS in resource-limited setting. *J Biomed Sci, 16*, 102. doi: 1423-0127-16-102 [pii]
10.1186/1423-0127-16-102

Odafe, S., Idoko, O., Badru, T., Aiyenigba, B., Suzuki, C., Khamofu, H., Chabikuli, O. N. (2012). Patients' demographic and clinical characteristics and level of care associated with lost to follow-up and mortality in adult patients on first-line ART in Nigerian hospitals. *J Int AIDS Soc, 15*(2), 17424. doi: 10.7448/IAS.15.2.17424
17424 [pii]

Osmand, D. (1998). Epidemiology of disease progression in HIV. *Available from: http://www.hivinsite*.

Palella, F. J., Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A., Holmberg, S. D. (1998). Declining Morbidity and Mortality among Patients with Advanced Human Immunodeficiency Virus Infection. *New England Journal of Medicine, 338*(13), 853-860. doi: doi:10.1056/NEJM199803263381301

Palombi, L., Marazzi, M. C., Guidotti, G., Germano, P., Buonomo, E., Scarcella, P., Program, D. (2009). Incidence and Predictors of Death, Retention, and Switch to Second-Line Regimens in Antiretroviral-Treated Patients in Sub-Saharan African Sites with Comprehensive Monitoring Availability. *Clinical Infectious Diseases, 48*(1), 115-122. doi: 10.1086/593312

Appendix A References

Pantaleo, G., Menzo, S., Vaccarezza, M., Graziosi, C., Cohen, O. J., Demarest, J. F., Fauci, A. S. (1995). Studies in Subjects with Long-Term Nonprogressive Human Immunodeficiency Virus Infection. *New England Journal of Medicine, 332*(4), 209-216. doi: doi:10.1056/NEJM199501263320402

Park, H. M. (2008). Univariate Analysis and Normality Test Using SAS, Stata, and SPSS, in University Information Technology Services (UITS) Center for Statistical and Mathematical Computing. 1-41. Retrieved from http://www.iuj.ac.jp/faculty/kucc625/documents/normality.pdf

Patel, D., Cortina-Borja, M., Thorne, C., & Newell, M. L. (2007). Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. *Clin Infect Dis, 44*(12), 1647-1656. doi: CID50007 [pii]
10.1086/518284

Peeters, M., Gueye, A., Mboup, S., Bibollet-Ruche, F., Ekaza, E., Mulanga, C., Delaporte, E. (1997). Geographical distribution of HIV-1 group O viruses in Africa. *AIDS, 11*(4), 493-498.

Pérez-Hoyos, Ferreros, Amo, Muga, Romero, de Olalla, & Hernández-Aguado. (2006). Survival and progression to AIDS in a seroconverter cohort in the post-highly active antiretroviral therapy era: effectiveness goes on. *AIDS, 20*(2), 289-291.

Pezzotti, Napoli, Acciai, Boros, Urciuoli, Lazzeri, & Rezza. (1999). Increasing survival time after AIDS in Italy: the role of new combination antiretroviral therapies. *AIDS, 13*(2), 249-255.

Pezzotti, P., et al. (1999). Increasing survival time after AIDS in Italy: the role of new combination antiretroviral therapies. *AIDS, 13*(2), 249-255.

Phillips, Lazzarin, Gonzales-Lahoz, Clumeck, Glauser, Proenca, Johnson. (1996). Factors associated with the CD4+ lymphocyte count at diagnosis of acquired immunodeficiency syndrome. *Journal of Clinical Epidemiology, 49*(11), 1253-1258. doi: http://dx.doi.org/10.1016/S0895-4356(96)00216-8

Phillips, Leen, Wilson, Anderson, Dunn, Schwenk, Sabin. (2007). Risk of extensive virological failure to the three original antiretroviral drug classes over long-term follow-up from the start of therapy in patients with HIV infection: an observational cohort study. *The Lancet, 370*(9603), 1923-1928.

Phillips, & Pezzotti. (2004). Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. *AIDS, 18*(1), 51-58. doi: 00002030-200401020-00006 [pii]

Plantier, J.-C., Leoz, M., Dickerson, J. E., De Oliveira, F., Cordonnier, F., Lemee, V., Simon, F. (2009). A new human immunodeficiency virus derived from gorillas. [10.1038/nm.2016]. *Nat Med, 15*(8), 871-872. doi: http://www.nature.com/nm/journal/v15/n8/suppinfo/nm.2016_S1.html

Podlekareva, D., Mocroft, A., Dragsted, U. B., Ledergerber, B., Beniowski, M., Lazzarin, A., group, E. s. (2006). Factors Associated with the Development of Opportunistic Infections in HIV-1–Infected Adults with High CD4+ Cell Counts: A EuroSIDA Study. *Journal of Infectious Diseases, 194*(5), 633-641. doi: 10.1086/506366

Porta, D., Rapiti, E., Forastiere, F., Pezzotti, P., Perucci, C. A., & Group, f. t. L. A. S. C. (1999). Changes in survival among people with AIDS in Lazio, Italy from 1993 to 1998. *AIDS, 13*(15), 2125-2131.

Porter, Babiker, Bhaskaran, Darbyshire, Pezzotti, & Walker. (2003). Determinants of survival following HIV-1 seroconversion after the introduction of HAART. *Lancet, 362*(9392), 1267-1274. doi: S0140673603145709 [pii]

Prime Minister's Department Malaysia, & United Nations Country Team. (2010). Malaysia: The Millennium Development Goals at 2010.

Puhan, M. A., Van Natta, M. L., Palella, F. J., Addessi, A., & Meinert, C. (2010). Excess mortality in patients with AIDS in the era of highly active antiretroviral therapy: temporal changes and risk factors. *Clin Infect Dis, 51*(8), 947-956. doi: 10.1086/656415

Quinn, T. C. (1996). Global burden of HIV pandemic. *Lancet, 348*, 99-106.

