# IMPACT OF VIRAL HEPATITIS ON CLINICAL OUTCOMES AND SURVIVAL TRENDS AMONG HIV/AIDS PATIENTS ON HAART AT HOSPITAL PULAU PINANG

**By**

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## *DEDICATION*

***I would like to dedicate my thesis***

***TO***

***MY COUNTRY…***

***MY FATHER…***

***MY MOTHER…***

***MY BROTHERS… and***

***MY FAMILY***

***For their unconditional love, encouragement patience and sacrifice during my study***

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**Ali Akhtar**

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| | |
|---|---|
| WHO | World Health Organization |
| UNAIDS | United Nations program on HIV/Acquired Immuno Deficiency Syndrome |
| HIV | Human Immunodeficiency Virus |
| AIDS | Acquired Immunodeficiency Syndrome |
| HBV | Hepatitis B |
| HCV | Hepatitis C |
| IVDUs | Intravenous Drug Users |
| HCC | Hepatocellular Carcinoma |
| ESLD | End Stage Liver Disease |
| HAART | Highly Active Antiretroviral Therapy |
| D4T | Stavudine |
| 3TC | Lamivudine |
| TDF | Tenofovir |
| EFV | Efavirenz |
| NVP | Nevirapine |
| AZT | Zidovudine |
| FTC | Emtricitabine |
| NRTI | Nucleoside Reverse Transcriptase Inhibitors |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitors |
| ARV | Antiretroviral |
| ALT | Alanine Transaminase |
| ALP | Alkaline Phosphatase |
| TAHOD | Treat Asia HIV Observational Database |

| | |
|---|---|
| CRC | Clinical Research Centre |
| NIH | National Institute of Health |
| MREC | Medical Research and Ethics Committee |
| HPP | Hospital Palau Pinang |
| SPSS | Statistical Package for Social Sciences |

# LIST OF PUBLICATIONS

## Journal Publications

1) **Ali Akhtar**, Amer Hayat Khan, Syed Azhar Syed Sulaiman, Chow Ting Soo, Muhammad Salman. Hepatitis B and HIV Co-infection: Prevalence and outcomes in Tertiary Care Hospital Malaysia. *Journal of Medical Virology* (Under review) Impact Factor 2.217

2) **Ali Akhtar**, Amer Hayat Khan, Syed Azhar Syed Sulaiman, Chow Ting Soo, Kashifullah Khan. Prevalence of HBV and HCV and their correlation with liver enzymes and CD4 cells among HIV positive individuals at Hospital Palau Pinang, Pinang, Malaysia
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3) **Ali Akhtar**, Amer Hayat Khan, Syed Azhar Syed Sulaiman, Chow Ting Soo, Kashifullah Khan. Influence of HCV Infection among HIV Positive Individuals Treated with Antiretroviral Therapy in Malaysia (Waiting for DG Health Malaysia Approval) {Targeted Journal: American Journal of Therapeutics (Impact Factor 1.290)}

### Conference Abstracts

1) Khan AH, Syed Sulaiman SA, **Akhtar A**, Adnan AS, Aftab RA
Impact of Hepatitis B on Human Immunodeficiency Virus Patients in Malaysia: A Retrospective Study. Abstract accepted at ISPOR 6th Asia Pacific Conference Beijing, China, 6-9 September 2014

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Chronic Hepatitis C Prevalence and its Correlation with CD4 Cells and Liver Enzymes among HIV Positive Patients: A Malaysian Scenario. Abstract accepted at ISPOR 6th Asia Pacific Conference Beijing, China, 6-9 September 2014

**KESAN JANGKITAN HEPATITIS DAN HASIL KLINIKAL SERTA TREND JANGKA HAYAT DI KALANGAN PESAKIT HIV/AIDS YANG MENGAMBIL UBATAN HAART DI HOSPITAL PULAU PINANG**

## ABSTRAK

Literatur yang sedia ada menunjukkan bahawa Hepatitis dengan atau tanpa Virus Kurang Daya Tahan (HIV) lazimnya berkongsi cara pemindahan dan masalah kesihatan awam yang utama di seluruh dunia. Matlamat kajian ini adalah untuk menilai prevalens HBV dan HCV di kalangan pesakit HIV positif, peramal yang terlibat dalam hasil klinikal dan trend kemandiran hidup di kalangan pesakit jangkitan bersama. Kajian ini termasuk 808 pesakit HIV positif dari unit penyakit berjangkit terlibat dalam kajian keratan rentas, retrospektif dari 2007-2012 yang dijalankan di Hospital Pulau Pinang (HPP). Data telah dikumpulkan melalui borang pengumpulan data yang disahkan.

Sejumlah 808 pesakit HIV positif telah dipertimbangkan untuk kajian ini dan dari jumlah itu, didapati 627 (77.6%) adalah lelaki dan 181 (22.4%) adalah perempuan. Kaum Cina merupakan kaum majoriti iaitu 500 (61.9%) pesakit berbanding dengan kaum Melayu iaitu 161 (19.9%) pesakit dan kaum India hanya mempunyai 104 (12.9%) pesakit. Secara keseluruhan, kebanyakan pesakit telah berkahwin dan ini merangkumi 380 (47.0%) orang, berumur di bawah 40 tahun iaitu 407 (50.4%) orang, perokok sebanyak 457 (56.6%) orang, bukan alkoholik sebanyak 499 (61.8%) orang dan penagih dadah bukan intravena pulak sebanyak 680 (84.2%) orang merupakan majoriti di kalangan populasi kajian. Cara pemindahan utama yang diperhatikan dalam kajian ini adalah melalui hubungan heteroseksual iaitu 572 (70.8%). Median (julat) kiraan sel CD4, ALT dan ALP populasi kajian ini masing-masing adalah 461 (11 - 956), 26 (6 - 226) dan 93 (44-495). Semua ubat rejimen yang digunakan dalam HAART untuk pesakit HIV adalah dari kumpulan nucleoside

