THE EFFECT OF ANTIRETROVIRAL ON AIDS PROGRESSION AMONG HIV-INFECTED PEOPLE IN PAHANG FROM 2011 TO 2020

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THE EFFECT OF ANTIRETROVIRAL ON AIDS PROGRESSION AMONG HIV-INFECTED PEOPLE IN PAHANG FROM 2011 TO 2020

By

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral Drugs
EC	Elite Controller
FSW	Female Sex Worker
HIV	Human Immunodeficiency Virus
NAR	National AIDS Registry
PWID	People Who Injecting Drug
PLHIV	People Living with HIV
SIV	Simian Immunodeficiency Virus

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KESAN ANTIRETROVIRAL TERHADAP PERKEMBANGAN KEPADA AIDS DALAM KALANGAN ORANG YANG DIJANGKITI HIV DI PAHANG DARI TAHUN 2011 HINGGA 2020

ABSTRAK

Latar belakang: ARV terbukti sangat berkesan dalam menunda perkembangan penyakit HIV. Kadar perkembangan AIDS menurun dengan penggunaan ARV. Kejadian AIDS pada era ARV didapati menurun berbanding era sebelum ARV. Sustainable Developmental Goal menyasarkan untuk menamatkan epidemic HIV/ AIDS menjelang 2030.

Objektif: Kajian ini dilakukan untuk menentukan median masa perkembangan HIV kepada AIDS dan kesan ARV terhadap perkembangan AIDS dalam kalangan orang yang dijangkiti HIV di Pahang dari tahun 2011 hingga 2020.

Metodologi: Ini adalah kajian kohort retrospektif yang menggunakan data sekunder *National AIDS Registry* (Pahang) dan *ARV Line Listing*. Kajian ini melibatkan penduduk Pahang yang berumur 15 tahun dan ke atas yang didiagnosis menghidap HIV dan didaftarkan di dalam *National AIDS Registry* (Pahang) antara 1 Januari 2011 hingga 31 Disember 2020. Maklumat pesakit dikemaskini sehingga 21 Februari 2021. Kaedah Kaplan Meier digunakan untuk menentukan masa median survival secara umum dan antara kumpulan berdasarkan status ARV . Model Regresi Bahaya Berkadaran Cox (Cox Proportional Hazard Model) digunakan untuk menilai kesan ARV terhadap perkembangan AIDS dan mengenal pasti faktor ramalan yang lain.

Keputusan: Analisis Kaplan Meier secara keseluruhan menunjukkan seiring bertambahnya waktu, jumlah acara dan kebarangkalian menurun. Tidak ada masa median untuk analisis Kaplan Meier ini. Kebarangkalian survival terendah adalah 0.790 pada 112.59 bulan. Dengan menggunakan Model Regresi Bahaya Berkadaran Cox, 2 model akhir dihasilkan; model 1 tanpa memasukkan CD4 dan model 2 dengan memasukkan CD4. Dalam kedua-dua model itu ARV adalah signifikan. Dalam model 1, faktor prediktif yang signifikan ialah ARV, dimana telah mengurangkan bahaya 0.598 atau 40.2% perkembangan AIDS. Menjadi etnik bukan melayu mengurangkan bahaya dengan faktor 0.561 atau 43.9%. Peningkatan usia dan dijangkiti melalui heteroseksual adalah faktor prediktif yang buruk untuk perkembangan AIDS. Orang yang dijangkiti HIV dalam golongan umur ≥36 tahun dan dijangkiti HIV melalui heteroseksual, masing-masing mempunyai faktor bahaya 1.343 dan 1.459 kali terhadap perkembangan AIDS. Model 2 menunjukkan, menerima ARV, mempunyai tahap pendidikan yang tinggi dan peningkatan bilangan CD4 adalah faktor ramalan yang signifikan untuk perkembangan AIDS dalam kalangan orang HIV. Golongan yang menerima ARV mempunyai 0.129 kali risiko terkena AIDS berbanding dengan kumpulan yang tidak menerima ARV. Kumpulan dengan tahap sekolah rendah, menengah dan tahap tinggi, masing-masing mempunyai 22.9%, 75.2% dan 88.8% pengurangan bahaya untuk mengalami AIDS berbanding dengan orang yang tidak berpendidikan. Dengan setiap peningkatan 50 bilangan CD4, penghidap HIV mempunyai 0.805 kali ganda risiko terkena AIDS.

