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**1 author:**

Ojunga Samson Okoth
Kenya Forest Research Institute

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*Case Report*

# The application of logistic regression in modeling of survival chances of HIV-positive patients under highly active antiretroviral therapy (HAART): A Case of Nyakach District, Kenya

**Ojunga Okoth Samson[1,6], Mose Nyandwaki[2], Peter Mutwiri[3], Otulo Wandera[4], Omollo Oriema[5] and Edgar Otumba[6]**

[1]Ministry of Devolution and Planning, P.O Box 30005 Nairobi, Kisumu.
[2]Kenya National Bureau of Statistic, P.O Box 30005-Nairobi
[3]Ministry of Trade, Weight and Measures department, P.O Box 36-60202 Nkubu-Kenya.
[4]Rongo University College, P.O Box 103-40405 Rongo, Kenya
[5]Ministry of Education, Kisumu County P.O Box 145 Pap Onditi 40111
[6]School of Mathematics, Applied Statistics and Actuarial science Maseno University, P. O. Box 333-40105, Maseno, Kenya.

*Corrsponding author email: mcojijosamsa@gmail.com

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***ABSTRACT***

**In Kenya the number of persons requiring antiretroviral Therapy (ART) in 2012 was over 90,000 while globally more than 1.4 million were under ART in the year 2012. Though ART treatment has decreased mortality of HIV associated deaths, there is still need for funding of ART services by donors and Ministry of health so as to prevent the loss caused by AIDS related deaths in the society. This study modeled using logistic regression the survival chances of the HIV positive patients under ART treatment in within Nyakach district. The study outlined the various socio-economic factors affecting the survival or death of the patients using logistic regression model. The sample of 320 patients was considered from patients from Katito health center from Nyakach district for a period of six months. The analysis of the data showed that risk factors consisting TB infection, kind of drug regimen, distance from the health facility, access to tap and portable water, the kind of marital status of patients and counselling session attendance by patients on ART affected their survival. Thus, the survival of patients under ART programs can be improved if we improve the access to socio-economic factors like access to water, setting up many health facilities too provide health services at close distance to the affected and also we can bring behavioral change among HIV patients to attend counselling session and get pieces of advices on correct health measures and be-haviours.**

**Keywords:** odds ratio, logistic regression, Log likelihood

## INTRODUCTION

Now it's almost three decades since the first case was reported, HIV/AIDs continue to be the most serious health issue facing the world. The UNAIDS by 2011 estimates that globally there are 34 million people living with HIV (Hoa 2011). In the last two decades, the Acquired Immune Deficiency Syndrome (AIDS) epidemic that is caused by the Human Immunodeficiency Virus (HIV) swept through sub-Saharan Africa with venom. Although mortality related to HIV has declined in recent years, 1.8 million people lost their lives due to HIV related complication in 2010 alone and many more continue being infected annually with 2.7 million new cases of HIV being reported in 2010 only (Hoa 2011). In 2011 over 1.6 million people were HIV infected in Kenya, even though adult prevalence declined from a high of 15 in 1998 to a current low of 6.2 (NACC and NASCOP 2012). The UNAIDS estimates that due to the use of ARVS close to 2.5 million deaths have been averted since 1995 [14]. In the year 2011 of the 1.6 million people estimated to be living with HIV in Kenya only 432,621 were on ARVs (Kimani, 2008). Since the epidemic began, HIV has claimed the lives of at least 1.7 million people in Kenya. In 2011, an estimated 49,126 people in Kenya died of AIDS-related causes. Hence this disease being one without any cure is accounting and responsible for the economical, social and health crisis especially among developing countries where it prevalence is still very high (Hosmer and Lemeshow 1989).

**Objectives of the study**

1. To determine the important social and economic factors affecting Survival of HIV patients under highly active antiretroviral therapy or HAART.
2. To determine a suitable model for predicting the chances of survival among the HIV positives attending ART clinic in Nyakach District.
3. To provide information for policy makers on the factors affecting survival of HIV positives taking ARVs.

**Multiple Logistic regression modeling**

In this study, we employed the use of Logistic regression to calculate the probability of survival of patient over the probability of death of patient and the results of the analysis are expressed in the form of an odds ratio. This study adopted a systematic random Sampling (Cochran 1977) method to collect representative sample of patients based on their identification number, clinic cards as they attend the HAART clinic in the health centre in Nyakach district.