Reverse transcriptase Perencat (NRTIs) dan Bukan nucleoside Reverse transcriptase Perencat (NNRTIs). Tenofovir (TDF) + Emtricitabine (FTC) + Efavirenz (EFV) merupakan pilihan gabungan dan diberi majoriti kepada pesakit iaitu 215 (26.6%) orang termasuk HIV-virus hepatitis B dan pesakit jangkitan bersama HIV-HCV. Dalam populasi kajian ini, didapati Tuberkulosis pulmonari adalah sebanyak 185 (27.4%), diikuti dengan pneumonia Pneumocystis 116 (17.2%) dan kencing manis 62 (9.2%). Prevalens keseluruhan HBV di kalangan populasi kajian ini adalah 86 (13%), termasuk 76 (11.4%) lelaki dan 10 (1.5%) perempuan. Majoritinya adalah kaum Cina 64 (9.6%), berumur 40 tahun ke atas sebanyak 48 (7.2%) dan bujang 42 (6.3%). Peramal yang terlibat dalam hasil klinikal jangkitan bersama HIV-HBV adalah jantina perempuan (OR = 2.015; p = 0.007), kumpulan umur > 40 tahun (OR = 0,559; p = 0.002), status perkahwinan bercerai (OR = 0.440; p = 0.039) dan bukan penagih dadah intravena (OR = 2,996; p = <0.001). Dalam trend hidup jangkitan bersama HIV-HBV, kadar kemandiran hidup didapati lebih tinggi dalam penagih dadah bukan intravena (p = 0.035). Didapati prevalens HCV adalah 18.4% di kalangan populasi kajian dan ini termasuk 122 (17.2%) lelaki dan 8 (1.1%) perempuan. Kaum Melayu 76 (10.7%) adalah majoriti di kalangan pesakit jangkitan bersama HIV-HCV diikuti dengan kaum Cina 36 (5.1%) dan India 14 (2.0%). Hasil klinikal pesakit jangkitan bersama HIV-HCV mempunyai peramal penting iaitu jantina perempuan (OR = 2.015; p = 0.002), kumpulan umur > 40 tahun (OR = 0,635; p = 0.007) dan bukan penagih dadah intravena (OR = 2,376; <0.001). Dalam trend kemandiran hidup pesakit jangkitan bersama HIV-HCV, didapati pesakit di bawah umur 40 tahun (p = 0,028) dan bukan penagih dadah intravena (p = 0.048) mempunyai kadar kemandiran yang lebih tinggi. Dalam populasi kajian ini, didapati prevalens jangkitan tiga kali ganda (HIV-HBV-HCV) adalah 2.4%.

Prevalens keseluruhan HBV adalah lebih rendah berbanding HCV di kalangan populasi kajian. Jantina, kumpulan umur dan pengguna dadah secara suntikan adalah peramal yang terlibat dalam hasil klinikal pesakit jangkitan bersama HIV-HBV dan HIV-HCV. Kadar kemandiran hidup yang lebih tinggi ditemui pada lelaki, penagih dadah bukan intravena dan berumur di bawah 40 tahun dalam trend kemandiran hidup pesakit jangkitan bersama.

**IMPACT OF VIRAL HEPATITIS ON CLINICAL OUTCOMES AND SURVIVAL TRENDS AMONG HIV/AIDS PATIENTS ON HAART AT HOSPITAL PULAU PINANG**

## ABSTRACT

The existing literature suggests that Hepatitis with or without Immunodeficiency Virus (HIV) shared common routes of transmission and major public health problems throughout the world. Aims of the present study are to evaluate the prevalence of Hepatitis B (HBV) and Hepatitis C (HCV) among HIV positive patients, predictors involved in the clinical outcomes and survival trends among cited co-infected patients. The present study includes 808 HIV positive patients from infectious disease unit in a retrospective, cross-sectional study from 2007 to 2012 conducted at Hospital Pulau Pinang (HPP). Data were collected through a validated data collection form.

Out of 808, there were 627 (77.6%) males and 181 (22.4%) were females. Chinese accounted for 500 (61.9%) patients in majority as compare to Malays accounted for 161 (19.9%) patients and Indians for a total of 104 (12.9%) patients. Majority of the patients were married 380 (47.0%), below the age of 40 years 407 (50.4%), smokers 457 (56.6%), non-alcoholic 499 (61.8%) and non-intravenous drug users 680 (84.2%) among the overall study population. The main route of transmission observed in the present study was heterosexual contact 572 (70.8%). The median (range) of CD4 cell count was 461 (11 - 956), ALT 26 (6 - 226) and ALP 93 (44 - 495) of the study population. All the regimens used in HAART for HIV patients were from Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) groups. Tenofovir (TDF) + Emtricitabine (FTC) + Efavirenz (EFV) were common choice in the majority of the

patients (215, 26.6%) including HIV-HBV and HIV-HCV co-infected patients. Pulmonary tuberculosis was observed 185 (27.4%) in the study population followed by Pneumocystis pneumonia 116 (17.2%) and Diabetes Mellitus 62 (9.2%). The overall prevalence of HBV among the study population was 86 (13%) including 76 (11.4%) males and 10 (1.5%) females. The majority was Chinese race 64 (9.6%), above 40 years of age 48 (7.2%) and single 42 (6.3%). Predictors involved in clinical outcomes of HIV-HBV co-infected patients were female gender (OR = 2.015; $p$ = 0.007), >40 years age group (OR = 0.559; $p$ = 0.002), divorced marital status (OR = 0.440; $p$ = 0.039) and non-intravenous drug users (OR = 2.996; $p$ = <0.001). Higher survival rates was found in non-intravenous drug users ($p$ = 0.035) in survival trends of HIV-HBV co-infected patients. HCV prevalence was found 18.4% among the study population including 122 (17.2%) males and 8 (1.1%) females. Malays accounted for 76 (10.7%) patients in majority among HIV-HCV co-infected patients followed by Chinese 36(5.1%) and Indians 14 (2.0%). Clinical outcomes of HIV-HCV co-infected patients have the significant predictors as female gender (OR = 2.015; $p$ = 0.002), >40 years age group (OR = 0.635; $p$ = 0.007) and non-intravenous drug users (OR = 2.376; <0.001). In survival trends of HIV-HCV co-infected patients higher survival rates was found in patients below 40 years of age ($p$ = 0.028) and non-intravenous drug users ($p$ = 0.048). Prevalence of triple infection (HIV-HBV-HCV) was found to be 2.4% in the study population.

