SURVIVAL TIME AND PROGNOSTIC FACTORS OF AIDS PATIENTS IN KELANTAN: 2010-2014

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By

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LIST OF ABBREVIATIONS

A	Accrual time
Adj. HR	Adjusted Hazard Ratio
Adj. RR	Adjusted Risk Ratio
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
AZT	Zidovudine
CI	Confidence Interval
CCRC	Cure and Care Rehabilitation Centre
CDC	Centre of Disease Control
CHR	Crude Hazard Ratio
F	Additional follow-up
FSW	Female Sex Worker
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IBBS	Integrated Biological Behavioural Surveillance
IDU	Intravenous drug user
LML	Log minus log
m	Ratio of prognostic to non-predictor group (from the population)
m1	Median survival time among predictor group (by literature)
m2	Median survival time among non-predictor group
MSM	Men having sex with men
MTCT	Mother-to-child transmission
NAR	National AIDS Registry
NGO	Non-governmental Organization
PCP	*Pneumocystis jrovecii* Pneumonia
PH	Proportional Hazard
PLHIV	People living with HIV
PMTCT	Prevention of mother-to-child transmission
PS	Power and sample size calculation
PWID	People who intravenous drug user
RNA	Ribonucleic acid
SD	Standard Deviation
STD	Sexual Transmitted Diseases

SPSS	Statistical Package for The Social Science
TG	Transgender
TB	Tuberculosis
UK	United Kingdom
US	United State
USM	University Sains Malaysia
WHO	World Health Organization

LIST OF SYMBOLS

>	More than
<	Less than
≥	More than and equal to
≤	Less than and equal to
=	Equal to
α	Alpha
β	Beta
ρ	p-value
%	Percentage

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ABSTRAK

MASA KEMANDIRIAN DAN FAKTOR-FAKTOR PROGNOSTIK PESAKIT AIDS DI KELANTAN: 2010-2014

Latar belakang: Kematian berkaitan AIDS ini masih menjadi kebimbangan di seluruh dunia serta di negeri Kelantan. Walaubagaimanapun masa kemandirian median dan faktor-faktor kebarangkalian yang menyumbangkan kepada risiko kematian di kalangan pesakit AIDS di Kelantan adalah tidak diketahui.

Objektif: Untuk menentukan keseluruhan masa kemandirian median dan faktor-faktor kebarangkalian kematian dalam kalangan pesakit AIDS di dalam populasi Kelantan dari tahun 2010 hingga 2014.

Kaedah: Satu kajian kohort retrospektif telah dijalankan pada Januari 2018 menggunakan data sekunder diperolehi daripada Pendaftaran AIDS Nasional bagi tempoh 1 Januari 2010 hingga 31 Disember 2014 dan susulan sehingga 31hb Mac 2015. Sebanyak 1073 data yang lengkap telah dipilih untuk analisa deskriptif dan analisa kemandirian. Analisa menggunakan kaedah Kaplan - Meier dan model Cox's regresi bahaya berkadar dengan anggaran bahaya nisbah dan 95% selang keyakinan digunakan.

Keputusan: Purata umur (SD) ketika diagnosis adalah 37.08(7.37) tahun. Sebahagian besar kes kebanyakannya adalah lelaki (87.0%), Melayu (87.5%), bujang (62.3%), menganggur (38.0%), status pendidikan menengah (78.1%) dan kes tanpa jangkitan HIV-TB (62.8%). Anggaran 53% kematian pesakit semasa waktu susulan. Masa median kemandirian keseluruhan ialah 11 bulan. Kebarangkalian kelangsungan hidup dalam tempoh 1 tahun, 2 tahun dan 5 tahun masing-masing adalah 49.1%, 47.8% dan

46.7%. Multivariat Cox regresi menunjukkan bahawa factor-faktor kebarangkalian kematian adalah berdasarkan umur 30-49 tahun (Adj. HR 1.57; 95% CI: 1.14, 2.16; p = 0.006), lelaki (Adj. HR 1.39; 95% CI: 1.07, 1.79; p = 0.012), menganggur (Adj. HR 1.40; 95% CI: 1.12, 1.75; p = 0.003) dan mempunyai jangkitan HIV-TB (Adj. HR 1.78; 95% CI: 1.37, 2.31; p < 0.001).

Kesimpulan: Keseluruhan masa kemandirian median dalam kalangan pesakit AIDS di Kelantan adalah masih rendah. Untuk meningkatkan kadar kemandirian hidup di kalangan pesakit-pesakit AIDS, segala usaha perlu dibuat untuk memastikan saringan awal, diagnosis awal, intervensi awal dan pengurusan yang komprehensif melibatkan permulaan rawatan HAART dengan segera dalam merawat pesakit HIV/AIDS sebelum berlakunya kematian berkaitan AIDS.

KATA KUNCI:

HIV/AIDS, keseluruhan masa kemandirian median, kadar kemandirian, faktor-faktor prognostik

ABSTRACT

SURVIVAL TIME AND PROGNOSTIC FACTORS OF AIDS PATIENTS IN KELANTAN: 2010-2014

Background: The AIDS death is still a worldwide concern as well as in Kelantan. However, the median survival time and predictor factors that contributing to risk of death among AIDS patients in Kelantan were unknown.

Objectives: To determine the overall median survival time and survival rate of AIDS patients and predictors factors of death in Kelantan population from 2010 to 2014.

Methodology: A retrospective cohort study was conducted in January 2018 using secondary data obtained from National AIDS Registry for the period of 1st January 2010 to 31st December 2014 and followed-up until 31st Mac 2015. A complete 1073 data was selected for descriptive analysis and survival analysis. Kaplan- Meier survival analysis and Cox's proportional hazard regression model with estimates of hazard ratio and 95% confidence interval were used.

