Factors Associated with Survival of HIV/HBV Co-infected Patients in Uganda

Ruth Atuhaire,[34] Leonard Atuhaire[35] and Yovani Lubaale[36]

Abstract

The main objective of the study was to identify factors that affect survival of HIV/HBV co-infected patients. The study used data from TASO Uganda. Patients who registered with the organization between 2005 and 2010 were followed to determine their survival. The covariates of study were age, education level, number of sex partners, Disease stage, weight, HBV related condition, being on ARV's. To estimate the survival function for every subgroup of each variable, the product- limit method developed by Kaplan and Meier was used (Kaplan and Meier, 1958) and a log rank test to compare the survivorship functions across several groups. Lastly,a proportional hazards model was used to examine the joint effect of the covariates on the duration of survival assuming a Gompertz distribution for the time variable. The study revealed the duration of survival for HIV/HBV co-infected patients increased with increasing weight. Patients who had Hepatocellular carcinoma or Cirrhosis at diagnosis were at an increased risk of death as compared to those who had chronic active hepatitis B. Patients on ARVs had an increased death rate as compared to those who were not on ARVs, because the study showed that majority of the Patients seek for treatment when they are infected with Carcinoma, the old stage of Hepatitis B. Given the fact that ARVs have been thought to make life better for HIV/AIDS patients, there is need for further research in this area. Patients who were educated had a reduced death rate as compared to the uneducated ones. Therefore, emphasis should be on designing Information Education Communication (IEC) materials to sensitize the uneducated HIV/HBV co-infected patients on effects of non compliance and unbalanced diets.

Keywords: HIV/HBV co-infected patients, survival analysis, Kaplan and Meier method, proportional hazards model, Uganda

[34] Makerere University Business School, P.O.Box 1337, Kampala, Uganda
[35] Makerere University Business School, P.O.Box 1337, Kampala, Uganda
[36] Makerere University Business School, P.O.Box 1337, Kampala, Uganda

1. Introduction

Hepatitis is an inflammation of the liver, most commonly caused by a viral infection. Hepatitis B is an infectious hepatitis caused by the hepatitis B virus (HBV). This infection has two possible phases; acute and chronic (Bonacini & Kurz, 2002). Acute hepatitis B refers to newly acquired infections; affected individuals notice symptoms approximately 1 to 4 months after exposure to the virus. Most people with acute hepatitis, symptoms resolve over weeks to months and they are cured of the infection. However, a number of people develop a very severe, life-threatening form of acute hepatitis called fulminant hepatitis. Chronic hepatitis B is an infection with HBV that lasts longer than 6 months. Once the infection becomes chronic, it may never go away completely (Bonacini & Kurz, 2002).

Approximately 90 to 95 percent of infected adults are able to fight off the virus so their infection is cured. Only about 5 to 10 percent of adults infected with HBV go on to develop chronic infection, and children are at much higher risk for chronic infection (Hoffmann & Thio, 1990). Studies have shown that up to 90 percent of infected young children will fail to clear the virus from their bodies and go on to develop chronic infection. About two-thirds of people with chronic HBV infection are chronic carriers. These people do not develop symptoms, even though they harbour the virus and can transmit it to other people. The remaining one third develop "active" hepatitis, a disease of the liver that can be very serious (Hoffmann, & Thio, 1990).

It is realized that the liver is an important organ that filters toxins out of the blood, stores energy for later use, helps with digestion, and makes substances that fight infections and control bleeding, and this liver has an incredible ability to heal itself, but long-term inflammation caused by HBV can result in permanent damage. Scarring of the liver is called cirrhosis, a condition traditionally associated with alcoholism but one that is also caused by chronic active hepatitis B infection. When this occurs, the liver can no longer carry out its normal functions and may fail completely. The only treatment for liver failure is liver transplant. According to WHO, (2004) report about 15 to 25 percent of people with chronic hepatitis B die of liver disease.

According to WHO (2006), people who are at an increased risk of being infected with the hepatitis B virus include : Men or women who have multiple sex partners, especially if they don't use a condom, Men who have sex with men , Men or women who have sex with a person infected with hepatitis B virus, People with other sexually transmitted diseases, People who inject drugs with shared needles, People who receive transfusions of blood or blood products, People who undergo dialysis for kidney disease, Institutionalized mentally handicapped people and their attendants, caregivers, and family members ,Health care workers who are stuck with needles or other sharp instruments contaminated with infected blood, Infants born to infected mothers

For those who do get sick, symptoms usually develop within 1 to 4 months after exposure to the virus. The initial symptoms are often similar to the flu. Common symptoms of hepatitis B include: Appetite loss, feeling tired (fatigue), nausea and vomiting, itching all over the body, pain over the location of the liver (on the right side of the abdomen, under the lower rib cage), Jaundice (a condition in which the skin and the whites of the eyes turn yellow in color), dark

urine (the color of cola or tea). Hepatitis B is among the causes of global mortality. It is spread as HIV an infectious killer of adults.

Infection with Hepatitis B is one of the common human infections worldwide. The association between Hepatitis B and HIV presents an immediate and grave public health and socioeconomic threat, particularly in the developing world. The impact of the two viral infections on resource-poor countries have ominous social and medical implications, and the already overstretched health services now have to face a tremendously increasing Hepatitis B problem (Hudson et al, 1988). HIV infection worsens the situation by increasing reactivation of chronic Hepatitis B infection in dually infected persons as well as favoring rapid progression of new infections in the HIV-infected. This also results in an increase of the risk of infection and a subsequent increase of cases in the general population (Hoffmann et al,1990).

The risk of death from Hepatitis B in Uganda has increased especially among HIV/HBV co-infected patients despite good clinical and microbiological response to Pegylated interferon alfa-2b Pegasys **(** Lalla et al, 1990 ; Hudson et al, 1988). The risk factors for this increased hepatitis B associated mortality however need to be studied further in Uganda, because they are important in improving treatment outcome among such patients.

The study was guide by the main objective to determine the factors associated with survival of HIV/HBV co-infected patients. The following hypotheses were tested: The survival of HIV/HBV co-infected patients is independent of socio demographic factors (age, number of sex partners, Education level, marital status) of the individual, and the survival of HIV/HBV co-infected patients is independent of clinical factors (HBV related conditions, ARVs, weight, WHO stage).

2. Literature Review

Hepatitis B is the most common serious liver infection in the world. Worldwide, an estimated two billion people have been infected with the hepatitis B virus (HBV), and more than 350 million have chronic (long-term) liver infections, of whom, more than 620,000 die from liver-related disease each year (WHO, 2004).

