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ORIGINAL RESEARCH

Joint Modeling of Incidence of Unfavorable Outcomes and Change in Viral Load Over Time Among Adult HIV/AIDS Patients on Second-Line Anti-Retroviral Therapy, in Selected Public Hospitals of Addis Ababa, Ethiopia

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Background: In Ethiopia, second-line anti-retroviral therapy (ART) for HIV/AIDS patients was started some years ago; however, few studies have reported the unfavorable outcomes of second-line ART. Therefore, this study aimed to assess the incidence and predictors of unfavorable outcomes and their association with change in viral load among adult HIV/AIDS patients on second-line treatment at selected public hospitals in Addis Ababa, Ethiopia.

Methods: A retrospective follow-up study was conducted at selected public hospitals in Addis Ababa, Ethiopia, on 421 HIV/AIDS patients on second-line ART from 2016 to 2021. Cox proportional hazard models with a linear mixed effect model were jointly modeled using the JM package of R software with time-dependent lagged parameterizations, and a 95% confidence interval was used to select significant variables.

Results: Overall, 89 HIV/AIDS patients developed unfavorable outcomes. The incidence density was 7.48/100 person-years (95% CI: 6.08, 9.2). Secondary and tertiary educational level (AHR=0.47, 95% CI: 0.25, 0.89, and AHR=0.27, 95% CI: 0.1, 0.72), CD4 count less than 100 cells/mm^3 (AHR=2.15, 95% CI: 1.21, 3.83), poor adherence (AHR=3.59, 95% CI: 1.73, 7.49), and TB comorbidity (AHR=2.23, 95% CI: 1.21, 4.14) at the start of second-line ART were significant predictors of incidence of unfavorable outcome. Time-dependent lagged value viral load was significantly associated with the risk of unfavorable outcome (AHR=1.28, 95% CI: 1.01, 1.63).

Conclusion: In the study area, the incidence of an unfavorable outcome of second-line ART was high. Secondary and tertiary educational level, CD4 count less than 100 cells/mm^3, poor adherence, and TB comorbidity at the start of second-line ART were significant predictors of incidence of unfavorable outcomes. Thus, strengthening routine viral load measurement, increase patient adherence, intensive counseling, and strong TB screening are needed in the study setting.

Keywords: second-line ART, viral load change, HIV/AIDS, joint modeling, Ethiopia

Introduction

The human immunodeficiency virus (HIV) is of serious global public health concern, having claimed about 33 million deaths to date. According to a WHO report, owing to gaps in HIV services, 690,000 people died from HIV-related causes in 2019, and 1.7 million people were newly infected.[1] According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) assessment on the global AIDS epidemic, 2020 targets will not be realized owing to deeply unequal achievement, and the COVID-19 pandemic risks throwing HIV progress off track. Since 2015, missed targets have

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resulted in 3.5 million additional HIV infections and 820,000 additional AIDS-related deaths compared with the situation if the world were on track to fulfill the 2020 goals.[2]

To ensure long-term HIV treatment success in Sub-Saharan Africa, there is a clear and increasing need for expanded access to third-line drug options. However, HIV treatment failure involving second-line regimens has extremely few options for further switching in resource-constrained situations, which is a severe concern.[3,4]

In Ethiopia, in 2017, 414,854 adults and 21,146 children under the age of 15 were taking ART. Even though there are limited data regarding second-line treatment failure and outcomes, it is essential to identify these in patients taking ART to plan early therapeutic switches to another available ART regimen.[4,5]

Globally, the incidence of unfavorable outcomes (treatment failure, losses to follow-up, and death) among patients on the second-line ART were differently reported in different countries. According to a study in Myanmar, 136 patients (17%), had an unfavorable outcome,[6] and in southern Vietnam, 60 patients (18.4%) experienced treatment failure at the end of the study period.[7]

At the end of 2020, there were an estimated 37.7 million (30.2–45.1 million) HIV-positive individuals worldwide, with almost two-thirds (25.4 million) living in the WHO African Region.[1] To reach the new proposed global 95-95-95 targets, we will need to redouble our efforts to avoid the worst-case scenario of half a million excess deaths in Sub-Saharan Africa. A retrospective study carried out in Southern Uganda reports that among 921 patients initiated on second-line treatment, 165 (17.9%) were lost to follow-up, with an incidence of 26.7 per 100 person-years (PY).[8]

In Ethiopia, in 2019, about 670,000 people were living with HIV and 12,000 people died from an AIDS-related disease.[9] Most of the Millennium Development Goal objectives linked to HIV/AIDS have been achieved by Ethiopia. However, the decline in the rate of mortality from HIV/AIDS has been slow.[10] In a study conducted in the Amhara region, out of 1192 HIV-positive individuals who were on second-line ART, 136 died in 3157 PY of follow-up.[11]

According to a multicenter study conducted in the Amhara region of Ethiopia, the cumulative incidence of losses to follow-up and death was 5.41% and 10.99%, respectively, over the entire period of follow-up.[12] Another study conducted in this area, the Amhara region, shows among 1011 patients on second-line treatment, 254 experienced treatment failure,[13] and a study conducted at the outpatient ART clinic at Adama Regional Hospital reports that out of 383 patients on second-line ART, 18.9% were lost to follow-up at the end of the follow-up period.[14]

The findings of a systematic review and meta-analysis show that high baseline viral load, advanced clinical stage of HIV at baseline, low peak CD4 cell counts at baseline (<100 cells/mm^3), and suboptimal adherence to second-line therapy were factors associated with the significantly increased occurrence of second-line ART failures.[15]

Second-line regimens are generally the last therapeutic option accessible for patients in resource-limited nations because third-line regimens are expensive and difficult to come by. Provision of ART by itself is not enough to control the problems of HIV. In addition to improving unfavorable outcomes (loss to follow-up, death, and treatment failure) of HIV patients on second-line treatment, thorough monitoring and evaluation are needed to satisfy the global strategy of ending AIDS as a public health danger by 2030 and to enable people to live longer with HIV.