Kesimpulan: ARV berkesan untuk menunda perkembangan HIV kepada AIDS. Pada era pasca ARV, strategi harus difokuskan kepada promosi kesihatan dan saringan yang

efektif, pengesanan awal penyakit, permulaan dan kepatuhan kepada rawatan ARV, untuk mencegah penularan HIV dan menghentikan perkembangan penyakit.

THE EFFECT OF ANTIRETROVIRAL ON AIDS PROGRESSION AMONG HIV-INFECTED PEOPLE IN PAHANG FROM 2011 TO 2020

ABSTRACT

Background: ARV was shown to be very effective in delaying HIV disease progression. The AIDS progression rate was decrease with the usage of ARV. There was decrease in incidence of AIDS in ARV ere compared to preARV era. Sustainable Developmental Goal is aiming to end HIV/AIDS epidemic by 2030.

Objectives: This study was conducted to determine median progression time from HIV to AIDS and the effect of ARV on progression to AIDS among HIV-infected people in Pahang from 2011 to 2020.

Methodology: This is a retrospective cohort study using secondary data of National AIDS Registry (Pahang) and ARV Line Listing. This study included Pahang population aged 15-year-old and above who was diagnosed with HIV and registered in National AIDS Registry (Pahang) between 1st January 2011 to 31st December 2020. Exclusion criteria were patients diagnosed with AIDS within 1 month of HIV diagnosis. Patients' vital status was updated until 21st February 2021. Kaplan Meier method was used to determine median progression time in general and between groups. Cox Proportional Hazard was used to assess the effect of ARV on AIDS progression and identify other predictive factors.

Result: Kaplan Meier analysis in overall shows as the time increase, the number of event and the probability decrease. There was no median time for this Kaplan Meier analysis. The lowest survival probability was 0.790 at 112.59 months. Using cox proportional hazard, 2 final model were produced; model without CD4 count and model with CD4 count. In both models, ARV was a statistically significant factor. In model 1, ARV has 0.598 times hazard or 40.2% decrease hazard of AIDS progression. Being non-Malay reduced hazard by a factor of 0.561 or 43.9%. Increase in age and getting infected through heterosexual were bad predictors of AIDS progression. HIV infected person in age group of ≥36 years old and being infected with HIV through heterosexual had 1.343- and 1.459-times hazard towards AIDS progression. Model 2 revealed ARV uptake, higher level of education and increasing in CD4 count are good predictors for AIDS progression among HIV persons. Person who received ARV had 0.129 times hazard of developing AIDS compared with a group who did not receive ARV. Person with primary level, secondary level and tertiary level of education had 22.9%, 75.2% and 88.8% decrease in AIDS progression respectively as compared to person with no education. With every increase of 50 CD4 count, HIV person had 0.805 times hazard of developing AIDS.

Conclusion: ARV was found to be effective in delaying HIV disease progression to AIDS. In the post ARV era, strategies should be focused on effective health promotion and HIV screening, early case detection, ARV initiation and adherence, in order prevent HIV transmission and halt disease progression.

CHAPTER 1

INTRODUCTION

1.1 HIV/ AIDS

Human Immunodeficiency Virus (HIV) infection was cross infection from animal to human. The disease originated in Kinshasa, the capital of the Democratic Republic of Congo circa 1920, which transmitted from chimpanzee to human via 'hunter' activities. Simian immunodeficiency virus in wild chimpanzees (SIVcpz) was transferred to humans by two mechanisms either during killing and eating of chimpanzee, or during hunting, their blood gets into people's cuts and wounds. Usually, SIV is eliminated by human body immune system. HIV-1 is an adaptation form of SIV when it successfully escapes the human body immune system which occasionally happen. On the other hand, HIV-2 is connected to a SIV strain in sooty mangabeys (Avert, 2019a).