The overall prevalence of HBV was lower than HCV among the study population. Gender, age groups and intravenous drug users are the predictors involved in the clinical outcomes of HIV-HBV and HIV-HCV co-infected patients. Higher survival rates were found in males, non-intravenous drug users and below 40 years of age patients in survival trends of the co-infected patients.

# CHAPTER 1

# INTRODUCTION

Human immunodeficiency virus (HIV) is a Ribonucleic acid (RNA) retrovirus that destroys and harms the cells of the human immune system by impairing their function (WHO, 2007a). Hepatitis B Virus (HBV) is a member of hepadnaviridae family and is a small virus having a partially double-stranded relaxed, circular DNA genome (Block *et al.*, 2007). Hepatitis C virus (HCV) belongs to flaviviridae family and it is hepatotropic RNA virus of the genus Hepacivirus (Kim *et al.*, 2013).

## 1.1 Human Immunodeficiency Virus (HIV)

### 1.1.1 Epidemiology

In past two decades, human immunodeficiency virus (HIV) has stormed across the world. Currently there are about 34 million people living with HIV and the death rate of people with AIDS since the starting of the epidemic is nearly 30 million (UNAIDS, 2012). However, in the year 2011, about 1.7 million people died of AIDS and there is a decrease of 24% since 2005 and of 20 % since 2001 in middle income countries while in East Asia there were 5 million people living with HIV. Furthermore, the two most populated nations like China and India there are relatively low frequency rates of HIV infections even into large numbers of people (UNAIDS, 2012). Over 20,000 HIV cases have stated since 1980 and half of them have died. In December 2011, total 20,091 HIV cases have been stated and among all 34% were female and 66% were male throughout the world (Mullen *et al.*, 2013).

In the United States, the epidemiology of HIV has transformed pointedly from the early 1980s. This disease is presently a disease of demographic variety and affecting many factors like genders, races, ages and including several behaviors that can transmit the risks of HIV infection and there are at least 50,000 new HIV infected cases reported each year and one-fifth of them do not know that they are HIV infected which is a alarming scenario (Moore, 2011). The estimated death rate of HIV infection is 15,529 people in the year 2010 and overall 636,000 people diagnosed with AIDS in the United States (CDC, 2013).

The first case of HIV in Malaysia was in 1986 when a Chinese male of 45 years old of an American origin was visiting the country and fell ill (UNGASS, 2010). The World Health Organization reports that Malaysia has been classified as "a concentrated epidemic" due to the persistent progression of HIV infection in the population of Injecting Drug Users. Moreover, a study showed that if no cautious plans and schemes been taken effectively against the increased growth of HIV infection, then in the year 2015 up to 300,000 HIV cases would be reported in Malaysia (Tham *et al.*, 2012).

### 1.1.2 HIV Transmission

HIV transmission at high risk in general population involves several transmitting routes like injecting drug users, female sex workers and men who have sex with men (Mumtaz *et al.*, 2013). HIV transmission also involves exposure to contaminated blood, sexual contact, from mother to child during pregnancy and breast milk (Bourinbaiar *et al.*, 1991).

In Malaysia the key way of HIV transmission is basically the use and sharing of needles by using intravenous drugs and secondly through heterosexual contact (Choy *et al.*, 2012). A survey conducted by the Ministry of Health in Malaysia showed that there were some delusions about transmission and prevention of HIV/AIDS in the country (Aung *et al.*, 2013).

### 1.1.3 Pathogenesis

HIV infection involves a single target cell infected with single virion entering the host cell. The ensuing course of infection can be examined in various ways like monitoring the symptoms such as adaptable infection, fever, blood levels of targeted cells and so on usually measured by PCR for viral RNA (Coffin *et al.*, 2013).

The pore formation is basically the actual fusion that takes place within minutes and with the help of reverse transcriptase enzyme the genome is reverse transcribed just after the core is disassembled. During this process various viral variants can be produced until the enzyme has no proof reading activity. As the molecules in the cytoplasm of the producer's cells and components of the cell surface that is actually a lipid bilayer are combined with new viral particle, the virions adapt the characteristics of the cells in which they were produced. The host cell molecules can determine the virus' phenotype in different ways like shape and replicative features in the next infection cycle (Simon *et al.*, 2006).

## 1.2 Hepatitis B Virus (HBV)

### 1.2.1 Epidemiology

The World Health Organization estimates that about 2 billion of the worldwide population exposed to HBV infection and 450 million people are infected chronically. While the occurrence of HBV infection is 45 % of the world population that includes Moldova as well and the rate of HBeAg detection is 8% and greater in the infected publics (Iarovoi *et al.*, 2008). The worldwide epidemiology of HBV shows that the number of HBV infected people is 360 million with chronic infection and the death rate is of HBV related diseases is 600,000 (Shepard *et al.*, 2006).

Some studies estimated that 350 million carriers having chronic infections of HBV are present globally and its occurrence varies in different regions showing various frequencies like from high (more than 8%), intermediate (2 to 7%) and low (less than 2 %) (Hou *et al.*, 2005). In common population the incidence of chronic HBV infection in Ireland and the Netherlands is ranges from 0.2% to 7 % (Hatzakis *et al.*, 2011). Hepatitis B virus infection is widespread in Asia with 50 % infected population and shows its high progression in China, Hong Kong and Malaysia (Kawsar *et al.*, 2002).

### 1.2.2 Transmission

The transmission route of HBV is sexual and percutaneous just like HIV so both have common routes of transmission (Thio, 2009). The two main routes of transmission of HBV are sharing needles and homosexuality (Sheng *et al.*, 2004).

According to the World Health Organization, the HBV transmission modes are through blood or body fluids of an infected person just like the transmission of HIV. Furthermore, there are several ways for HBV transmission like sexual contact, perinatal, mother to child and through insecure use of injections and transfusions (WHO, 2014).