Rabkin, J. G., McElhiney, M., Ferrando, S. J., Van Gorp, W., & Lin, S. H. (2004). Predictors of Employment of Men With HIV/AIDS: A Longitudinal Study. *Psychosomatic Medicine, 66*(1), 72-78. doi: 10.1097/01.psy.0000108083.43147.6d

Rachlis, A. R., & Zarowny, D. P. (1998). Guidelines for antiretroviral therapy for HIV infection. Canadian HIV Trials Network Antiretroviral Working Group. *CMAJ, 158*(4), 496-505.

Ramalingam, S., Kannangai, R., Raj A, A., Jesudason, M. V., & Sridharan, G. (2002). Rapid Particle Agglutination Test for Human Immunodeficiency Virus: Hospital-Based Evaluation. *J. Clin. Microbiol., 40*(4), 1553-1554. doi: 10.1128/jcm.40.4.1553-1554.2002

Rapiti, E., Porta, D., Forastiere, F., Fusco, D., Perucci, C. A., & Group, f. t. L. A. S. C. (2000). Socioeconomic Status and Survival of Persons with AIDS before and after the Introduction of Highly Active Antiretroviral Therapy. *Epidemiology, 11*(5), 496-501.

Ratner, L., Haseltine, W., Patarca, R., Livak, K. J., Starcich, B., Josephs, S. F., Wong-Staal, F. (1985). Complete nucleotide sequence of the AIDS virus, HTLV-III. [10.1038/313277a0]. *Nature, 313*(6000), 277-284.

Reeves, J. D., & Doms, R. W. (2002). Human immunodeficiency virus type 2. *Journal of General Virology, 83*(6), 1253-1265.

Resino, S., J, M. B., Gurbindo, D., Tomas Ramos, J., Antonio Leon, J., Jose Mellado, M., & Angeles Munoz-Fernandez, M. (2003). Viral load and CD4+ T lymphocyte response to highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children: an observational study. *Clin Infect Dis, 37*(9), 1216-1225. doi: CID30854 [pii] 10.1086/378804

Riyarto, S., Hidayat, B., Johns, B., Probandari, A., Mahendradhata, Y., Utarini, A., Flessenkaemper, S. (2010). The financial burden of HIV care, including antiretroviral therapy, on patients in three sites in Indonesia. *Health Policy Plan, 25*(4), 272-282. doi: 10.1093/heapol/czq004 czq004 [pii]

Rizzardi, De Boer, Hoover, Tambussi, Chapuis, Halkic, Pantaleo. (2000). Predicting the duration of antiviral treatment needed to suppress plasma HIV-1 RNA. *J Clin Invest, 105*(6), 777-782. doi: 10.1172/JCI9079

Rosenberg, E. S., Billingsley, J. M., Caliendo, A. M., Boswell, S. L., Sax, P. E., Kalams, S. A., & Walker, B. D. (1997). Vigorous HIV-1-Specific CD4+ T Cell Responses Associated with Control of Viremia. *Science, 278*(5342), 1447-1450. doi: 10.1126/science.278.5342.1447

Rosner, B. (2000). *Fundamentals of Biostatistics* (5 ed.): Harvard University.

Rougemont, M., Stoll, B. E., Elia, N., & Ngang, P. (2009). Antiretroviral treatment adherence and its determinants in Sub-Saharan Africa: a prospective study at Yaounde Central Hospital, Cameroon. *AIDS Res Ther, 6*, 21. doi: 10.1186/1742-6405-6-21 1742-6405-6-21 [pii]

Saraceni, V., King, B. S., Cavalcante, S. C., Golub, J. E., Lauria, L. M., Moulton, L. H., Durovni, B. (2008). Tuberculosis as primary cause of death among AIDS cases in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis, 12*(7), 769-772.

Appendix A References

Sarna, A., Pujari, S., Sengar, A. K., Garg, R., Gupta, I., & Dam, J. (2008). Adherence to antiretroviral therapy & its determinants amongst HIV patients in India. *Indian J Med Res, 127*(1), 28-36.

Schwarcz, Hsu, Vittinghoff, & Katz. (2000). Impact of protease inhibitors and other antiretroviral treatments on acquired immunodeficiency syndrome survival in San Francisco, California, 1987-1996. *Am J Epidemiol, 152*(2), 178-185.

Sepkowitz, K. A. (2001). AIDS — The First 20 Years. *New England Journal of Medicine, 344*(23), 1764-1772. doi: doi:10.1056/NEJM200106073442306

Shanthi, A. G., Damodharan, J., & Priya, G. (2007). Depression and coping: A study on HIV positive men and women. *Sri Ramachandra Journal of Medicine, 15-19*.

Shisana, O., Zungu-Dirwayi, N., Toefy, Y., Simbayi, L. C., Malik, S., & Zuma, K. (2004). Marital status and risk of HIV infection in South Africa. *S Afr Med J, 94*(7), 537-543.

