Epidemiological Study of Risk Factors of HIV Using General Hospital UDI as a Case Study

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ABSTRACT

This study explores the epidemiological study and risk factors of HIV based on a synthesis of recent studies that employ the Cox proportional hazards regression model. The research highlights significant variables influencing HIV progression, survival and treatment outcomes. Key findings indicate that functional statuses (bedridden) are critical predictors of HIV progression to AIDS and overall survival. Antiretroviral therapy (ART) has a substantial impact on reducing mortality risk among HIV patients, underscoring its importance in HIV management. The patients from geographical location Ezeagu are linked to poorer outcomes and higher mortality rates. The Cox model effectively captures the complex interplay of these variables, providing valuable insights into HIV epidemiology and identifying high-risk groups that require targeted interventions. These findings emphasize the need for comprehensive HIV care programs that address both medical and social determinants of health. The use of advanced statistical models like the Cox regression continues to be instrumental in unraveling the multifaceted nature of HIV and guiding public health strategies to mitigate its impact.

Keywords: Cox proportional Hazard, HIV progression treatment outcomes adherence, Time to Event

INTRODUCTION

HIV management and other support services begin with HIV counselling and testing (HCT). It gives clients the chance to learn more about the human immune deficiency virus and to find out their HIV status. (HIV). People living with HIV/AIDS (PLWHA) benefit from it by receiving the necessary behavioural changes, psychological support and emotional assistance. HCT lessens the stigma attached to HIV in the society and promotes social inclusion (FMOH, 2011).

Through the provision of physical access to HIV-related services, the Nigerian government sought to deliver HIV counseling to at least 80% (about 80 million) of the sexually active population by 2015. Notwithstanding the client- and provider-initiated counselling and testing methodologies' uptake, there was a relatively low demand for HIV Counselling Test (HCT) in the nation (FMOH, 2011; UNAIDS, 2016). The causes for the low acceptance of HIV Counselling Test (HCT) in Nigeria include the scarcity of HIV testing kits, end users' incorrect perceptions of HIV Counselling Test (HCT) centres, and the insufficient number of facilities offering HCT services (NACA, 2010a).

Although the prevalence of HIV has decreased over the past ten years, it is still a public health concern in Nigeria. Despite the low prevalence of HIV among adults (3.4%), the nation has the second-largest HIV epidemic in the world based on population, after South Africa (UNAIDS, 2016). Eighty percent of HIV infections in Nigeria are caused by heterosexual sexual activity; however, as more people use intravenous drugs and engage in same-sex relationships, the risk of HIV infection rising to forty percent increases (NACA, 2015). Thus, there is a need to raise awareness and step up efforts to improve Nigerians' understanding of HIV. HIV infection amongst HCT clients has been linked to factors such as age, gender, marital status, educational attainment, and awareness of the virus (Zheng et al, 2010; Peltzer, 2012).

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Nigerians are generally well-informed about HIV (FMOH, 2013), however their comprehensive knowledge of HIV prevention is low (24 percent for women and 34 percent for men), which is lower than the average for West and Central Africa (UNICEF, 2011). Educational attainment and socioeconomic standing were linked to thorough understanding of HIV prevention (UNICEF, 2011).

As of 2007, 33.2 million people were projected to be infected with HIV worldwide. (WHO AIDS, 2007) With almost two-thirds (68%) of all HIV-positive individuals residing in this region, Sub-Saharan Africa continues to be the most impacted continent by the worldwide AIDS pandemic. Furthermore, sub-Saharan Africa accounted for more than 75% of AIDS-related deaths in 2007. It is thought that the 1980s marked the beginning of the HIV epidemic in Nigeria. Reports of the first cases of AIDS in Nigeria date back to 1986. It was projected that 4.4% of Nigerians were living with HIV/AIDS at the end of 2006. (Federal Ministry of Health, 2005). AIDS is typically the result of untreated HIV infections. Patients are now able to live longer because to recent developments in HIV treatment. Therefore, long-term HIV/AIDS consequences, such as cardiovascular (CV) issues, are more common in HIV-positive patients. When highly active antiretroviral therapy (HAART) was introduced in the mid to late 1990s, it significantly decreased HIV-associated morbidity and mortality in individuals receiving treatment, preventing them from dying of opportunistic infections. (Palella et. al, 1998 and Mocroft et. al, 1998).

