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Modeling Treatment Outcomes of HIV/AIDS Patients on Highly Active Antiretroviral Therapy in Northern Region of Ghana

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Abstract

The study sought to assess the effects of covariates on the survival time of HIV patients on Highly Active Antiretroviral Therapy (HAART). The average age of patients is 36.09 years with a standard deviation of 10.31, the minimum and maximum ages were 11 and 84 years, respectively. Majority (69.30%) of HIV patients on HAART were females. Weight, HIV Type, WHO Stage, TB result and Age are the main factors that influence CD4 count of HIV/AIDS patients. For every unit increase in age of a patient, survival decreases by 3.00%. The survival time for a female patient is 13.50% higher than that of a male patient. There is a need for patients on HAART to be educated on proper management of their personal lifestyle, including weight management, to improve treatment success.

Keywords

HIV/AIDS, HAART, Machine Learning Techniques, Tuberculosis, CD4 Counts

1. Introduction

Acquired Immune Deficiency Syndrome (AIDS) is caused by the Human Immunodeficiency Virus (HIV). HIV impairs the biological defense of the body against opportunistic diseases like pneumonia and Tuberculosis (TB). A person can have HIV infection for a very long time without showing any signs of illness. Nonetheless, a person can spread the illness to other people through sexual contact while they are still asymptomatic [1]. Also, a pregnant or nursing woman who is infected can pass the illness to her child. HIV can also be transferred through drug use, sharing needles used for injections, and transfusions of tainted blood. The presence of opportunistic infections is used to define AIDS. The disease kills almost all infected people, especially those not on treatment [2].

When the immune system does not have enough CD4 cells, it cannot fight against illness and infections. Despite broad attempts to combat the disease, HIV/AIDS is still a major public health concern worldwide [3]. The fact sheet 2020 [4], published more than three decades ago, estimates that more than 75 million individuals have been infected with HIV since the epidemic began in the 1980s and 36 million have died from HIV-related illnesses. According to estimates from the Joint United Nations Programme [4], thirty-eight million people were living with HIV worldwide in 2021. Out of this figure, 36.7 million were adults and 1.7 million children below fifteen years old, while fifty-four percent (54%) were women and girls. In 2020, eighty-four percent (84%) of those with HIV were aware of their status, eighty-seven percent (87%) of those with HIV were receiving antiretroviral therapy, and 90% of those receiving treatment had their viral load suppressed.

Antiretroviral Therapy (ART) was available to 25.4 million people by the end of 2019, up from 6.4 million in 2009 and 67% of people living with HIV were getting treatment, including two-thirds of HIV-positive adults and over half of HIV-positive adolescents under the age of 14. Seventy-eight percent (78%) of females and sixty-one (61%) of males got access to treatment after the age of 15. In 2019, 84% of pregnant women living with HIV had access to antiretroviral medications [4].

The introduction of highly active antiretroviral medication has been linked to decreasing HIV/AIDS-related mortality. This highly efficient treatment extends the infection expectancy of HIV-infected individuals from 12 to 25 years [5]. Treatment with HAART can help reduce virus replication while also boosting the ability of the immune system to fight off infections. Because of this, HIV/AIDS is currently seen as something that can be lived with but not cured. The advent of HAART to manage HIV infection has altered the course of the disease [4].

Since medication metabolism is affected by several factors such as the burden of co-infection for example, tuberculosis, viral subtypes, and genetic background, the efficiency of HAART differs by country. The survival rates of HIV patients reported by different studies are therefore inconsistent, although most studies have indicated that HAART considerably lowered the risk of the disease progression from HIV to AIDS and mortality [6]. In terms of public health, it is critical to know how long it takes on average for an HIV-positive person to develop AIDS and how long an AIDS patient may expect to live on HAART. No widespread agreement or extensive evidence exists yet for an accurate estimation of the HIV-infected person's survival rate based on data from various situations [7]. Untreated HIV infection, on the other hand, worsens immunodeficiency and makes people more susceptible to infections, including tuberculosis, according to the World Health Organization [8], HIV is a prominent source of morbidity and mortality in many countries, primarily in Sub-Saharan Africa and increasingly in Asia and South America. As a result, the TB and HIV/AIDS programmes have similar goals. General health service providers receive assistance from TB and HIV programmes.