Sieleunou, I., Souleymanou, M., Schonenberger, A. M., Menten, J., & Boelaert, M. (2009). Determinants of survival in AIDS patients on antiretroviral therapy in a rural centre in the Far-North Province, Cameroon. *Trop Med Int Health, 14*(1), 36-43. doi: 10.1111/j.1365-3156.2008.02183.x TMI2183 [pii]

Silverberg, M. J., Leyden, W., Quesenberry, C. P., Jr., & Horberg, M. A. (2009). Race/ethnicity and risk of AIDS and death among HIV-infected patients with access to care. *J Gen Intern Med, 24*(9), 1065-1072. doi: 10.1007/s11606-009-1049-y

Smith, Staszewski, Sabin, Nelson, Dauer, Gute, Gazzard. (2004). Use of viral load measured after 4 weeks of highly active antiretroviral therapy to predict virologic outcome at 24 weeks for HIV-1-positive individuals. *J Acquir Immune Defic Syndr, 37*(1), 1155-1159. doi: 00126334-200409010-00006 [pii]

Smurzynski, M., Wu, K., Benson, C. A., Bosch, R. J., Collier, A. C., & Koletar, S. L. (2010). Relationship between CD4+ T-cell counts/HIV-1 RNA plasma viral load and AIDS-defining events among persons followed in the ACTG longitudinal linked randomized trials study. *J Acquir Immune Defic Syndr, 55*(1), 117-127. doi: 10.1097/QAI.0b013e3181e8c129

Spacek, L. A., Griswold, M., Quinn, T. C., & Moore, R. D. (2003). Total lymphocyte count and hemoglobin combined in an algorithm to initiate the use of highly active antiretroviral therapy in resource-limited settings. *AIDS, 17*(9), 1311-1317. doi: 10.1097/01.aids.0000060369.78202.66

Stebbing, J., Gazzard, B., & Douek, D. C. (2004). Where does HIV live? *N Engl J Med, 350*(18), 1872-1880. doi: 10.1056/NEJMra032395 350/18/1872 [pii]

Stebbing, J., Sawleshwarkar, S., Michailidis, C., Jones, R., Bower, M., Mandalia, S., Gazzard, B. (2005). Assessment of the efficacy of total lymphocyte counts as predictors of AIDS defining infections in HIV-1 infected people. *Postgrad Med J, 81*(959), 586-588. doi: 81/959/586 [pii] 10.1136/pgmj.2004.030841

Sterling, Vlahov, Astemborski, Hoover, Margolick, & Quinn. (2001). Initial Plasma HIV-1 RNA Levels and Progression to AIDS in Women and Men. *New England Journal of Medicine, 344*(10), 720-725. doi: doi:10.1056/NEJM200103083441003

Taiwo, B. O., Li, X., Palella, F., Jacobson, L. P., Margolick, J. B., Detels, R., Phair, J. P. (2009). Higher risk of AIDS or death in patients with lower CD4 cell counts after virally suppressive HAART. *HIV Medicine, 10*(10), 657-660. doi: 10.1111/j.1468-1293.2009.00739.x

The UK Collaborative HIV Cohort Steering Committee. (2010). Late diagnosis in the HAART era: proposed common definitions and associations with mortality. *AIDS, 24*(5), 723-727 710.1097/QAD.1090b1013e328333fa328330f.

Thompson, M. A., Aberg, J. A., Cahn, P., Montaner, J. S., Rizzardini, G., Telenti, A., Schooley, R. T. (2010). Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA, 304*(3), 321-333. doi: 10.1001/jama.2010.1004
304/3/321 [pii]

Toure, A., Khanafer, N., Baratin, D., Bailly, F., Livrozet, J. M., Trepo, C., Vanhems, P. (2012). First presentation for care of HIV-infected patients with low CD4 cell count in Lyon, France: risk factors and consequences for survival. *AIDS Care, 24*(10), 1272-1276. doi: 10.1080/09540121.2012.656574

Trkola, A., Dragic, T., Arthos, J., Binley, J. M., Olson, W. C., Allaway, G. P., Moore, J. P. (1996). CD4-dependent, antibody-sensitive interactions between HIV-1 and its co-receptor CCR-5. [10.1038/384184a0]. *Nature, 384*(6605), 184-187.

UNAIDS. (2010). Global Report, Fact Sheet.

UNAIDS. (2012). Report on the Global AIDS epidemic.

UNAIDS, & WHO. (2004). UNAIDS/WHO Policy Statement on HIV Testing.

UNGASS. (2010). Country Progress Report – Malaysia, Reporting period: January 2008 – December 2009.

UNGASS. (2012). GLOBAL AIDS RESPONSE 2012: Country Progress Report January 2010 – December 2011. Malaysia March 2012.

University of South Florida. (2008). Institutional Review Board: Waiver or Alteration of Informed Consent. Florida: Division of Research Integrity and Compliance.

Vallabhaneni, S., Chandy, S., Heylen, E., & Ekstrand, M. (2012). Reasons for and correlates of antiretroviral treatment interruptions in a cohort of patients from public and private clinics in southern India. *AIDS Care, 24*(6), 687-694. doi: 10.1080/09540121.2011.630370

Van den Broeck, J., Cunningham, S. A., Eeckels, R., & Herbst, K. (2005). Data cleaning: detecting, diagnosing, and editing data abnormalities. *PLoS Med, 2*(10), e267. doi: 04-PLME-PF-0256 [pii] 10.1371/journal.pmed.0020267

Vicknasingam, B., Narayanan, S., & Navaratnam, V. (2009). The relative risk of HIV among IDUs not in treatment in Malaysia. *AIDS Care, 21*(8), 984-991. doi: 915041492 [pii] 10.1080/09540120802657530

Volberding, P. A., & Deeks, S. G. (2010). Antiretroviral therapy and management of HIV infection. *Lancet, 376*(9734), 49-62. doi: 10.1016/S0140-6736(10)60676-9 S0140-6736(10)60676-9 [pii]

Volberding, P. A., Levine, A. M., Dieterich, D., Mildvan, D., Mitsuyasu, R., & Saag, M. (2004). Anemia in HIV infection: clinical impact and evidence-based management strategies. *Clin Infect Dis, 38*(10), 1454-1463. doi: 10.1086/383031 CID31909 [pii]