### 1.2.3 Pathogenesis

HBV is a kind of noncytopathic virus and there are various factors that influencing the pathogenesis of HBV including its co-infection with other viruses most particularly of HIV and Hepatitis C (HCV) while there is a difference between the controlling of patients infected with dual viruses and patients infected with a single virus (Cheruvu *et al.*, 2007). There are eight genotypes of HBV from (A-H) varying geographically and have impact on disease progression and outcomes of treatment and the disease expressions during chronic HBV infection depend on the balance between the virus and immune responses of the host (Puoti *et al.*, 2006).

## 1.3 Human Immunodeficiency Virus and Hepatitis B Virus Co-infection

Studies reported that about 10% of HIV infected patients are co-infected with chronic HBV although the occurrence of HIV-HBV co-infection differs globally (Kellerman *et al.*, 2003; Uneke *et al.*, 2005). There are more than 350 million individuals having HBV infection chronically worldwide (WHO, 2007) and nearly 33 million people are HIV infected (UNAIDS, 2008). In United States the estimated rate of HIV infected individuals is 1.25 million (Te *et al.*, 2010). There are higher rates of co-infection detected in the areas having common prevalence of chronic HBV infection like in Asia and Sub Saharan Africa (Uneke *et al.*, 2005). Chronic

HBV infection in the United States is not common and the rate of this infection is greater among the adults having intravenous and sexual transmission routes (Brito *et al.*, 2008). It is estimated that 10 % persons of HIV infected patients out of 40 million are co-infected with chronic HBV throughout the world (Thio, 2009).

In HIV co-infected patients, the progression of hepatitis B is categorized through the increased frequency of active viral replication. There is a continuous reduction in CD4 cell counts as certainly the viral replication is enhanced and linked to reduced cellular immune response in contrast of HBV in the progression of untreated HIV infection. Furthermore, there is a reduction in inflammation reaction and normal or slightly levels of liver enzymes are elevated in response to weak immune response (Boesecke *et al.*, 2010).

HIV and HBV have shared mode of transmission so their co-infection is very common (Thomas *et al.*, 1994). In HBV infected individuals the treatment outcome of HIV-1 infection is not understood properly. Some studies reported that there is a reduction in the development of liver disease and might be predictable since the pathogenesis of HBV infection is supposed to be mediated immunologically (Thio *et al.*, 2002; Webster *et al.*, 2000).

In HIV infected patients, the HBV infection is considered as opportunistic infection and this co-infection can cause severe interactions because HIV weakens the cellular immunity following a greater replication of HBV infection increases replication of HIV by stimulation of transcriptional factor and inflammatory cytokines (Sheng *et al.*, 2004).

In the United States and Western Europe, the infection of HBV is acknowledged in 5 to 16 % of the persons infected with HIV (Alter, 2006; Thio, 2003). Co-infection of HIV and HBV enhanced the risk of liver-related morbidity. However, HIV induced the weakening of innate and adaptive immunity so lower occurrences of natural loss of HBV surface antigen (HBsAg) have been observed (Kim *et al.*, 2012). Natural history of hepatitis B virus changes by the co-infection of HIV-1 with higher serum HBV DNA and lower levels of alanine aminotransferase (ALT) leading the increased rates of cirrhosis predominantly in those individuals with low CD4 T cell counts (Lewin *et al.*, 2009).

The levels of viral replication in chronic hepatitis B virus carriers relates with the existence of detectable antigen of HBV in serum. In the reported studies related to co-infection of HIV with HBV carriers the frequency of loss of HBeAg positivity determined the natural history of HBV replication. In HBV carriers among HIV infected persons there is a lower rate of tendency has been reported. In a study another measure of viral replication in the lowering rate of detectable HBV DNA in serum was found to be considerably reduced in HIV-infected HBV carriers (Gilson *et al.*, 1997).

The HBV and HIV co-infection enhances the mortality as well as morbidity in comparison with those caused by other mono infections (Hoffmann *et al.*, 2007). There are higher levels of hepatitis B viremia in individuals co-infected with HIV. Moreover, approximately five times fast progression to hepatitis B infection, hepatocellular carcinoma and cirrhosis in patients with HIV as compare to individuals infected with only hepatitis B virus (Kourtis *et al.*, 2012).

## 1.4 Hepatitis C Virus (HCV)

### 1.4.1 Epidemiology

It is estimated that 130 million people are infected with HCV globally. In addition, the occurrence of HCV is about 27% of cirrhosis and 25% of Hepatocellular carcinoma (HCC) worldwide (Alter, 2007). Both the temporal and geographic differences are there in the trends of HCV infections. Overall general average prevalences (1.0%-1.9%), of HCV infections have been seen in various countries like United States (Alter, 2002), Spain (Domínguez *et al.*, 2001), Australia (Dore *et al.*, 2003), Italy (Sagnelli *et al.*, 2005) and Japan (Sun *et al.*, 2001). The reported rate of high prevalence (15%-20%) of HCV infection is in Egypt (Abdel-Aziz *et al.*, 2000) and lowest widespread (0.01%-0.1%) is in the Scandinavia and the United Kingdom (Frank *et al.*, 2000; Shepard *et al.*, 2005). Globally it is estimated that about 150 million people are infected with HCV and about 350,000 deaths occur due to HCV (Zidan *et al.*, 2012).

### 1.4.2 Transmission

The main mode of HCV transmission is repetitive percutaneous exposure to blood through injecting drug use and transplantation or transfusion from infected donors. A less active mode of HCV transmission is through mucosal contacts to serum-derived fluids (e.g. sexual contact with an infected partner) or blood and by needle sticks (Alter, 2007). The main route of childhood HCV transmission is from mother to infant and this transmission is ranges from 3% to 10%. The transmission risk is high among the women at delivery and HIV co-infected (Cottrell *et al.*, 2013). About 20 % of HCV infections are not explained particularly in non-injecting drug users (Aaron *et al.*, 2008). About 20 % of patients with HCV denied the common

risk factors like intravenous drug use and other exposures although the main route of transmission for HCV infection was intravenous drug use (Tohme *et al.*, 2012).

