QUALITY ADJUSTED LIFE YEARS(QALYs) ESTIMATION FOR HIV PATIENTS ON ART IN KENYA.

ABSTRACT

Aims: This study seeks to estimate QALYs for HIV/AIDS patients on ART in Kenya to evaluate the impact of ART. Previous studies in Kenya have majorly focused on Disability Adjusted Life Years (DALYs) as the health outcome measure of interest for patients on ART. The QALYs values are important as they form a basis for evidence based decision making and policy formulation in the country with regards to HIV/AIDS.
Study design: The study involved secondary data obtained from a retrospective follow up study on hospital records of HIV/AIDS patients enrolled for ART from 2005 to 2017.
Place and Duration of Study: Jomo Kenyatta University of Agriculture and Technology, between January 2019-April 2023
Methodology: The study involved a retrospective study of 3000 patients on ART in Kenya from the period of 2005-2017. All the records are in terms of random patient id and in no way is the privacy and anonymity of patients is compromised. The inclusion criteria is patients who had complete information on the covariates used in the model over the follow up period. The proxy utility function method was used to estimate the QALYs for HIV/AIDS patients on ART. The total QALY gained by each patient is separately calculated and aggregated to get the average QALYs gained by all patients.
Results Sex, Age, Marital Status and weight are significant predictors of survival of HIV Patients on ART in Kenya. Being on ART therapy resulted in a gain of 9.688313 QALYs for HIV/AIDS patients. The association parameter estimate is-0.0345, the negative value implies that increase in the values of CD4 count results in decrease in the hazard of death for HIV patients on ART therapy
Conclusion: The proxy utility function methodology is appropriate for the calculation of QALYs values for HIV patients on ART. It has the advantage of introducing patient level variability in the course of utilities and the utility values of each patient on ART can be calculated at each time point. Since ART results in the improvement in QALYs of patients, efforts should be directed towards ensuring patients who are enrolled onto the therapy continue with it for sustained health and non health benefits.

Keywords: Effectiveness, Health, Survival, Covariates

1. INTRODUCTION

Africa carries an estimate of 25% of world's disease burden but only has access to less than 1% of the global health expenditure. For any given set of interventions for a disease, the challenge that arises is that resources are scarce. Human Immunodeficiency Virus (HIV) is

one of the diseases that imposes a large disease burden to the continent. In Kenya, there has been great progress in the use of biomedical, non-biomedical, structural and behavioral approaches in the prevention, diagnosis and treatment of HIV/AIDS over the past 2 decades. This has resulted in HIV translating from a terminal illness to a chronic disease.

There were 1.5 million people living with HIV(PLWHIV) in Kenya in 2020, including 50% who were on ART treatment, (UNAIDS Data,2021). According to HIV estimate reports of 2020, there were 52,800 new infections in the country. Considering the public health impact of chronic HIV infections adherence to ART treatment are vital HIV control measures. However, ART treatment is expensive and requires access to medical facilities and care. Moreover, it has been noted that there is a level of non-adherence to ART regimens by some PLWHIV.

Kenya aims at achieving the global targets of zero new infections, zero AIDS- related deaths and zero discrimination. Higher levels and efficient use of these scarce resources are needed to get the AIDS pandemic response back on track towards the global goal of ending AIDS by 2030. This necessitates quantifying the health and non- health impact of ART on PLWHIV.

Economic evaluation is as an important tool for comparing alternative interventions in terms of resource use and the outcomes as it is a decision-making strategy, (Drummond and Rudmik,2013). The Ministry of Health (MoH) in Kenya has adopted the evidence- informed approach in the advocacy, planning and budgeting for HIV/AIDS response at the national and county levels. Evidence based policy making emphasizes on the increasing need for economic evaluation of funds spent on disease interventions.