In the United States, hepatitis B is largely a disease of young adults aged 20-50 years. About 800,000 to 1.4 million Americans are chronic hepatitis B virus carriers, and the disease causes about 3, 000 deaths each year (Hudson et al, 1988). The good news is that infection with HBV is usually preventable because there is an effective vaccine. Use of the vaccine has resulted in an 82 percent decrease in the number of new infections reported in the United States each year.

The problem of Hepatitis B and its related conditons in any country has been responsible for much of the deaths especially among people with HIV/AIDS and therefore the study to find out the factors associated with the survival of people co-infected with HIV/AIDS and HBV was inevitable. Globally, 600,000 were the estimated deaths (in 2002), 70% estimated HepB3 coverage and 92% of the countries integrated HepB in routine immunization (WHO, 2004).

According to the AMREF (1999), while there are around 25 million HIV-infected persons in sub-Saharan Africa, there are also an estimated 50 million with chronic hepatitis B virus (HBV)

infection. The scale-up of' HIV treatment with antiretroviral medication (ARVs) in Africa should result in substantial reductions in morbidity and mortality. In developed countries, however, improved survival with highly active antiretroviral therapy (HAART) has been associated with notable increases in mortality due to liver disease among HIV-infected persons. Also, persons co-infected with hepatitis viruses have significantly higher liver-related toxicity with ARVs compared to persons infected with HIV alone as well as protocol investigated predictors of liver disease among co-infected participants (Feld et al, 2005).

Hepatitis and HIV have been closely linked since the emergence of AIDS. HIV infection has contributed to a significant increase in the worldwide incidence of Hepatitis B (UNAIDS, 1996). About 25 million people in sub-Saharan Africa are infected with HIV and about 50 million with chronic HBV, and patients with both viruses face a dreadful progressive decline in cell-mediated immunity, this greatly increases the risk of developing liver related diseases in co-infected individuals and leading to more frequent deaths involvement and atypical radiographic manifestations. It is further observed that although some HIV-related infections are both treatable and preventable, incidence rates continue to rise in developing nations where HIV infection and Hepatitis B are endemic and resources limited like Uganda.

According to Feld et al. (2005), globally Hepatitis is among the most common opportunistic infection affecting HIV-seropositive individuals and it is the most common cause of death in patients with AIDS and Hepatitis B virus (HBV) being the leading cause of chronic liver disease and liver-related death worldwide, with the majority of these cases occurring in areas of Africa and Asia where HBV prevalence is high. Many of the countries that are affected by hepatitis B are also affected by a high HIV burden, leading to frequent HIV/HBV co-infection. The consequences of co-infection, including increased liver-related morbidity and mortality, increased hepatitis B viral replication, immune reconstitution to HBV in the setting of antiretroviral therapy, and hepatotoxicity from antiretroviral drugs, are especially important in regions with expanding antiretroviral programmes. (Hoffmann et al, 1999). It is further noted that in some areas of sub-Saharan Africa, the rates of co-infection exceed 1,000 per 100,000 population (Dye et al, 1999). They observed that Hepatitis B case rates have increased in sub-Saharan Africa since 1985. It is argued that these increases were relatively greater as HIV seroprevalence increased.

According to WHO (2006), a person who is HIV-positive and infected with Hepatitis B virus has a very high likelihood to become sick with chronic Hepatitis B than someone infected with Hepatitis B virus who is HIV-negative (Moore et al, 1988). Co-infections accounts for about 13 percent of AIDS deaths worldwide. The report further indicated that in Africa, HIV is the single most important factor determining the increased incidence of Hepatitis B. It is common to find a patient with HIV having Hepatitis B in Uganda (Bwogi et al, 2009). Such a situation lowers the immunity of that patient and makes him vulnerable to other opportunistic infections, which required a study to find out the factors associated with the survival of Hepatitis B and HIV co-infected patients so that they can be mitigated.

ART in HIV-Hepatitis B patients; In a study that was done to assess the Liver in HIV in Africa, it was noted that as access to antiretroviral therapy improves across the African continent,

liver disease is emerging as an important cause of morbidity and mortality among HIV-infected individuals. Although coinfection with hepatitis B virus (HBV) and hepatitis C virus (HCV), along with highly active antiretroviral therapy (HAART)-induced hepatotoxicity appear to be the major causes of liver disease in this population, other diseases endemic to Africa with hepatic manifestations are influenced by HIV infection (Feld et al, 2005).

Feld et al. (2005) noted that although highly effective therapy exists for both HIV and HBV, concomitant administration is fraught with difficulties. Problems arise when giving these therapies concomitantly and many physicians delay highly active antiretroviral therapy (HAART) for two or more months to minimize the risk of toxic side effects. It is known that patients with low CD4 counts are at increased risk of progression and mortality, and are also more prone to side effects and toxicity from therapy.

Sex **differences** and Hepatitis B; According to WHO (2002) report, Hepatitis B and Tuberculosis is responsible for more female deaths around the world than any other infectious disease. The report further indicates that worldwide apart from TB, Hepatitis B is also a single killer of young women; causing maternal mortality in developing countries to increase.

In a study that was done in Africa by Bwogi et al, (2003) , it was found out that gender related differences at presentation existed and one-year outcomes after the initiation of HBV treatment showed no difference in survival. Also, Hepatitis B virus (HBV) is the leading cause of chronic liver disease and liver-related death worldwide, with the majority of these cases occurring in areas of Africa and Asia where HBV prevalence is high. Many of the countries that are affected by hepatitis B are also affected by a high HIV burden, leading to frequent HIV/HBV co-infection.

The consequences of co-infection, including increased liver-related morbidity and mortality, increased hepatitis B viral replication, immune reconstitution to HBV in the setting of antiretroviral therapy, and hepatotoxicity from antiretroviral drugs, are especially important in regions with expanding antiretroviral programmes. Little data, however, are available on HIV/HBV co-infection from regions with high chronic hepatitis B prevalence. However, in a prospective study that was carried out to determine treatment outcome in an unselected cohort of HBV patients admitted at Children's Hospital Boston and Zomba General Hospital in Malawi, death rates were similar in men and women (Harries et al, 1998). Although WHO (2002) and Bwogi et al. (2003) indicated a difference in survival based on sex, the study by Harris et al. (1998) did not show any differences in survival of the patients based on sex. Therefore it remained unclear whether sex is a factor that influenced the survival of HIV-HBV co-infected patients that this study intended to find out.