Result: The mean (SD) age was 37.08 (7.37). The patients were predominantly males (87.0%), Malays (87.5%), single (62.3%), unemployed (38.0%), with background of secondary education (78.1%) and cases without HIV-TB co-infection (62.8%). Approximately 53% of the patients death during follow-up. The overall median survival time was 11 months. The probability of survival in 1-year, 2-year and 5-year were 49.1%, 47.8%, and 46.7% respectively. Multivariate Cox regression showed that significant prognostic factors were age 30-49 years (Adj. HR 1.57; 95% CI: 1.14, 2.16; p=0.006), male (Adj. HR 1.39; 95% CI: 1.07, 1.79; p=0.012), unemployed (Adj. HR

1.40; 95% CI: 1.12, 1.75; p=0.003) and HIV-TB co-infection (Adj. HR 1.78; 95% CI: 1.37, 2.31; p<0.001).

Conclusion: The overall median survival time among AIDS patients in Kelantan was still low. To increase the survival among AIDS patients, every effort need to be made to ensure early screening, early diagnosis, early intervention and comprehensive management involving initiating HAART treatment as soon as possible in treating HIV/AIDS patients before they progress to AIDS-related death.

KEYWORDS:

HIV/AIDS, overall median survival time, survival rate, prognostic factors

CHAPTER 1

INTRODUCTION

1.1 HIV/AIDS

Globally, human immunodeficiency virus (HIV) still being address as a threat to the public health problem (WHO,2017). However, the Acquired immunodeficiency syndrome (AIDS) is no longer public health concern due to the successfully and advance of modern antiretroviral therapy (ART) that effectively suppressing HIV within a person's body. Finding found that patient with HIV can live longer with any manifestation of AIDS (Cahill and Valadéz, 2013). The AIDS is a term which applies to the most advanced stages of HIV infection that can damage body's immune system (WHO,2017).

AIDS as a result of profound immunosuppression causing the HIV-infected individuals vulnerable to opportunistic infections, secondary neoplasms and neurologic manifestation. As in case definition for infectious diseases in Malaysia, an adult (age more than 12 years old) is considered to have AIDS if tested positive for HIV antibody, and one or more of the following is present: (1)10% body weight loss or cachexia, with diarrhoea or fever, or both, intermittent or constant, for at least 1 month, not known to be due to a condition unrelated to HIV infection; (2) Cryptococcal meningitis; (3) Pulmonary or extra-pulmonary tuberculosis; (4) Kaposi sarcoma; (5) Neurological impairment that is sufficient to prevent independent daily activities not known to be due to a condition unrelated to HIV infection (for example, trauma or cerebrovascular accident); (6) Candidiasis of the oesophagus (which may

presumptively be diagnosed based on the presence of oral candidiasis accompanied by dysphagia); (7) Clinically diagnosed life-threatening or recurrent episodes of pneumonia, with or without etiological confirmation; and (8) Invasive cervical cancer (MOH, 2017).

1.1.1 The natural history of HIV

The natural history of untreated HIV varies widely. The treatment planning and preventive strategies are depending on the long term development of non-progression of HIV and viral control (Sabin and Lundgren, 2013). A better understanding of the epidemiological triad that involving the host, agent and environmental factor is crucial in providing the prevention and control of the disease spread.

The dynamic interaction of the agent-host can be explained through the progression of disease. It's started from the susceptible infected of the host with the agent typically HIV-1. The acute phase or so called primary infection of adults HIV infection occur after 3 to 6 weeks of infection followed by chronic phase. Most of the HIV patient are asymptomatic with a CD4+ count of 350-800 cells/mm^3 in chronic phase. The primary infection may symptomatic and or asymptomatic which usually correlate with faster progression. The antibodies usually appear two to four weeks later (Lavreys *et al.*, 2002). The self-limited illness that occur in primary infection showing the nonspecific symptoms such as fever (80%), malaise (68%), arthralgia (54%), maculopapular rash (51%), myalgia, oral ulcers and pharyngitis whereas neurological complications such as Guillaine Barre´syndrome and Bell's palsy occasionally occur. Most of the symptoms resolved after 7-10 days. Some of the patient develop more severe symptoms that usually associated with opportunistic infection such as *Pneumocystis jirovecii* pneumonia (PCP) or oesophageal candidiasis with the CD4+

count below 200 cells/mm^3 (Lewthwaite & Wilkins, 2009). This phase recognized by detection of lower CD4+ T cells but the virus production and viremia was at higher level. When the dissemination of virus occurs, there was a sharply decrease of the CD4+ cell count in the peripheral blood. These is where the prolonged period of clinical latency occurs.

In the stage of clinical latency period, the individual doesn't show any symptoms but the HIV replication, CD4 depletion and viral evolution continues and lasting for several years. The United Kingdom (UK) study done by Mandalia *et al*. shows that asymptomatic individual can live up to more than 7 years presumably because of stable CD4+ cell counts. Patients also can have persistent lymphadenopathy and many patients have minor opportunistic infections such as oral thrush (candida) or herpes zoster (Lewthwaite & Wilkins, 2009). The crisis phase begins when there are clinical features of persistent lymphadenopathy with significant constitutional symptoms such as fever, rash and fatigue. It shows the decompensation of immune system with increase production of viral replication.