In Ethiopia, a few studies in the area have documented the incidence of unfavorable outcomes of HIV patients on second-line ART, but no studies have been conducted to assess the relationship between the longitudinal biomarker viral load and incidence of unfavorable outcomes among HIV/AIDS patients on second-line ART. Therefore, this study aimed to identify risk factors for the incidence of unfavorable outcomes and model the association with change in viral load among adult HIV/AIDS patients on second-line treatment at selected public hospitals in Addis Ababa, Ethiopia.

Methods

Study Design and Setting

A retrospective follow-up study was conducted among HIV patients aged 15 years and above between September 11, 2016, and February 27, 2021, at public hospitals in Addis Ababa, Ethiopia. Based on the 2007 census, the estimated population size of Addis Ababa was 3,384,569. There are 10 public hospitals in Addis Ababa.[16] Out of these 10 public hospitals, Zewditu Memorial Hospital and St. Paul's Hospital Millennium Medical College were selected for the current study. The selected hospitals had the highest number of clients on second-line ART. Around 7200 (1006 on second-line

ART) and 4700 (514 on second-line ART) HIV patients from Zewditu Memorial Hospital and St. Paul's Hospital Millennium Medical College, respectively, were on ART at the time of data collection.

Population and Sample

The source population in this study was all HIV/AIDS patients on second-line ART having follow-up at the selected public hospitals in Addis Ababa, whose age was greater than or equal to 15 years. The study population was all newly diagnosed HIV/AIDS patients on second-line ART at the selected public hospitals in Addis Ababa from September 11, 2016, to February 27, 2021. All enrolled adult HIV patients on second-line treatment during the study period, followed for at least 6 months and with at least two measurements of viral load, were included. Patients whose date of second-line ART initiation was unknown, those for whom the date of unfavorable outcomes was unknown, and those with incomplete data on variables were excluded from the study.

The sample size was determined using the Schoenfeld formula for survival parts,[17] using STATA 14 statistical software by considering predictors significantly associated with time to treatment failure from previous studies,[18,19] and using the Diggle formula for longitudinal measurement parts.[20] It was calculated under the following statistical assumptions: two-sided significance level (α) of 5%, power 90%, $Z\alpha/2$ value at 95% CI 1.96, $q1$: the proportion of subjects that are in group 1 (exposed), $q0$: the proportion of subjects that are in group 2 (unexposed); $1-q1$, HR: hazard ratio, and the probability of an event (E). Accordingly, a final sample size of 463 was obtained. Then, the study subjects were selected using a simple random sampling technique through computer-generated random numbers.

Sampling Procedure

There were 1520 HIV patients on second-line ART in the selected hospitals. Using the proportional allocation method, from the study sample size of 463, we aimed to select 306 and 157 HIV patients on second-line ART from Zewditu Memorial Hospital and St. Paul's Hospital Millennium Medical College, respectively. Finally, 421 patients (279 from Zewditu Memorial Hospital and 142 from St. Paul's Hospital Millennium Medical College) who fulfilled the inclusion criteria were included in the study (Figure 1).

Study Variables

For this study, the incidence of unfavorable outcomes and the repeated viral load measurement were the two outcome variables. The independent variables were: socio-demographic characteristics (sex, age, educational level, marital status, occupational status, religion), and clinical and immunological variables (functional status, CD4 count, TB coinfection, adherence, BMI, WHO stage) at the start of second-line therapy (at the switch). Additional variables were: second-line regimen, opportunistic infections, izoniazid (INH) use, co-trimoxazole preventive therapy (CPT) use, number of first-line regimen changes, duration on first-line ART, type of first-line regimen before the switch, and time-varying endogenous covariates: repeatedly measured viral load, recorded as the number of viral copies per milliliter.

Time to the unfavorable outcome was defined as the time from starting the second-line ART initiation to treatment failure, loss to follow-up, or death, whichever occurred first. The event was defined as patients who developed unfavorable outcomes during the follow-up time. Unfavorable outcomes include treatment failure, loss to follow-up, and death in patients who were on second-line ART.[6] If a patient developed at least one of these three outcomes, he or she was considered as having unfavorable outcomes.

For this study, death was defined as recorded death in a patient who was on second-line ART.[18] Loss to follow-up was defined as a patient who had not received repeat ART for 3 months or longer and was not yet classified as "dead" or "transferred out".[18] Treatment failure included virological failure. Real treatment failure should be estimated by virological failure using viral load. Virological failure was defined as a persistently detectable viral load exceeding 1000 copies/mL (two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of using ART.[21] Censored patients were defined as those who were transferred out or event free at the end of the study.