The current epidemic of HIV started in the mid- to late 1970s. People was getting infected through direct contact with body fluids, especially blood of person with HIV infection. People who belongs to population who have higher risk of having HIV infection are called key populations. Homosexual men; people who inject drugs (PWID); inmates and other closed environments, sex workers and their clients, and transgender people are identified as key population**.** Until today, HIV is still a big global public health concern, with around 33 million death reported so far. UNAIDS reported there were 38.0 million HIV infected people around the globe in 2019 (UNAIDS, 2020).

The first AIDS case in Malaysia was reported in 1986. Since then, it becomes major public health concern. Until December 2018, cumulative number of reported HIV, AIDS and HIV/AIDS related death are 118 883, 25 925 and 43 843 respectively. The expected number of people living with HIV (PLHIV) in Malaysia was 87 041, and 75 040 of whom were notified through the national surveillance system. Only 55% have accessibility to antiretroviral (ARV) (Anita & Chai, 2019).

All HIV infection will progress to acquired immunodeficiency syndrome (AIDS) if left untreated. AIDS progression is different from one individual to others and it can take many years to develop. In Malaysia, Infectious Disease Prevention and Control Act 1988 has listed AIDS as mandatory notifiable disease. For surveillance purpose in Malaysia, an adult (over the age of 12) is considered to have AIDS if tested positive for HIV antibody, and having one or more of the following symptoms : (1) 10 percent body weight loss or cachexia for at least 1 month, with diarrhoea or fever, or both, intermittent or continuous, not owing to a condition unrelated to HIV infection; (2) Cryptococcal meningitis; (3) Pulmonary or extra-pulmonary tuberculosis; (4) Kaposi sarcoma; (5) Neurological impairment that prevents independent daily activities and is not known to be caused by a condition unrelated to HIV infection (such as trauma or a cerebrovascular accident); (6) Candidiasis of the oesophagus (which may presumptively be diagnosed based on the presence of oral candidiasis accompanied by dysphagia); (7) With or without cause, clinically diagnosed life-threatening or repeated episodes of pneumonia; and (8) Invasive cervical cancer. HIV positive case with signs of AIDS should be notified to the nearest

District Health Office via submission of the notification form within a week (7 days) (Ministry of Health Malaysia, 2017)

1.1.1 Natural history of HIV

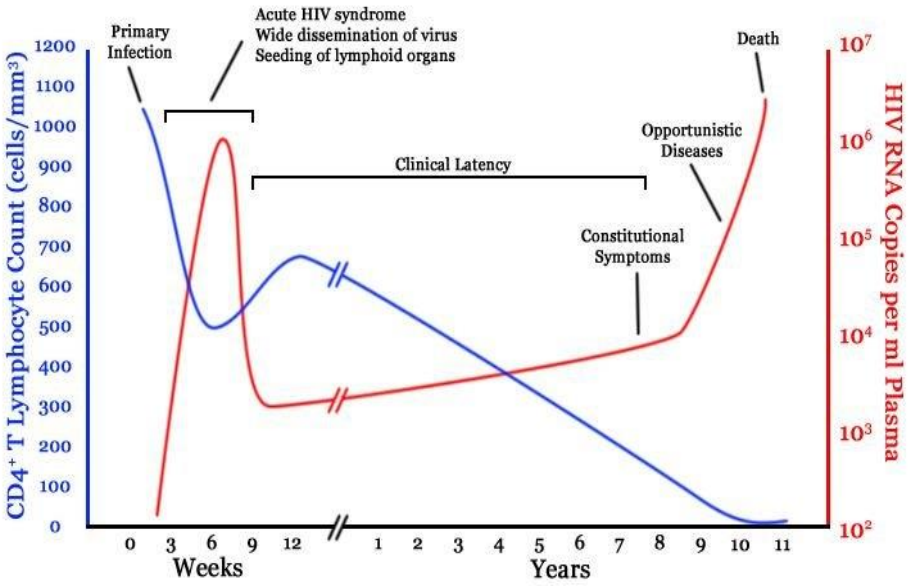

Figure 1.1 Natural History of HIV

The figure 1.1 summarize the natural history of HIV. It is divided into 4 stages, susceptibility stage, subclinical stage, clinical disease stage and the last one recovery/ disability/death stage.