TB programmes are already overburdened because of the rise in TB cases caused by the infection of people with HIV. The influence of HIV on TB control programmes reveals many flaws. There is an increase in the number of difficult-to-diagnose cases of pulmonary TB, including extra-pulmonary and smear-negative TB. More people are experiencing negative side effects from medications. Because of other curable HIV-related infections, mortality and morbidity are also increasing [5].

The red ribbon has become a global symbol indicating solidarity with those living with AIDS. It is there to show how the HIV/AIDS program in Ghana has evolved from one that focused almost exclusively on prevention to one that prioritizes prevention while also including a full program of prevention, care, and support. However, changing the direction of Ghana's AIDS pandemic is very possible. Instead of spreading through the air, water, or insects, the virus is propagated through specific human behaviors. More than 95% of our adults between the ages of 15 and 49 are uninfected, and all of these healthy men and women may take proactive measures to stay safe from HIV. Thus, this study seeks to model the outcomes of HIV/AIDs patients on HAART in the Northern Region of Ghana.

2. Methodology

2.1. Data Source and Management

The study used secondary data of 1296 HIV/AIDS patients registered for HAART at Tamale Teaching Hospital from January 1, 2011 to December 31, 2017. This hospital is a referral center for health facilities in the North East, Upper West, Upper East, and Savanna regions of Ghana. The hospital features a separate wing for HIV/AIDS patients who are receiving treatment.

A typical missing data issue in survival analysis is censoring, which arises because we don't know how long an individual may expect to live in the real world. Each participant's censored observation's usefulness is limited by chance. The data was coded and analyzed using R-Studio version 4.2.3 and SPSS-21. The following variables were included in the study:

Survival Time (dependent variable): Determined by subtracting date of diagnosis from date of death.

Socio-Demographic Characteristics: Age, Gender (male or female), Education (Primary, JHS/SHS, Tertiary), Marital Status (Married or Unmarried), and Religion (Christian or Muslim).

Patient Characteristics: HIV Type (HIV Type 1 or HIV Type 2), Weight, Smoking (Smoking/Not Smoking), Alcohol (Drinking or Not Drinking), TB (Yes/No), Hypertension (Yes/No), Asthma (Yes/No), Hepatitis (Yes/No), Disclosure (Yes/No), CD4 Count, WHO Stage 1 or 2 (1&2, 3&4), Status of Patients (Dead or Alive).

2.2. Akaike's Information Criteria

The Akaike's Information Criteria (AIC) is given:

$$\text{AIC} = 2K - 2\ln(L)$$

where K is the number of independent variables in the model. The default K is 2, so model with one independent variable will have K as $2+1=3$, and so on.

L denotes the maximum value of the likelihood function for the model. For model selection, the one with the smaller AIC value is selected [5].

2.3. Schwarz's Bayesian Criterion

The Schwarz Bayesian Criteria (SBIC) is given by

$$\text{BIC} = -2 * L + \text{Log}(N) * K$$

where $\log()$ has the base-e called the natural logarithm and N is the number of examples in the training dataset. The BIC enacts a better consequence to estimate model parameters than that of AIC [5].

2.4. Accelerated Failure Time Model

The Accelerated Failure Time Model (AFT) was used for modeling the data. Four main distributions were used in identifying the best model, which include Weibull, Log-logistic, Exponential and Log-normal. The AFT model is represented in the Log-linear form as:

$$\log(T) = \mu + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p + \sigma\varepsilon$$

where

T = Time-to-event (Failure time),

β_i = Regression coefficients $i = 1, 2, 3, \cdots, p$,

x_i = Explanatory variables $i = 1, 2, 3, \cdots, p$,

μ = The intercept,

σ = The scale parameter,

ε = The disturbance or error term [5].

Model Assumptions

1) Censored observations are accepted by the model.

2) It demands multiplicative (proportional) predictors with regard to event time.

3) It also posits a constant for the projected time ratios.

2.5. Goodness of Fit Test

According to the results of the accuracy measures, AIC and BIC showed smaller values for Log-normal and a higher Log-likelihood estimate, as seen in **Table 1**. This is an indication that Log-normal accelerated time model provides the best fit for the data. Details of the results for the comparative performance of the distributions are contained in **Table 1** below.

Table 1. Goodness of fit for AFT models.