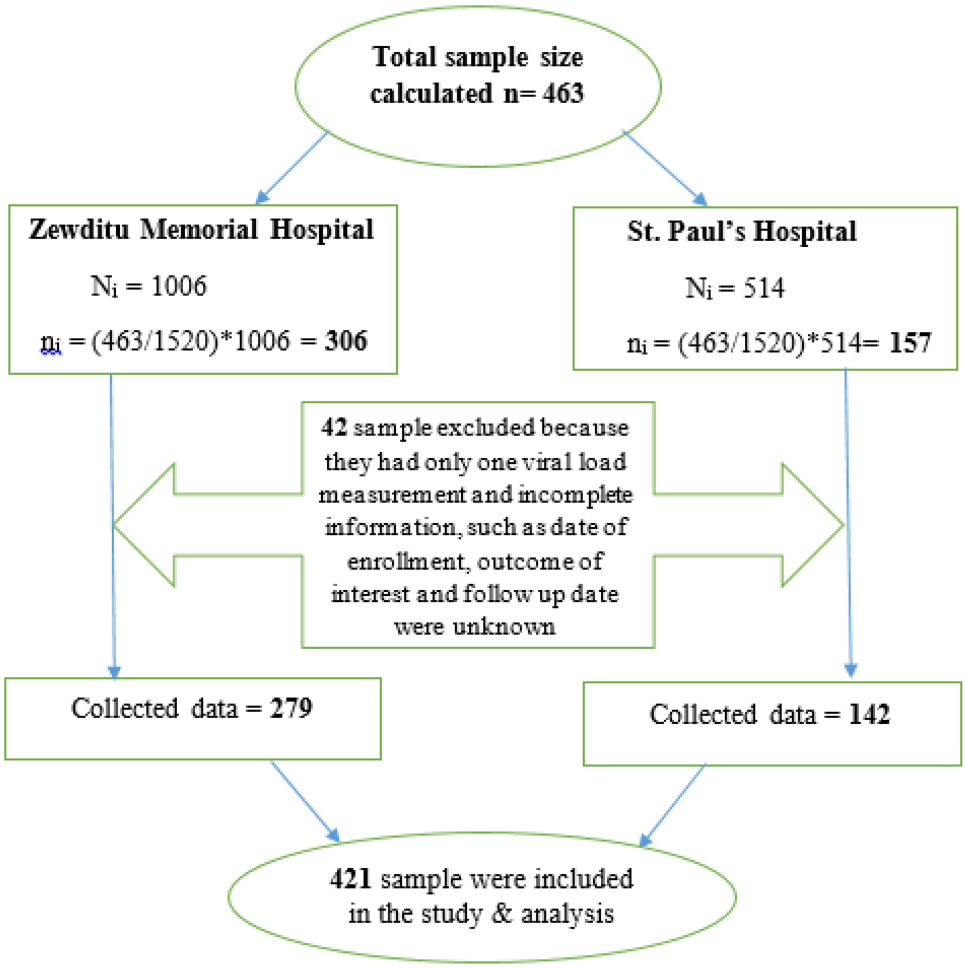

Figure 1 Proportional allocation of sample size among selected public hospitals in Addis Ababa, Ethiopia.

Depending on the percentage of drug dosage calculated from a monthly total dose of ART drugs, adherence was categorized as good, fair, or poor. Good drug adherence was defined as ≥95% or <2 missed drug doses out of 30 doses or ≤3 missed drug doses out of 60 doses; fair drug adherence as 85–94% or 2–4 missed drug doses out of 30 doses or 4–9 missed drug doses out of 60 doses; and poor drug adherence as <85% or ≥5 ART missed drug doses out of 30 doses or >9 ART missed drug doses out of 60 doses. Based on the WHO classification, normal weight is BMI from 18.5 to 24.99 kg/m^2, mildly underweight from 17 to 18.49 kg/m^2, moderately underweight from 16 to 16.99 kg/m^2, and severely underweight <16 kg/m^2; overweight is >25 kg/m^2.

Data Collection Procedures and Quality Control

To obtain relevant data, a checklist for reviewing patient charts was created. Secondary data regularly recorded from patients followed up at the hospitals provided the data for this analysis. Health professionals from the ART clinic were designated as data collectors, and data were obtained by evaluating patient follow-up charts and cards. The Health Management Information System (HMIS) card number was used to identify individual patient cards.

To confirm the quality of the data, a preliminary review was conducted among 5% of the sample size of the selected hospitals. Then, the adequacy of the checklist was evaluated and unclear questions were modified before actual data collection. To ensure consistency, 2 days of training were given to data collectors and supervisors before data collection. The assigned supervisors undertook monitoring and supervision every day to check the consistency and completeness of the data.

Data Management and Statistical Analysis

Data entry was performed using EpiData version 4.6.0.0 and then exported to R statistical software version 4.1.0 for further analysis. To describe the study population, descriptive statistics such as means, medians, standard deviations, IQRs, percentages, and frequencies were used. Graphical methods and frequency tables were also used for descriptive data. Using the Kaplan–Meier (KM) method, the median time to the unfavorable outcome was estimated and the incidence density was computed as the number of new cases divided by patient-months at risk. The log-rank test was used to compare survival times between groups of categorical variables. Before fitting the survival sub-model, proportional hazard assumptions were checked graphically using the cumulative log hazard plot and statistically using the Schoenfeld residual test.