Site of disease and survival; Mcmahon et al. (1990) have shown that survival time of HIV-HBV co-infected patients is associated with the site of HBV disease. In their study using the log rank test, the median survival was shortest in patients with both hepatocellular carcinoma and cirrhosis, followed by those who had active hepatitis B alone and then those who had only URTI. In a proportional hazards regression analysis, which adjusted for CD4+ count, hepatocellular carcinoma disease was among the factors independently associated with shorter survival.

Giovanni et al, (2003) concluded that the site of HBV had no significant influence on the survival of the HIV HBV co-infected patients and therefore, there were no differences in survival of the patients who had active hepatitis B and those who had URTI. They used the Kaplan-Meier technique and the generalised log-rank test to construct and compare the survival probabilities curves of the two groups. This was also a concern for the researcher in this study to find out whether site of the URTI had an influence on the survival of the HBV and HIV co-infected patients.

Hepatitis B related condition**;** Hepatocellular carcinoma (HCC, also called malignant hepatoma) is a primary malignancy (cancer) of the liver. Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules (lumps that occur as a result of a process in which damaged tissue is regenerated), leading to loss of liver function. Cirrhosis is most commonly caused by alcoholism, hepatitis B and C, and fatty liver disease, but has many other possible causes. Glomerulosclerosis is Inflammation of the glomeruli, caused often by an autoimmune disease, but it can also result from infection, and the most common signs of glomerulosclerosis are proteinuna and kidney failure. USAID,(2006) and Feld et al(2005).

3. Methodology

This section shows data source, study participants, data processing and analysis. The data used in this study was from records of HIV/HBV patients registered with TASO Uganda. Patients who were considered in this study are those registered between April 2005 and June 2010 and had been on treatment for at least 60 days. Time from the date of enrollment to the date of death or censoring was taken as the response variable for survival analysis. The covariates of interest included; age, number of sex partners, marital status, education level, occupation, ethnic group, HB related condition, weight, Disease stage and being on ARVs. The Study participants were all TASO clients who were HIV/HBV infected, attending TASO between April 2005 and June 2010.

Raw data was received from TASO in Microsoft Access and then was exported from Access to STATA for analysis. Data was declared as survival data with death as the failure variable and the time from the enrollment to death/censoring as the time variable. To achieve the desired objectives, different methods of data analysis were employed. These included description of the variables used in the study in form of frequency tables, examination of the relationship of individual variables with time to death and model estimation (multivariate survival analysis).

Descriptive statistics were used to summarize characteristics of the study population. Continuous and discrete variables were summarized into standard deviations, modes, ranges, medians, and means. Nominal and ordinal variables were summarized into frequencies, percentages and medians, and confidence intervals presented.

Examining the individual relationship of each variable to survival, and estimating the survival function for every subgroup of each variable, the product- limit method developed by Kaplan and Meier was used (Kaplan and Meier, 1958). The product- limit method estimates the survivorship function, S(tj) at time tj, which is the probability of surviving up to the time tj. The Kaplan-Meier or PL estimator for survival distribution is of the form;

$$S(t_j) = \prod_{i=1}^{j} \left(1 - \frac{d_i}{r_i}\right) \quad \text{.....(3.1)}$$

Where t_j is the time of the j[th] death

r_i is the number at risk at time t_i

d_i is the number dying at time t_i

To compare the survivorship functions across several groups, the log rank test was used. The log rank test is based on a set of scores (W_i) assigned to the observation. The scores are functions of the logarithms of the survival function estimated at t_i using:

$$e(t_i) = \sum_{j \le t_i} \frac{m_{(j)}}{r_{(j)}} \quad \text{.....(3.2)}$$

Where m_j is the number of failure times.

r_j is the number at risk.

And the scores W_i are given by

$$W_i = \begin{cases} 1 - e(t_i) & \textit{for an uncensored observation} \\ -e(t_i) & \textit{for an observation censored at } t \end{cases}$$

The log rank test depends solely on the sum S of the W scores in any of the groups.

The variance of S is given as:

$$Var(S) = \left\{ \sum_{j=1}^{k} \frac{m_{(j)}(r_{(j)} - m_{(j)})}{r_{(j)}} \right\} \frac{n_1 n_2}{(n_1 + n_2)(n_1 + n_2 - 1)} \quad \text{.....(3.3)}$$

Where n_1 is the number of observations in group 1

n_2 is number of observation in group 2

k is number of distinct failure times (Lee, 1992)

Therefore the log rank test statistic, L, is represented as

$$L = \frac{S}{\sqrt{Var(S)}} \quad \text{.....(3.4)}$$

which follows an asymptotically standard normal distribution under the null hypothesis.

The test statistic, L, has a critical region $L<Z_{\alpha}$ if S is obtained from group 1 and $L>Z_{\alpha}$ otherwise.

The Nelson-Aalen estimator due to Nelson (1972) and Aalen (1978) was employed to estimate the cumulative hazard functions for different group variables instead of survivor functions (Kaplan-Meier estimators). The Nelson-Aalen estimator has better small-sample properties than Kaplan-Meier and it is given by

$$\hat{H}(t) = \sum_{j|t_j \le t} \frac{d_j}{n_j} \quad \text{.....(3.5)}$$

Where n_j is the number at risk at time t_j, d_j is the number of failures at time t_j, and the sum is over all distinct failure times less than or equal to t.

Its standard error is given by

$$Var\{\hat{H}(t)\} = \sum_{j|t_j \le t} \frac{d_j}{n_j^2} \quad \text{.....(3.6)}$$

And the confidence intervals are $\hat{H}(t)\exp\{\pm z_{\alpha/2}\hat{\phi}(t)\}$, where

$$\hat{\phi}^2(t) = \frac{Var\{\hat{H}(t)\}}{\{\hat{H}(t)\}^2} \quad \text{.....(3.7)}$$

Estimates the asymptotic variance of $\ln \hat{H}(t)$ and $z_{\alpha/2}$ is the $(1-\alpha/2)$ quantile of the normal distribution.

Theoretically, the survival and cumulative hazard functions are related by

$$S(t) = \exp\{-H(t)\}$$

or $$H(t) = -\ln\{S(t)\} \quad \text{.....(3.8)}$$

Klein and Moeschberger (2003) observed that for survival function and cumulative hazard function, both the Kaplan-Meier estimator and the Nelson-Aalen estimator are consistent estimates. These statistics are asymptotically equivalent. Also according to Hosmer and Lemeshow (1999), the Nelson-Aalen estimator of the survival function is always greater than or equal to the Kaplan-Meier estimator. However, the Kaplan-Meier estimator has a shortcoming that once the estimator is zero, it remains zero regardless of future activity. The Nelson-Aalen estimator does not suffer from this problem, since it will increase with every failure event, even after the Kaplan-Meier estimate would have reached zero.