The Quality adjusted life years (QALYs) is the recommended metric to be used in cost effectiveness analysis for health outcome evaluation by several decision- making bodies, (Sanders et al,2016). It is a single measure of both morbidity and mortality and defines health in terms of time spent in health states, that is, it represents preferences for health status and duration of the effect of the intervention. QALYs is a useful measurement standard of assessing the value of an intervention given scarcity of resources, (Neumann and Cohen,2018). To estimate the QALYs gained when receiving an intervention, the health utilities at different health states are calculated. The health utility weights lie between 0 signifying death and 1 signifying perfect health.

There are different approaches to calculating the health-related quality of life such as Euroqol-5D (Balestroni and Bertolotti,2012), Health Utility Index (Horsman et al., 2003), SF-6D (SF-36 Brazier et al,2002). The methodology of calculating QALYs employed in this research is the proxy utility function introduced by (Deo and Grover, 2019). The proxy utility function is preferable in cases where the survival data is accompanied with longitudinal measurements on certain covariates in order to incorporate the joint modelling of survival and longitudinal models. This approach also allows for patient level variability in the course of the utilities even in particular states thus QALYs gained by each patient on ART can be calculated separately.
It is vital to measure the change in QALYs as individuals receive ART treatment for HIV/AIDS infection in order to understand the health and non-health impact of the life-long ART intervention on the patients' health. Moreso studies on cost effectiveness of ART treatment with QALYs as the health outcome measure for Kenya are yet to be conducted.

In Kenya, for HIV/AIDS, effectiveness of ART treatment has been done from an epidemiological perspective. There is little research that has been carried out on the health and non-health impact of the ART treatment on patients with QALYs as the outcome measure.

2. MATERIAL AND METHODS

Study Design

The study involved secondary data obtained from a retrospective follow up study on hospital records of HIV/AIDS patients enrolled for ART from 2005 to 2017.

Study Population

The study conducted a retrospective analysis of cohort data from a sample of 4500 people living with HIV(PLHIV) on ART in Kenya. Individual patient records were used but no identification number to maintain anonymity. We included patients aged 18 years and above at ART initiation dates. We excluded patients with incomplete information about exact date of death, date of collection of Viral Load, CD4 count and lost to follow up. The patients who were alive at the end of the study period were right censored during their last hospital visit. This reduced the study sample to 3000 patients. We further extracted demographic characteristics such as age, gender, marital status and weight.

Statistical Analysis

The secondary data was entered, cleaned, and managed using of R software. QALYs represents a day spent in good health and measures the health effect/health outcome of a medical intervention. To calculate the QALYs, this study used the proxy utility approach developed by Deo and Grover(2019). This approach is suitable as it allows for the joint modelling of the longitudinal variables observed during follow up visits and the time to event of interest which in this case is death. The biomarker that has been used as a measure of disease progression is the CD4 count for each patient during the follow up visits.

Joint Modelling of Longitudinal and Time-to-Event Data

Joint Model Specification

Let;

n : number of patients enrolled on the ART therapy.

T_i^* : True observed event time for i^{th} patient on ART therapy.

C_i : Censoring time for i^{th} patient on ART therapy.

T_i : event time for the i^{th} patient on ART therapy where T_i = min (T_i^* ; C_i)

$\rho_i = I(T_i^* \leq C_i)$: the event indicator which takes value 1 when the event has occurred and 0 when observation is censored.

$y_i(t)$:value of the observed longitudinal outcome for patient i on ART therapy at time *t.*

t_{ij} j^{th}occasion (time point) at which longitudinal response variable is observed for i^{th} patient (j = 1, 2, ..., n) i.e., number of times, and the time points at which longitudinal responses
are recorded for a patient on ART therapy can differ among patients on ART therapy.

y_{ij}: value of the longitudinal outcome for i^{th}patient on ART therapy at t_{ij}

$m_i(t)$: unobserved value of the longitudinal outcome for i^{th} patient on ART therapy at time *t.*