Condom use and other HIV/AIDS preventative measures are always met with opposition among commercial drivers in Nigeria, despite the high level of knowledge on HIV/AIDS and the growing awareness of the danger of HIV infection (Oyedunni et. al, 2011 and Michael 2013). Nigeria ranks third in the world among countries with the highest number of HIV/AIDS patients, behind only South Africa and India (Michael 2013). The HIV epidemic in Nigeria progressed from the early stages, when the prevalence rate was less than 5% across all subpopulations, to the concentrated stage, where the rate is greater than 5% in high-risk populations, and finally to the generalised stage, where the rate is higher than 5% among pregnant women visiting clinics (FMOH, 2019). According to data given by the Nigerian government, 1.4% of adults in the country between the ages of 15 and 49 are HIV positive. 2.8% was the national HIV prevalence, according to earlier estimates. An estimated 1.9 million persons in Nigeria are HIV positive, according to NAIDS and the National Agency for the Control of AIDS. Although 1.4% of persons in Nigeria between the ages of 15 and 49 have HIV, women are more than twice as likely to have the virus than men in the same age range (1.9% versus 0.9%). Between the ages of 20 and 24, young women are more than three times more likely than young men to be living with HIV. This is the age range in which the gender disparity in HIV prevalence is most pronounced. The fresh data is 0.2%. Preventing new HIV infections in children has been the focus of significant efforts in recent years (Adebobola et. al, 2014).

Here we examine HIV epidemiology trends and risk factors in Udi local government area (LGA) of Enugu State Nigeria using Cox proportional hazard model,

The Cox proportional hazards regression model, introduced by Sir David Cox in 1972, is a cornerstone in survival analysis and has profound implications in various scientific fields, including medical research, engineering, and economics. It is a semi-parametric model used to investigate the association between the survival time of subjects and one or more predictor variables. (Cox, 1972).

Survival analysis focuses on the time until an event of interest occurs, such as death, relapse, or failure. Unlike traditional regression models, which predict a continuous or categorical outcome, the Cox model accounts for the time dimension and the possibility of censored data, where the event of interest has not occurred by the end of the study. (Kleinbaum & Klein, 2012).

METHODOLOGY

Hazard Function

The *hazard function*, $h(t|X)$, represents the instantaneous risk of an event occurring at time t, given that the individual has survived up to time t, and depends on covariates X. It is defined as:

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$$h(t \mid X) = \lim_{\Delta t \to 0} \frac{P(t \le T < t + \Delta t \mid T \ge t, X)}{\Delta t} \quad 1$$

Where T is the time to the event, and X represents the covariates (e.g., age, gender, CD4 count, etc.).

Cox Proportional Hazards Model

The Cox Proportional Hazards model assumes that the hazard function can be expressed as a product of a baseline hazard function $h0(t)$ and an exponential term that accounts for the covariates:

$$h(t|X) = h0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta p X p) \quad 2$$

Where:

$h(t|X)$ is the hazard at time t for an individual with covariates $X = (X1, X2, \ldots, Xp)$,

$h0(t)$ is the baseline hazard function, and $\beta 1, \beta 2, \ldots, \beta p$ are the regression coefficients.

$$h(t/X) = h_0(t)exp(\beta_1 Age + \beta_2 Sex + \beta_3 Functional\ Status + \beta_4 CD4 + \beta_5 TB\ Co - Infected + \beta_6 Employment\ Status + \beta_7 Regimen + \beta_8 Mortality + \beta_9 Adherence\ to\ Drug + \beta_{10} Location) h(t/X)$$

Partial Likelihood Estimation

The regression coefficients β in the Cox model are estimated by maximizing the partial likelihood function. The partial likelihood for the i-th event time is obtained as in equation 3

$$L(\beta) = \prod_{i=1}^{k} \frac{\exp(\beta^T X_t)}{\sum_{j \in R(t_i)} \exp(\beta^T, X_j)} \quad 3$$

Where:

Xi are the covariates for the individual experiencing the event at time ti , $R(ti)$ is the risk set, i.e., the set of individuals still at risk at time ti . The log-partial likelihood is maximized to obtain the estimates of β, which quantify the effect of each covariate on the hazard.