1.1.1(a) Susceptibility Stage

HIV transmission occur when virus expose to mucosa surface or via percutaneous inoculation(Shaw & Hunter, 2012). It transmitted through sexual activity, blood product and vertically (from mother to child) during pregnancy, delivery and/or breast feeding (World Health Organization (WHO), 2020).

The main route of HIV transmission is having sex or sharing syringes and other injection equipment with PLHIV. The risk of infected by HIV is varies depends on type of exposure. Anal sex is higher risk to get HIV from vagina sex and the receptive

(bottom) is much riskier than insertive (top) (*CDC*, 2016). The transmission rate of HIV from a mother living with HIV to her child is range between 15% to 45% during pregnancy, through delivery or breastfeeding (WHO, 2020) .

1.1.1(b) Subclinical Stage

In this stage, host has been infected by HIV, the pathogenesis of disease is taking place but no symptoms shown yet. This stage is divided into two phases, primary infection and chronic infections.

During primary infections phase, HIV attack CD4 cells inside the lymph nodes to reproduce multiple times. This process leads to swelling and enlargement of lymph nodes with the new cells and virus. CD4 cell burst and release the new virus to the systems and this new virus attack other CD4. This leads to high level of viral load and decrease level of CD4. The level of viral load can be higher than 10 million copies/ml. At this time the person is very infectious.

Then, sero-conversion take place, where the immune system activated and produce antibodies. Acute sero-conversion period is period from HIV infection to anti HIV-antibodies detection. About 50-70% of people have symptoms and the rest is asymptomatic (Jameson *et al.*, 2018). These are usually flu-like symptoms, including fever and lethargy. Some people required hospitalization due to very serious infections. The number of CD4 counts increase and viral load level decrease in trend. Duration of sero-conversion usually 3 weeks (Cohen *et al.*, 2011), but can be up to 12 weeks. Study in china shows that the mean time for antibodies formation was 43.90 with 95% CI (37.30, 50.50) days (Kong *et al.*, 2019).

After six months, HIV infection enters the chronic phase. This phase progress slowly compares to the primary phase. The CD4 count will continuously drop and viral load will continuously increase with the time. The risk of a serious infection increases

with the CD4 count drops. The incubation period varies from less than 1 year to more than 15 years. It depends on many factors such as age, transmission risk and CD4 count (Chen *et al*., 2015).

1.1.1(c) Clinical disease stage

When the immune system strikes enough, the CD4 count becomes lower than 200, serious infection, opportunistic infection set in and the person develop AIDS. Among the sign and symptoms of AIDS are unknown cause of severe weight loss (>10% of presumed or measured body weight), unidentified reason of chronic diarrhoea for more than one month, and persistent fever without clear aetiology (over 37.6°C on and off or continuous, for more than one month), persistent oral candidiasis oral hairy leucoplakia, newly diagnose with pulmonary tuberculosis, very serious bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia), acute necrotizing ulcerative stomatitis, gingivitis or periodontitis, unknown cause anaemia or chronic thrombocytopenia, Kaposi's sarcoma (WHO, 2007).

AIDS progress faster in a person who has acute retroviral illness and shorter seroconversion time as compared to a person with longer seroconversion time(Spivak *et al.*, 2010). HIV incubation period varies between several months and can be up to 13 years. A study conducted among those who were bisexual and homosexual in Amsterdam, (using Markov model) revealed that the median time from seroconversion to AIDS was 8.3 years (95% CI, 8.1, 8.6). In this study they developed a model to predict median time according to CD4 level. Result revealed that the median time varied between 1.9 years with 95% CI (1.8, 2.3) and 10.9 years with 95% CI (10.7, 11.4) (Hendricks, 1999) . Another study in Guinea-Bissau, West Afrika reported the median progression time to AIDS was 6·2 years (95% CI 5·4, 7·1) in HIV-1- infected

person and 14·3 years (10·7, 18·0) in HIV-2- infected person (p<0·0001) (Esbjörnsson *et al.*, 2019).