The crisis phase is the final phase that characterized by catastrophic breakdown of host defences, a marked increase in viremia and clinical disease. Patients may present with fever of more than one month's duration, fatigue, weight loss and diarrhoea with the CD4+ cell count reduced below 500 cell/$mm^{3.}$ Patients may prone to serious opportunistic infections and develop secondary neoplasms and/or neurologic manifestations. This is so-called AIDS defining condition (Figure 1.1). The Centre of Disease Control (CDC) guidelines define AIDS as any HIV-infected individual with CD4+ cell counts less than or equal to 200 cell/mm^3. The total years of survival from the HIV infected person to the diagnosis of AIDS is approximately 8-10 years (Sabin

& Lundgren, 2013). A study reported that the survival of AIDS patient to death without any intervention is approximately within two years (Poorolajal *et al.*, 2016).

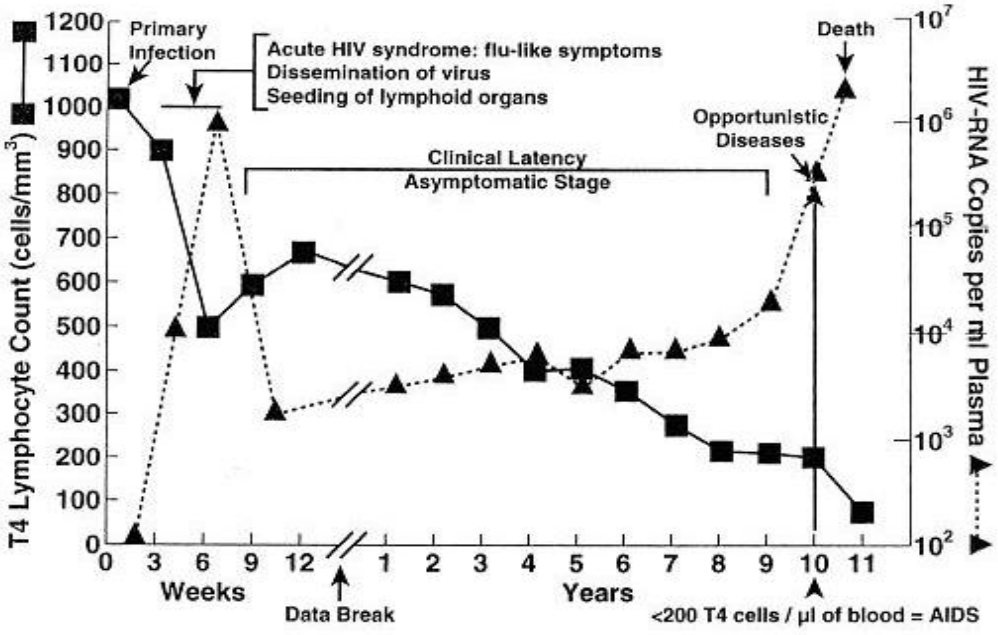

Figure 1.1: The typical clinical course of HIV disease

1.1.2 Risk Factor

The risk factors of HIV are depending on the types of exposure and behaviour. The infectious agent of HIV involve transmission from person-to-person through unprotected penile-vaginal or penile-anal intercourse; the use of HIV-contaminated injecting and skin-piercing equipment, including sharing of needles and syringes by people who inject drugs; vertical transmission from mother to infant during pregnancy, delivery or breastfeeding and transfusion of infected blood or its components. The heterosexual HIV infection is the main contributor of mode of transmission in Sub-Saharan Africa and South-East Asia Region that mostly affected the young women (CDC, 2015).

The updates information of Ministry of Health Malaysia "Ending AIDS in Malaysia" shows the changing pattern of HIV transmission from the people who inject drugs (PWID) to the sexually transmitted HIV infection mostly men having sex with men (MSM). This evidence supported by the latest Integrated biological and behavioural surveillance survey (IBBS) in 2014. The IBBS is done mainly to establish information that contributes towards developing an evidence- informed response to HIV and AIDS that was initially conducted in 2009. Total of three round of IBBS survey was done. At initial part the IBBS survey was concentrate for three key population which is PWID, female sex worker (FSW) and transgender (TG) then for second and third round focusing on wider group which included the MSM people. This survey was successfully being implemented countrywide in 2012 and 2014.

The IBBS done in 2014 reported that the HIV prevalence among PWID declining from 22.1% to 16.3% in 2009 and 2014 respectively. Whereas, the HIV prevalence among MSM was increasing from 3.9% in 2009 to 8.9% in 2014. The other groups that contribute to the increase of HIV transmission through sexual are FSW and TG which showing the percentage of 10.5% in 2009 and 7.3% in 2014, later is 9.3% in 2009 and 5.6% in 2014 respectively (NSPEA, 2015). However, in IBBS 2014 even though nationally showed slowly declining HIV transmission through PWID but Kelantan is still dominated by PWID with HIV prevalence 44.7% followed by Terengganu (30.0%), Johor (27.1%) and Kuala Lumpur (21.3%). Penang (1.6%) and Melaka (1.7%) were among the lowest HIV prevalence in PWID. Kuala Lumpur (17.1%) and Pahang (14.5%) is the state mostly predominant by sexually transmitted of HIV infection mainly FSW and lowest in Perak (0.6%). In 2014, the prevalence among MSM and TG were highest in Kuala Lumpur which 22.0% and 10.6% respectively (NSPEA, 2015).

1.2 HIV/AIDS incidence, mortality and survival

In the past 30 years there are a lot of achievement and programmes being done to combat HIV/AIDS but yet it's still remains a major threat to the public health (GBD, 2015). However, HIV/AIDS is no longer among the world's top 10 causes of death (WHO, 2017). AIDS mortality has been declining at a steady pace, from peak of 1.9 million in 2005 to 1.0 million in 2016 about 48% declining of the AIDS-related death (UNAIDS, 2017). There is no cure and vaccine yet for this moment but the global response is to reduce the burden of the disease to those infected and to prevent further infections spread.