Hazard Ratio

The hazard ratio (HR) compares the hazard functions for two individuals with different covariates X_1 and X_2. It is shown as in equation (4).

$$HR(X_1, X_2) = \frac{h(t \mid X_1)}{h(t \mid X_2)} = \exp(\beta^T (X_1 - X_2)) \quad 4$$

This provides a multiplicative interpretation of the effect of covariates on the hazard.

Survival Function Estimation: Kaplan-Meier Estimator

The Kaplan-Meier estimator is a non-parametric method used to estimate the survival

function $S(t)$, which represents the probability that a subject survives beyond time t. The survival function is given by:

$$S(t) = P(T > t) \quad 5$$

The Kaplan-Meier estimator for the survival function is defined as:

$$s(t)=\prod_{t_i \le t}\left(\frac{n_i-d_i}{n_i}\right) \qquad 6$$

Where: *ti* are the distinct event times

di is the number of events at time *ti* ,

ni is the number of individuals at risk just before time *ti* .

The Kaplan-Meier estimator accounts for censored data by only considering event times for individuals who experience the event of interest (e.g., death) while appropriately adjusting for the number of individuals at risk.

Model Assumptions and Diagnostics

Proportional Hazards Assumption

The Cox model assumes that the hazard ratios between individuals with different covariates remain constant over time. This is known as the *proportional hazards assumption*, mathematically expressed as:

$$\frac{h(t \mid X_1)}{h(t \mid X_2)}=\exp\left(\beta^T\left(X_1-X_2\right)\right) \qquad 7$$

This assumption implies that the effect of the covariates is multiplicative with respect to the baseline hazard function and does not vary with time.

Goodness-of-Fit

The goodness-of-fit of the Cox model can be assessed using the following methods:

Likelihood Ratio Test

This test compares the full model (with covariates) to a reduced model (without covariates). The likelihood ratio statistic is given by

$$L(r)=-2\log\left(\frac{L_0}{L_1}\right) \qquad 8$$

Where L_0 is the likelihood of the reduced model, and L_1 is the likelihood of the full

model.

The impact of multiple factors on the risk of HIV infection will be studied, it will include covariates such as age, sex, functional status, CD4, TB co-infected, employment status, regimen, mortality, adherence to drug and location in the model. The coefficients (β_i) will help quantify the association between each covariate and the risk of HIV infection.

$$h(t/X) = h_0(t)exp(\beta_1 Age + \beta_2 Sex + \beta_3 Functional\ Status + \beta_4 CD4 + \beta_5 TB\ Co-Infected + \beta_6 Employment\ Status + \beta_7 Regimen + \beta_8 Mortality + \beta_9 Adherence\ to\ Drug + \beta_{10} Location) \qquad (11)$$

By fitting this model to epidemiological data, researchers can identify significant risk factors and predict the likelihood of HIV infection under various conditions.

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ANALYSIS AND RESULTS

The dataset comprises 1000 individuals from four local government areas (LGAs) named Udi, Agbani, Ezeagu, and Oji River receiving treatment at the General Hospital Udi. Each individual has associated data on various demographic and clinical factors, such as sex, age, functional status, CD4 count, tuberculosis co-infection, employment status, treatment regimen, adherence to drugs, mortality, time to HIV infection

Descriptive Statistics

The following key points summarize the data distribution and the result is presented in Table 1.

The dataset is evenly split between males and females. Individuals are categorized as less than 20 years or 20 years and older. There are three categories - walking, ambulatory, and bedridden. Individuals are categorized as having CD4 counts less than 200 or 200 and above. Presence or absence of Tuberculosis co-infection was also investigated. **Employment Status was categorised as** Public servant, self-employed, or unemployed. **Regimen, that is** Treatment lines, whether the individuals adhered to their prescribed drug regimen was also studied. **Mortality rate was also measured and Time to HIV Infection** is measured in years.