Multivariate analysis was performed to determine the factors associated with the survival time of the patients. A proportional hazard model was fitted.
The proportional hazard model is of the form;

$$h(t \mid \mathbf{x}_j) = h_0(t)\exp(\mathbf{x}_j\boldsymbol{\beta}_x) \quad \text{.....(3.9)}$$

Where $h_o(t)$ is the baseline hazard function,
$\mathbf{X}_{js}$ are the covariates,
t is time to death of an individual.

Different proportional hazard models were fitted assuming three distributions of the survival time. The three distributions considered were the exponential, Weibull and Gompertz. The hazard functions of these distributions are the following:

Exponential: $h(t) = \lambda,\ \lambda>0$.....(3.10)
Weibull: $h(t) = \lambda\gamma t^{\gamma-1},\ \gamma>0$.....(3.11)
Gompertz: $h(t) = \exp(\lambda + \gamma t)$.....(3.12)

The best fit among the three distributions was selected by comparing the AIC values of the observed data under the three distributions.

AIC = 2k -2(log likelihood) ..... (3.13)

Where k is the number of free parameters in the model. The model with the minimum AIC value was chosen as the best model to fit the data (Akaike,1973).

4. Findings of the Study

This section presents the results of the analysis as described in chapter three. It tries to explain the factors associated with survival of HIV/HBV co-infected Patients. The characteristics of the patients considered were grouped into socio-demographic age, sex, marital status, Education, occupation and number of sex partners. It further presented the clinical factors for the patients at baseline.

A total of 347 Patients were included in this study, of these there were more females 53.5 percent compared to males. Many patients were married 47.8 percent and a small number had never married 3.6 percent. The study further indicated that 61.4 percent attained primary school education. At least 23.6 percent attained secondary school education and only 11.8 percent had no formal education. The mean age of the patients was 37 years. The minimum age being 23 years and maximum 71 years. Most of the patients in the study were aged above 40 years 43.2 percent. The study further showed that 74.2 percent of the patients had atleast 2 sexual partners, only 25.8 percent had atmost 1 partner.

Table 4.1: Distribution of HIV/HBV patients by socio-demographic characteristics

Variable	Number	Percentage
Sex		
Female	186	53.5
Male	161	46.5
Total	347	100.0
Age group (years)		
20-29	72	20.7
30-39	125	36.1
>=40	150	43.2
Total	347	100.0
Marital status		
Never married	12	3.6
Married	166	47.8
Divorced/Separated	101	29.0
Widowed	68	19.6
Total	347	100.0
Education level		
None	41	11.8
Primary	213	61.4
Secondary	82	23.6
Tertiary	11	3.2
Total	347	100.0
Occupation		
None	77	22.1
Paid employee	93	26.8
Peasant	107	30.7
Other	70	20.4
Total	347	100.0
Number of sex partners		
At most 1	90	25.8
At least 2	257	74.2
Total	347	100.0

Most of the patients were not on ARVs (80.1%) at baseline. Information on Disease stage of HIV reveals that three quarters of the patients (76.2%) were in stage III (immunity is compromised and opportunistic infections are rampant like HIV/AIDS), 14.7 percent were in stage II and only 9.1 percent were in stage IV. The results further show that most of the cases had Hepatocellular Carcinoma (53.7%) and a few patients had Cirrhosis (7.4 %). The mean weight of the patients was about 51kg. The minimum weight of the patients was 29kg and the maximum was 90kg. Majority of the patients in the study weighted 50kg and above (52.5%).

Table 4.2: Distribution of HIV/HBVpatients by baseline clinical conditions

Variable	Number	Percentage
Weight (kg)		
< 50	165	47.5
>= 50	182	52.5
Total	**347**	**100.0**
ARVs		
No	278	80.1
Yes	69	19.9
Total	**347**	**100.0**
Disease stage		
II	51	14.7
III	264	76.2
IV	32	9.1
Total	**347**	**100.0**
HBV related condition		
Chronic active hepatitis	75	21.7
Hepatocellular Carcinoma(HCC)	186	53.7
Cirrhosis	27	7.4
Urinary Track Infections(URTI)	59	17.2
Total	**347**	**100.0**

Using *Kaplan-Meier* survival time analysis and the log rank test methods, the results of the relationship of individual variables with time to death were presented as shown in the tables below. The tables displayed the number and percentage of failures and the mean survival time for different covariates, that is, sex, age, marital status, education level, occupation, number of sex partners, HBV related condition, weight, Disease stage and ARVs. In addition, the tables displayed the value of the log-rank statistic and its level of significance used to assess the differences in the survival functions of selected variables across the levels of particular variables.

It was observed that survival was different across different categories of marital status (p=0.02.). The marital status of a patient seemed to significantly affect the duration of survival. It can be observed that widowed patients had the highest proportion failure, followed by the divorced/separated. It is also surprising that the never married had the least failure time. The table further shows that survival was different across different levels of education (p=0.05). The level of education of a patient seemed to affect the duration of survival. Furthermore, the number of sex partners had a significant effect on the duration of survival (p=0.01).

Survival time was not significantly different across different categories of sex, age group and occupation of HIV/HBV co infected patients (p>0.05). This implies that these factors seemed not to affect the duration of survival for HIV/HBV co infected patients.

Table4.3: Relationship between socio-demographic variables with survival time

Variable	Patients	No. of failures	% failures	Mean survival time (days)	Log rank χ^2	P
Sex					**0.07**	**0.79**
Female	186	10	5.4	1098		
Male	161	9	5.6	864		
Age group					**2.76**	**0.25**
20-29	72	4	5.6	1076		
30-39	125	6	4.8	915		
>=40	150	11	7.3	1080		
Marital status					**9.95**	**0.02**
Never married	12	1	8.3	821		
Married	166	11	6.6	909		
Divorced/Separated	101	13	12.9	1079		
Widowed	68	18	26.5	1051		
Education level					**7.81**	**0.05**
None	41	4	9.8	1041		
Primary	213	12	5.6	1072		
Secondary	82	3	3.7	912		
Tertiary	11	1	9.1	857		
Occupation					**2.38**	**0.50**
None	77	5	6.5	1073		
Paid employee	93	6	6.5	909		
Peasant	107	7	6.5	1106		
Other	70	6	8.6	858		
Number of sex partners						
At most 1	90	6	6.7	1093	**1.03**	**0.01**
At least 2	257	72	28.0	848		

Survival time was found not to be different by gender of patient, age group and occupation at 5 percent level of significant (P-values>0.05). This is in agreement with Harries et al, (1998) whose study on HBV patients admitted at Children's hospital Boston and Zomba General hospital in Malawi, death rates were simillar in men and women, hence more research needed.