Walensky, R. P., Wolf, L. L., Wood, R., Fofana, M. O., Freedberg, K. A., Martinson, N. A., Losina, E. (2009). When to start antiretroviral therapy in resource-limited settings. *Ann Intern Med, 151*(3), 157-166. doi: 0000605-200908040-00138 [pii]

Wang, Wang, L., Wu, Z., Guo, W., Sun, X., Poundstone, K., & Wang, Y. (2010). Estimating the number of people living with HIV/AIDS in China: 2003-09. *Int J Epidemiol, 39 Suppl 2*, ii21-28. doi: 10.1093/ije/dyq209 dyq209 [pii]

Wang, Wang, N., Li, D., Jia, M., Gao, X., Qu, S., Smith, K. (2009). The 2007 Estimates for People at Risk for and Living With HIV in China: Progress and Challenges. *J Acquir Immune Defic Syndr, 50*(4), 414-418. doi: 10.1097/QAI.0b013e3181958530

Watts, J. M., Dang, K. K., Gorelick, R. J., Leonard, C. W., Bess, J. W., Jr., Swanstrom, R., Weeks, K. M. (2009). Architecture and secondary structure of an entire HIV-1 RNA genome. *Nature, 460*(7256), 711-716. doi: nature08237 [pii] 10.1038/nature08237

Whiteside, A. (2001). Demography and economics of HIV/AIDS. *British Medical Bulletin, 58*(1), 73-88. doi: 10.1093/bmb/58.1.73

WHO. (2003). A public health approach to Antiretroviral treatment: Overcoming constraints. Geneva.

WHO. (2004). Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach (2003 revision). Geneva.

WHO. (2006a). Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a public health approach.

WHO. (2006b). Antiretroviral therapy of HIV infection in adults and adolescents in resource-limited settings: recommendations for a public health approach (2006 revision). Geneva.

WHO. (2007a). AIDS Epidemic Update.

WHO. (2007c). Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children.

WHO. (2007d). WHO and UNAIDS announce recommendations from expert consultation on male circumcision for HIV prevention.

WHO. (2008). Worldwide prevalence of anaemia 1993–2005. WHO Global Database on Anaemia.

WHO. (2009). AIDS Epidemic Update.

WHO. (2010a). Antiretroviral therapy for HIV infection in adult and adolescent, recommendations for a public health approach, revision.

WHO. (2010b). Global Report: UNAIDS Report on the Global AIDS Epidemic.

WHO. (2011). Global HIV/AIDS response: Epidemic update and health sector progress towards Universal Access. Progress Report 2011.

Williams, B. G., Lloyd-Smith, J. O., Gouws, E., Hankins, C., Getz, W. M., Hargrove, J., Auvert, B. (2006). The potential impact of male circumcision on HIV in Sub-Saharan Africa. *PLoS Med, 3*(7), e262. doi: 05-PLME-RA-0709R2 [pii]
10.1371/journal.pmed.0030262

Wong, Chan, & Lee. (2004). Delayed Progression to Death and to AIDS in a Hong Kong Cohort of Patients with Advanced HIV Type 1 Disease During the Era of Highly Active Antiretroviral Therapy. *Clinical Infectious Diseases, 39*(6), 853-860. doi: 10.1086/423183

Wong, Lye, D. C., Lee, C. C., & Leo, Y. S. (2011). Acute HIV infection in Singapore: predominance of men who have sex with men. *Singapore Med J, 52*(12), 860-863.

Wood, E., Montaner, J. S., Chan, K., Tyndall, M. W., Schechter, M. T., Bangsberg, D., Hogg, R. S. (2002). Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996. *AIDS, 16*(15), 2065-2072.

Xiang, J., Wünschmann, S., Diekema, D. J., Klinzman, D., Patrick, K. D., George, S. L., & Stapleton, J. T. (2001). Effect of Coinfection with GB Virus C on Survival among Patients with HIV Infection. *New England Journal of Medicine, 345*(10), 707-714. doi: doi:10.1056/NEJMoa003364

Yamaguchi, J., Coffey, R., Vallari, A., Ngansop, C., Mbanya, D., Ndembi, N., Brennan, C. A. (2006). Identification of HIV type 1 group N infections in a husband and wife in Cameroon: viral genome sequences provide evidence for horizontal transmission. *AIDS Res Hum Retroviruses, 22*(1), 83-92. doi: 10.1089/aid.2006.22.83

Yelin, E. H., Greenblatt, R. M., Hollander, H., & McMaster, J. R. (1991). The impact of HIV-related illness on employment. *Am J Public Health, 81*(1), 79-84.

Zhang, M., Shang, H., Wang, Z., Cui, W. G., & Hu, Q. H. (2010). Natural history of HIV infection in former plasma donors in rural China. *Front Med China, 4*(3), 346-350. doi: 10.1007/s11684-010-0102-x

Appendix A References

Zhou, J., & Kumarasamy, N. (2005). Predicting short-term disease progression among HIV-infected patients in Asia and the Pacific region: preliminary results from the TREAT Asia HIV Observational Database (TAHOD). *HIV Medicine, 6*(3), 216-223. doi: 10.1111/j.1468-1293.2005.00292.x

Appendix B: Ethical Approval

JAWATANKUASA ETIKA PERUBATAN

PUSAT PERUBATAN UNIVERSITI MALAYA
59100 LEMBAH PANTAI
KUALA LUMPUR

TEL : 03-79492565
03-79494422 SAMB. 3214, 3209
FAX : 03-79545682

11 Mei 2007 Rujukan: HU-61/12/1-1

Prof. Madya Awang Bulgiba Awang Mahmud
Jabatan Perubatan Kemasyarakatan & Pencegahan

Tuan

SURAT PEMAKLUMAN KEPUTUSAN PERMOHONAN MENJALANKAN PROJEK PENYELIDIKAN
Identification Of Determinants For Progression To AIDS in HIV Patients Receiving Anti-Retroviral Treatment.
MEC Ref. No.: 565.22

Dengan hormatnya saya merujuk kepada perkara di atas.