Globally, an estimated 36.7 million people living with the HIV infection at the end of 2016 with the HIV prevalence 0.8% among adults (UNAIDS, 2017). In 2016, reported 1.8 million newly infected with HIV (WHO, 2017). From the start of epidemic till now an estimated 78 million people suffering from HIV infection and from that 35 million people have died because of AIDS-related illness. New HIV infection has declined by 50% between 2000 and 2015 while the number of HIV/AIDS related deaths stabilized during the same period. About 16% of reduction in number of AIDS death across the global population since 2010 (UNAIDS, 2017). The most affected countries with the HIV infection was the African region with the estimated number of people living with HIV was about 25.6 million in 2016 (WHO, 2017). Survival probabilities of progression from AIDS onset to AIDS-related death between patient with Highly Active Antiretroviral Therapy (HAART) and without HAART have change. Reported from meta-analysis research of 57 studies, an estimated the 6-year survival those from AIDS onset to AIDS-related death in patient receive HAART and who did not were 78% and 18% respectively (Poorolajal *et al.*, 2016).

In Western Pacific region, the estimated number of people living with HIV (PLHIV) was 1.28 million in 2010 and the number increase to 1.48 million in 2016. However, the prevalence still low, 0.1% which mask the high HIV infection among key affected population. The new infection of HIV also decreases from 120,000 in 2000 to 97,000 in 2016. The AIDS-related death reported have been declining over the past year from 65,000 in 2005 to 39,000 in 2016. China is the main country that contributed to the higher new HIV infection which was 63.02% out of 37 countries in Western Pacific Region. Reported data from year 2000 to 2015 for Western Pacific the increased use of antiretroviral therapy (ART) corresponds with the decrease in AIDS-related deaths. As ART use increased up to 50% in 2015, AIDS-related deaths began to slow and decrease to 40,000 cases ("Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015," 2016).

The first reported case of AIDS in Malaysia was in 1986 (UNAIDS, 2016). Since then, the cumulative number of AIDS-related death from year 1989 to 2016 were 18,827 with people diagnosis of AIDS were 23,717 (GARPR, 2016). In 2016, almost 50% reduction of the new HIV infection as compared to year 2000 from 12,000 to 5700 cases. The AIDS-related death was 7000 in 2016. Same as other countries the survival of AIDS patients in Malaysia was markedly improving after ART treatment or HAART was introduced in 1996 (Mat Shah *et al.,* 2012). Since then, the natural history of HIV/AIDS as well as morbidity and mortality pattern have changed (May and Ingel (2011). The HIV-infected person experiencing immune reconstitution and prolonged survival as result of HAART. New antiretroviral with lesser side-effect facilitated adherence to treatment and contributed to increasing life expectancy (Nakagawa *et al.,* 2013). In Malaysia, survival analysis research done by Lubis *et al*.

(2013) reported that the data from 845 HIV-infected patients aged ≥20 years on ART in a large teaching hospital in Malaysia from 1989 to 2009 was survived up to 72.7% if the viral load less or equal than 50 copies/ml. The mean survival time was 130.9 (95% CI: 123.4, 138.3) month. The triple drug ART used to treat HIV patients and to lower viral load to ≤50 copies/ml was the significant modifiable predictors of death in Malaysian HIV patients.

Kelantan is among the five states that account for almost two thirds (62%) of all people living with HIV (PLHIV) in Malaysia. The epidemic snapshot Kelantan 2016 database showed that the cumulative number of AIDS cases from year 2001 to 2016 was 2,255 cases and the AIDS-related death was 174 cases in 2016. There is no survival analysis done yet in Kelantan up to this date.

1.3 Malaysian AIDS Surveillance and National AIDS Registry

The AIDS surveillance system in all states in Malaysia is active and comprehensive. It involves both public and private medical care providers including hospitals, health clinic, physicians, general practitioners and laboratories. All cases of HIV, AIDS and AIDS-related death diagnosed by registered medical practitioners are mandatorily notifiable as stipulated by Prevention and Disease Control Act 1988.

This surveillance system aims to better characterize the newly diagnosed HIV population and to facilitate the public health follow up. The sources of notification include health facilities, routine HIV testing among people who inject drugs in drug rehabilitation centres and prisons, tuberculosis (TB) and sexually transmitted diseases (STD) patients, pregnant women attending antenatal clinics and blood donors. The system was upgraded to web-based notification in 2001.

The Ministry of Health established the National AIDS Registry (NAR) in 2009. It is intended to replace the existing surveillance system designed to function as a streamlined and effective national HIV programme monitoring mechanism that able to capture detailed disaggregated data continuously and systematically. The registry captures data on each HIV patient relating to their socioeconomic background, risk factor, date of confirmation, contact information, AIDS-related symptoms etc. The data was entered since 2000 taken from manual registration HIV/AIDS report. The data includes all notifiable HIV, AIDS and AIDS death by government and private hospital according to every state but only the HIV/STD/Hep C Unit of respective state and administrator, HIV/STI Section of Disease Control Division, Ministry of Health Malaysia able to access the data with the ID number and password to enter the system.