1.1.1(d) Recovery, disability, death stage

Without treatment, all AIDS patients will die. During the early era of AIDS, in the absence of treatment, median survival time for AIDS were 26 weeks after the first presentation. A study conducted in Kelantan, Malaysia showed the overall median survival time for AIDS was 11 months (Ngah *et al.*, 2019). Another study in India showed median survival time for HIV patients from diagnosis was around 12 years from the date of HIV detection and around 4.3 years from the date of ART registration (Bajpai R *et al.*, 2014).

1.1.2 ARV and other prognostic factors of AIDS Progression

First ARV drug that has been used to treat HIV/AIDS was azidothymidine (AZT) in 1987. Due to its side effect, it was only approved to be used in an advanced HIV person. In 1996, a combination of 3 types of ARV called as highly active antiretroviral therapy (HAART) was proven to be effective. Within a few years of the initial International AIDS Society–USA recommendations being published, there was a significant reduction in morbidity and death associated with the increased usage of protease inhibitor-containing regimens. Initially the drug was very expensive which cost US$ 20 000 per person per year. The UNAIDS Drug Access Initiative was launched in December 1997 as a result of a dialogue initiated by Peter Piot of the Joint United Nations Programme on HIV/AIDS (UNAIDS) with the pharmaceutical industry in 1995 to work toward delivering antiretroviral therapies at reasonable prices in poor countries. This initiative enables the first patients treated with the drugs in Cote d'Ivoire and Uganda in early 1998. In 2000 the price for the first line regime was

US$1200. In 2003 , the cost decrease to US$ 150–250 per year for the first line regimens when fixed-dose combination therapies was introduced, giving the competition to pharmaceutical company (Vella *et al.*, 2012). The low cost of ARV made is accessible to many people.

Globally, at the end of 2019, 81% of PLHIV being diagnosed, and 67% of them were on ARV therapy. This equal to an estimated 25.4 million of the 38.0 million people living with HIV (World Health Organization (WHO), 2020).

ARV is effective in preventing AIDS progression. A study conducted in Canada observed that for every 100 individuals who were actively on ARV, the estimated AIDS rate decreased by 2.48% (estimated rate ratio 0.9752; 95% CI 0.9679; 0.9826) and for every 1% increase in the number of individuals suppressed on ARV, the AIDS rate decreased by 1.95% (estimated rate ratio 0.9805; 95% CI 0.9737; 0.9874) (Montaner *et al.*, 2014). Another study conducted in Brazil showed the incidence of AIDS is lower in ARV era as compared to pre-ARV era, where AIDS incidence decrease from 12.8 to 5.0 per 1000 person-years between 1992 and 2003 (Tancredi & Waldman, 2014) .

Apart from ARV, there are many other factors contribute to HIV disease progression. Among of them are transmission factors, CD4 count (Jiang *et al.*, 2013; Tancredi & Waldman, 2014), age (Jiang *et al.*, 2013; Hamidi *et al.*, 2017; Tancredi & Waldman, 2014), marital status, harm reduction (Luo *et al.*, 2019), educational level, black and brown skin colour (Tancredi & Waldman, 2014), nutritional status (Carter *et al.*, 2015) and psychological status (Yousuf *et al.*, 2020).

1.2 Problem statement and rationale of study

Pahang is the eighth state that reported the highest number of PLHIV cases in Malaysia(Anita & Chai, 2019). In the last 10 years, Pahang shows decline in reported HIV cases along with Terengganu and Kelantan. In 2019, Pahang only contributes 3.1% of overall new HIV reported cases;11th of the overall rank(Suleiman, 2019). Only 168 cases were reported in that year, which shows 56% decrement compared to reported cases in 2010, which was 382 cases.

However, yearly HIV report revealed that the number of AIDS cases in Pahang was still high. More than 100 AIDS cases were registered every year from 2011 to 2019 except in 2018 the number is slightly low (80 cases) although antiretroviral (ARV) has been given universally since 2006. Thus, is ARV program in Pahang not effective?