**Basic concepts and notation**

**i.** Odds: In an experiment of chance the odds in favour of an event is the number of ways in which the event could occur, divided by the number of ways in which it could fail to occur. The odd is the ratio of the probability that the event of interest occurs to the probability that it does not. This is often estimated by the ratio of the number of times that the event of interest occurs to the number of times that it does not.

**ii.** Logit: The log odds (logit) are the natural logarithm (log to the base e) of the odds. The logit has a symmetrical range: a positive sign means the odds are in favour; a negative sign means the odds are against.

**iii.** Log likelihood: 'likelihood' is a probability, specifically the probability that the observed values of the dependent may be predicted from the observed values of the independents. Like any probability, the likelihood varies from 0 to 1. The log likelihood (ll) is its log and varies from 0 to minus infinity (it is negative because the log of any number less than 1 is negative).

**Literature Review**

**Highly Active Anti-retroviral Therapy**

The main focus of this literature review in on previous studies about the determinants of HIV/Aids mortality and socio economic factors that contribute to the death of AIDS patients on ART treatment. Initially most AIDS patients were found in Kenya's urban centres, but the situation revised such that 62 % of the country's HIV/Aids cases are now in rural areas. According to report of a study on the in-hospital mortality rates of HIV patients on the causes of mortality and characteristics of inpatients at Kamuzu Central Hospital (KCH) in Lilongwe, life expectancy of HIV-infected patients primarily depended on the natural history of the HIV infection (Akinkuotu and Roemer 2011). Peter Kipkurui (Yegon 2008) on his study on the measures of dealing with malnutrition and anemia to improve survival and curb early mortality in Kenya, revealed that HIV death of HIV positive patients starting ART in rural clinics of South Rift Valley is still a challenge (Yegon 2008). The world Health Organization Publication report of 2008 (World Health Organization 2011) on early loss of HIV-infected patients on potent antiretroviral therapy program in low-income countries used Logistic regression to examine the association between the follow-up program and economic situation of the poor countries. This report indicated that better ART outcomes which included higher programme retention rates may only be obtained in services that have smaller numbers of patients, showing that high number of patients on ART therapy has much socio-economic risks factors affecting their survival. Several other reports described mutual relationship between demographic and clinical treatment on the follow-up outcomes among a cohort of HIV-infected at a large HIV care program (Chao-Ying (1974). A publication of Journal of Aids (Nachega 2005) on HIV-infected adults in Soweto, South Africa, indicated that out of 105 HIV clinic patients evaluated, 70% of were not on ART, 89 % had good knowledge about the cause of HIV infection and 83 % knew about modes of transmission. Fifty-nine percent reported they were not worried about ART side effects. 65% agreed that missing ART doses can lead to disease progression. Ninety percent had disclosed their HIV sero-status to 1 or more persons, but only 62 % with a current sexual partner reported having told that partner their status, hence showing a greater margin on knowledge on ART and HIV/Aids. In most developing countries the epidemic is greatly embedded with age, sex, poverty and cultural issues. A study of the United State National surveillance (Palella et al., 1998) data in 1998 showed greater reductions in morbidity and mortality associated with the acquired immunodeficiency syndrome (AIDS). The analysis of data on 1255 patients, each of whom had at least one CD4+ count below 100 cells per cubic millimeter, which were seen at nine clinics specializing in the treatment of human immunodeficiency virus (HIV) infection in eight U.S. cities from January 1994 through June 1997, indicated that mortality among the patients declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in the second quarter of 1997. These declines in morbidity and mortality were attributable to the use of more intensive antiretroviral therapies (Nachega 2005). In South Africa projections suggested that about 6 million people were infected with HIV by the year 2005 and that without treatment intervention the mortality rate of HIV/AIDS will reach over 800,000 deaths per year by 2013 (Dorrington et al., 2002) . Hence the government of South Africa has proposed to increase access to highly active antiretroviral therapy (HAART) to alter this trend (Dorrington et al., 2002). The report of a study in Eldoret, Kenya to determine important factors that affect antiretroviral drug adherence among HIV/AIDS male and female adult patients (18 years and above) attending Moi Teaching and Referral Hospital, Eldoret, Kenya indicated that the key factors affecting adherence are; being away from home, being busy and forgetting. It was recommended that patients should be educated on the importance of strict adherence to the prescribed doses of ARVs as a suitable measure of intervention. (Hoa Mai 2011) on his masters thesis on adherence once on HAART by patients noted that although the measurement of adherence of ART adherence is critical in both ART intervention and clinical research, there is no 'gold standard' by which to measure adherence to medication hence the need to study all the factors that surround the patients lifestyle affecting their survival (adherence to drugs) after being introduced on HAART. A publication in the Journal of Clinical Oncology in 2001 elaborated a (Beata et al., 2001) multivariate analyses based on the cox proportional hazards model of the survival of HIV patients from the length the time they start chemotherapy to their death from various causes while on ART. The analyses were also conducted with the use of exact logistic regression to model the proportion of patients who were alive at the end of follow-up. The Harvard school of public health publication (Harvard school of public health 2006) on Multinomial logistic regression analyses examined the association of demographics and sexual risk behaviors across the tripartite groups. Women with a history of sexually transmitted diseases were more likely to experience violence and depression both alone and jointly. Women who had two or more sexual partners in the last 30 days (OR=2.26) and women who had an early onset of alcohol use (OR = 2:50) were at an increased risk for having the full tripartite of drug use, violence and depression. Never being married was a protective factor for the full tripartite. As expected, more risk factors were found among women who had the full tripartite than among women with one or two of the factors. The co-existence of the tripartite factors and sexual risk behaviors may indicate a need to ultimately provide more specialized prevention and intervention efforts to combat HIV infection. This area of research may improve our understanding of the numerous obstacles to HIV intervention among drug-using populations. Perhaps because most large scale treatment providers have few resources available to track missing patients, most studies treat patient attrition as a side issue and focus solely on describing those patients who are retained. Recently studies (Kilbourne et al., 2002) has even focused mainly on clinical, immunological and virological data, but little is known about social, economic and demographic factors influencing loss on patients on ART treatment which this study is proposed to focus