Model	AIC	BIC	Log-likelihood
Exponential	1298.51	1376.01	−633.90
Weibull	1288.52	1371.19	−628.00
Log-normal	**1284.14**	**1366.81**	**−625.70**
Log-logistics	1287.52	1370.19	−627.50

3. Results

The age group 31 - 40 has the highest number (40.20%) of HIV infections, followed by the age group 21 - 30 years and above 60 years recorded the lowest HIV infections. Again, it revealed that 162 (25.40%) and 477 (74.60%) of males and females respectively had primary education, 139 (31.60%) of males and 301 (68.40%) of females had JSS/SHS education while 97 (44.70%) and 120 (55.30%) of males and females respectively had Tertiary education while 11% representing both males and females had no formal education at the time of enrolment into HIV care. See Table 2 for more details.

Table 2. Demographic statistics of HIV/AIDs patients.

Variables	Category	Male (%)	Females (%)
Age Distribution	11 - 20	16 (30.80)	36 (69.20)
	21 - 30	51 (14.40)	304 (85.60)
	31 - 40	164 (31.50)	357 (68.50)
	41 - 50	103 (41.40)	146 (58.60)
	51 - 60	53 (58.90)	37 (41.10)
	60+	11 (37.90)	18 (62.10)
Education	Primary	162 (25.40)	477 (74.60)
	JSS and SHS	139 (31.60)	301 (68.40)
	Tertiary	97 (44.70)	120 (55.30)
Marital Status	Married	283 (34.80)	530 (65.20)
	Not Married	115 (23.80)	368 (76.20)
HIV Type	HIV Type 1	387 (31.00)	863 (69.00)
	HIV Type 2	1 (25.00)	3 (75.00)
	HIV Types 1&2	10 (23.80)	32 (76.20)
Disclosure	Disclose	333 (29.90)	781 (70.10)
	Not Disclose	65 (35.70)	117 (64.30)
WHO Stage	1&2	329 (33.70)	646 (66.30)
	3&4	69 (21.50)	252 (78.50)
Status of Patient	Alive	360 (29.80)	848 (70.20)
	Dead	38 (43.20)	50 (56.80)
Total	Per Category	398 (30.70)	898 (69.30)

Close to fifty-four percent (53.60%) and 46.30% of males and females respectively have tuberculosis, while 368 representing 29.70% and 872 (70.30%) respectively for males and females did not have tuberculosis. Details of the results are contained in Table 3.

Table 3. Comorbidities of HIV/AIDS.

Variables	Category	Male (%)	Female (%)	Total (%)
Smoking	Smoking	24 (92.30)	2 (7.70)	26 (2.01)
	Not Smoking	374 (29.40)	896 (70.60)	1270 (97.99)
Alcohol	Drinking	48 (42.90)	64 (57.10)	112 (8.64)
	Not Drinking	350 (29.60)	834 (70.40)	1184 (91.36)
TB Result	Yes	30 (53.60)	26 (46.40)	56 (4.32)
	No	368 (29.70)	872 (70.30)	1240 (95.68)
Hypertension	Yes	12 (36.40)	21 (63.60)	33 (2.55)
	No	386 (30.60)	877 (69.40)	1263 (97.45)
Asthma	Yes	2 (50.00)	2 (50.00)	4 (0.31)
	No	396 (30.70)	896 (69.30)	1294 (99.69)
Hepatitis	Yes	4 (30.80)	9 (69.20)	13 (1.00)
	No	394 (30.70)	889 (69.30)	1283 (99.00)

To identify the main factors that influence CD4 count of HIV/AIDS patients. CD4 count though a continuous variable, is split into two levels (as ≤350 and >350 copies/mL). For the purposes of validation of the model, the entire dataset was divided into two sets (that is, training dataset and test dataset). The train data set, consisting of 908 (70%) of the 1296 patients, was used to build the model. A decision tree was created with the help of "rpart.plot" function to explain how the variables considered as explanatory variables impact CD4 count. Also, the model is used to predict the outcome variable based on the test dataset. Table 4 shows the prediction results of Rpart model.

Table 4. Prediction results of the Rpart model.