Table 1 frequency distribution of characteristics of 1000 patients diagnosed of HIV

Characteristics		No of patients	Percentage
Location	Agbani	241	24.1
	Oji River	221	22.1
	Ezeagu	283	28.3
	Udi	255	25.5
Sex	Female	495	49.5
	Male	505	50.5
Age	<20	487	48.7
	>=20	513	51.3
Functional status	Ambulatory	303	30.3
	Walking	347	34.7
	Bedridden	350	35.0
CD4 Count	<200	532	53.2
	>=200	468	46.8
TB_CoInfected	Yes	508	50.8
	No	492	49.2
Employment Status	Public Servant	353	35.3
	Self Employed	321	32.1
	Unemployed	326	32.6
Regimen	1a	111	11.1
	1b	119	11.9
	1c	93	9.3
	4a	113	11.3
	4b	103	10.3
	5a	122	12.2
	5b	110	11.0
	6a	108	10.8
	6b	121	12.1
Adherence	Adherent	512	51.2
	Non-Adherent	488	48.8

The distribution of patients across different locations is fairly even. The highest number of patients are from Ezeagu (28.3%), while the lowest is from Oji River (22.1%). The sex distribution is almost equal. Similarly, the age distribution is almost equal, with a slight majority of patients being older than 20 years (51.3%) This

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue IV April 2025

distribution shows that nearly an equal number of patients were ambulatory, bedridden, or walking. Walking means being able to walk, bedridden means the patient is confined to bed, and Ambulatory means they can walk but with some limitations. A notable portion of patients is bedridden, indicating a significant degree of illness. Slightly more patients have a CD4 count lower than 200, which suggests a weaker immune system in the majority of individuals. Low CD4 counts are associated with more advanced HIV and worse health outcomes. About half of the patients have TB co-infection. TB is a common opportunistic infection in HIV patients and can complicate treatment and prognosis. Employment status is spread fairly evenly, with public servants being the largest group. The high number of unemployed patients (326) could indicate socioeconomic difficulties, often common in populations with serious health issues. The treatment regimens are distributed across multiple categories, with Regimen 5a (12.2%) having the highest number of patients, followed by 6b (12.1%) and then 1b (11.9%) . These regimens likely refer to specific antiretroviral treatments (ART) used in the cohort. Adherence to treatment is crucial in HIV management, and the almost equal split between adherent and non-adherent patients suggests that adherence is a major issue in this population. Non-adherence can lead to poor health outcomes and increased mortality.

Time To Event (Survival Analysis or Time to Event Data)

Table 2 The Time to Event Data and its Measures

mean	Median	SD	Mortality rate
9.64	6.28	10.4	0.497

Mean Time to Event: 9.64 months (on average, it took about 9.64 months for an event to occur, potentially death or another relevant outcome in the study). Median Time to Event: 6.28 months (half of the individuals experienced an event within 6.28 months, meaning the distribution is skewed right due to the longer average). Standard Deviation of Time to Event: 10.4 (the spread of times to event is quite high, indicating a lot of variation. Some individuals experienced events much sooner, while others took a lot longer). Mortality Rate: 0.497 (around 49.7% of the individuals in the dataset have died during the observation period).

Survival Analysis

Kaplan-Meier survival analysis stratified by local government area:

Coxph (formula = surv_object ~ GeographicalLocation + Sex + Age + Functional Status + CD4 +

TB_Co Infected + Employment Status + Regimen + Adherence, data = HIV_data)

Table 2 Parameters of the model and its Significance

		coef	exp(coef)	se(coef)	z	Pr(>|z|)
Geographical Location	Ezeagu	-0.327641	0.720622	0.135581	-2.417	0.0157*
Geographical Location	Oji River	-0.155247	0.856204	0.124974	-1.242	0.2142
Geographical Location	Udi	-0.200555	0.818277	0.127222	-1.576	0.1149
Sex	Male	-0.011570	0.988497	0.092154	-0.126	0.9001
Age	>=20	-0.071854	0.930667	0.091955	-0.781	0.4346
Functional Status	Walking	-0.189550	0.827332	0.112124	-1.691	0.0909
Functional Status	Bedridden	-0.233448	0.791799	0.114727	-2.035	0.0419*
CD4	>=200	0.024491	1.024793	0.091767	0.267	0.7896
TB Co Infected	Yes	0.009112	1.009154	0.091269	0.100	0.9205
Employment Status	Self Employed	-0.066739	0.935440	0.110993	-0.601	0.5476
Employment Status	Unemployed	-0.091220	0.912817	0.111413	-0.819	0.4129
Regimen	1b	-0.174751	0.839666	0.189891	-0.920	0.3574
	1c	0.018807	1.018985	0.205044	0.092	0.9269
	4a	0.034996	1.035616	0.187809	0.186	0.8522
	4b	0.039552	1.040345	0.195365	0.202	0.8396