Bersama-sama ini dilampirkan surat pemakluman keputusan Jawatankuasa Etika Perubatan yang bermesyuarat pada 17 Januari 2007 untuk makluman dan tindakan tuan selanjutnya.

Sekian, terima kasih.

Yang benar

Setiausaha
Jawatankuasa Etika Perubatan
Pusat Perubatan Universiti Malaya

s.k Dekan
Fakulti Perubatan

Appendix B Ethical Approval

PUSAT PERUBATAN UNIVERSITI MALAYA
ALAMAT: LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEFON: 03-79494422, 03-79494422 KEBEL: UNIHOS, KUALA LUMPUR
FAX NO: 6-03-79545682

NAME OF ETHICS COMMITTEE/IRB: Medical Ethics Committee, University Malaya Medical Centre ADDRESS: LEMBAH PANTAI 59100 KUALA LUMPUR	ETHICS COMMITTEE/IRB REFERENCE NUMBER: 565.22
PROTOCOL NO: TITLE: Identification Of Determinants For Progression To AIDS in HIV Patients Receiving Anti-Retroviral Treatment.	
PRINCIPAL INVESTIGATOR: Prof. Madya Awang Bulgiba 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: 19 December 2006
[ ] Study Protocol	Ver date:
[ ] Confidential Information Brochure	Ver date:
[ ] Patient Information Sheet	Ver date:
[ ] Consent Form	Ver date:
[ ] Questionnaire Form	Ver date:
[ ] Data Collection Form	Ver date:
[ ] Advertisement/Payment & Compensation to Subjects	Ver date:
[✓] Investigator(s) CV's (Prof. Madya Awang Bulgiba 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: 17th January 2007

s.k Dekan
Fakulti Perubatan

Timbalan Dekan (Penyelidikan)
Fakulti Perubatan, Universiti Malaya

Setiausaha
Jawatankuasa Penyelidikan Pusat Perubatan
Fakulti Perubatan, Universiti Malaya

.....
PROF. LOOI LAI MENG
Chairman
Medical Ethics Committee

Appendix B Ethical Approval

PUSAT PERUBATAN UNIVERSITI MALAYA
ALAMAT: LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEFON: 03-79494422, 03-79494422 KEBEL: UNIHOS, KUALA LUMPUR
FAX NO: 6-03-79545682

MEDICAL ETHICS COMMITTEE COMPOSITION, UNIVERSITY MALAYA MEDICAL CENTRE

Date: 17th January 2007

Member (Title and Name)	Occupation (Designation)	Male/Female (M/F)	Tick (✓) if present when above items were reviewed
Chairperson: Prof. Looi Lai Meng	Representative Dean/Director	Female	✓
Secretary: Puan Mariam Mansor	Pengurus Kanan (Pentadbiran) PTJ UH Diagnostik	Female	
Members: 1. Prof. Madya Jamiyah Hassan	Deputy Director	Female	
2. Prof. Tan Chong Tin	Representative Head Of Department Of Medicine	Male	✓
3. Prof. Mohd. Hussain Habil	Head of Department of Psychological Medicine	Male	✓
4. Dr. Colin Ng Leong Liong	Representative Head of Department of Surgery	Male	
5. Prof. Zahurin Mohamed	Head of Department of Pharmacology	Female	✓
6. Puan Grace Xavier	Lecturer, Faculty of Law	Female	✓
7. Puan P. Devashanti	Representative Pengurus Kanan, PTj Farmasi	Female	✓
8. YBhg. Datin Aminah Pit Abdul Rahman	Public Representative	Female	✓
9. Madam Ong Eng Lee	Public Representative	Female	✓

Comments: The MEC of University Malaya Medical Centre is operating according to ICH GCP guideline and the Declaration of Helsinki. Members no. 6, 8 & 9 are representatives from Faculty of Law in the University of Malaya and the public, respectively. They are independent of the hospital or trial site.

.....
PROF. LOOI LAI MENG
Chairman
Medical Ethics Committee

Appendix C: Kelulusan Tajuk Thesis

UNIVERSITI MALAYA

UM.M/PD/644/15

10 Januari 2013

Rahayu Lubis (MHA060016)
Jabatan Perubatan Kemasyarakatan & Pencegahan
Fakulti Perubatan
Universiti Malaya

Tuan/Puan,

KELULUSAN TAJUK TESIS

Dengan ini dimaklumkan bahawa Fakulti dalam mesyuaratnya pada 9.1.2013 telah meluluskan tajuk tesis tuan/puan seperti berikut:-

"DETERMINANTS OF DISEASE PROGRESSION IN AIDS PATIENTS RECEIVING TREATMENT IN THE UNIVERSITY OF MALAYA MEDICAL CENTRE"

Sekian, terima kasih.