Longitudinal sub-model: Linear mixed effects model

The linear mixed effects model for the i^{th} patient on ART therapy according to Rizopoulo(2010), can be defined as:

$$y_i(t) = m_i(t) + \varepsilon_i(t)$$

And

$$= x_i^T\beta + Z_i^T b_i + \varepsilon_i(t) \sim N(0, \sigma^2)$$

where,

β : vector of the unknown fixed effects parameters,

b_i : vector of random effects,

x_i^T : transposed row vectors of the design matrices for the fixed effects,
Z_i^T : transposed row vectors of the design matrices for the random effects, random effects follow a multinomial normal distribution,
$\varepsilon_i(t)$ denotes the error terms which are assumed to be independent of b_i
$m_i(t)$denotes the value of the longitudinal outcome for the i^{th} patient on ART therapy at time t and is assumed to be free of any measurement error.

Survival sub-model: Time dependent Cox PH

The Time dependent Cox PH model for the i^{th} patient according to Rizopoulos (2010), can be defined as:

$$h_i(t_i|m_i(t), w_i) = h_0(t)\exp(\gamma^T w_i + \alpha m_i(t))$$

where,
$h_0(t)$ denotes the baseline risk function,
w_i is a vector of baseline covariates,
γ is a vector of coefficients corresponding to the baseline covariates,
α is the association parameter which measures the association between the risk of occurrence of the event of interest and the longitudinal outcome variable.

Parameter Estimation of the Longitudinal sub-model and the survival sub-model

parameters of both the longitudinal and survival sub model, they are jointly estimated using the maximum likelihood estimation by maximizing the joint likelihood function of the survival component and the longitudinal component.

proxy utility function

The proxy utility function developed Deo and Grover(2019) is defined as a function of changes in the longitudinal measures of the time dependent covariate. The association parameter
α estimated from the survival sub-model gives the effect of the change in the longitudinal measure on the utility of the patient on ART therapy and the effect of changes in the longitudinal covariate on the risk of death. From the Cox-PH survival sub-model, the exponential of the estimated coefficients represents extent of change in the odds in favor of the event of interest which is death per unit change in the covariate value.
Thus, for the exponential of the association parameter estimate, the inverse is taken as the proxy effect of change in the value of the time dependent covariate on utility of each patient on ART therapy.
The utility function for the i^{th} patient on ART therapy at time *t* is then defined as:

$$U_i(t) = U_{oi} + \exp(\widehat{\alpha}).\sum_t \left[\frac{y_i(t) - y_i(t-1)}{y_i(t-1)}\right]$$

Where: $U_{o1} = \frac{y_{oi}}{K}$ is the base utility of the i^{th} patient on ART therapy at the start of the study, y_{oi} is the baseline observed value of the time dependent covariate and K is the cut-off value of the longitudinal covariate beyond which it is considered to be in a medically normal range.

Calculation of QALY

According to Deo and Grover (2019), the utility values can be classified on either the basis of the observed covariate values and the ones calculated from the predicted values of the covariate in the case of censoring. Considering a discount rate of d%, (3%), QALY is given by:

$$QALY_I = U_{oi} + \sum_{t=2}^{T_i^*} U_i(t-1)\,(1+d)^{-t}$$

Ethical Considerations

We used data with no personal identification for the analysis to maintain anonymity. We sort ethical approval from the JKUAT Institutional Scientific and Ethical Review Committee

(ISERC) and the use of this data complies with the ethical guidelines defined for administrative and secondary data.

3. RESULTS AND DISCUSSION

Study Design

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Statistical Analysis

The secondary data was entered, cleaned, and managed using of R version 5.0.2 software. QALYs represents a day spent in good health and measures the health effect/health outcome of a medical intervention. To calculate the QALYs, this study used the proxy utility approach developed by Deo and Grover (2019). This approach is suitable as it allows for the joint modelling of the longitudinal variables observed during follow up visits and the time to event of interest which in this case is death. The biomarker that has been used as a measure of disease progression is the CD4 count for each patient during the follow up visits.