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume X Issue IV April 2025

	5a	0.011629	1.011697	0.179889	0.065	0.9485
	5c	-0.104708	0.900587	0.192905	-0.543	0.5873
	6a	-0.053181	0.948208	0.193789	-0.274	0.7838
	6b	0.182795	1.200569	0.192441	0.950	0.3422
Adherence	Non-Adherent	0.046933	1.048052	0.091164	0.515	0.6067

Table 3 Confidence Interval for the coefficients of the Model

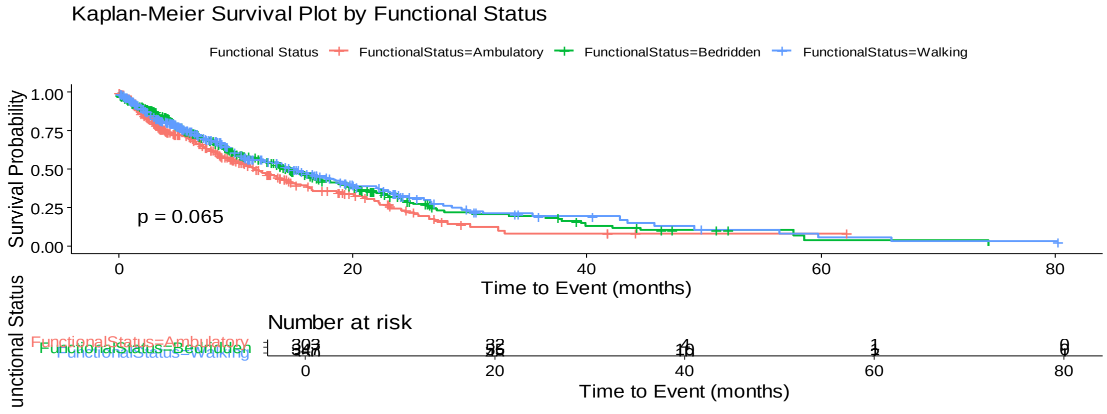
Parameters		exp(coef)	exp(-coef)	lower.95	upper.95
Geographical Location	Oji River	0.7206	1.3877	0.5525	0.9400
	Ezeagu	0.8562	1.1679	0.6702	1.0938
	Udi	0.8183	1.2221	0.6377	1.0500
Sex	Male	0.9885	1.0116	0.8252	1.1842
Age	>=20	0.9307	1.0745	0.7772	1.1145
Functional Status	Bedridden	0.8273	1.2087	0.6641	1.0307
	Walking	0.7918	1.2629	0.6324	0.9915
CD4	>=200	1.0248	0.9758	0.8561	1.2267
TB_Co Infected	Yes	1.0092	0.9909	0.8439	1.2068
Employment Status	Self Employed	0.9354	1.0690	0.7526	1.1628
	Unemployed	0.9128	1.0955	0.7338	1.1356
Regimen	1b	0.8397	1.1909	0.5787	1.2183
	1c	1.0190	0.9814	0.6818	1.5230
	4a	1.0356	0.9656	0.7167	1.4964
	4b	1.0403	0.9612	0.7094	1.5257
	5a	1.0117	0.9884	0.7111	1.4394
	5b	0.9006	1.1104	0.6171	1.3144
	6a	0.9482	1.0546	0.6486	1.3863
	6b	1.2006	0.8329	0.8233	1.7506
Adherence	Non-Adherent	1.0481	0.9542	0.8766	1.2531