Node	Split	N	Loss	Yval	(yProb)	
1)	Root	908	235	≤350	(0.7411894	0.2588106)
2)	Weight < 57.5	591	126	≤350	(0.7868020	0.2131980)
4)	WHO Stage < 1.5	485	93	≤350	(0.8082474	0.1917526)
8)	Age ≥ 24.5	439	78	≤350	(0.8223235	0.1776765)*
9)	Age < 24.5	46	15	≤350	(0.6739130	0.3260870)
18)	Weight < 50.5	41	10	≤350	(0.7560976	0.2439024)
36)	TB Result ≥ 1.5	39	8	≤350	(0.7948718	0.2051282)*
37)	TB Result < 1.5	2	0	>350	(0.0000000	1.0000000)*
19)	Weight ≥ 50.5	5	0	>350	(0.0000000	1.0000000)*
5)	WHO Stage ≥ 1.5	106	33	≤350	(0.6886792	0.3113208)
10)	HIV Type < 2.5	103	30	≤350	(0.7087379	0.2912621)*
11)	HIV Type ≥ 2.5	3	0	>350	(0.0000000	1.0000000)*
3)	Weight ≥ 57.5	317	109	≤350	(0.6561514	0.3438486)
6)	Weight < 84	312	105	≤350	(0.6634615	0.3365385)*
7)	Weight ≥ 84	5	1	>350	(0.2000000	0.8000000)*

Note: * denotes terminal node.

Twenty-six percent (26%) of the patients had CD4 count less than 350 copies/mL. On weight of patients, sixty-five percent (65%) of the patients were less than 58 kg, and if a patient's weight is less than 58 kg, the patient has 21% chance of recording a CD4 count less than 350 copies/mL. Thirty-five percent (35%) of the patients were at least 58 kg, and if a patient is 58 kg or more, the patient has 34% chance of recording a CD4 count less than 350 copies/mL. Details of the results are contained in Figure 1.

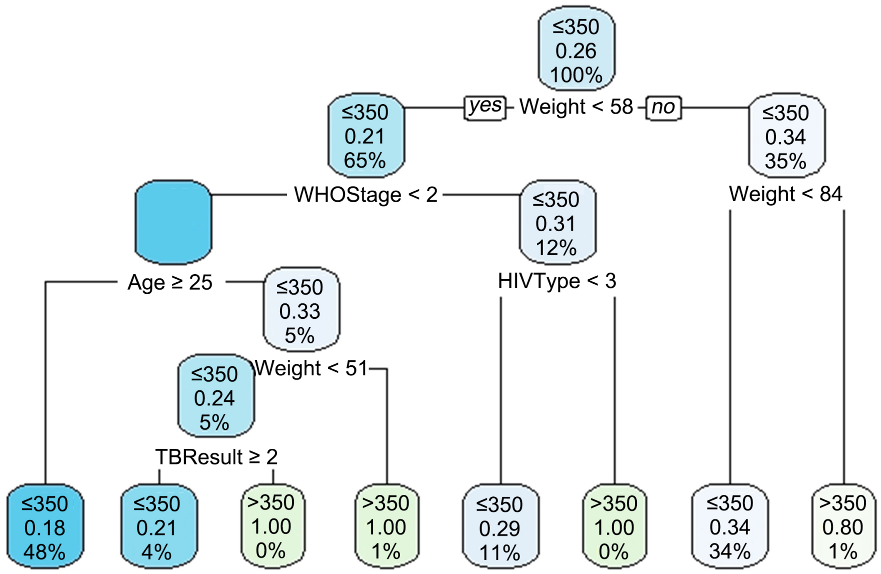

Figure 1. Decision tree for CD4 count of HIV/AIDS patients.

Log-Normal Distribution

Following the selection of the Log-normal distribution as the best model for analyzing the data, it was used to analyze the HIV/AIDS data with Stepwise selection using "StepAIC" function in R. With the StepAIC function, Age, Gender, Weight and WHO Stage emerged as the only four variables that have significant effect on the survival time. See Table 5 for more details.

Table 5. Step AIC selection of Log-normal distribution.

Variables	Coef.	L95%	U95%	Std. Error	Exp (Coef.)	P
(Intercept)	4.8035	2.3423	7.2647	1.2557	121.9317	0.0001
Age	−0.0317	−0.0611	−0.0023	0.0150	0.9688	0.0348
Gender (Ref: Male)	0.7598	0.0819	1.4377	0.3459	2.1379	0.0280
Weight	0.0361	0.0109	0.0613	0.0129	1.0367	0.0050
WHO Stage (Ref: Stage 1&2)	1.1476	0.2182	2.0771	0.4742	3.1507	0.0155

An additional analysis was conducted by interacting with some covariates in the Log-normal model to identify possible interactive effects among the explanatory variables. The results revealed that disclosure and the interaction term "Weight ×

Disclosure" significantly affect the treatment outcome of HIV/AIDS patients. Details of the results are contained in Table 6.