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Parameter Estimation of the Longitudinal sub-model and the survival sub-model

parameters of both the longitudinal and survival sub model, they are jointly estimated using the maximum likelihood estimation by maximizing the joint likelihood function of the survival component and the longitudinal component.

proxy utility function

The proxy utility function developed [4] is defined as a function of changes in the longitudinal measures of the time dependent covariate. The association parameter α estimated from the survival sub-model gives the effect of the change in the longitudinal measure on the utility of the patient on ART therapy and the effect of changes in the longitudinal covariate on the risk of death. From the Cox-PH survival sub-model, the exponential of the estimated coefficients represents extent of change in the odds in favor of the event of interest which is death per unit change in the covariate value.

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Calculation of QALY

According to[4], the utility values can be classified on either the basis of the observed covariate values and the ones calculated from the predicted values of the covariate in the case of censoring. Considering a discount rate of d%, (3%), QALY is given by:

$$QALY_I = U_{oi} + \sum_{t=2}^{T_i^*} U_i(t-1)\,(1+d)^{-t}$$

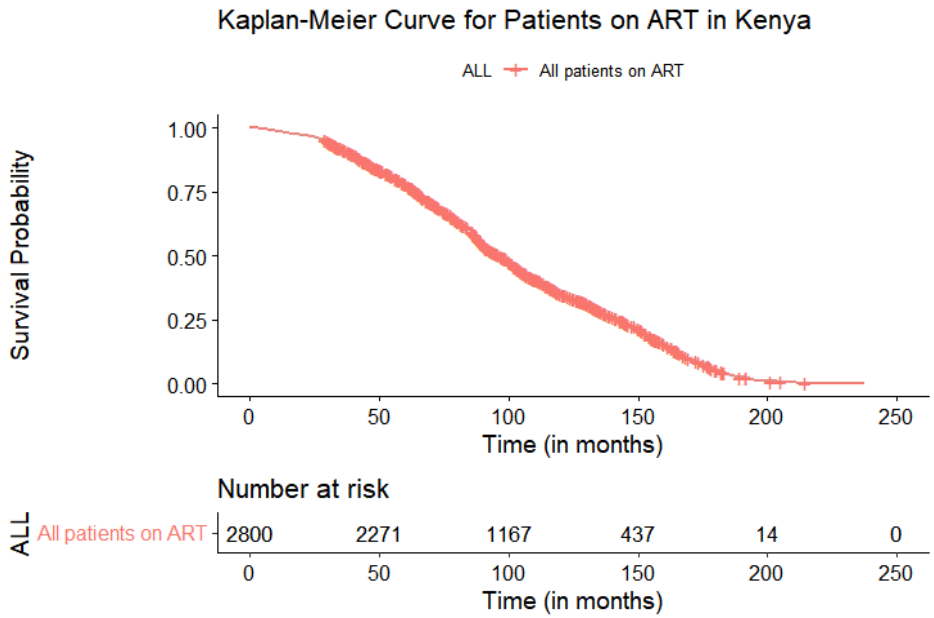

Fig. 1. KM curve for survival of HIV/AIDS patients on ART in Kenya

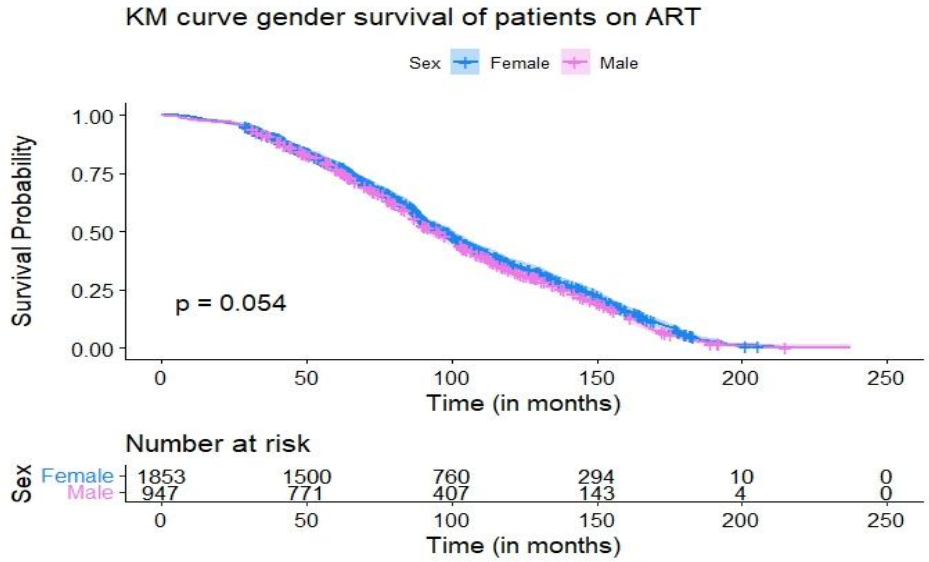

Fig. 2. KM curve for survival based on gender for HIV/AIDS patients on ART in Kenya

Table 1. Description of independent variables included in the model

Covariate name	Description	Levels (if a factor)
Number of Participants	Total number of patients (3000)	
ID	Patient ID code	None
Otime	Time of observation in months calculated from the date of registration (a time dependent covariate)	NA
Sex	A variable with two levels, Male and Female	0=Female 1=Male
Age	Age at baseline	NA
Marital Status	A variable with two levels, Married and Not married	0=Not married 1=Married
Weight	Weight at each visit	NA

Table 2. Results of the joint longitudinal and survival sub-model

Covariate	Longitudinal Sub-model		Survival Sub-model	
Intercept	Coefficient Estimates	p-value	Coefficient Estimates	p-value
Otime	112.310	<.0001***	-	-
Sex(Female)	-14.6147	<.0001***	-0.0435	0.0324**