Under the longitudinal sub-model, the individual and average changes in viral load over time were calculated before fitting the linear mixed model. The normality of the longitudinal outcome was checked using a Q-Q plot and histogram. It was found to be normally distributed after log transformation. Sensitivity analysis was used to handle missing values.

The linear mixed model for the longitudinal outcome and Cox proportional hazard model for the survival sub-model were fitted. Using the JM package of R software, joint models were fitted with time-dependent lagged parameterizations to estimate the effects of the viral load change on the risks of unfavorable outcomes. To determine the relationship between longitudinal viral load change and unfavorable outcomes, the association parameter (alpha value) from a fitted joint model was used. A significance level of 0.05 for all statistical tests was used as a cut-off point. For the longitudinal sub-model, model fitness was checked using marginal residuals, and for the survival sub-model, model adequacy was checked using Cox Snell residuals for checking overall fit. The likelihood ratio test and Akaike information criterion (AIC) were applied for model selection.

Ethical Considerations

Ethical clearance and approval were obtained from the Institutional Review Committee of the College of Medicine and Health Sciences, University of Gondar. Permission letters were obtained from medical directors of the selected hospitals to access the patients' medical records. Owing to the retrospective nature of the study and the fact that all data were taken from patients' medical records, the Institutional Review Committee of the University of Gondar and the respective hospitals waived the requirement for informed consent. Confidentiality was maintained at all levels of the study and data were held on a secure password-protected system.

Results

Socio-Demographic Characteristics

Data from the 463 patients who were on second-line ART between September 11, 2016, and February 27, 2021, were reviewed and collected. Forty-two records of patients were excluded because they had only one viral load measurement and had incomplete information, such as the date of enrollment, the outcome of interest, or the follow-up date being unknown. The final analysis was conducted on 421 patients.

At the start of second-line ART, the mean (SD) age of patients was 41.1 (10.8) years and males constituted 195 (46.32%). The majority of study participants, 327 (77.67%), were followers of the Orthodox religion and 225 (53.44%) were non-government employees. Among the participants, 164 (38.95%) were married and 66 (15.68%) had no formal education (Table 1).

Characteristics During and After the Switch to Second-Line Treatment

Patients were switched to second-line treatments because of virological failure, immunological failure, clinical failure, and drug toxicity of first-line treatment. The most common reasons were virological failure (62%), followed by clinical and virological failure (14.25%), and a combination of immunological and virological failure (11.88%) (Table 2).

At the beginning of second-line ART, 388 (92.16%) of the patients were started on a lopinavir (LPV/r) boosted protease inhibitor second-line regimen and 33 (7.84%) received an atazanavir (ATV/r)-based regimen. The mean (SD)

Table 1 Socio-Demographic Characteristics of Patients on Second-Line ART at Public Hospitals in Addis Ababa, Ethiopia, September 11, 2016, to February 27, 2021

Variables	Category	Frequency	Percent (%)
Age	15–29 years	58	13.78
	30–45 years	217	51.54
	>45 years	146	34.68
Sex	Male	195	46.32
	Female	226	53.68
Religion	Orthodox	327	77.67
	Muslim	38	9.03
	Protestant	54	12.83
	Catholic	2	0.48
Marital status	Single	126	29.93
	Married	164	38.95
	Divorced	71	16.86
	Widowed	49	11.64
	Separated	11	2.61
Educational level	No formal education	66	15.68
	Primary	142	33.73
	Secondary	154	36.58
	Tertiary	59	14.01
Occupational status	Government employed	36	8.55
	Non-government employed	225	53.44
	Jobless	59	14.01
	Student	44	10.45
	Housewife	49	11.64
	Other	8	1.90

Note: Other = driver, daily laborer.

Table 2 Reasons for Switching to Second-Line ART at Public Hospitals in Addis Ababa, Ethiopia, September 11, 2016, to February 27, 2021

Reasons for Switching	Frequency	Percent (%)
Virological failure	261	62
Clinical and virological failure	60	14.25
Immunological and virological failure	50	11.88
Clinical, immunological, and virological failure	19	4.51
Clinical and immunological failure	9	2.14
Drug toxicity only	9	2.14
Immunological failure only	9	2.14
Clinical only	4	0.95

weight of participants at the start of second-line ART was 57.2 (11.5) kg. Besides, 174 patients (41.33%) had a CD4 count below 100 cells/mm^3 and the majority, 351 (83.37%), had good or fair clinical adherence (≥85%).

In addition, at the start of second-line ART, 313 (74.35%) of the patients were in WHO clinical stage I or II, 64 (15.2%) were in WHO clinical stage III, and 44 (10.45%) were in WHO clinical stage IV (Table 3).

Incidence of Unfavorable Outcome

Study participants were followed for a median follow-up period of 32.9 months (IQR 25.9−40.7) after switching to second-line ART. Out of 421 study participants followed for a maximum of 54.03 months, a total of 89 patients (21.14%) had developed unfavorable outcomes in 14,282.03 person-months or 1190.17 PY of observations. Among the

Table 3 Characteristics of Patients During and After the Switch to Second-Line ART at Public Hospitals in Addis Ababa, Ethiopia, September 11, 2016, to February 27, 2021