The time to death for HIV/HBV co-infected patients depended on someone's weight (p=0.01). Weight was categorized into two groups that is, those below 50kg and those who were 50kg and above. The survival time increased with increase in weight. It is also evident that survival was different among those patients who were on ARVs and those who were not (p=0.03). The mean survival time was higher among those who were not on ARVs as compared to those who were on

ARVs. The baseline HBV related condition of the patients seemed to have a significant effect on their survival (p=0.04). Those ones who had chronic active hepatitis had a longer mean survival time (1107days) as compared to the rest, as was studied by Jordan et al,(2005).

Generally, patients who were in Disease stage II had a longer mean survival time (1110days) as compared to those who were in Disease stage III and IV. However, the baseline Disease stage seemed not to have a significant effect on the survival of HIV/HBV co-infected patients (p=0.19).

Table 4.4: Relationship between baseline conditions with survival time

Variable	Patients	No. of failures	% failures	Mean survival time (days)	Log rank χ^2	P
Weight					**5.96**	**0.01**
< 50	165	14	8.5	885		
>= 50	182	8	4.4	1114		
ARVs					**4.72**	**0.03**
No	278	16	5.8	1105		
Yes	69	6	8.7	872		
Disease stage					**3.28**	**0.19**
II	51	1	2.0	1110		
III	264	20	7.6	1088		
IV	32	2	6.3	910		
HBV related condition					**10.17**	**0.04**
Chronic active hepatitis	75	4	5.3	1107		
Hepatocellular Carcinoma(HCC)	186	17	9.2	796		
Cirrhosis	27	2	7.4	819		
URTI	59	3	5.1	898		

Nelson-Aalen estimator was also employed to give the visual picture of cumulative hazard functions of different variables under different categories.

Hazard estimate by Sex; It was observed that though the cumulative hazard functions converged at the beginning of the analysis time, females had a lower hazard than males. This implies that females took longer to die as compared to males.

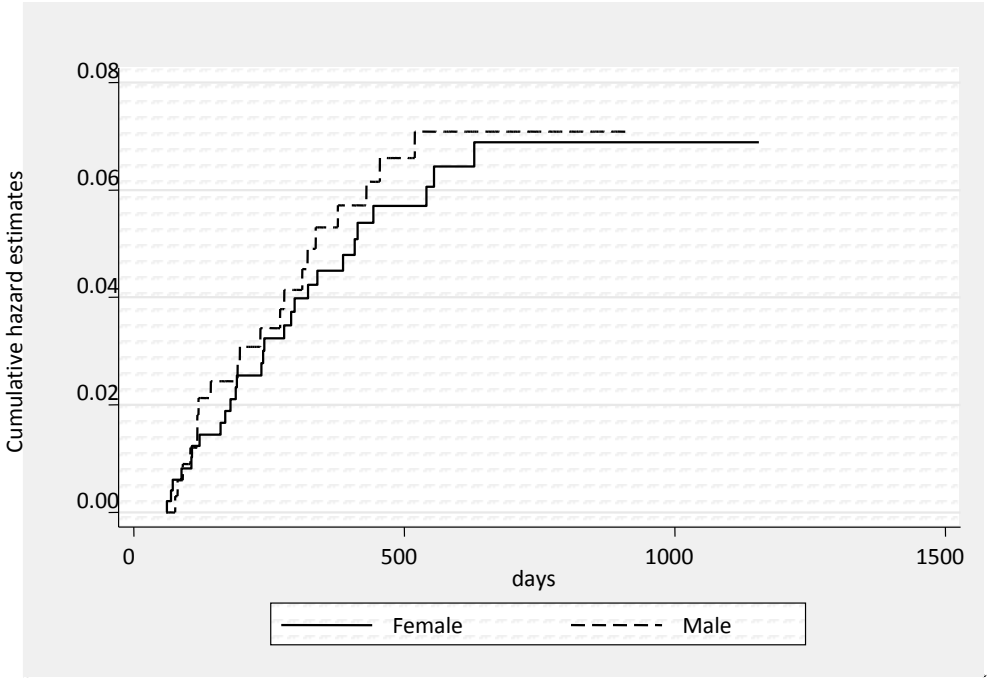

Figure 4.1: Nelson-Aalen cumulative hazard estimates by sex

The hazard estimate by age increased with increasing age at the beginning . As time went on, the hazard for those aged 30-39 years decreased and then stabilized. Then the hazard for the ones aged 20-29 years increased and later stabilized. The hazard continued to increase among the older patients (>= 40years) but stabilized at the end. Old patients who were aged 40 years and above had a higher hazard as compared to the rest. The hazard was highest for patients who were widowed and lowest for those who were married. This implies that married take longer to die than the widowed.