Table 4 Result of the Goodness of fit Test

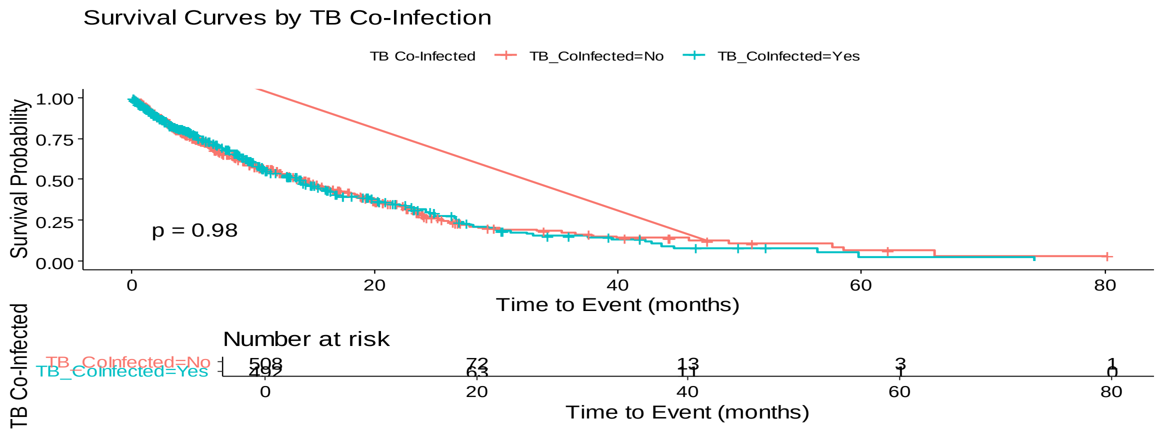
Coefficient of Concordance	0.549	Se = 0.015	
Likelihood ratio test	17.44	Df = 20	P = 0.6
Wald test	17.54	Df = 20	P = 0.6
Score (log rank) test	17.63	Df = 20	P = 0.6

The results from Tables 2, 3 and 4 showed the output of Cox Proportional Hazard Model which is commonly used in survival analysis to explore the relationship between survival time of subjects and one or more predictor variables. From the results, the geographical location (Ezeagu) and Functional Status (Bedridden) of the patients are significant.

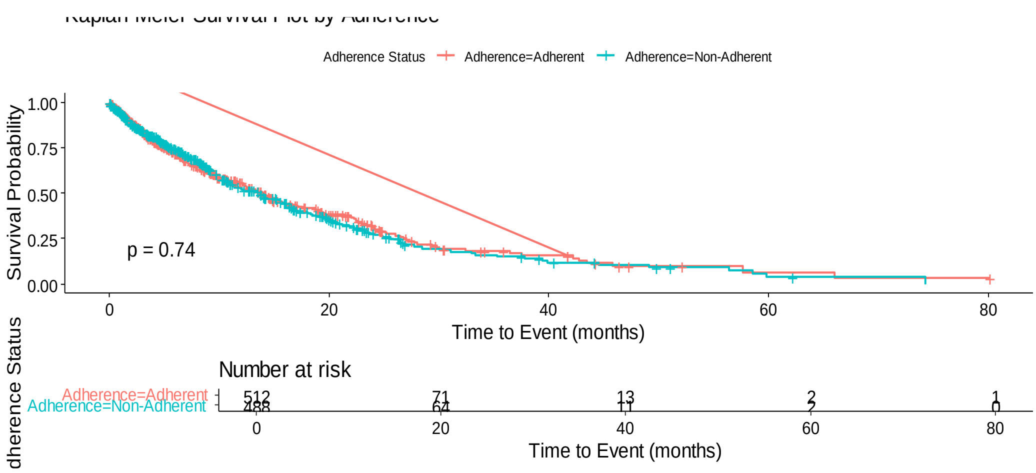
The Kaplan-Meier survival plot was done on functional status, TB co-infection and on patient's adherent to treatment and the results are shown in figure 1A – 1C



A: Survival Plot by Functional Status from General Hospital, Udi



B Survival Plot by TB Co-Infection of Patients at General Hospital, Udi.



C: Survival Plot by Adherence from General Hospital, Udi.

Figure 1: Survival Plots for the characteristics under study

The plot suggests that there is a trend toward different survival probabilities based on functional status. The group with the highest survival probability appears to be those who are walking, followed by ambulatory, and then bedridden patients. Also the bedridden group shows the steepest decline in survival probability, indicating a poorer prognosis compared to the other groups.