Variables	Category	Frequency	Percent (%)
Second-line regimen	LPV/r based	33	7.84
	ATV/r based	388	92.16
BMI at switch	Normal	285	67.7
	Mild	102	24.23
	Moderate	34	8.08
TB status	No TB	371	88.12
	TB present	50	11.68
CD4 at switch	<100 cells/mm^3	174	41.33
	≥100 cells/mm^3	247	58.67
WHO stage at switch	Stage I/II	313	74.35
	Stage III	64	15.20
	Stage IV	44	10.45
Adherence at switch	Good/fair (≥85%)	351	83.37
	Poor (<85%)	70	16.63
Functional status at switch	Working	340	80.76
	Ambulatory	63	14.96
	Bedridden	18	4.28
Opportunistic infection	No	350	83.14
	Yes	71	16.86
INH used	No	363	86.22
	Yes	58	13.78
CPT used	No	181	42.99
	Yes	240	57.01

total unfavorable outcomes, 44 (49.44%) were treatment failures (virological failure), 16 (17.98%) were deaths, and 29 (32.58%) were categorized as lost to follow-up. The incidence density was 7.48/100 PY (95% CI: 6.08, 9.2). The survival probability of the patients was high at the start of the follow-up and decreased as follow-up increased (Figure 2). The cumulative probability of survival of study participants was 0.965 at 20 months, 0.858 at 30 months, 0.717 at 40 months, and 0.639 at the end of the study.

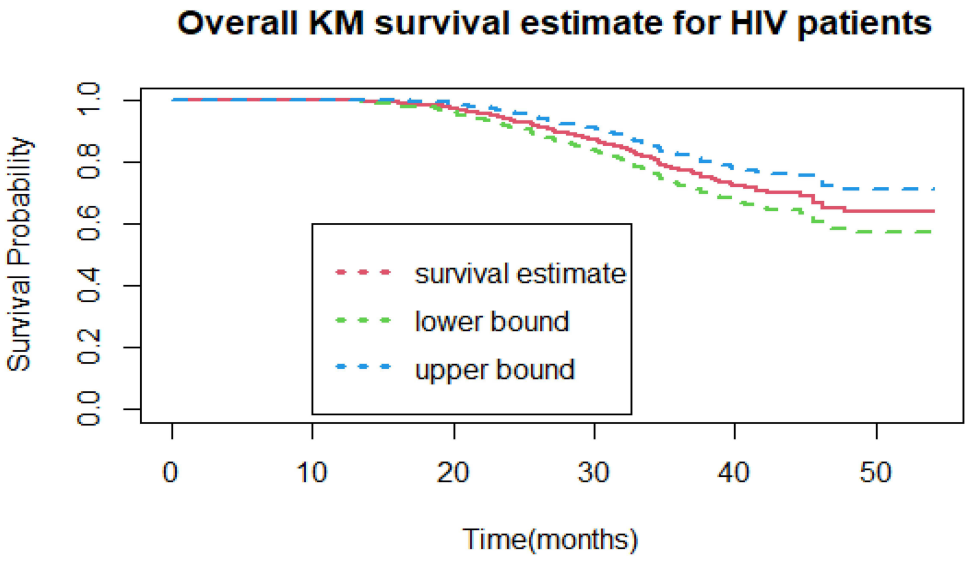

Figure 2 Overall Kaplan–Meier survival curve for patients on second-line ART at public hospitals in Addis Ababa, Ethiopia, September 11, 2016, to February 27, 2021.

Exploring Longitudinal Viral Load Change

During the study period, a minimum of two and a maximum of nine viral load measurements were taken. This implies that data were unbalanced and there was a different number of measurements per subject. Individual profile plots reveal that there is variability of viral load within and between patients. The random intercept model is reasonable, and as the trajectory of viral load over time for the patients was not constant, it suggests that considering a mixed model with random slope is important (Figure 3). The mean profile plot for viral load indicates that changes in viral load over time are not linear. So, imposing a linear mixed model may be too restrictive and produce unsatisfactory results. Therefore, we used a natural cubic spline to longitudinal model, which handles the correlation that is not handled by random effects and yields satisfactory results. The mean viral load among HIV patients on second-line ART who had unfavorable outcomes was higher than in those who did not develop unfavorable outcomes (Figure 4).

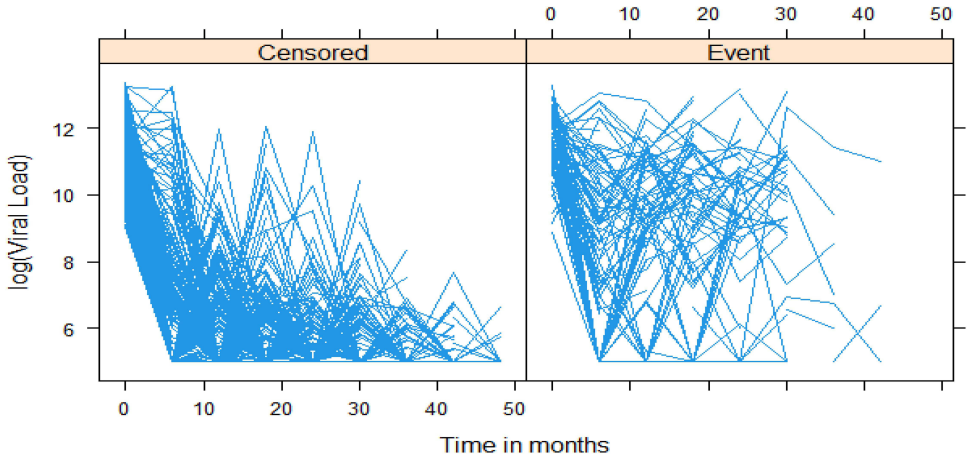

Figure 3 Individual profile plot by status for patients on second-line ART at public hospitals in Addis Ababa, Ethiopia, September 11, 2016, to February 27, 2021.