Besides the passive notification from government hospitals, clinic and private setting, the HIV/STI/Hep C Unit also conducted an active case detection by doing the outreach program screening cooperated with non-governmental organization (NGO). The programmes were through testing and screening programmes include routine HIV screening of all donated blood, blood products and organs, opt-out antenatal screening, routine testing of inmates in drug rehabilitation centres and prisons, testing of TB and STI patients, clients of harm reduction programme, contacts of HIV infected persons, and voluntary premarital testing. The notification form received from various sources mentioned will be verified by the Epidemiologist or Public Health Specialist of HIV/STI/Hep C Unit at every district before the respective district registered to the National AIDS Registry and further analyses by the HIV/STD/Hep C Unit at every respective state.

1.4 Problem statement

There were studies done with regards to survival of HIV/AIDS patients and looking the prognostic factors of survival worldwide. Reports of improved survival among persons living with AIDS were well documented in most of the literature in the late 1990s especially after the ART initiation.

Recently studies from Western countries showed improvement in survival among the AIDS patients. The striking pattern of improving the prevalence and incidence worldwide with the increase of the ART coverage highlighted that the changes in the patient survival ("Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies," 2008).

In Malaysia, HIV epidemics still concentrated with the key affected population (sex workers, men having sex with men, transgender persons and people who use drug). Hence, identification of current survival status and the factors influencing the survival among AIDS patient was crucial since no such study has been carried out in Malaysia.

Locally, there was no population-based study done yet to evaluate the survival and prognostic factors of AIDS patient. Even though the prognostic factor of death research finding from Western Countries were numerous, but it may not readily be adapted to Malaysia and Kelantan per say as the outcome of AIDS depends on a multitude of factors ranging from sociodemographic factors and clinical characteristics. It is therefore critical to conduct this survival time analysis among AIDS patients to meet the need for region-wide information.

1.5 Rationale of study

The impact of HIV response should be assessed by monitoring changes in AIDS-related death over time. By identification of prognostic factors of death in AIDS patient will help to guide HIV/AIDS prevention, care and treatment programmes in Kelantan as well. It can guide clinician for prompt treatment in order to reach the target of National Strategic Plan of Ending AIDS 2016-2030 (NSPEA) which are 90% of key affected population tested for HIV and know their result, 90% of PLHIV receive ART and 90% of people on ART achieve viral suppression.

So, with the detail of survival time among AIDS patients can help the clinician to use the local data to convince patient about overall prognosis of AIDS survival. It's also can be used as a guidance in planning further management. Therefore, we will be able to improve the survival time among the AIDS patient in Kelantan and hence alert the health care professional to diagnoses AIDS as early as possible. Moreover, the research done in Malaysia only focusing on the survival with regards of treatment modalities. In this study, the broader factor can be included to see the survival of the AIDS patients either increase or decrease with regards of the other modalities such as sociodemographic factors and HIV-TB co-infection as these variables are available and complete in our secondary data in National AIDS Registry.

Meanwhile, the determination of survival time and prognostic factors of death among AIDS patient information will serve several purposes: 1) increase knowledge on the medical and public health level determinants of survival after AIDS diagnosis; 2) to enhance planning and allocations of resources for HIV/AIDS services; and 3) provide the detection of changes that may help in the success of the services and the area of gaps for improvement of the survival times among AIDS patients. There was

still lack of research done on survival among AIDS patients in Malaysia and no study done yet at Kelantan state. So, the primary aim of this study was to determine the survival time and survival rate as well as the prognostic factors of AIDS patients in Kelantan.

1.6 Research questions

I. What is the median survival time of AIDS patients in Kelantan?

II. What is the survival rate of AIDS patients in Kelantan?

III. What are the prognostic factors of AIDS patients in Kelantan?

1.7 Objectives

1.7.1 General objective

To determine the overall median survival time and prognostic factors of AIDS patient in Kelantan from 2010-2014.

1.7.2 Specific objectives

1. To determine median survival time of AIDS patients in Kelantan diagnosed between 2010-2014.
2. To determine the survival rate of AIDS patients in Kelantan
3. To determine the prognostic factors (sociodemographic and HIV-TB co-infection) of death among AIDS patients in Kelantan.

1.8 Hypothesis

1.8.1 Alternative hypothesis

There are an association between prognostic factors (sociodemographic and HIV-TB co-infection) with the death among AIDS patients in Kelantan.

CHAPTER 2

LITERATURE REVIEW

All the literature searches pertaining to survival, HIV/AIDS and the prognostic factors were widely done by using search engines such as PubMed, Science Direct, Springer Link and Ebcohost. Various searching strategy was applied such as combination of terms with the use of Boolean operators (AND, OR, NOT). The entire literature search published from 2000-2017 were included. Key words used were HIV/AIDS, median survival time, survival rate and predictors of death.

2.1 The Infectious Agent: Human Immunodeficiency virus

The causative agent for AIDS is Human immunodeficiency virus (HIV). The HIV is a retrovirus that contains only RNA. The HIV is a human retrovirus belonging to the lentivirus family including feline immunodeficiency virus, simian immunodeficiency virus, visna virus of sheep, and the equine infectious anaemia virus which has two types known as HIV-1 and HIV-2. The HIV-1 is the most common types of infectious agent that contribute to worldwide AIDS epidemic. The later type is much less common and less virulent, but eventually produces clinical findings similar to HIV-1 (Sharp & Hahn, 2011). The HIV-1 type itself has two broader groups, designated M (major) and O (outlier). The most common form of group M are further divided into subtypes A through J which have differing geographic distributions but all produce AIDS similarly. Subtypes B most common form in Western Europe and United States and E most common form in Thailand. The different subtypes also exhibit different in mode of transmission. For example, the subtype E is spread predominantly by

heterosexual contact (male-to-female), presumably because of its ability to infect vaginal sub epithelial dendritic cells. Compare to the subtype of B, the virus best transmitted by introduction of infected monocytes and lymphocytes due to poorly grows of the subtypes in the dendritic cells (Robbins, 2003).