Yang benar,

AMINAH HJ. NAFIAH
Penolong Pendaftar (Pascaijazah)
Fakulti Perubatan

s.k. Ketua, Jabatan Perubatan Kemasyarakatan & Pencegahan

Profesor Awang Bulgiba Awang Mahmud - Penyelia
Jabatan Perubatan Kemasyarakatan & Pencegahan

Cik Nurhazrin Zanzabir
Penolong Pendaftar, Institut Pengajian Siswawah

JMD/gp/kelulusan tajuk tesis/disertasi - 2013

Timbalan Dekan (Pascaijazah), Fakulti Perubatan, Universiti Malaya, Lembah Pantai, 50603 Kuala Lumpur, MALAYSIA
Tel: (603) 79492108 • Faks: (603) 79676684 • E-mail: medic_admin@um.edu.my • http://medicine.um.edu.my

Appendix D: Accepted manuscript

Predictors of death in Malaysian HIV-infected patients on anti-retroviral therapy

Rahayu Lubis, Awang Bulgiba, Adeeba Kamarulzaman, Noran N. Hairi, Maznah Dahlui, Devi Peramalah

PII: S0091-7435(13)00019-4
DOI: doi: 10.1016/j.ypmed.2013.01.006
Reference: YPMED 3532

To appear in: *Preventive Medicine*

Please cite this article as: Lubis Rahayu, Bulgiba Awang, Kamarulzaman Adeeba, Hairi Noran N., Dahlui Maznah, Peramalah Devi, Predictors of death in Malaysian HIV-infected patients on anti-retroviral therapy, *Preventive Medicine* (2013), doi: 10.1016/j.ypmed.2013.01.006

Appendix E: Conference presentation

1st Asia Pacific Clinical Epidemiology and Evidence-Based Medicine Conference

Tuesday, 3 April, 2012 08:52
From: "apceebm1@ummc.edu.my" <apceebm1@ummc.edu.my>
To: rahayu_lubis@yahoo.com

Dear Rahayu Lubis, Registration ID: 201194

Title of the submitted abstract: PREDICTORS OF SURVIVAL IN MALAYSIAN HIV-INFECTED PATIENTS ON ANTI-RETROVIRAL THERAPY (T1)

We are pleased to inform you that your abstract entitled PREDICTORS OF SURVIVAL IN MALAYSIAN HIV-INFECTED PATIENTS ON ANTI-RETROVIRAL THERAPY (T1) has been accepted for Oral presentation in the 1st Asia Pacific Clinical Epidemiology and Evidence-Based Medicine Conference to be held from 06 Jul 2012 to 08 Jul 2012 in Kuala Lumpur, Malaysia.

In order to confirm your participation in this conference as a presenter, we must receive your registration fee before prior to the conference. Please take note that the deadline for registration fee payment for presenter (oral or poster) is 31st May 2012. The presenter who did not pay for the registration fee after the deadline will be regarded as self-withdrawal from the presentation and the abstract will not be included in the conference proceedings. If you make payment before 30th April 2012, you can enjoy the early bird rate as stated in our conference website (http://apceebm.um.edu.my).

Please note that the main theme of your paper may have changed following our review of your abstract. We will be informing you of further details regarding the poster presentation guidelines within the next few weeks.

We thank you for submitting your abstract for consideration at our conference and we look forward to meeting you in Kuala Lumpur.

Yours sincerely,
Assoc. Prof.Dr. Wong Yut Lin
Chairman of Scientific Committee
1st Asia-Pacific Clinical Epidemiology and Evidence Based Medicine Conference
Julius Centre University of Malaya
c/o Department of Social and Preventive Medicine
Faculty of Medicine, University of Malaya
50603 Kuala Lumpur, Malaysia

Tel: +603-7967-3793/3797 Fax: +603-7967-4975
Email:apceebm1@ummc.edu.my

Appendix E Conference presentation

To: Dr Rahayu Lubis
Department of Social and Preventive Medicine
University of Malaya
Malaysia

26th October 2010

RE: Acceptance letter of abstracts for ASIALINK-CE & EBM conference: 'Clinical Epidemiology and Evidence-Based Medicine in Global Perspective'

Dear Dr Rahayu Lubis,

We are delighted to inform you that your abstract "Progression to AIDS in HIV patients seen in the University of Malaya Medical Centre" has been accepted for oral presentation at the Asialink conference 'Clinical Epidemiology and Evidence-Based Medicine in Global Perspective'.

Please register your attendance to the Scientific Congress as soon as possible if you have not done so. Information regarding registration, housing, program and presentation guidelines can be found at our website www.asialink-ce.org.

We look forward to welcoming you in Bali.

With regards,

Professor Sudigdo Sastroasmoro
ChairmainAsiaLink-CE Indonesia
Professor of Pediatrics

Organizing Committee, Asia Link Conference
Asialink Clinical Epidemiology & Evidence-Based Medicine
Center for Clinical Epidemiology & Evidence-Based Medicine (CEEBM)
Cipto Mangunkusumo Hospital- Faculty of Medicine University of Indonesia
2nd floor Building-H Jl. Diponegoro 71 Jakarta 10430
Website: www.asialink-ce.org and www.ceebm.org email: info@ceebm.org
Tel/Fax: (+62) 21 316 1760 mobile sms: (+62) 812 1004 9009 (dr. Tifauzia)
(+62) 838 9931 2097 (Mega) (+62) 856 777 9587 (dr. Devi)

Appendix E

CONFIRMATION LETTER
(ORAL PRESENTER)

No. Ref : 5126/H2.F10/HMI.00/2010

Dear Rahayu Lubis

The 42nd APACPH Conference Organizing Committee is pleased to confirm regarding your abstract title: DETERMINANTS OF PROGRESSION TO DEATH AFTER AIDS DIAGNOSIS IN UNIVERSITY OF MALAYA MEDICAL CENTRE, KUALA LUMPUR

Topic:HIV/AIDS Prevention

is **ACCEPTED** for **ORAL PRESENTATION**

Date: 26th November 2010 Time: 2.15 pm –3.45pm

Room: Bandung Room, BICC, Nusa Dua, Bali, Indonesia

The 42nd APACPH Conference will be held from November 24 to 27, 2010 in Bali International Conference Centre (BICC), Nusa Dua, Bali, Indonesia. You can check the abstract notification acceptance on our website: http://www.apacph2010.org/pages/notifications-abstract-acceptance.php

The Asia-Pacific Academic Consortium for Public Health is one of the most important academic consortiums in the Asia - Pacific region. The 42nd APACPH Conference is expected to have the participation of more than 1000 public health professionals and academicians from more than 22 countries. Please kindly respond on your availability by **completing the registration form and ONLINE payment** on our website: http://www.apacph2010.org/pages/registration-form.php.