Table 6. Estimates of Log-normal distribution with interaction-AFT model.

Variables	Coef.	L95%	U95%	Std. Error	Exp. (Coef.)	P
Intercept	14.3577	6.4282	22.2872	4.0457	1719801.	0.0004
Age	−0.0306	−0.0597	−0.0015	0.0148	0.9699	0.0391
Gender (Ref: Male)	0.7586	0.0860	1.4312	0.3432	2.1352	0.0271
Weight	−0.1355	−0.2684	−0.0027	0.0678	0.8733	0.0456
Disclosure (Ref: Not)	−5.1817	−9.1943	−1.1692	2.0472	0.0056	0.0114
WHO Stage (Ref: Stage 1&2)	1.1611	0.2382	2.0840	0.4709	3.1935	0.0137
Weight: Disclosure	0.0925	0.0216	0.1633	0.0361	1.0969	0.0105

4. Discussion

This study involved 1296 HIV patients on HAART at the Tamale Teaching Hospital. Out of this figure, 898 (69.00%) were females, whilst 398 (31.00%) were males with adults aged 21 - 50 years representing 86.80% of total infections. This shows that, majority of patients are females. This is in line with National HIV and AIDS Strategic Plan 2021-2025 of Ghana where patients' population is projected to increase by about 3.3% between 2020 and 2025 with more females living with HIV than males, that is 67.30%, 67.50% and 67.63% of females than males in 2023, 2024 and 2025 respectively [9]. The females are generally vulnerable to HIV/AIDs infection due to their genetic make-up. Florom-Smith *et al.* [10] also reported similar findings that 14.2% of females against 7.5% males, and 11.1% among adults aged 15 to 49 years. Another study in South Africa reported 26.30% and 14.80% respectively for females and males as relative HIV/AIDS infections within the age group of 15-49. Clearly, HIV/AIDs infection is higher among females than males.

Among the patients who were married, 283 (34.80%) and 530 (65.20%) were males and females respectively. Majority of female patients were married, contradicting the findings of a study in South Africa [11], where the highest HIV incidence rate was found in the cohabiting group, which was 10.80 times higher than that of those married and living together. Also, about 85.00% of the patients under study disclosed their HIV status to either of their partners or family members. About 74.00% of those who disclosed their HIV status were males, whilst 64.00% of those who did not disclose their status were females. The results show that about 75.00% of the patients were classified as WHO Stage 1 (1 or 2). Females accounted for 66.30% of (1 or 2), while 78.50% of the female patients were classified as WHO Stage 2 (3 or 4). Out of the 1,296 patients, 6.80% of them died within the study period, as seen in Table 2.

The decision tree revealed the following five variables as significant in predicting HIV/AIDS treatment outcomes: Weight, HIV Type, WHO Stage, TB result and Age. Figure 1 revealed that 26% of the patients had CD4 count less than 350 copies/mL. On weight of patients, sixty-five percent (65%) of the patients were less than 58 kg, and if a patient's weight is less than 58 kg, the patient has 21% chance of recording a CD4 count less than 350 copies/mL. Thirty-five percent (35%) of the patients were at least 58 kg, and if a patient is 58 kg or more, the patient has 34% chance of recording a CD4 count less than 350 copies/mL. However, 34% of the patients were below 84 kg, and if a patient is below 84 kg, the chance of recording a CD4 count below 350 copies/mL is 34%. Among patients with weight of at least 84 kg, the chance of recording a CD4 count beyond 350 copies/mL for a patient is 80%. Also, 5% of the patients were less than 51 kg, and if a patient is below 51 kg, the chance of recording a CD4 count less than 350 copies/mL is 24%. However, 1% of the patients were at least 51 kg, and this group of patients had 100% chance of recording CD4 count more than 350 copies/mL.

On WHO Stage of patients, fifty-three percent (53%) of the patients had WHO Stage 1&2 symptoms, and if a patient is at WHO Stage 1&2, the patient has 19% chance of recording a CD4 count of less than 350 copies/mL. However, 12% of the patients had WHO Stage 3&4 symptoms, and if a patient is at WHO Stage 3&4, the patient has 31% chance of recording a CD4 count of less than 350 copies/mL.