Emergence of HIV infection started since 1980s originated from a man in Kinshasa, in the Democratic Republic of Congo collected from his blood around 1959. In the beginning, mostly believes that the source of HIV is come from 'homosexual'. However, research found that HIV is related to Simian Immunodeficiency Virus (SIV) which is originated from non-human primate progenitor and not because of long misguided associations of it being a "gay flu," disease of immigrants or commonly called homosexual and intravenous drug users. The SIV having similar way with HIV attack the immune system but happen to the monkeys and apes (Sharp & Hahn, 2011). The researcher reported that the type HIV-1 is related to the strain of SIV found in chimpanzees and strain of SIV in sooty mangabeys closely related to HIV-2. The accepted theory behind the changing of SIV to HIV was started since 1999, where the researcher found that the virus was transferred to human from chimp when their blood getting into as a result of hunted chimp killed and eaten by them. The genetic evidence show the virus evolved and adapted in the new host (human). SIV became transmissible to humans and developed into HIV (Worobey *et al.*, 2010).

2.1.1 Structure of HIV

The structure of mature HIV is a spherical shape of virion that consists of a bar-shaped electron dense core containing the viral genome; two short strands of ribonucleic acid (RNA) each 9200 nucleotide bases long, encased with the enzymes reverse transcriptase, protease, ribonuclease, and integrase within an outer lipid envelope

derived from a host cell (Figure 2.1). The outer coat of virus consists of two layers of lipids which is the outer ‘spike’ consist of different protein that embedded in the viral envelope called glycoprotein and the transmembrane. The transmembrane is needed in the process of cell fusion whereas the glycoprotein is crucial when the virus has to attach to the host cell to start the replication process.

The basic components of HIV consist of three important and major genes called: envelope glycoprotein (env), group specific antigen (gag), and pol (reverse transcriptase, protease and integrase) which code for various viral proteins. The env genes form an envelope precursor protein gp160 which undergoes proteolytic cleavage to the outer envelope glycoprotein gp120. The gp120 responsible for tropism to CD4+ receptors. The transmembrane glycoprotein gp41 combined with glycoprotein gp120 to the target cell's membrane. The gag gene develops the proteins of the matrix p17, the "core" capsid p24, and the nucleocapsid p7. The pol gene synthesis the important enzymes such as reverse transcriptase p51 and p66, integrase p32, and protease p11. The antibody recognizes the p24 that used to diagnose HIV infection in blood screening (Fajardo-Ortiz *et al.*, 2017). Other than three standard retroviral genes, HIV contains other several genes named tat, rev, vif, nef, vpr, and vpu which regulate the synthesis and assembly of infectious viral particles. The replication of the virus that can produce up to 1000-fold increase in viral genes transcription done by the product of tat (transactivator) gene. The activation intracellular kinase activity mainly T-cell activation, viral replication and viral infectivity is particularly done by the nef protein and also needed for progression of HIV infection in vivo (Figure 2.2).

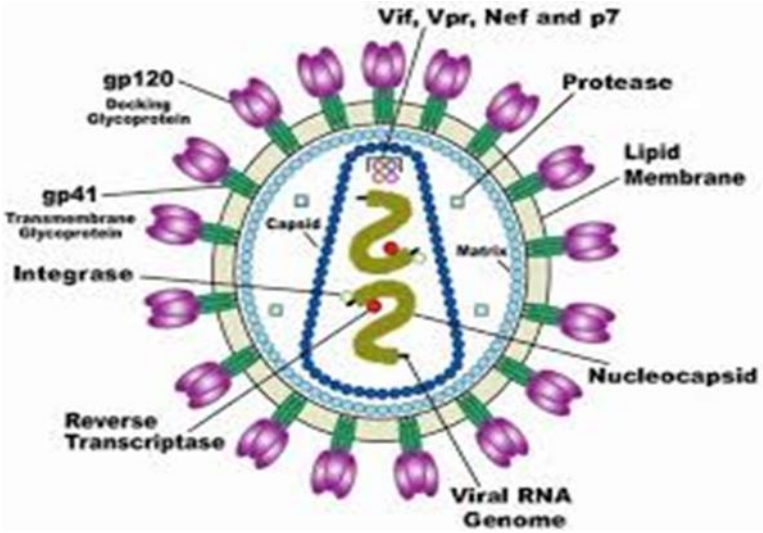

Figure 2.1: Virus HIV structure

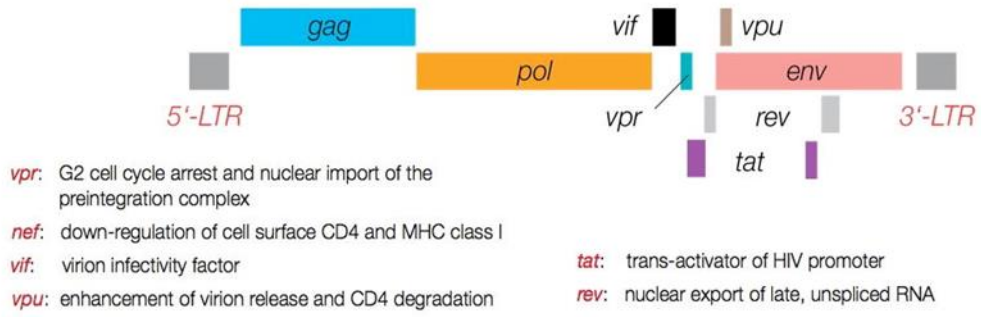

Figure 2.2: The HIV genome

2.1.2 Pathogenesis of HIV

The immune-pathogenesis of HIV disease are particularly causing the immunosuppression that primarily affecting cell-mediated immunity. This result from the infection and subsequently loss of CD4+ T cells as well as impairments in the function of surviving helper T cells. The coreceptor of CD4 receptor also known as chemokine responsible for HIV infection. However, binding to CD4 is not sufficient for infection without the HIV envelope gp120 also bind to the coreceptors to facilitate