Information regarding official hotels can be found on: http://www.apacph2010.org/pages/official-hotel.php. The conference venue, Bali International Conference Centre (BICC) is adjoining with the Westin Resort Nusa Dua Hotel.

If you need additional information, please contact: **Ede Surya Darmawan/Fatma Lestari** Tel: +62-21-78849036; Fax: +62-21-78849036; +62-21-7863472; Email: info@apacph2010.org

Sincerely yours,

Prof Tomiko Hokama
President, APACPH
Former Dean, Graduate School of Health Sciences, University of the Ryukyus

Bambang Wispriyono, Ph.D
Conference Chair, 42nd APACPH Conference
Dean, Faculty of Public Health
Universitas Indonesia

Appendix E

41st APACPH Conference-Acceptance Notice

Tuesday, September 15, 2009 10:38 AM

From: "41st APACPH Conference Secretariat" judychou@elitepco.com.tw

To:rahayu_lubis@yahoo.com

Acceptance Notice for Poster Presentation September 15, 2009

Dear Dr. Rahayu Lubis,

On behalf of the 41st APACPH Conference Organizing Committee, I am very pleased to inform you that your following abstract has been accepted as one of the 41st APACPH Poster Presentation.

Please reply & confirm your participation (by completing the reply form below) before September 25, 2009 for our following preparation of the program. Please be aware that, there should be at least one author to complete the registration process before October 15, 2009 for your abstract; if no registration is done by the deadline, the presentation will NOT be scheduled for the conference.

Please feel free to contact us if you have any further inquiry or assistance required.

Yours sincerely,

41st APACPH Conference Secretariat
Judy Chou
Tel: +886-2-8502-7087 ext. 27
Fax: +886-2-8502-7025
E-mail: apacph2009@elitepco.com.tw

Appendix E

Tentative date and time of oral presentation in APACPH Conference

Tuesday, 14 October, 2008 15:41

From:
"Moy Foong Ming" <moyfm@ummc.edu.my>
To:
rahayu_lubis@yahoo.com

Dear Sir/Madam,

Please find the file for the tentative schedule of your oral presentations.

Please be reminded that the presentation and inclusion of abstracts in the proceedings are subjected to your payment of registration fees.

The deadline of payment has been extended to 20 October 2008.

Thank you.

Regards,
Dr Moy FM
Secretariat
APACPH Conference

Date	Session/Room	Time starts	Time ends	Theme	Theme Title
8-Nov	F12	1115	1300	C	HIV/AIDS prevention and control

FNAME	SNAME	REGISTER	KL ID	REQUEST	Day
Rahayu	Lubis	Oral	KL_O_071		8-Nov
			TITLE		THEME
A 21-Year Review Of Hiv/Aids Patients Seen In The University Of Malaya Medical Centre					C

Appendix F: WHO Clinical Staging

Source: (WHO, 2007b, 2007c)

Primary HIV Infection

Asymptomatic
Acute retroviral syndrome

Clinical Stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical Stage 2

Moderate unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrheic dermatitis
Fungal nail infections

Clinical Stage 3

Unexplained severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhea for >1 month
Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant)
Persistent oral candidiasis (thrush)
Oral hairy leukoplakia
Pulmonary tuberculosis (current)
Severe presumed bacterial infections (eg, pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
Unexplained anemia (hemoglobin <8 g/dL)
Neutropenia (neutrophils <500 cells/µL)
Chronic thrombocytopenia (platelets <50,000 cells/µL)

Clinical Stage 4

HIV wasting syndrome, as defined by the CDC (see Table 3, above)
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site)
Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
Extrapulmonary tuberculosis

Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Cryptococcosis, extrapulmonary (including meningitis)
Disseminated nontuberculosis *Mycobacteria* infection
Progressive multifocal leukoencephalopathy
Candida of the trachea, bronchi, or lungs
Chronic cryptosporidiosis (with diarrhea)
Chronic isosporiasis
Disseminated mycosis (eg, histoplasmosis, coccidioidomycosis, penicilliosis)
Recurrent nontyphoidal *Salmonella* bacteremia
Lymphoma (cerebral or B-cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy
Symptomatic HIV-associated cardiomyopathy
Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis

Appendix G Evidence Table

Question: HIV/AIDS progression, Risk factors of death, Survival time, Achieving VL ≤ 50 copies/ml

Authors	Years	Place	Study design	sample	Outcome
Lifson, et al	2012	USA	Retrospective cohort	1600	Risk of death: Age > 40: HR 1.32 OI: HR 1.93 CD4 < 50 : HR 2.97 (ref. CD4 > 500) VL: HR 1.36 per log 10 increase Hb < 12: HR 1.36
Fregonese, et al	2012	Thailand	Prospective cohort	1578	Median age: 33 years Risk of death: Anemia: HR 4.90 CD4 < 50: HR 3.1 VL > 1000: HR 2.8
Toure, et al	2012	France	Prospective cohort	3569	Risk of death: CD4 < 200: HR 5.81 (ref. CD4 > 200) Male: HR 1.28 (ref. Female) Age: 30-39: HR 1.72 (ref. Age < 30 years) 40-49: HR 2.14 50-59: HR 2.03 > 60: HR 4.75
Jim Young, et al	2012	Europe	Retrospective and Prospective Cohort	75336	Reduce risk of death: CD4 < 200: HR 0.35 CD4 200 - < 350: HR 0.81 CD4 350 - < 500: HR 0.74 CD4 > 500: HR 0.96