Age	-3.2305	0.0007***	0.0087	0.0014***
Marital Status (Married)	-9.3230	0.003**	-0.2367	0.0179 **
Weight	-	-	-0.0654	<.0001***
Association	-	-	-0.0345	<.0001***

*** Significant at 1% level of significance; ** Significant at 5% level of significance; * Significant at 10% level of significance.

Figure 1 shows the Kaplan Meier Survival curve of all patients on ART in Kenya. There is a higher mortality at inception of ART but it reduces with time.
Table 1 gives a description of the variables/covariates which is the observation time, the gender, the age, the marital status and weight of patients on ART used in the proxy utility function to obtain the QALYs values.

From Figure 2, the Kaplan Meier Survival curve women are at a higher risk but also have a higher survival probability indicating better adherence to ART therapy than men.
From Table 2, we observed that the estimate of association parameter between the longitudinal measures on CD4 count and the survival sub-model is highly significant at 1% level of significance and its -0.0345, the negative value implies that increase in the values of CD4 count results in decrease in the hazard of death for HIV patients on ART therapy.

A discount rate of 3% per annum has been used in the calculation of QALY. Converting this rate into effective monthly rate, we have d = .03/ 12 = 0.0025. we calculate the total QALY gained by each patient after getting enrolled in the ART program. Total QALY gained by first ten patients came out as 10.901880, 11.954010, 8.516071, 15.887459, 15.201133, 11.542711, 9.413716,12.484717, 6.148211, 13.491893 years respectively. The average of total QALYs of all patients is calculated to get the mean QALY gain due to ART treatment which is 9.688313.

4. CONCLUSION

We conclude that, on an average, patients gain 9.688313 QALYs, discounted at 3% per annum, after getting enrolled in ART program till the time they reach the average life expectancy of HIV patients in Kenya. More interventions focused on ensuring adherence to ART therapy are needed.

ETHICAL CONSIDERATIONS

We used data with no personal identification for the analysis to maintain anonymity. We sort ethical approval from the JKUAT Institutional Scientific and Ethical Review Committee (ISERC) and the use of this data complies with the ethical guidelines defined for administrative and secondary data.

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