### 1.4.3 Pathogenesis

There are several diseases related with HCV infection like hepatocellular carcinoma, fibrosis and autoimmune diseases and considering the immune responses from other members of the Flaviviridae family. HCV is classified as a member of a genus Hepacivirus based on the similar patterns of hydrophobicity and homology (Chambers *et al.*, 1990; Houghton *et al.*, 1991). After the prime infection of flavivirus the persistent infection is infrequent in addition with HCV. The previous trends of chronic HCV infection are those with prolonged lobular inflammation and portal tracts of changing severity. The composition of infiltrate is primarily CD8+ T cells (Marrogi *et al.*, 1995). In chronic HCV hepatitis there is an acidophilic degeneration inside the intact plates and formation of apoptotic bodies shown by hepatocytes. Proliferation and damage to the bile duct may also happen. Hepatitis C virus can act with iron to stimulate liver damage (Freeman *et al.*, 2001).

## 1.5 Human Immunodeficiency Virus and Hepatitis C Co-Infection

Globally estimated rate of infections caused by Hepatitis C was 130 million with an overall prevalence of 3% and about 4 to 5 million people are co-infected with HIV. Moreover, the prevalence of HCV among injection drug users (IDU) is about 72% to 95 %, 1% to 12% in MSM (in men who have sex with men) and 9% to 27% in heterosexuals among HIV infected persons in the US and Western countries (Alter, 2006). There are 15 to 45 % persons clear the HCV virus after acute infection and the rate of individuals is 20% to 30% with persistent viremia develop liver

fibrosis, and potentially cirrhosis, following liver failure, and hepatocellular carcinoma (Operskalski *et al.*, 2011).

The occurrence of HCV co-infection in individuals infected with HIV is high and ranges from 10 to 40%, and can be increased up to 80 % in highly exposed regions (Cohen, 1999; Greub *et al.*, 2000). Both the HIV and HCV are having shared transmission routes particularly through injection drug use and the receipt of blood transfusions or products so there is a high association in HIV and HCV co-infection. Furthermore, in AIDS defining events there found an increased progression of death rates in co-infected patients with HCV (Anderson *et al.*, 2004).

It is reported in most studies that HIV has adverse effects on natural history of hepatitis C virus infection and there is an association between HIV infection with higher HCV viral loads, hepatitis B virus persistence and increased risk of end stage liver disease (ESLD) in most studies (Bica *et al.*, 2001; Martín-Carbonero *et al.*, 2001; Thomas *et al.*, 2000). The levels of HCV-RNA become higher after co-infection with HIV. Literature shows that in HIV infected patients the HCV-RNA levels are higher with lower CD4+ counts than 200/$mm^3$as compared to patients infected with HIV having higher CD4+ counts (Thomas, 2005; Thomas *et al.*, 1996).

The infection of hepatitis C virus is frequently prevalent in the population of HIV infected individuals with one third of Americans infected with HIV and worldwide 7 million are being co-infected (Soriano *et al.*, 2010). Now the leading cause of death is chronic HCV infection after the complications associated with AIDS among the individual of HIV infection in the regions where highly active antiretroviral therapy (HAART) is available (Taylor *et al.*, 2012).

HIV-HCV co-infected individuals have numerous consequences for clinical administration and care; First of all there is a high viral load of HCV in HIV co-infected individuals. Secondly the risk of hepato-toxicity increases with hepatitis C virus under ART, predominantly with drugs like, nevirapine and can affect the choice of timing and therapy. Thirdly, there might be precipitation in Hepatitis C virus immune reconstitution occurrences by the use of HAART in HCV infected persons, and may also be reduced immune recovery in co-infected individuals (Yami *et al.*, 2011).

In HIV-HCV co-infected patients, there is a reduction in HCV specific T-cell responses, an outcome consistent with a higher rate of development to chronicity in these patients (Rehermann, 2007). The responses of T-cell in chronic hepatitis C are usually weak. There is weaker $CD4^+$ and $CD8^+$ responses seem in co-infected patients and even after CD4 cell counts recover in response to HAART, these responses are not restored (Rotman *et al.*, 2009).

On the pathogenesis of hepatitis C virus infection the effects of HIV-1 are harmful and contain a higher rate of viral persistence and hepatic decompensation, increased rates of viral loads and a faster rate of fibrosis progression (Kim *et al.*, 2009).

Literature shows that there are higher levels of HCV in the blood of HIV infected patients following a rapid progression to liver diseases related to hepatitis C virus and higher risk of liver disease and cirrhosis. In addition, HCV is now considered as adaptable infection in HIV infected people (Martín-Carbonero *et al.*,

2001). Strader (2005) reported that in HIV-HCV positive patients, an increased progression in liver diseases related to hepatitis C virus and the effect of HCV on the development of HIV infection seems to be minimal to modest.

### 1.6 Highly Active Antiretroviral Therapy (HAART)

The name given to the insistent treatment regimens used to stop the development of HIV disease and to suppress replication of HIV virus is Highly Active Antiretroviral Therapy (HAART). According to WHO, antiretroviral therapy course of action, lower CD4 count or below 350 cell/$mm^3$ in all HIV infected patients should be started on ART (WHO, 2010a). The area of HIV medicine is continuously changing and developing. The improvements made in more than last two decades have reformed. All the medication and preventive cares necessary for antiretroviral therapy are not available in all regions (Samuel *et al.*, 2006).

Antiretroviral drugs were introduced Malaysia in different stages; in 1989 zidovudine was available followed by didanosine and zalcitabine in early 1990s and stavudine and lamivudine in mid 1990s and HAART drugs were available in 2006 in Malaysia and are of three types named as NRTI, NNRTI and PI (Shah *et al.*, 2012). There were three specific drugs authorized as "government use order" providing to all government hospitals were didanosine, zidovudine and the combination of lamivudine and zidovudine since 2004 (UNGASS, 2010). On the basis of patient-centered outcomes highly active antiretroviral therapy has been seemed to be cost effective (Montaner *et al.*, 2006).