**Logistic regression**

Logistic regression was first proposed in the 1970s as alternative techniques to overcome limitations of ordinary least square (OLS) regression in handling dichotomous outcome. It became available in statistical packages in the early 1980s. Logistic regression has been used in epidemiological research, where often the outcome variable is presence or absence of some disease. Epidemiologic studies are frequently cross-sectional, simple, fast and are inexpensive in design and when the outcomes are binary, then logistic regression have been used for these analysis which results in odds ratio being frequently reported in situations where incidence or prevalence ratios are estimable, despite the fact that they are "biologically interpretable only insofar as it estimates the incidence-proportion or incidence-density ratio" (Greenland 1987). From a survey done by the authors in the International.

Journal of Epidemiology and in the Revista de Sade Pblica (So Paulo, Brazil) published in 1998, 221 original articles were found and among these, 110 (50%) were based on cross-sectional studies, and 45 (20%) on longitudinal studies. Logistic regression was used for the analysis of 37 (34%) and 10 (22%) of these studies, respectively. We have, therefore, that an important proportion of such studies end up reporting odds ratios, the effect measure yielded by logistic regression, rather than prevalence or incidence ratios. Additionally, logistic regression is often used for the sake of control of confounding and adjustment of interactions (Axelson et al., 1994). Studies assessing the adherence to highly active antiretroviral therapies (HAART) in a cohort of French patients infected by HIV through injection drug use (IDU), and the impact on adherence of buprenorphine ambulatory drug maintenance treatment (DMT), has been widely introduced since 1996, with methodology of univariate and logistic regression with adjusted odds ratios (OR) used to compare characteristics of non-adherent versus adherent patients. In French, the results of the 164 patients, 34.8% took less than 80% of the prescribed HAART doses during the previous week and the decrease in viral load after initiation of HAART was signicantly lower among non-adherent patients. After adjustment by logistic regression, non-adherence was associated with younger age, alcohol consumption, frequency of negative life-events during the prior 6 months and active drug use. However, IDU in buprenorphine DMT reached higher levels of adherence (78.1%) than ex-IDU (65.5%), although this difference did not reach statistical signicance.Hence concluding Prescription of buprenorphine DMT may increase adherence to HAART among HIV-infected opiate-dependent patients. Multiple logistic regression has also been used to determine the association between HIV and vital status 12 months after starting treatment (HAART) controlling for covariates which showed that there was no significant difference in 12-month survival between patients with and without HIV. However, HIV-positive patients not on ARVs had significantly poorer 12-month survival than did either HIV-positive patients on ARV treatment (p = 0:05) or HIV-negative patients (p < 0:01). There was no difference in 12-month survival between HIV-positive patients on ARV treatment and HIV-negative patients (p = 0:44) (Charlotte et al., 2011).