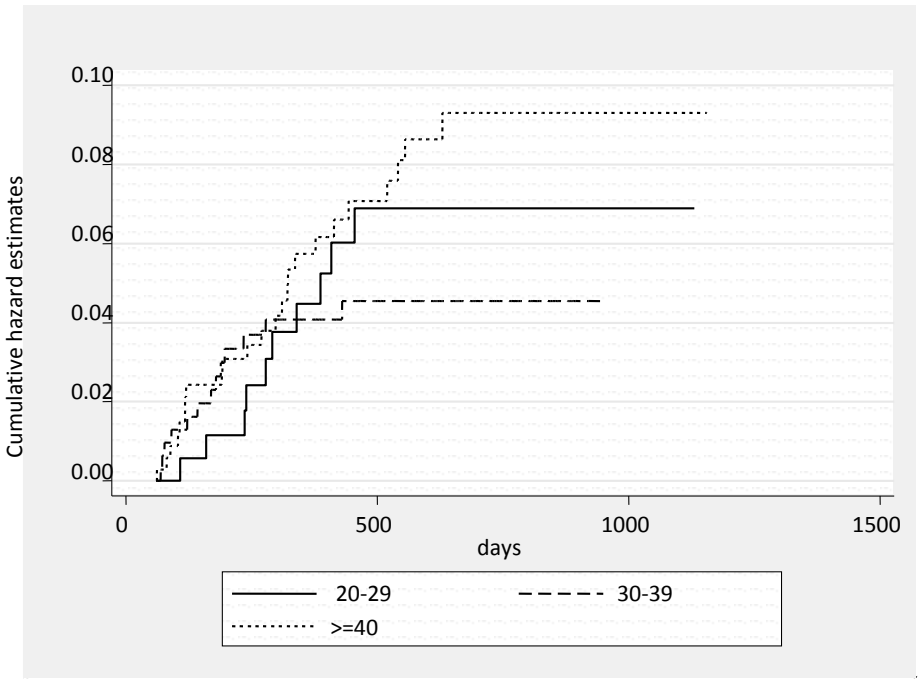

Figure 4.2: Nelson-Aalen cumulative hazard estimates by age group

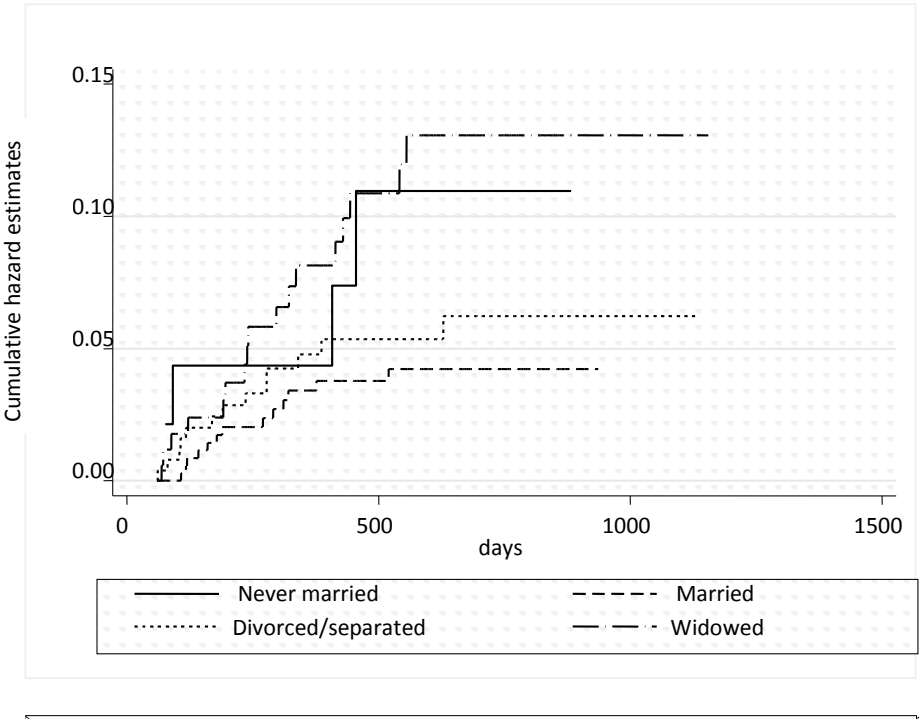

Figure 4.3: Nelson-Aalen cumulative hazard estimates by marital status

The hazard was highest among those patients with no formal education as compared to those who attained different levels of education.

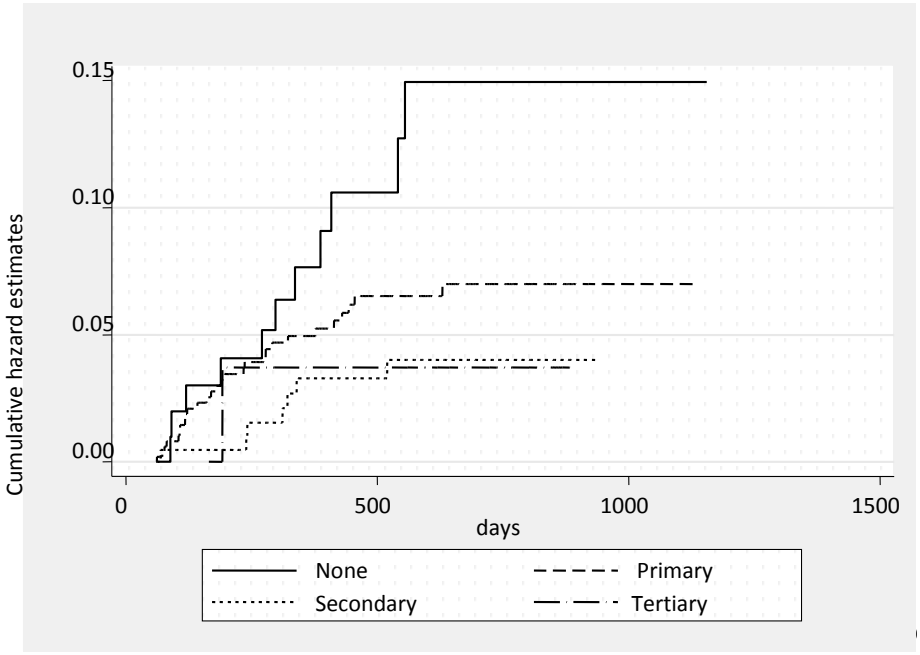

Figure 4.4: Nelson-Aalen cumulative hazard estimates by education level

50kg had their hazard lower than that of patients with a lower weight. Also, HIV/HBV co-infected patients who were not ARVs had their hazard lower than that of those who were on ARVs.