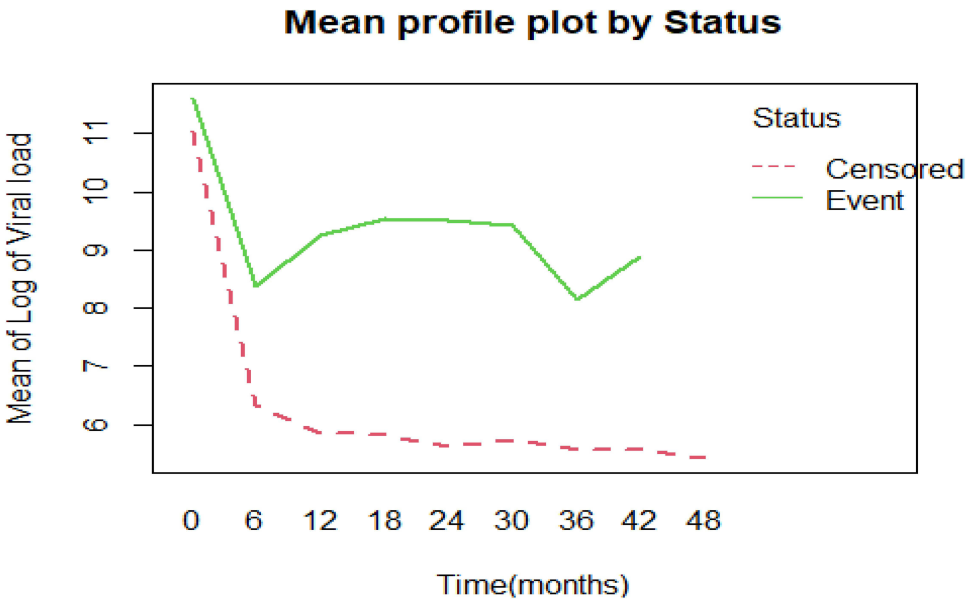

Figure 4 Mean profile plot viral load by the status of unfavorable outcome for patients on second-line ART at public hospitals in Addis Ababa, Ethiopia, September 11, 2016, to February 27, 2021.

Model Diagnosis and Comparisons

The proportional hazard assumptions were checked using the cumulative log hazard plot and the Schoenfeld residual test method. Both methods indicated that the proportional hazard assumption was satisfied. The normality of the data was checked using a Q-Q plot. It showed that viral load was not normally distributed. Then, transformation was applied using the log-transformation method and normally distributed data were obtained. Overall, the model fit for the Cox proportional hazard model was reasonable, as evidenced by the Cox Snell residual plot. The linear mixed effect model was assessed by the marginal residuals of the fitted values and showed a good fit.

To handle missing values in longitudinal data, sensitivity analysis was applied using multiple imputations and complete case analysis. The Cox proportional hazard model for survival sub-model and the linear mixed effect model with only random intercept for the longitudinal sub-model was selected as a better model, based on model assumption with the lowest AIC (Table 4). Then, to express the correct relationship between the risk of unfavorable outcome and change in viral load, the linear mixed effect model with only random intercept and the Cox proportional hazard model were jointly modeled using the time-dependent 6-month lagged parameterizations under piecewise PH-GH specifications of the baseline risk function. A joint model with time-dependent lagged parameterizations under a complete case analysis approach gave a better fit and was selected as the final model based on the AIC value. The 6-month lagged parameterization was used because the first measurement for the viral load was taken after the sixth month and data were managed by the 6-month interval (Table 5).

Predictors of Unfavorable Outcome and Its Association with Viral Load Change

The results showed that the 6-month lagged value of the viral load was significantly associated with the risk of unfavorable outcomes. Educational level, TB comorbidity, CD4 count, and poor adherence at the start of second-line ART were variables that were found to be significant predictors of the incidence of unfavorable outcomes.

Patients with secondary and tertiary educational levels had a reduced hazard of an unfavorable outcome, by 53% (AHR=0.47, 95% CI: 0.25, 0.89) and 73% (AHR=0.27, 95% CI: 0.1, 0.72), respectively, compared to patients with no formal education. The risk of unfavorable outcome was 2.23 times higher (AHR=2.23, 95% CI: 1.21, 4.14) among patients who had started second-line ART with TB comorbidity compared to those who had no TB. The hazard of experiencing unfavorable outcomes was 3.59 times higher (AHR=3.59, 95% CI: 1.73, 7.49) for patients who started second-line ART with poor adherence compared to those with good/fair adherence levels. Patients who started second-line ART with a CD4 count below 100 cells/mm^3 had a 2.15 times (AHR=2.15, 95% CI: 1.21, 3.83) higher likelihood of unfavorable outcome compared to patients who started second-line ART at a CD4 count of 100 cells/mm^3 or above. The value of viral load in the body over the past 6 months was significantly associated with the current risk of unfavorable outcomes from the selected joint model with time-dependent lagged parameterization

Table 4 Model Comparison for Longitudinal and Survival Sub-Models, and Sensitivity Analysis