Modifications in the treatment of HIV infection, predominantly in the HAART have very much decrease mortality and enhanced the quality of life for a

number of HIV/AIDS positive individuals. In addition, several studies in the recent years reported their concern on the factors related with the non-adherence to HAART and also examined the procedures of predicting medication adherence noticeably less consideration has been dedicated to how adherence changes over time (Carrieri *et al.*, 2001; Howard *et al.*, 2002; Levine *et al.*, 2005).

About 10 % of the patients experience a drug related liver injury after the initiation of HAART with an increase level of liver transaminases up to five times than the normal limit (Vogel *et al.*, 2007). Luckily, most of the elevations of liver transminases are only temporary and rarely direct to clinically severe symptoms or the termination of HAART . There is an increase risk of HAART related toxicity in the patients co-infected with HCV therefore, if possible then antiretroviral drugs like stavudine, didanosine and full-dose ritonavir with high risk of hepatotoxicity should be avoided (Qurishi *et al.*, 2003). In general the significance of HAART is far compensating the risk of hepatotoxicity. This is possibly on account of immune reconstitution of highly active antiretroviral therapy (Vogel *et al.*, 2008).

It has been always challenging to decide that when to start treatment in an HIV-infected individual. On the other hand, initiation of treatment should be started at any beginning point of the course of disease, earlier to a time when loss of CD4 cells is such that there is a considerable risk of clinical development (Clumeck *et al.*, 2008). Evidence suggest there were low clinical progression rates although the CD4 cell count remained more than 200 cells/µl but also increased quickly at lower levels, strategies of most initial treatment suggested that there would be delayed in treatment until the CD4 cell count had fallen below 200 cells/µl (Sabin *et al.*, 2009).

The majority of doctors trained in treating HIV in Malaysia considering the antiretroviral (ARV) strategies released by WHO which suggested that all patients start antiretroviral therapy when their CD4 count lower to 200 cells/ mm3 or lower, at which position many previously show symptoms of HIV disease and other opportunistic infections. Moreover, the usual ART treatment of choice at present practiced in Malaysia comprises of the combination of two nucleoside reverse-transcriptase inhibitors (NRTIs), in general either zidovudine (AZT) + lamivudine (3TC) or stavudine (d4T) + 3TC with a nonnucleoside reverse-transcriptase inhibitor (NNRTI), normally either nevirapine (NVP) or efavirenz (EFV ). However, a generic combination of triple drug which is extensively accessible and of low cost called SLN (stavudine + lamivudine + nevirapine) (WHO, 2010b).

## 1.7 Problem Statement

For over years, people all over the world have debated about the association between human immunodeficiency virus and chronic viral hepatitis. Patients with human immunodeficiency virus can be under a great risk to develop viral hepatitis especially in those with lowered CD4 counts. Therefore, the ignorance of this problem may lead to serious health complications with increased risk of mortality rate in human immunodeficiency virus infected population. All these factors prompt the efforts to investigate the prevalence of Hepatitis B and C among HIV/AIDS patients, associated risk factors involved in the clinical outcomes and survival trends of HIV-HBV and HIV-HCV co-infected Malaysian population.

## 1.8 Rationale of the Study

The link between human immunodeficiency virus and chronic viral hepatitis is considered controversial, therefore, many questions to be addressed related to this association. Best to researcher's knowledge there is no published data that investigate the association between human immunodeficiency virus and chronic viral hepatitis (B and C) in Malaysia. Furthermore, internationally very limited data is available on survival trend among HIV/AIDS patients with viral hepatitis co-infection. Based on this information, the current study is aimed to evaluate the epidemiological connection between human immunodeficiency virus and chronic hepatitis (B and C) among the Malaysian population. Moreover, present study investigates the associated factors involved in the clinical outcomes and survival trends of HIV-HBV and HIV-HCV co-infected patients which are being treated with HAART.

## 1.9 Significance of the Study

The results of the current study provide the baseline data for future studies that focused on the association between the human immunodeficiency virus and chronic viral hepatitis. Moreover, current study may support the background of practitioners about the possibility of developing chronic viral hepatitis especially hepatitis C among the human immunodeficiency virus infected population. It could also help to reduce the hepatitis occurrence in human immunodeficiency virus infected patients by attracting the attention of the involved risk factors and to avoid the clinical complications of HIV and Hepatitis association. On the other hand, present study also gives an idea for HIV infected patients and possible risk factors involved in the clinical outcomes and survival trends of the patients due to these combinations.

## 1.10 Study Objectives

1) To determine the prevalence of hepatitis B among HIV population of the study
2) To evaluate the prevalence of hepatitis C among HIV infected population of the study
3) To determine factors that involved in the clinical outcomes of the study population.
4) To evaluate the survival trend among HIV/AIDS and Hepatitis co-infected population.

# CHAPTER 2

# LITERATURE REVIEW

Following chapter aims to shed light on previously conducted studies, on prevalence of Hepatitis B and C among HIV/AIDS patients; predictors involved in the clinical outcomes of HIV-HBV and HIV-HCV co-infected patients and survival trends of HIV-HBV and HIV-HCV co-infected patients.

## 2.1 Prevalence of Viral Hepatitis among HIV infected individuals

Mohammadi *et al.* (2009) conducted a descriptive, cross-sectional study from January 2007 to January 2008 in Iran reported the prevalence of HBV and HCV among the HIV positive patients. In that study 391 HIV positive individuals were included in which 358 were males and 33 were females. The prevalence of HBV was observed in 57 (14.5%) and HCV in 282 (72%) of the total study population. Study concluded that 72% of the patients were HIV-HCV co-infected and 14.5% patients were co-infected with HIV-HBV. A significant correlation was seen in the co-infected patients depending on different variables which include age, sex, marital status, occupation, exposure.