This Kaplan-Meier plot demonstrates that there is no significant difference as indicated by the overlapping survival curves and the high p-value of 0.98. This suggests that TB co-infection does not impact survival outcomes in this dataset

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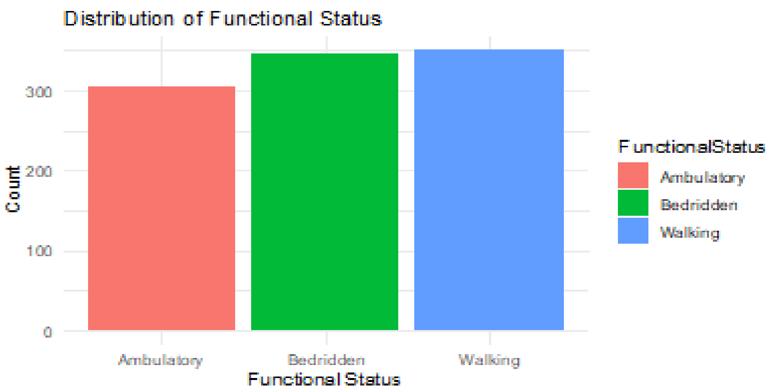
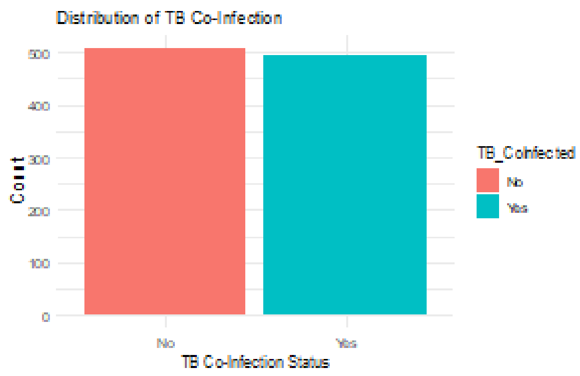
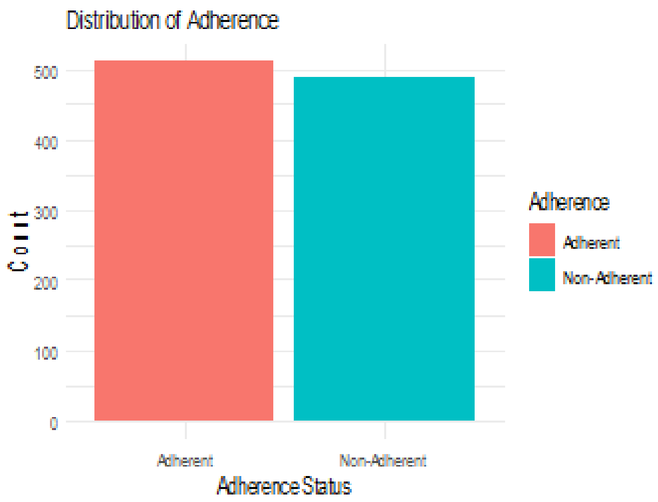
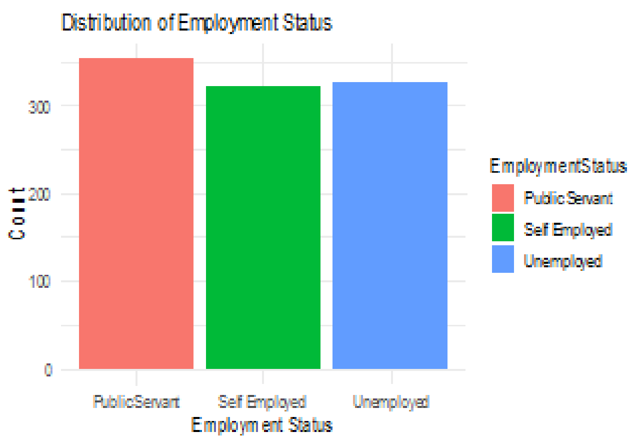
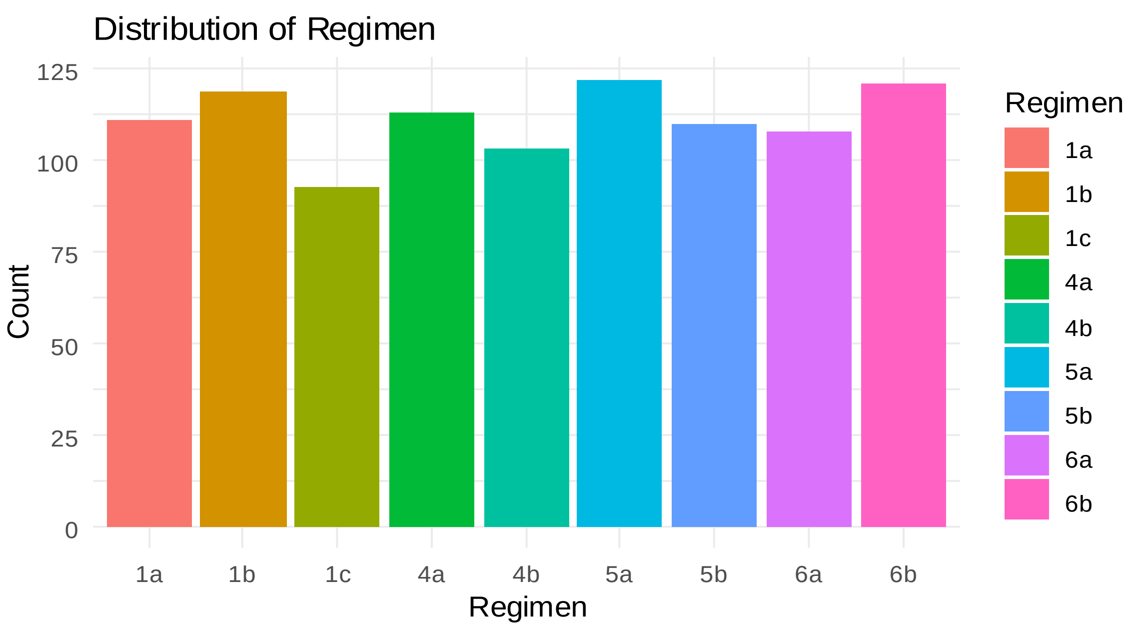
The plot showed an observed trend where adherent patients have better survival probabilities than non-adherent patients, suggesting that adherence to treatment may be beneficial for patient outcomes.