cell entry. Chemokines are cell surface fusion-mediating molecules. Such coreceptors include CXCR4 and CCR5. Their presence on cells can aid binding of the HIV envelope glycoprotein gp120 act as infection promoter. Initial binding of HIV to the CD4 receptor is mediated by conformational changes in the gp120 subunit, but such conformational changes are not sufficient of fusion. The fusion of HIV happens when the conformational change of gp41 subunit produce by chemokine receptors. The differences in chemokine coreceptors that are present on a cell also explains how different strains of HIV may infect cells selectively. The process of infection to lymphocytes was done by T-tropic strains which selectively interact with CXCR4 chemokine corereceptor. The M-tropic strains of HIV interact with the CCR5 chemokine coreceptor to infect macrophages. Dual tropic HIV stains have been identified. In some cases, when there was a resistance to HIV infection probably due to CCR5 mutation. The capability of this routes produce HIV resistance may increase the ability of virus to infect cells easier.

Most of the patient develop the stage of clinical AIDS when the CD4 lymphocyte count drops below 200/microliter. It has been determined that approximately 100 billion new viral particles are produced every day and one to two billion CD4+ T cells die each day. The loss of CD4+ cells can occur by both increased destruction and reduced production (Robbin, 2003).

2.1.3 Transmission

The most commonly mode of transmission of HIV infection is by sexual contact, either homosexually or heterosexually but again about 85% type HIV-1 all are coming from heterosexual transmission (Simon *et al.*, 2006). Solely change the perception that HIV transmission is a disease of homosexual. Same reported by Center

for Disease Control, United State (US) in 1983 (Greene, 2007). The virus enters to the body through the lining of the vagina, vulva, penis, rectum, or mouth during sexual contact. The other mode of transmission is through contact with infected blood or blood products, or tissues from transfusion and transplants. The sharing needle or syringes during intravenous drug use are other blood-borne routes. Mother-to-child transmission of HIV is the spread of HIV infection from infected mother to child during pregnancy, childbirth or breastfeeding. According to the WHO the transmission rate mother-to-child transmission is range from 15% to 45% without any intervention.

The systemic review study on HIV modes of transmission found that 13 out of 29 countries that have been reported shows the low-risk group are more vulnerable to HIV transmission (26-63%) and female sex workers (FSW) still remain low (median 1.3%) and the people with intravenous drug user (PWID) even they are the largest contributor to HIV transmission in early-phase of endemic reported to have low overall HIV prevalence. The sexual contact through men who have sex with men show increasing size in population and the annual fraction of new HIV infections reported varies across region (range 0.1 to 82%) (Shubber *et al.*, 2014).

2.1.4 Progression to AIDS

The progression of HIV to AIDS presentation is still debatable. The asymptomatic HIV infection to develop AIDS varies from patient to patient and the determinants are not clearly stated. The identification of AIDS started in 1981 when there are young gay men in US sick and on the point of death after suffering from an opportunistic infection. The speculation stated that AIDS was originated from Haiti as appearance of AIDS in Haiti. Late 1982, epidemiologic evidence reported that AIDS transmitted by bodily fluids and contaminated blood. A true cause of AIDS found after

immunological intervention show the level of CD4 T cell rapidly decrease to the level of 200 cell/mm^3 make them prone to opportunistic infection and various malignancy (Greene, 2007). The previous study reported that the reduced number of T-helper lymphocytes, increase T-suppressor lymphocytes and reduced amount of serum antibody to HIV are the most likely determinants of progression of AIDS (Desalu, 2002).

2.2 HIV/AIDS burden

The incidence and mortality of HIV/AIDS as public health concern is mostly common indicator for the disease burden. The HIV/AIDS is one of the disease attributable to the total disability mainly in Southern Sub-Saharan African countries (GBD, 2016). The changing pattern HIV/AIDS burden reported based on the global burden of disease study 2015 shows the global HIV incidence peak in 1997, 3.3 million new infections and declining fast between 1997 and 2005. Since then the incidence was steadily constant about 2.6 million per year. However, in 2015 the number of people living with HIV/AIDS increasing and reached to 38.8 million (GBD, 2016).

Sub-Saharan Africa with only small population but yet a largest contributor to global burden of HIV infection (71%). The new infection still high even reported the declining of the trends from 2.2 million in 2005 to 1.5 million in 2013 (Kharsany & Karim, 2016a). The declining of the incidence was corresponding with the antiretroviral therapy (ART) coverage. The evidence is based on study done by Reniers *et al.* (2014) reveal from data of seven members of the Network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA Network) cover populations ranging from 20000 to 200000 in size. The study was carried out to see

the mortality trend from period of 2000 to 2011 which cover the pre- and post-ART era. The mortality rate ratio in early 2000s (pre-ART era) varied between 8.4 to 21.2 whereas post-ART era ranged from 2.4 to 6.6.

Malaysia is one of the faster growing HIV epidemics in the East Asia and Pacific region, from three cases in 1986 dramatically increase to 91,362 cases of HIV-infection, 16,352 AIDS cases and 12,943 AIDS-related deaths by end of 2010 (NSPEA, 2017). Again same as other countries, the introduction of ART in early 1990s gives a new dimension on the survival of people living with HIV from death sentences toward manageable chronic condition (Huang & Hussein, 2004).