An epidemiological study conducted in Zambia by Kapembwa *et al.* (2011) to assess the prevalence of HBV and HCV among HIV infected patients. Researcher included 323 HIV infected patients in a tertiary care hospital of Lusaka, Zambia. Demographic, medical and laboratory data was collected to determine the risk factors of co-infection. Out of 323 HIV infected patients 32 (9.9%) were co-infected with HBV and 4 (1.2%) co-infected with HCV. Patients with hepatitis B co-infection were more likely to be <40 years (84.4% vs. 61.4%; $P = 0.01$) as compared to HIV mono

infected patients. Mild to moderately increased AST/ALT (40-199 IU/L, 15.8% vs. 5.4%; $P = 0.003$) was observed in patients co-infected with active hepatitis B. Risk factors associated with HCV co-infection was not determined in this study due to low prevalence of disease. Study concluded that the regular screening of HIV infected patients for hepatitis B virus in southern Africa.

A study in Gambia to determine the seroprevalence of HBV and HCV in HIV-infected subjects as the prevalence of HIV-Hepatitis co-infection is not well documented in sub-Saharan Africa. A total of 190 individuals with AIDS and 382 without AIDS patients were tested retrospectively for the presence of HBV and HCV co-infection. The prevalence of HBV in HIV-positive subjects was 12.2%. The CD4 count <200cells/μL had higher HBV DNA viral load as compared to higher CD4 count (log 4.0 vs. log 2.0 DNA copies/ml, $p < 0.05$) in HIV-HBV co-infected individuals. Seroprevalence of HCV was 0.9% among HIV-infected patients. The prevalence of HBV carriers in general population is similar to the HIV infected Gambians while HIV-HBV co-infected population had lower CD4 count and elevated liver enzymes as compared to the general population (Jobarteh *et al.*, 2010).

Yanagimoto *et al.* (2012) conducted a retrospective multicentre analysis in Japan reported that 6% of HIV infected individuals were co-infected with hepatitis B after that they included 252 patients infected with HIV from six hospitals of Japan. The main route of transmission was observed in homosexual contact followed by heterosexual contact [186 of 252; (74%)], the mean age of patients was 39.5 ± 9.6 years and the proportion of males was very high as compared to females [243 of 252; 96%)]. Advance liver disease with the complication of ascites, hepatocellular

carcinoma and hepatic encephalopathy developed in three patients among 252 HIV-HBV co-infected patients. A comparison between treated patients with antiretroviral treatment along with anti-HBV drugs and untreated patients the liver function was worse in the patients who were treated than untreated however, platelet counts and albumin levels were similar observed in both groups. Study concluded that the antiretroviral treatment along with anti-HBV drugs in HIV-HBV co-infected patients may retard the progression of the disease and prevent liver related death in such co-infected patients.

The prevalence of HBV co-infection in HIV positive individuals and its impact on all-cause deaths, progression of disease, liver related deaths and its response towards antiretroviral treatment was assessed by Konopnicki *et al.* (2005). Data was collected from 72 European HIV centers included 9802 patients. Global mortality and liver-related mortality, incidence of AIDS, time to viral load <400 copies/ml and time to 25% CD4 cell count increase after initiation of the HAART treatment and then compared between HBsAg negative and positive individuals. Total 498 (8.7%) patients were found to be HBeAg positive. The incidence rate of newly diagnosed AIDS patients was similar in HBeAg negative and positive patients (3.4 and 3.3/100 person-year respectively). The incidences of liver related and all-cause morbidities were significantly greater in HBeAg positive patients (0.7 and 3.7/100 person-years respectively) as compared to HBeAg negative patients (0.2 and 2.6/100 person-years respectively). In 1679 patients HBeAg status did not influence immunological or viral responses after the initiation of HAART. The study concluded that the prevalence of HBV among HIV individuals was 9% and chronic

infection of HBV significantly increases liver-related mortality in HIV-1 infected population.

A cross-sectional study was conducted to evaluate the prevalence of HBV in HIV infected patients and impact of antiretroviral therapy in Thailand. A total of 403 individuals were enrolled with mean age of 42.3 years and 60.3% were male. HBV co-infection was observed in 33(8.2%) patients with median (IQR) CD4 cell count of 395 (277-555) cells/$mm^3$. The patients receiving ART had the prevalence of HBV 6.1% and the prevalence without ART was 11.4%. The AST levels before the initiation of ART (OR = 1.020, 95% CI (1.007-1.034); p = 0.003) and undetectable HIV RNA at the time of screening (OR = 0.243, 95% CI (0.068-0.870); p = 0.030) were significantly associated with the HBV co-infection. HBV co-infection was not significantly associated with the liver enzymes. The study concluded that the screening of HBV among HIV individuals should not be omitted and screening should be performed before the initiation of the ART (Chotiprasitsakul *et al.*, 2010).

Adewole *et al.* (2009) carried out a study in National hospital in Abuja, Nigeria to evaluate seroprevalence of hepatitis B and hepatitis C among HIV infected patients and its impact on pattern of presentation. Total 260 HIV positive patients were enrolled in the study to figure out the prevalence of HBV and HCV. Patients were co-infected with HBV were 30 (11.5%) while 6 (2.3%) were co-infected with HCV however, only 4 (1.5%) were triple infected observed in the study and the overall prevalence of viral hepatitis among HIV positive patients was 15.4%. Patients younger than 40 years of age were more affected in study and the odd ratios for females being co-infected was 1.2 (25% Vs 75%) with the *p* value of 0.03. There

was no significant difference in the mean levels of liver enzymes (ALT, AST) among the difference cohorts. In co-infected groups the mean CD4 count was (106cells/$mm^3$) significantly differs as compared to the HIV mono-infected patients (171cells/$mm^3$). The highest value of CD4 count (260cells/$mm^3$) was observed in HIV-HCV co-infected patient. Adewole concludes that the HIV-HCV prevalence may be due to intravenous drug abusers and HIV-HBV co-infection was common in present study which should be under major consideration before the starting and choice of therapy.