## Model building

While simple logistic regression analysis is the regression application with one dichotomous outcome and one independent variable, multiple logistic regression analysis was applied where there is a single dichotomous outcome or more than one independent variable as described by Hosmer and Lemeshow in their description of logistic regression analysis and its applications6. Considering k independent variables affecting the survival of the patients denoted by the vector of factors affecting patients under HAART treatment clinic. The conditional probability that denoted the outcome (Dead/Alive while on ART) was present was denoted by: $p(y = 1/x) = p(x)$.

The dependent variable are either the patients are dead or surviving while on HAART while the Independent variables ranges from the marital status, education level, source of income, source of water, lighting source, CD4 Count, WHO Stage, Weight of patients, TB Cases, Counselling sessions attended, Drug regimen, Alcohol/drugs abuse, HIV status of partner, Distance to health facility, Nature of the road to health facility, and religion affiliation. The logit of the multiple logistic regressions is given by the equations (Dave 2006) below:

$$g(X) = \beta_0 + \beta_1 x_1 + ....... + \beta_k x_k \quad ........3.1$$

While the probability of survival of HIV positive patient is also given by;

$$p(x) = \frac{\exp(\beta_0 + \beta_1 x_1 + ....... + \beta_k x_k)}{1 + \exp(\beta_0 + \beta_1 x_1 + ....... + \beta_k x_k)}$$

..............................3.2

The odds ratio is a measure of effect size, describing the strength of association or non-independence between two binary data values as outlined below:

$$odds = p/1-p = \frac{probability(survival)}{1 - probability(survival)} = \frac{pr\{survival/eventoccurs}{pr(eventsdoesnotoccurs/death)}$$

...3.3

and

$$probability(events) = odds(event)/1 + odds(event) ......$$

...3.4

also

$$oddsratio = \frac{oddsofsurvival}{oddsofdeath} \quad .........................3.5$$

Unlike other measures of association for paired binary data such as the relative scores, the odds ratio treated the two variable being compared symmetrically, and estimated using some type of non random samples (Agresti 1996). The logit function is defined by: $\log it(p) = \log\left(\frac{p}{1-p}\right)$ ..........3.6

The odds of survival is

$$\frac{p(x)}{1 - p(x)} = \exp(\beta_0 + \beta_1 x_1 + ....... + \beta_k x_k) \ ...$$

...................................3.7

The log of odds of survival equals

$$\log \frac{p(x)}{1 - p(x)} = \exp(\beta_0 + \beta_1 x_1 + ....... + \beta_k x_k)$$

.....................................3.8

The probabilities ranges between zero and one, Odds ranges between zero and infinity, but the Logit of transformation ranges between negative infinity and

**Table 1**. Variables in the Final Model

| | | β | SE | Wald | df | Sig. | Exp | 95% C I Lower | Upper |
|---|---|---|---|---|---|---|---|---|---|
| Step | Marital | | | 6.560 | 3 | .087 | | | |
| | Marital(1)-M | -2.817 | 1.232 | 5.225 | 1 | .022 | .060 | .005 | .669 |
| | Marital(2)-M | -1.616 | 1.134 | 2.031 | 1 | .154 | .199 | .022 | 1.834 |
| | Marital(3)-M | -1.723 | 1.365 | 1.593 | 1 | .207 | .179 | .012 | 2.591 |
| | Water(1)-W | -1.775 | .670 | 7.027 | 1 | .008 | .169 | .046 | .630 |
| | DISTANCETOHEALTHCE NTRE(1)-DHF | -3.670 | 1.591 | 5.323 | 1 | .021 | .025 | .001 | .576 |
| | COUNS | | | 11.714 | 2 | .003 | | | |
| | COUN(1)-Coun | -3.005 | 1.353 | 4.931 | 1 | .026 | .050 | .003 | .703 |
| | COUN(2)-Coun | .082 | 1.229 | .004 | 1 | .947 | 1.086 | .098 | 12.084 |
| | REGIMEN(1)-Re | 2.340 | .776 | 9.083 | 1 | .003 | 10.379 | 2.266 | 47.531 |
| | TB(1) | -2.227 | 1.039 | 4.591 | 1 | .032 | .108 | .014 | .827 |
| | CONSTANT | 8.788 | 2.410 | 13.293 | 1 | .000 | 6.55E3 | | |