Survival sub-models				
Model	**Cox**	**Log logistic**	**Weibull**	**Exponential**
AIC	792.19	792.79	803.75	938.64
Longitudinal sub-models				
Model		**AIC**	**Log-likelihood ratio**	
Random intercept model		9611.565	−4791.783	
Random intercept and slope model		9717.542	−4849.771	
Sensitivity analysis				
Model		**AIC**	**Log-likelihood ratio**	
Multiple imputation		11,608.31	−5772.155	
Complete case analysis		10,563.92	−5249.595	

Table 5 Survival Sub-Models with Time-Dependent Lagged Parameterizations for HIV Patients on Second-Line ART at Public Hospitals in Addis Ababa, Ethiopia, September 11, 2016, to February 27, 2021

Variables	Category	Event	Censored	AHR (95% CI)	*p*-Value
Sex	Male	51	144	1	
	Female	38	188	1.06 (0.65, 1.72)	0.815
CD4 count at switch	≥100 cells/mm^3	20	227	1	
	<100 cells/mm^3	69	105	2.15 (1.21, 3.83)	0.009
Adherence at switch	Good/fair (≥85%)	29	322	1	
	Poor (<85%)	60	10	3.59 (1.73, 7.49)	0.006
Functional status at switch	Working	42	298	1	
	Ambulatory	34	29	1.76 (0.91, 3.39)	0.095
	Bedridden	13	5	1.57 (0.53, 4.66)	0.413
Educational level	No formal education	41	25	1	
	Primary	24	118	0.95 (0.52, 1.76)	0.879
	Secondary	18	136	0.47 (0.25, 0.89)	0.02
	Tertiary	6	53	0.27 (0.1, 0.72)	0.009
BMI	Normal	24	261	1	
	Moderate	41	61	1.76 (0.92, 3.39)	0.09
	Severe	24	10	1.66 (0.63, 4.41)	0.308
WHO stage at switch	Stage I/II	45	268	1	
	Stage III	22	42	0.74 (0.35, 1.56)	0.429
	Stage IV	22	22	0.49 (0.22, 1.1)	0.085
Opportunistic infection	Yes	32	39	1	
	No	57	293	1.09 (0.62, 1.93)	0.765
TB status	No	40	331	1	
	Yes	49	1	2.23 (1.21, 4.14)	0.01
Second-line regimen	LPV/r based	16	17	1	
	ATV/r based	73	315	0.52 (0.27, 1.01)	0.052
Association parameter (lag of 6 months)					
Associate (6-months lagged value)				1.28 (1.01, 1.63)	

under complete case analysis. The risk of experiencing unfavorable outcomes increased by 28% (AHR=1.28, 95% CI: 1.01, 1.63) if the viral load had increased by a unit (log_{10}/mL) in the past 6 months (Table 6).

Discussion

This study was carried out to determine the incidence and predictors of unfavorable outcomes, together with the effect of the viral load change, on the risk of unfavorable outcomes among HIV patients on second-line ART at selected public hospitals in Addis Ababa, Ethiopia. Factors such as educational level, TB comorbidity, CD4 count, and poor adherence at the start of second-line ART were found to be significantly associated with the risk of unfavorable outcomes. In addition, the 6-month lagged value of viral load was significantly associated with the risk of unfavorable outcomes.

In our study, 21.14% (cumulative incidence) of patients had developed unfavorable outcomes, with an incidence rate of 7.48 per 100 PY observations. The result of the overall incidence in the current study is in line with previous studies conducted in Asian and African countries, which reported incidences of 72.3 per 1000 PY of observation in Northern Ethiopia[19] and 7.9 patients per 100 PY follow-up in Myanmar,[6] while rates of treatment failure and mortality per 100 PY were 8.8 and 1.1, respectively, in Asia.[22] However, the incidence of unfavorable outcomes was lower than in a meta-analysis conducted in Sub-Saharan Africa (15 per 100 PY),[15] and in studies carried out in the Amhara region, Ethiopia (9.86 per 100 PY),[13] and in South Africa.[23] The cumulative incidence of this study is greater than that in a study conducted in Northwestern Ethiopia, which was 61.7 per 1000 PY.[18] This discrepancy may be due to the different follow-up periods for the studies. Another possible reason could be that this study identified treatment failure using viral load as

Table 6 Longitudinal Sub-Models with Time-Dependent Lagged Parameterizations for HIV Patients on Second-Line ART at Public Hospitals in Addis Ababa, Ethiopia, September 11, 2016, to February 27, 2021

Fixed Effects	Category	Beta	*p*-Value	95% CI
Intercept		10.94	<0.0001	(10.18, 11.7)
ns (Time, 2)1		−7.45	<0.0001	(−7.82, −7.09)
ns (Time, 2)2		−0.043	0.85	(−0.47, 0.39)
Weight at switch	≤45	1		
	>45	−0.011	0.03	(−0.02, −0.001)
Second-line regimen	LPV/r based	1		
	ATV/r based	−0.75	0.0009	(−1.19, −0.31)
CD4 count at the switch	≥100 cells/mm^3	1		
	<100 cells/mm^3	1.001	<0.0001	(0.76, 1.24)
CPT used	Yes	1		
	No	0.079	0.51	(−0.16, 0.32)
Variance component				
SD of intercept	0.95			
SD of residual	1.78			
SD of ns (Time, 2)1	0.19			
SD of ns (Time, 2)2	0.22			

Abbreviations: ns, natural cubic spline; CPT, co-trimoxazole preventive therapy; SD, standard deviation; CI, confidence interval.

the diagnostic criterion, which is explained in the recent WHO definition. In the previous studies, immunological and clinical markers were mainly used to assess treatment failure, which can shorten the time of diagnosis.