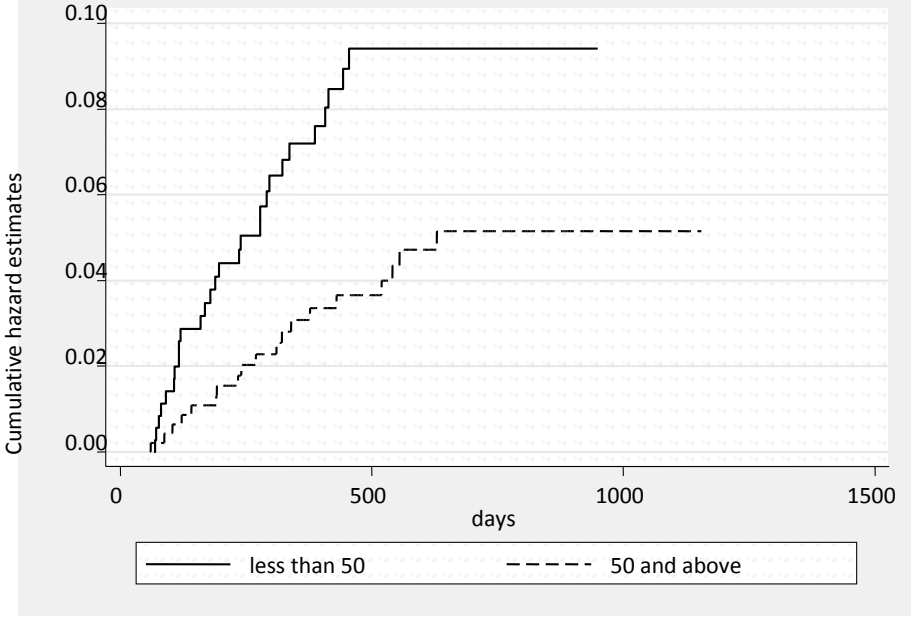

Figure 4.5 Nelson-Aalen cumulative hazard estimates by weight

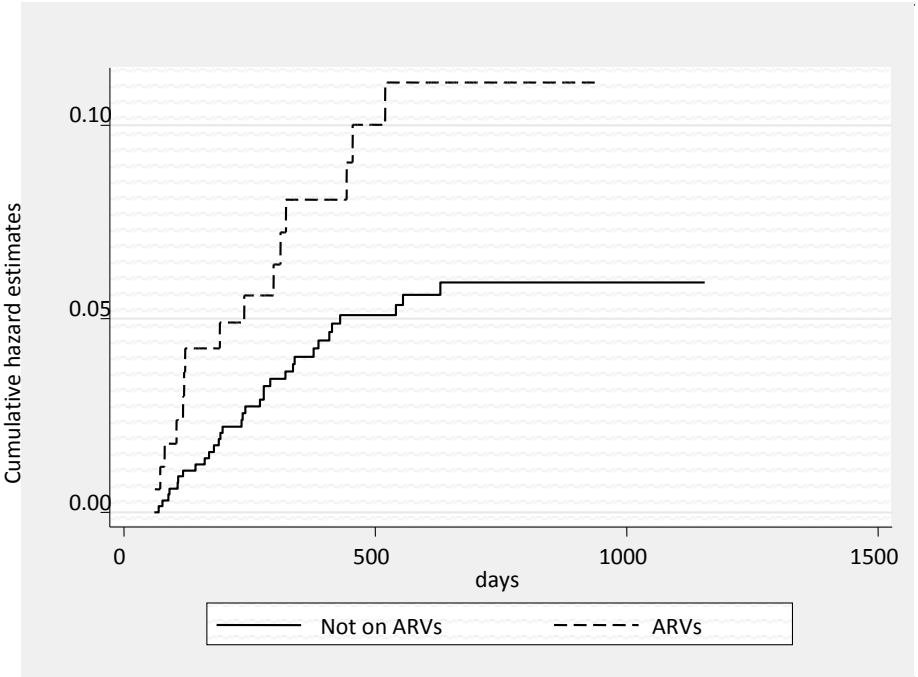

Figure 4.6: Nelson-Aalen cumulative hazard estimates by ARVs

The hazard was highest among patients who were in WHO stage III and was lowest among those who were in WHO stage II. It is also observed that at the beginning of the analysis time, patients with hepatocellular carcinoma had a higher hazard than the other patients who had other baseline HBV related conditions but as time went on, their hazard became constant and those ones who had glomerulonephritis had a higher hazard as compared to the rest.

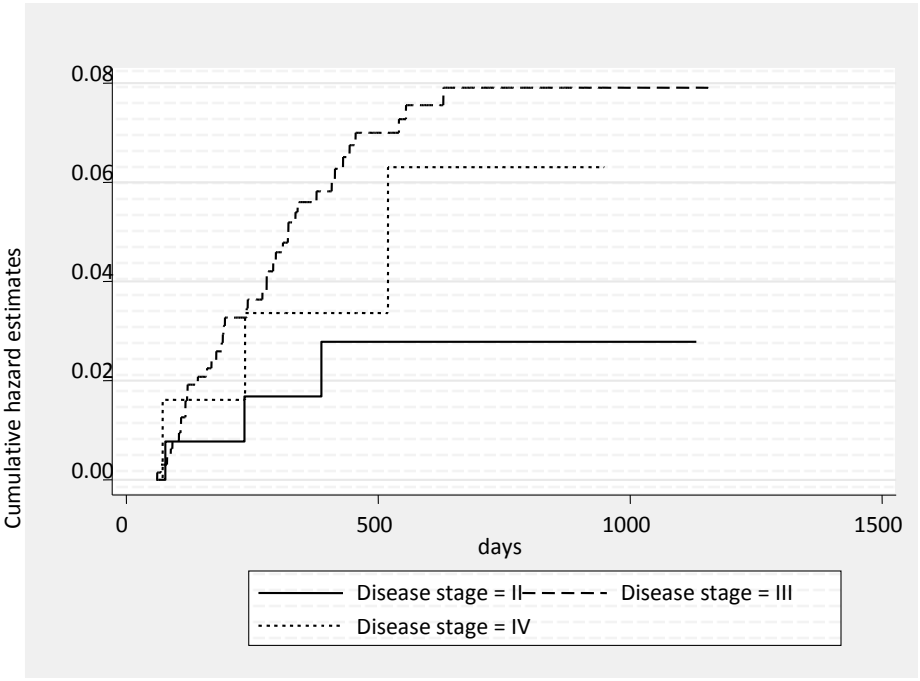

Figure 4.7 Nelson-Aalen cumulative hazard estimates by Disease stage

Using the log rank test to test for equality of survival functions, weight, being on ARVs, HBV related condition, education level and marital status were found to significantly affect survival. A Gompertz proportional hazards model, which had the minimum AIC value, was considered as the best model to determine factors associated with the survival of HIV/HBV patients.