On Age of patients, 48% of the patients were at least 25 years old. A patient who is at least 25 years old has 18% chance of recording a CD4 count less than 350 copies/mL. Patients younger than 25 years represent 5% of the total population of patients in the study. A patient less than 25 years has 33% chance of recording a CD4 count less than 350 copies/mL.

On TB status of patents, 4% of the patients did not have TB, and for a patient without TB, the chance of recording CD4 count less than 350 copies/mL is 21%. On HIV type, those with HIV-Type 1 or 2 represent 11% of the patients, and for a patient who is HIV type-1 or HIV type-2, there is 29% chance of recording a CD4 count less than 350 copies/mL (see **Figure 1**).

Also, Age, Gender, Weight, Disclosure, and WHO Stage, including the interaction term (Weight × Disclosure), significantly affect the survival time of HIV patients. An increase in age of a patient is associated with a decrease in survival time. For every unit increase in age, survival time reduces by 3.01%. Female patients have longer survival time than males [5]. An increase in weight of a patient is associated with a decrease in survival time. A unit increase in weight corresponds to a decrease in risk of survival by 12.70%. Patients who gain weight have the tendency to default on clinical visit for HAART medication and it confirms an earlier result [12]. This may explain the reason for the negative relation between weight of a patient and the survival time.

Patients who disclosed their HIV status tend to have shorter survival time than their counterparts who did not disclose. That is, risk of death of a patient who disclosed his/her HIV status is 0.56% lower than that of a patient who did not disclose. This is because disclosing one's HIV status may lead to stigmatization by the family or the community. This stigmatization may affect the patient psychologically. This feeling of shame and isolation has the tendency of discouraging the patient to continue with the HAART medication [10] [13], HIV patients classified under WHO Stage 3&4 have longer treatment time than those under WHO Stage 1&2. The chance of survival for patients classified under WHO Stage 3&4 is 19.40% higher than those classified under WHO Stage 1&2.

Patients who disclose their HIV status with an increase in weight, tend to have shorter survival time than those who do not disclose. In effect, this means that survival time for a patient who disclosed his/her HIV status and with a unit increase in weight has 9.70% risk higher than the one who did not disclose but recorded a unit increase in weight, which is in line with [5]. One would have thought that because the main effects of weight and disclosure, which are negative on the log survival time, their interaction would have also been negative on the log survival time, but this is not the case. This may be as a result of the fact that, the intent of disclosure is for the advantage of the patient in the sense that the patient may receive some sort of support from the person to whom the status is disclosed. It could be moral support, financial support, or any support that would help the patient to cope with the sickness. It is expected that once the patient receives these supports and continues taking the antiretroviral drugs, his/her weight will improve, which will then lead to an increase in the survival time [13].

With respect to comorbidities of HIV, 30 (53.60%) and 26 (46.30%) for males and females respectively were diagnosed with tuberculosis, while 368 representing 29.70% and 872 (70.30%) respectively for males and females did not have tuberculosis. This revealed an HIV/TB co-infection of 56 (4.32%), the results agree with other researchers [5] [14] [15]. Also, the results show that equal proportion of males and females who are living with asthma are also HIV positive, contrary to findings from Uganda by Kirenga *et al.* [16], which reported asthma prevalence of 15.50% among persons living with HIV and 9.10% among those without HIV. The results also show that about 31.00% of male and 69.00% of female HIV patients were diagnosed with hepatitis, representing 1.00% of the patients in the hospital. This figure is a little below the prevalence rate of hepatitis of 2.45% and 16.70% in the Northern and Western regions of Ghana [17]. About ninety-eight (97.45%) of HIV/AIDs patients did not have hypertension, 21 female HIV patients, representing 63.60% had hypertension compared to 36.40% of male positives. This is similar to findings of past research [18] [19]. There is therefore a need for all stakeholders to intensify their efforts and commitment in mitigating the HIV/AIDS menace.

5. Conclusion

The study revealed that Age, Gender, Weight, Disclosure, WHO Stage and Weight × Disclosure are the significant determinants of the survival times of patients. Also, patients whose CD4 Count is above 408 cells/mm^3 have 92.00% chance of surviving, while those below 408 cells/mm^3 have 22.00% chance of surviving. The common comorbidities of HIV/AIDS are tuberculosis, hepatitis, hypertension, and asthma. It is therefore essential for various stakeholders to intensify education for these patients for better outcomes.

Data Availability

The data is available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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