Rougemont, et al	2012	Myanmar and Zimbabwe	Retrospective cohort	1090	Mortality rate of TB-HIV: 28.9 per 100 person years Risk of death: Low BMI: HR 4.05 (ref. High BMI)
Ghate, et al	2011	India	Prospective cohort	457	Risk of death: Age > 35 years : RR 1.97 CD4≤ 100: RR 33.20 TB: RR 2.38 ART naive: 5.60
Auld, et al	2011	Mozambique	Retrospective cohort	2596	Median age: 34 years Risk of death: Male: HR 1.5 (ref. Female) Weight < 45 kg: HR 2.1(ref. > 60 kg) WHO stage 4: HR 1.7 (ref. Stage ½)
Althoff, et al	2010	USA	Prospective cohort	12196	Immune response decreased with increasing age (ref. 18- < 30 years) (30-<40): HR: 0.91 (40-<50): HR: 0.86 (50-<60): HR: 0.90 (≥ 60 yr):HR: 0.81
Obirikorang, et al	2009	Ghana	Prospective case control comparative	228	Positive Pearson's correlation Hb and CD4 ($r^2 = 0.1755$; $p < 0.0001$)
Bo Taiwo, et al	2009	Chicago	Prospective cohort	121	Time to achieve VL < 50 copies: 0.99 years Median age 42 years Risk of death: CD4 ≤ 200: HR 22.8 (ref. CD4 > 350)

Appendix G

Desilva M, et al	2009	Nigeria	Retrospective cohort	1552	Risk of death: Male: HR 1.77 CD4 < 50 : HR 3.28 TB-HIV: HR 3.53 Unemployment: HR 1.79
Grigoryan, et all	2009	USA	Retrospective cohort	27572	Three years survival : Male: IDU (87.3%): MSM (91.6%) Female: IDU (89.5%): heterosexual (93.3%)
Jaen, et al	2008	Spain	Retrospective and Prospective Cohort	3427	Median age 35.5 years Risk of death: CD4 < 200: HR 3.79 VL ≥ 100000 : HR 1.84 HAART 2001-2004: HR 0.52
Candiani, et al	2007	Brazil	Prospective cohort	371	Rate of OI: 18.32 per 100person years Risk of OI: No HAART: HR 5.4 (ref. HAART) CD4 < 15%: HR 0.3 (ref. > 15%) VL > 100000: HR 4.7 (ref. VL < 100000)
Geretti, et al	2006	UK	Prospective cohort	1386	74.5% patients achieving a VL < 50 copies Time to achieve VL < 50 by regimen: -2NRTIs+1NNRTI : 0.3 (0.2-0.5) years -2 NRTIs+1PI/r :0.4 (0.2-0.5) years -2NRTIs+1PI : 0.6 (0.3-1.0) years -Others : 0.3 (0.2-0.5) years
Hall, et al	2006	USA	Prospective Cohort	262,744	Risk to death: White: HR 1.15 (ref. Non Hispanic) American Indian: HR= 1.33 Hispanic: HR= 1.16

					Reference age 13-19 years Age 50-59 yr, HR = 3.66 Age ≥ 60, HR = 5.91
Perez-Hoyos, et al	2006	Spain	Retrospective cohort	2838	Risk of death: IDU: HR 2.17
Bonnet et all.	2005	France	Prospective cohort	709	Risk of progression: Older age: HR of 1.2 by 10 years CD4 < 50: HR of 13.0 (ref. CD4 > 350) CD4 50- 199: HR 5.1
Wong , et al	2004	Hongkong	Retrospective cohort	581	Survival time Pre-HAART era: 29.8 months HAART era: more than70 months Risk of death after CD4 <200 cell/µL: Age 50-59 yr: HR 2.31
Anastos , et al.	2004	USA	Prospective cohort	1132	Risk of death: Women with CD4 <200 all cause: HR 2.66 AIDS Death: HR 47.61
Cole, et al	2003	USA	Prospective cohort	1498	Risk of death No HAART, HR= 0.81
Egger, et al	2002	Europe	Prospective Cohort study	12574	Risk of death Age ≥ 50 years: HR 3.09 IDU: HR 2.44(ref. MSM) Heterosexual: HR 0.84 CDC stage C: HR 2.07(ref. stage A/B)
Jacobson , et al	2002	USA	Retrospective cohort	679	Risk of death: CD4 < 200: HR 2.29 Age > 45 years: HR 1.81

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Schwarcz, SK, et al	2000	California	Prospective and Retrospective Cohort	5686	Survival time: 15 months (ART without PI) 31 months (ART with PI) Risk of death: Age ≥ 40 years: HR 1.43 Homosexual IDU: HR 1.33 History of OI: HR 1.97
Li Y, et al	2000	Australia	Retrospective cohort	4814	Survival Time: In 1991: 16 months in 1991- 1996: 17.7 months in 1996: 27.7 months Risk of progression: Age > 45 years: HR 1.54
Rapiti E, et al	2000	Italy	Retrospective cohort	1474	Risk of death: SES level III: HR 2.81 SES level IV: HR 2.55 Females in the level IV: HR 4.85 IDU in level III: HR 4.54 IDU in level IV: HR 4.68
Pezzotti P, et al	1999	Italy	Prospective Cohort	771	Risk of death Monotherapy: HR 1.54 Double therapy: HR 0.61 Triple therapy: HR 0.36
Darby, et al	1996	UK	Retrospective Cohort	1216	10 year survival: Age < 15 years = 86% Age 15-34 years = 72% Age 35-54 years = 45% ≥ 55 years = 12%