2.3 Overall median survival time and survival rate of AIDS

The overall median survival time showed the first observed time at which the cumulative survival was 50% or less. In other word its refers to how long the patients survive with a disease in general or after a certain factor such as treatment. It is the time which can be expressed either in months or years when half the patients are expected to be alive. Meaning that the chance of surviving beyond that time is 50%.

In Somali Region, Eastern Ethiopia, a retrospective cohort study done by Bereket Damtew *et al*. (2015) analysed the survival patients who started ART between December 1, 2007 and December 31, 2011 at Kharamara hospital. Most of the cases were female patient 485 (58.4%). Out of total study population, 87 (11.1%) patients died during the five-year follow-up period, with majority of deaths 49(56.3%) occurring in the first 3 months. This study revealed the median survival time for event (death) was 20.7 months. The estimated mortality was 8.4%, 9.8%, 11.3%, 12.7% and 14.1% at 6, 12, 24, 36 and 48 months respectively.

The study done by Carvour *et al*. (2015) on the both retrospective cohort data from statewide cohort, Lowa for the period of 1982-2008 and a university-based validation cohort during the period 1984–2009. This study identifies the survival of AIDS-related neurologic disease between male and female for both cohorts were poor. The median survival time was 1.13 years for the statewide cohort and 3.04 years for the university-based cohort respectively. In the statewide cohort documented that median survival time was lower for women (median: 0.78 years, range: 0.00 to 11.38 years) than for men (median: 1.30 years, range: 0.00 to 19.04 years) through Kaplan-Meier analysis. In the university-based cohort, the rate of death was non-significantly higher for women than for men (Adj. HR: 1.44, 95% CI: 0.44 to 4.72, n = 171).

Further, Marin *et al.* (2003) in a subsequent sample of 3930 adult AIDS cases from 18 cities in seven states representing all regions of Brazil were randomly select cases diagnosed in 1995 and 1996 reported dramatic improvement in survival. This retrospective cohort study finding was compared with data from a previous national study of survival among 2135 adult Brazilian AIDS patients diagnosed in 1982–1989. Out of 3930 cases in the original sample, only 2821 AIDS patients studied. Twenty percent of them are female (763) with median age of 33 years. The median survival for AIDS cases diagnosed in 1995 is 18 months and cases diagnosed in 1996 had much better survival (median survival: 58months). The median survival time for AIDS patients in 1995 and 1996 combined was found to be 36 months. The previous study of survival among adult Brazilian AIDS patients in 1982 to 1989 found a median survival of 5.1 months.

Based on survival analysis study by Melo L.S *et al*. (2008), all the patients whose cases were notified over the study period from 1997 to 2004, the probability of

survival for the 597 subjects was 82%. This study was carried for those who died over eight years of Highly Active Antiretroviral Therapy, at a Referral Center in Northeast Brazil. There was a 75% probability of survival for up to 66 months. Among the 597 patients whose cases were notified as AIDS, 150 (25%) progressed to death.

Further analysis study of the survival looking in different perspective which is the survival of AIDS patient after diagnosis *Pneomocystis carinii* pneumonia (PCP) in United States. The data was obtained from 11 state and local department of United State for period of 1992-1998 done by Dworkin *et al*. (2001). This study was based on the data collection began in 1990 (Atlanta, Dallas, Houston, San Antonio, Denver, Detroit, Los Angeles, New Orleans, and Seattle), 1991 (New York City), and 1992 (Bayamon, Puerto Rico) through 1999 showed an improvement in survival with more recent year of diagnosis with PCP. Twelve-month survival increased from 40% during 1992–1993 to 44% during 1994–1995 and then to 63% during 1996–1998. The survival in 1-year was increasing in trend from 40% to 68% in 1992 to 1998 respectively.

In Malaysia, the hospital-based study done by Lubis *et al.* (2013). They studied 845 HIV- infected patients aged more than 20 years. This cohort study looking retrospectively the medical records of patient in large teaching hospital from 1989 to 2007 and followed up through 2009. From the finding noted were predominantly aged between 20 and 39 years (70.4%), were male (78.2%) and were Chinese (67.3%) while 48.5% were married, 67.5% had at least secondary education, 49.2% were professional or non-manual workers. About 74% had CD4<200 cells/µl and 55.5% had viral load (VL)≥100,000 copies/ml. This study was focusing on the survival of HIV infected patient on antiretroviral therapy. The mean survival time in this cohort was 130.9 (95%

CI 123.4, 138.3) months. The cumulative survival was more than 50%, so this study unable to calculate the median survival time. The survival rate of HIV infected patients on ART were 70.6% and 62.3% in 5-year and 10-year survival.

Table 2.1: Summary of literature review overall median survival time and survival rate of AIDS patient

Study location	**Database (years)**	**Overall median survival (months)**	**Survival rate**	**Author, Year**
Somali Region, Eastern Ethiopia	HIV/AIDS patients on ART at Kharamara hospital: PLHIV to death (2007-2011)	20.7	1-year: 90.2% 2-year: 88.7% 3-year:87.3% 4-year:85.9%	(Bereket Damtew *et al.*, 2015)
Iowa, United State of America	Surveillance data HIV/AIDS reporting system: Neuro-AIDS to death (Statewide cohort:1982-2008 University-based cohort: 1984-2009)	13 (Statewide cohort) 36 (university-based cohort)	Not stated in the study	(Carvour *et al.*, 2015)