In line with sustainable development goal, Malaysia is aiming for ending AIDS by 2030 with 3 zero vision. The zeroes are zero new HIV case, zero discrimination and zero AIDS related death (Ministry of Health, 2015). To make this ambition comes true it is very important to know the factors affected AIDS progression in order to prevent AIDS and subsequently prevent AIDS related death.

As far as we know, there was no population-based study was published in regards to evaluate the effect of ARV on AIDS progression in Malaysia. This will be a baseline study for further research in the future. This study also may be used as a guideline for decision making in HIV control program specifically in Pahang.

1.3 Research Question

This research was conducted to answer below questions:

1. What is the median time for progression to AIDS among HIV – infected people in Pahang?
2. What is the effect of ARV upon disease progression?

1.4 Research Objectives

1.4.1 General Objective

To determine median progression time from HIV to AIDS and the effect of ARV on progression to AIDS among HIV-infected people in Pahang from 2011 to 2020.

1.4.2 Specific Objectives

1. To determine the median time for progression to AIDS among HIV – infected people in Pahang.
2. To determine the effect of ARV on progression to AIDS among HIV- infected people in Pahang

1.5 Hypothesis

1.5.1 Alternative Hypothesis

There is an association between ARV and progression to AIDS among HIV-infected people in Pahang.

CHAPTER 2

LITERATURE REVIEW

Literature search widely done in search engine such as PubMed using MeSH terms. A combination of keywords related to the subject of 'factors associated with progression to AIDS' were used with Boolean operators (OR and AND) in PubMed's advanced search builder. The entire literature searches published from 2010-2020 were included. Keywords used were HIV, AIDS, median time and associated factor.

2.1 HIV

2.1.1 HIV Virus

HIV virus and its subtypes are retrovirus and belongs to a large family of ribonucleic acid (RNA) lentiviruses. They cause a disease characterized by immunosuppression or central nervous system involvement and long latency before become symptomatic (Sierra *et al.*, 2005).

There are 2 types of HIV, HIV-1 and HIV-2. HIV -2 is less virulence and has slower acting (Whiteside, 2016). Their genetic sequences only partially homologous. A *vpu* gene in HIV-1, similar to SIV in chimpanzee, while the *vpx* gene in HIV-2 is like sooty mangabey retrovirus. Each type of HIV is further divided into several groups. HIV-1 has 4 groups; M, N, O and P. Group M is further divided into 10 subtypes. The genetic diversity between subgroups can be up to 30%. HIV-2 was first isolated in 1986 from Portuguese patient. However, this virus infection was most common in West African countries and barely found in Western Europe and other places that originated from West Africa. HIV-2 has 9 subtypes, labelled A through I. Group A is the most infectious worldwide and together with group B they account for pandemic spread. Both

HIV-1 and HIV -2 can be detected by enzyme immunoassay (EIA) and confirmatory assay (Seitz, 2016).

2.1.2 HIV Transmission

HIV was transmitted from human to human through 3 modes: 1) sexual, 2) parenteral 3) vertical (from mother to child through pregnancy, delivery of breast feeding). Sexual accounts for 75-85% of causes of HIV transmission. Table 2.1 below shows the risk of infection according to mode of transmission(Whiteside, 2016).

Table 2.1 Mode of transmission and the risk of infection

Mode of transmission	Risk of infection
Sexual transmission	
Female to male	1:700 to 1:3000
Male to female	1:200 to 1:2000
Male to male	1:10 to 1:1600
Fellatio	0 to 6:100
Parenteral Transmission	
Transfusion of infected blood	95:100
Needle-sharing	1:150
Needle stick	1:200
Needle stick/AZT PEP	1:10000
Transmission from mother to infant	
Without AZT treatment	1:4
With AZT treatment	< 1:10

Systematic review done in 2014 estimated the risk of transmission after 10000 exposure(Patel *et al.*, 2014). Table 2.2 shows the detail of estimation according to exposure routes.