Anbazhagan *et al.* (2010), carried out a study in south Tamil Nadu, India to evaluate the seroprevalence of HCV among HBV, hepatitis delta virus (HDV) and HIV positive patients. Among 1012 samples, 512 were clinically diagnosed with liver diseases and 500 were apparently healthy individuals were enrolled for HCV screening. The seroprevalence of HCV among study population was found to be 29 (5.6%). Co-infection of HCV-HBV, HCV-HIV, HCV-HBV-HIV were found in 8, 6 and 4 patients respectively. The majority of the patients were males in HCV-HBV co-infection and females were in the majority in HCV-HIV and HIV-HBV-HCV co-infections. The mean AST and ALT levels in HCV positive patients were 49 ± 10.1 and 42.1 ± 8.3 IU/L respectively. In HCV-HBV, HCV-HIV, HCV-HBV-HIV co-infected patients the mean ALT level was 58.0 ± 03.16, 56.78 ± 4.401 and 64.37 ± 4.01 IU/L respectively. Study concludes that the routine screening of HCV should be done in addition to HIV and HBV and regular surveillance to monitor and prevent these types of blood-borne viruses.

Seyed Alinaghi *et al.* (2011) conducted a study in Iran during 2004-2005 to determine the seroprevalence of HBV and HCV among HIV infected individuals. A

total of 201 blood samples were taken from HIV positive patients to evaluate the prevalence of HBV and HCV. 27 (13.4%) patients were HBsAg positive, 60 (29.8%) were anti-HBc positive and anti-HBs was observed in 23 (11.4%) patients. Anti-HCV Ab positive patients were 135 (67.2%). The majority of HIV-HBV and HIV-HCV co-infected patients were intravenous drug users; 61.2% and 85.1% respectively ($p$<0.0001). The minimum prevalence of both HBV and HCV among the study population were observed in HIV patients wife's (8%) ($p$<0.0001). Present study concluded that the co-infections with HBV and HCV were significant with the HIV/AIDS in Iran and suggested to evaluate the risk factors involved in these co-infections.

Reuter *et al.* (2011), established a prospective study to evaluate the prevalence and characteristics of hepatitis B and C among HIV positive treatment-naïve individuals. A total of 918 patients were enrolled in the study from RESINA-cohort, Germany. All clinical parameters and blood samples were taken prior to start the antiretroviral therapy. HBV, HBsAg and HBV DNA were found in 43.4% (398/918), 4.5% (41/918) and 6.1% (34/554) patients respectively. HCV positive patients were 10.6% (97/918) in the study. HCV positivity was associated with non-African ethnicity, IVDU route of transmission, abnormal liver enzymes elevation and low viral load of HIV. Both HBV and HCV correlated with HIV resistance mutations ($p$ = 0.001 and $p$ = 0.028). Study concludes that the prevalence of HBV and HCV among HIV treatment-naïve patients was very high. Moreover, the patients should be routinely screened for HBV and HCV before the initiation of HIV treatment. HIV resistance mutations were significantly associated with the HBV and HCV positive status.

## 2.2 Clinical outcomes of HIV and viral hepatitis co-infected patients

Zhou *et al.* (2007) established a study in the Asia-Pacific region to determine the prevalence of HBV and HCV, their impact on antiretroviral therapy and rate of mortality among the HIV positive individuals using the data from The TREAT Asia HIV Observational Database (TAHOD). Among 2979 TAHOD patients, the overall prevalence of HBV and HCV both was approximately 10%. After initiation of antiretroviral therapy the mean CD4 count after 180 days was118.8cells/µL while the patients co-infected with either HBV or HCV had lower but non-significant increase in the CD4 count as compared to HIV mono infected patients. Median time was 148 days to reach undetectable viral load (<400 copies/mL) and was not associated with either HBV or HCV. The patients co-infected with HCV had increased mortality (unadjusted hazard ratio, HR 2.80, *P=0.007*) using univariate analysis. However, there was no association between HBV and HCV with the increase in the mortality rate. In the multivariate model both HBV and HCV showed independently associated with the increase in the level of Alanine transaminase (ALT). The study concluded that the impact of hepatitis on virological and immunological responses and disease progression among this Asian cohort are similar to that reported in the western countries. Morbidity and mortality needs to be monitored among these co-infected patients.

A study was conducted in central Italian prisoners by La Torre *et al.* (2007) from the period of 1995 to 2000 to determine HIV, HBV and HCV co-infection determinants. HIV-HBV, HIV-HCV and HBV/HCV co-infections were observed in 31 (2.9%), 42 (4%) and 203 (17.9%) inmates, respectively. These co-infections were significantly associated with the smoking habits (OR = 3.73; p = 0.033; OR = 1.42; p

= 0.088; OR = 4.25; p = 0.053), status of drug addiction (OR = 16.02; p = 0.012; OR = 4.15; p < 0.001; OR = 23.57; p = 0.002) and Italian nationality (OR = 7.05; p = 0.009; OR = 2.31; p <0.001; OR = 4.61; p = 0.04). Informational and educational programs for inmates reduce the prevalence of such infections in jails.

Mendes-Correa *et al.* (2011) established a study in Brazil to evaluate the clinical and virological variables associated with HBV viremia and HBeAg status in HIV-HBV co-infected patients. A retrospective cross-sectional study was conducted in two outpatient clinics located in Sao Paulo, Brazil included HIV-HBV co-infected patients which were under treatment between 1994 to 2007. Total 86 HIV-HBV co-infected patients were included in study and among those 48 (56%) were on combination therapy included tenofovir (TDF) and lamivudine (LAM). HBeAg positive patients were 42 (48.9%) and 44 (51.1%) HBeAg negative. TDF treatment longer than 12 months was associated with undetectable HBV DNA viral load ($p$ = 0.047) assessed by multivariate analysis.

Thibault *et al.* (2013) conducted a multicenter cross-sectional study in 19 French University hospitals from January to December 2007. HBV load, genotype, epidemiological and clinical variables of 223 patients co-infected with HIV-HBV were investigated. The mean age of patients was 42 years and mostly was male 82%. Genotype division (A 52%, E 23.3%, D 16.1%) was associated with geographic origin, risk factors and co-infection with other hepatitis viruses. High proportion of patients (74.7%) under antiretroviral treatment was receiving a drug that had anti-HBV activity, including 47% receiving tenofovir (TDF). Advanced liver disease was