infinity. Hence modeling the probability *p* with logistic function is equivalent to fitting a linear regression model in which the continuous response *y* which has been replaced by the logarithm of the odds of success for a dichotomous random variable.
The odds in favour of survival for multiple regressions is outlined below as:

$$\ln\left(\frac{p}{1-p}\right) = \ln\left(e^{g(x)}\right) = (\beta_0 + \beta_1 x_1 + ....... + \beta_k x_k) \cdots$$

……………3.9

Then the probability of death of HIV positive patient on HAART is given as:

$$(1-p(x)) = \frac{1+\exp(\beta_0+\beta_1 x_1+.......+\beta_k x_k) - \exp(\beta_0+\beta_1 x_1+.......+\beta_k x_k)}{1+\exp(\beta_0+\beta_1 x_1+.......+\beta_k x_k)}$$

$$= \frac{1}{1+\exp(\beta_0+\beta_1 x_1+.......+\beta_k x_k)}$$ …….3.10

Since the observations are assumed to be independent, the likelihood function is obtained as the product of the terms given in expression as below

$$l(\beta) = \sum_{i=1}^{n} \text{p(xi)}^{\text{yi}} (1 - \text{p(xi)})^{1-\text{yi}}$$

…………………………………3.11

And the log likelihood defined as

$$l(\beta) = \ln l(\beta) = \sum_{i=1}^{n} \text{(yi)p(xi)} + (1 - \text{yi})\ln(1 - \text{p(xi)})$$ ..3.12

To find the value of that maximizes (L (β)) we differentiate (L (β)) with respect to β's and set the resulting equation to zero.

Letting $\hat{\beta}$ denotes the solution to these equations, then the fitted model value for the multiple Logistic regression model are $\hat{p}$ ($x_i$), the values of this expression in the above equation is

Computed using $\hat{\beta}$ and $\chi_i$ shown below

$$\hat{p}(xi) = \frac{e^{e(xi)}}{1+e^{e(xi)}}$$ ………………………3.13

## RESULTS

### Introduction

The overall best logistic regression model for this set of data emphasizes that both socio-economic and biological factors affect the survival status of patients on HAART within Nyakach district. The estimated coefficients ( β's) for the covariates in the final model, their standard error and the odd ratio corresponding to each of the estimated β' s are given in the following table 1 above.
The final model expressed as log odds of survival of HIV positive patient on HAART as shown below:

$$\log\left(\frac{p}{1-p}\right) = 8.788 - 2.227TB(1) + 2.40\,\text{Re}(1) - 3.005Coun(1) - 3.670DHF(1) - 1.755W(1) - 2.817M(1)$$

### Result interpretation

(i) **TB Cases**(1)

Though it's known that Tuberculosis (TB) remains a major public health problem and it's believed that the TB infection reduces the survival of the HIV positive patient on HAART. According to equation 3.1 ($\beta_1$), the value of Exp($\beta_1$) is 0.108 which implies that a one unit in patients infection by TB decreases the odds that the HIV positive Patients on HAART will survive by 0.108.The output for the 95% Confidence Interval for the $\beta_1$ is -2.227 1.96 1.039=(-4.263,-0.191) and for odds ratio ($e^{4:263}$; $e^{0:191}$)=(0.014,0.826),hence we conclude a negative association between the patients who contacted TB and probability of their survival of while on HAART in Nyakach district.