This bar chart in figure 2 demonstrates that the study's patient population is equally distributed across three functional statuses: Ambulatory, Bedridden, and Walking. Each group consists of roughly 330 individuals, indicating a balanced design in the dataset. This balance is advantageous for analyzing how different functional statuses might influence outcomes, as seen in the Kaplan-Meier survival analysis provided earlier.

The bar chart illustrates that the majority of the patients is not co-infected with TB, with only minority having a TB co-infection. This difference in group sizes can impact the statistical power and reliability of any analyses comparing these groups, as demonstrated by the Kaplan-Meier plot where no statistically significant difference was found.

The bar chart provides a clear visual representation of the distribution of adherence status within the study population, highlighting the disparity between the two groups. This imbalance has significant implications for the interpretation of the Kaplan-Meier survival curves as seen in the charts.

SUMMARY AND CONCLUSION

Neither sex nor age showed a significant impact on HIV-related mortality. This indicates that these demographic factors alone do not strongly influence survival outcomes in this cohort. Geographical location Ezeagu indicates higher risk of mortality. It emphasized the need for localized public health strategies. Continuous monitoring and tailored interventions based on local needs can help address specific challenges. Maintaining mobility and activity is crucial. Those who are bedridden face significantly higher risks, necessitating interventions to improve functional capabilities. Immune Function (CD4 Count) also did not significantly affect mortality. While CD4 count is typically an important marker of immune function in HIV patients, its lack of significant effect in this study could be due to effective treatment regimens and healthcare interventions. This insignificant result TB Co-infections might suggest effective management of co-infected patients, potentially due to integrated care programs for HIV and tuberculosis. Employment status does not significantly affect mortality. It may be as a result of positive effect of governmental and non-governmental interventions on easy accessibility of antiretroviral therapy. Poor adherence is not significant, emphasizes the need for more investigation on patients' drug adherence.

Future research should focus on longitudinal studies and the integration of additional variables, such as genetic factors and lifestyle behaviors, to further refine our understanding of HIV epidemiology.

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