Estimation of Quality Adjusted Life Years (QALYs) for HIV Patients on Art in Kenya Using Proxy Utility Function

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

Aims: This study seeks to estimate QALYs for HIV/AIDS patients on ART in Kenya to quantitatively evaluate the health impact of ART treatment on patients. 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 2022.

Methodology: The study involved a retrospective study of 3000 patients on ART in Kenya from the period of 2005-2017. All the patient records are identified using random patient id ensuring the privacy and anonymity of patients. The inclusion criteria is patients who had complete information on the covariates used in the model during follow up. The joint modelling of the longitudinal and survival data of each patient was applied and the results applied to proxy utility function to estimate the QALYs for patients on ART. To get the average QALYs gained by all patients, we aggregate the total QALYs from each patient. R. Software version 4.0.2 was used in the analysis.

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 implying that increase in the values of CD4 count results in a decrease in the hazard of death for HIV patients on ART therapy.

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**Conclusion:** The proxy utility function methodology is appropriate for the calculation of QALYs values for HIV patients on ART. It has the advantage of allowing utilities of each patient to vary and are calculated at every time point. Since ART results in the improvement in QALYs of patients, efforts should be directed towards ensuring patients who are enrolled for 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 the disease burden in the world 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 in 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 [1].

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 was a level of non-adherence to ART regimens by some PLWHIV. [2].

Kenya aims at achieving the HIV/AIDS global targets of ending AIDS by 2030 through zero new infections, zero discrimination and zero AIDS related deaths. Higher levels and efficient use of scarce resources are needed to get the AIDS pandemic response under control [3]. 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 Rudnik,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 national and county levels. Evidence based policy making emphasizes on the increasing need for economic evaluation of funds spent on disease interventions.

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 [4]. 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 [5]. To estimate the QALYs gained when receiving an intervention, 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 [6], Health Utility Index [7], SF-6D, SF-36 [8]. The methodology of calculating QALYs employed in this research is the proxy utility function introduced by Deo and Grover [9]. The proxy utility function is preferable in cases where there is information on survival data and longitudinal measurements on certain covariates in order to incorporate the joint modelling of survival and longitudinal sub models. This approach also allows for variability at the patient level 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, [10]. 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 ART treatment on patients with QALYs as the outcome measure. This study seeks to estimate QALYs for HIV/AIDS patients on ART in Kenya to quantitatively evaluate the health impact of ART treatment on patients.

2 Materials and Methods

2.1 Study design

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

2.2 Place and duration of study

Jomo Kenyatta University of Agriculture and Technology, between January 2019-April 2022.

2.3 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 on the exact date of death, covariates, viral load, CD4 count and lost to follow up. 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.

2.4 Statistical analysis

The secondary data was entered, cleaned, and managed using R software version 4.0.2. 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 [9]. This approach is suitable as it allows for the joint modelling of the longitudinal variables observed during follow up visits and the time to death. The biomarker that has been used as a measure of disease progression is the CD4 count for each patient during follow up visits.

2.5 Joint modelling of longitudinal data and survival data

2.5.1 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 (\( j = 1, 2, \ldots, n \)) 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 \( t \).
2.5.2 Longitudinal sub-model: Linear mixed effects model

The linear mixed effects model for the $i^{th}$ patient on ART therapy according to Rizopoulos [11], can be defined as:

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

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

where,

- $\beta$: 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,
- $\epsilon_i(t)$ 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.

2.5.3 Survival sub-model: Time dependent Cox PH

The Time dependent Cox PH model for the $i^{th}$ patient according to Rizopoulos [11], can be defined as:

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

where,

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

2.5.4 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 [12-18].

2.5.5 Proxy utility function

The proxy utility function developed Deo and Grover [9] is defined as a function that incorporates changes in the longitudinal measures of the time dependent covariate. The association parameter $\alpha$ 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 [19-24].

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:

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

### 2.5.6 Calculation of QALY

According to Deo and Grover [9] 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:

$$QALY_i = U_{oi} + \sum_{t=2}^{\tau_i^*} U_i(t - 1)(1 + d)^{-t}$$

Table 1. Description of independent variables included in the model

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

Table 1 gives a description of the variables/covariates which is the observation time, gender, age, marital status and weight of patients on ART used in the proxy utility function to obtain QALYs values.

### 3 Results and Discussion

Fig. 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.

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

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Longitudinal Sub-model</th>
<th>Survival Sub-model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient Estimates</td>
<td>p-value</td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otime</td>
<td>112.310</td>
<td>&lt;.0001***</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>-14.6147</td>
<td>&lt;.0001***</td>
</tr>
<tr>
<td>Age</td>
<td>-3.2305</td>
<td>0.0007***</td>
</tr>
<tr>
<td>Marital Status</td>
<td>-9.3230</td>
<td>0.003***</td>
</tr>
<tr>
<td>Weight</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Association</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

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

From Fig. 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 $\hat{\alpha}$ of association parameter between the longitudinal measures on CD4 count and the survival sub-model is significant at 1% level of significance and its value -0.0345 implies that increase in the values of CD4 count results in decrease in the hazard of death for HIV patients on ART therapy.

3.1 Calculation of QALY results

We used a discount rate of 3% per annum which is equivalent to an effective monthly rate, $d = 0.03/12 = 0.0025$, in the calculation of QALY. 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 mean QALY gain due to ART treatment is 9.688313.

4 Conclusion

We conclude that, on an average, HIV patients on ART treatment in Kenya gain 9.688313 QALYs, 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 Approval

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.

Acknowledgements

The authors report no conflicts of interest in this work. No funding was received to perform this study.

Competing Interests

Authors have declared that no competing interests exist.

References


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