(ii) **Drug Regimen**(1)

The case of increase in the patients on 2nd Line treatment (2F2B,AF1B,CF2A,AS2A) changes the odds of Survival chances of HIV positive patients on HAART by a multiplicative factor equal to $e^{2}$ given by $e^{2:340}$, i.e. by 10.379(increasing by approximately ten and third times that the HIV positive client on HAART will survive). The 95% Confidence Interval for the $\beta_2$ is 2.340 1.96 0.776=(0.819,3.850) and for odds ratio ($e^{0:819}$; $e^{3:850}$) =(2.268,46.993),hence we conclude a positive association between the patients on 2nd line treatment and their probability of survival while on HAART in the district.

(iii) **Counseling session**(1)

The equation 3.1 shows the value of Exp($\beta_3$) as 0.05 which implies that a one unit in-crease in the number of HIV positive patients who does not know about counseling and does not attend counseling within the month decreases by 0.05 the odds of HIV positive patient's survival while on HAART. The 95% Confidence Interval for the $\beta_3$ is -3.005 1.96 1.353=(-5.657,-0.353) and for odds ratio ($e^{5:657}$; $e^{0:353}$)=(0.003,0.703),hence we conclude a negative association between the patients who does not know about counseling and their possible survival while on HAART in Nyakach district.

(iv) **Distance to Health facility**(1)

Access to prompt and adequate treatment offered in health facilities remains key complement to the survival of HIV positive on HAART within Nyakach district, when these facilities are far off the services are out of reach of many deserving patients. The result show the value of Exp($\beta_4$) as 0.025 which implies that a one unit increase in distance to health facility over 5 km decreases the odds of the HIV positive patient's survival while on HAART by 0.025. The 95% Confidence Interval for the $\beta_4$ is -3.670 1.96 1.591=(-6.788,-0.552) and for odds ratio ($e^{6:788}$; $e^{0:552}$)=(0.001,0.576),hence we conclude a negative association between the patients who are far from health facilities and possible survival while on HAART.

(v) **Access to piped water**(1)

The value of Exp($\beta_5$) was 0.169 which implies that a one unit increase in lack of access to piped water decreases the odds of the HIV positive patient's survival while on HAART by 0.169.The 95% Confidence Interval for the $\beta_5$ is -1.775 1.96 0.670=(-3.088,-0.462)and for odds ratio ($e^{3:088}$; $e^{0:462}$)=(0.046,0.630), hence we conclude a negative association between the patients who do not have access to piped water and probability of survival while on HAART.

(vi) **Marital types**(1)

The value of Exp($\beta_6$) was 0.060 for widowed patients which implies that a one unit increase in the numbers of widowed patients decreased the odds of the HIV positive patient's on HAART by 0.060.The 95% Confidence Interval for the $\beta_6$ is -2.817 1.96 1.232=(-5.232,-0.402) and for odds ratio ($e^{5:232}$; $e^{0:402}$)=(0.005,0.669) ,hence we conclude a negative association between the patients who are widowed and their survival while on HAART.

## CONCLUSION AND RECOMMENDATION

These socio-economic factors may not be clinically important but because they alert the physicians to the help improve the survival chances of the patients on HAART. It is interesting to note that the overall best logistic regression model does not include the some risk factors like CD4 Count, WHO Stage, Weight of the patients and other key clinical risk factors which had dominated the research world on HIV/Aids. Most of the past research studies of HIV/Aids patients had concentrated on only the clinical risk factors as key primary predictors in the survival chances of HIV positive patients on HAART. The logistic regression method of analysis of the data collected from the patients attending ART Clinic in Nyakach district indicated that the main factors that affect the survival/death status of HIV patients who are on HAART include; access to clean and portable water, the TB cases among the patients, Drug regimen, marital status of HIV positive patients, the distance to the health facilities and the number of counseling session each patients are able to attended within a month. It's important to indicate that most patients with poor health indicators like low weight and who have HIV-positive partners are less likely to survive as indicated from the study. Since the main aim of HAART is to improve the status of HIV-positive individuals taking drugs, its is important to research more on the socio-economic risk factors that are normally excluded by epidemiologist as less significant even though this study shows that they are significant using the logistic regression model. Thus its of great importance to include all the risk factors ranging from biological, social, behavioral and economical factors in order to revert the current death still witnessed of the HIV positive patients even while on HAART and enhance their survival. Hence the demonstration that logistic regression model can be used as a basis of understanding,modelling and studying the other socio-economic factors that affect the survival of HIV positive patients on HAART.

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