Table 4.4: Estimated Gompertz proportional hazards model

Number of observations = 747 LR χ^2 (12) = 30.42

Log likelihood = -209.74796 Probability > χ^2 = 0.0024

Variable	Hazard. Ratio	Standard error	P	95% Confidence Interval	
Weight	0.960	0.018	0.033**	0.925	0.997
ARVS					
Yes	1.956	0.658	0.046**	1.011	3.783
No	1.000				
Education level					
No education	1.000				
Primary	0.558	0.207	0.115	0.270	1.153
Secondary	0.321	0.161	0.245	0.119	0.581
Tertiary	0.338	0.360	0.024**	0.041	2.734
Marital status					
Never married	1.000				
Married	0.505	0.296	0.245	0.160	1.594
Divorced/Separated	0.561	0.335	0.333	0.174	1.809
Widowed	1.096	0.624	0.872	0.358	3.347
HBV related condition					
Chronic active hepatitis	1.000				
Hepatocellular Carcinoma(HCC)	2.161	0.980	0.089*	0.888	5.258
Cirrhosis	1.223	0.898	0.784	0.289	5.161
URTI	1.350	0.573	0.079*	0.587	3.103

* * Significant at 5% * Significant at 10%

The weight of patients was significantly associated with survival after controlling for other factors. A one-kilogram increase in weight reduced the hazard by 4 percent. The survival of the patients increased with increasing weight. This is because massive loss of weight is a sign of lost immunity which comes as a result of increased viral load hence a result of reduction in the CD4 count, and an individual is prone to opportunistic liver infections. Massive loss of weight can be used to predict time to death. Being on ARVs was seen to be significantly associated with the survival of HIV/HBV co-infected patients after adjusting for other factors (p=0.046). The hazard increased by 96 percent for an individual who was on ARVs as compared to one who was not on ARVs. This implies that patients on ARVs tended to die faster than the ones who were not on ARVs. This could be that patients on ARVs are very sick and therefore their immune system is too low to fight opportunistic infections like Hepatitis B. It could also be a result of interaction between ARVs and HBV drugs which leads to toxicity in the body. Overlapping toxicity profiles may result in the interruption or alteration of Hepatitis B and HIV regimens with potential subsequent microbiological or virological failure. This finding is consistent with Dean et al. (2002) who found out that HIV/HBV co-infected patients on ARVs and Hepatitis B therapy

concomitantly were significantly more likely to suffer an adverse event leading to interruptions in Hepatitis B/HIV therapy.

Also Moore et al. (2007) in their study found out that Hepatitis B and TB remain important cause of illness and death in patients receiving ART in Uganda. He noted however, that both appear to decline markedly, after 6 months of ART. Therefore HIV/HBV as well as HIV/TB co-infected patients should be entered in care early enough to prevent advance stages of Hepatitis B and TB. Patients who had hepatocellular carcinoma at baseline had their hazard increased by a factor of 2.16 as compared to those who had chronic active hepatitis B (p=0.057). Those ones who had Cirrhosis had their hazard increased by a factor of 1.22 as compared to those who had chronic active hepatitis B (P=0.079). In this study, patients who had hepatocellular carcinoma were at a high risk of death as compared to those who had chronic active hepatitis B. Similarly patients who had Cirrhosis were also at a high risk of death as compared to those who had chronic active hepatitis B. This could be due to the fact that patients with hepatocellular carcinoma have cancer that is acute and it affects the liver system causing pain in the body. Therefore a patient can easily die if not attended to immediately. Cirrhosis affects many other parts of the body, apart from the liver and ascites (fluid retention in the abdominal cavity) is the most common complication of cirrhosis, and is associated with a poor quality of life, increased risk of infection, and a poor long-term outcome. Other potentially life-threatening complications are hepatic encephalopathy (confusion and coma) and bleeding from esophageal varices.

Under normal circumstances, the disease is diagnosed late when it has reached its advanced stages. The diagnosis of Hepatitis B has never been easy as there is a very wide range of clinical features. The advent of HIV related Hepatitis B, with many unusual presenting features, has added significantly to the diagnostic difficulties. Therefore patients with Cirrhosis are at a higher risk of death due to late diagnosis or poor diagnosis of the disease.
This is in agreement with a study that was done by Mcmahon et al. (1990) when they found out that Cirrhosis was independently associated with shorter survival as compared to chronic active hepatitis B.

Patients with tertiary education had their hazard reduced by a factor of 0.66 as compared to those with no education after controlling for other factors (p=0.024). In this study, educated patients were at a reduced risk of death as compared to the uneducated ones. This could be attributed to the fact that educated people may have access to better treatment since they can afford medical expenses than the uneducated. The educated may also understand the usefulness of the treatment as well as having nutritious diets as compared to the uneducated. These patients should be encouraged to take the drugs as well as nutritional foods.

5. Summary, Conclusions and Recommendations

The main objectives of this study were to determine the socio-demographic and clinical factors responsible for the differentials in the survival of HIV/HBV co-infected patients. In order to establish the relationship between socio-demographic and clinical factors with survival, the log rank test was used. Education level, weight, being on ARVs and HBV related condition were found to have a statistically significant effect on the duration of survival. The hazard was highest among patients who were in the Disease stage III and lowest among the Disease stage II. A 1

kilogram increase in weight reduced the hazard by 4% and the hazard increase by 96% for an individual on ARV's as compared to one not on ARV's. Patients who had hepatocellular carcinoma and cirrhosis had increased hazards than those who had active hepatitis B. Patients with tertially education had their hazard reduced by 66% as compared to those who had no education at all.

The risk factors for death in HIV/HBV co-infected patients included being on ARVs and HBV related condition, weight, the level of education. HIV/HBV co-infected patients on ARVs had an increased death rate as compared to those who were not on ARVs. This finding is consistent with Dean et al. (2002) who found out that HIV/HBV co-infected patients on ARVs and HBV therapy concomitantly were significantly more likely to suffer an adverse event leading to interruptions in HIV/HBV therapy.

Patients who had Hepatocellular carcinoma or Cirrhosis at diagnosis were at an increased risk of death as compared to those who had chronic active hepatitis B. This is in agreement with a study that was done by Giovanni B Gaeta et al. (2003) when they found out Hepatocellular carcinoma (HCC, also called malignant hepatoma) is a primary malignancy (cancer) of the liver. Most cases of HCC are secondary to either a viral hepatitide infection (hepatitis B or C) or cirrhosis (alcoholism being the most common cause of hepatic cirrhosis), and that the usual outcome is poor, because only 10 - 20% of hepatocellular carcinomas can be removed completely using surgery. If the cancer cannot be completely removed, the disease is usually deadly within 3 to 6 months. Increasing weight among the HIV/HBV co-infected patients was associated with longer survival time. Also patients who were educated had a reduced death rate as compared to the uneducated ones.

The HBV-HIV drugs are considered very effective if a patient eats a balanced diet and comply with prescribed doses at the right time. Most of the educated people are working and therefore can afford treatment and balanced diets unlike the uneducated. Therefore, emphasis should be on designing Information Education Communication (IEC) materials to sensitize the uneducated HIV/HBV co-infected patients on effects of non compliance and unbalanced diets. Patients on ARVs had an increased death rate as compared to those who were not on ARVs, the explanation for this is that most Patients sought use of ARVs when in final stages of Hepatitis B and have already developed Cirrhosis which easily develops into liver cancer. This study therefore should be carried to see if Patients with cirrhosis should or should not be put on ARVs.

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