The incidence of unfavorable outcomes in patients with a CD4 count below 100 cells/mm^3 was higher than in patients with a CD4 count of 100 cells/mm^3 or above at the initiation of second-line ART. This finding is in line with studies conducted in Northern Ethiopia,[19] North West Ethiopia,[18] South Africa,[24] and Vietnam.[7] This may be related to the fact that patients with low CD4 count have a higher probability of developing different opportunistic infections. This probably raises the possibility of an unfavorable outcome.

Adherence status at the time of the switch was found to have a strong association with the risk of unfavorable outcomes. This study showed that the incidence of unfavorable outcomes was higher in patients with poor adherence compared to patients with good/fair adherence levels. This result is consistent with previous studies conducted in Vietnam,[7] India,[25] and the Amhara region, Ethiopia.[13] It is reasonable to believe that strong adherence to ART is critical to the outcome of HIV treatment.[26] This is because patients with poor adherence to drug treatment may fail to take drugs as prescribed by the health professional. This can be explained by the anti-retroviral drug concentration in the blood being insufficient to reduce viral RNA replication in the case of non-adherence.

Another important result that was found to have a significant association with the incidence of unfavorable outcomes was TB coinfection. This finding is consistent with studies conducted in South Africa[23] and Northern Ethiopia.[19] Possible reasons for this are TB itself being an indicator of clinical failure, and drug interactions occurring between protease inhibitors and rifampicin. Rifampicin is a potent liver enzyme inducer, which reduces the serum levels of protease inhibitors, and concurrent use can lead to treatment failure.

In addition, the incidence of an unfavorable outcome in a patient with no formal education was higher compared to patients with secondary or tertiary educational levels. Although no studies have assessed the association of education with the risk of unfavorable outcomes, there are studies showing that education is related to the risk of loss to follow-up and mortality. Studies were conducted in the Amhara region[11] and in Northern Ethiopia,[27] in which HIV patients who were illiterate had a high risk of mortality compared to those with tertiary education. Regarding loss to follow-up, studies in Benishangul-Gumuz, Ethiopia,[28] and in India[29] showed that ART patients who have no formal education were more likely to be lost to follow-up than those with educational status of college and beyond. One possible reason for this is that

patients with a higher level of education may have a better understanding of the importance of compliance with their drugs than those with a low educational level. In addition, if they have no formal education, patients may not appreciate the benefits of ART and more effort will be needed to make them adhere to the therapy, so they are at high risk of loss to follow-up.

In this study, the time-dependent lagged value parameterization of joint modeling showed that the past 6 months' value of viral load in the body was significantly associated with the current risk of unfavorable outcomes. Although no study has assessed the strength of association of longitudinal viral load change with the risk of an unfavorable outcome, some studies have shown that the unfavorable outcome is related to viral load. Research conducted in Nigeria showed that an unfavorable outcome was related to HIV RNA viral load.[30] In addition, a study conducted in India showed that high baseline viral load was associated with poor treatment outcome in terms of failure to achieve virological suppression.[31] An increased viral load may indicate drug resistance or rapid progression of viral replication,[32] and may relate to an unfavorable outcome.

The aims of this study were to provide vital information to policymakers and program planners designing control programs on virological failure, loss to follow-up, and death in HIV patients on second-line ART. The public health importance of this study is that it seeks to raise retention and extend care and to minimize and prevent the economic losses related to third-line ART among patients on second-line ART, by identifying the variables that are significantly associated with unfavorable outcomes, including longitudinal change in viral load.

This study used viral load to detect true treatment failure because the real treatment failure should be estimated by virological failure. Most previous studies used clinical and immunological failure criteria, which lack both sensitivity and specificity to detect failure. Despite our study having the strength to estimate the incidence of unfavorable outcomes and its association with viral load using advanced modeling, it is not free from limitations. As the present study was based on secondary data obtained from patient medical records, important variables such as hemoglobin, behavioral factors, and nutritional status, which are assumed to have an association with unfavorable outcome, were not well recorded. Because viral load measurement began recently, there are not enough repeatedly measured viral load data to demonstrate the perfect association of viral load with unfavorable outcomes. Besides, "unfavorable outcomes" was a composite outcome of virological failure, death, and loss to follow-up, which might overestimate the rate of unfavorable outcomes.

Conclusion

The incidence of unfavorable outcomes among HIV patients on second-line ART in this study was high. Unobserved true 6-month lagged parameterization values of viral load change had significant associations with risk of unfavorable outcome. Secondary and tertiary educational level, poor adherence at the start of second-line ART, CD4 count less than 100 cells/mm^3, and TB comorbidity were found to be significant predictors of incidence of unfavorable outcomes. Therefore, addressing significant predictors to prevent unfavorable outcomes, strengthening routine viral load measurement, increasing patient adherence, intensive counseling, and strong TB screening are needed in the study setting. In addition, to improve both understanding about the importance of compliance with their drugs and knowledge about their use and benefits, it is important for patients to increase their educational level.

Abbreviations

AHR, adjusted hazard ratio; AIC, Akaike information criterion; ART, anti-retroviral therapy; BMI, body mass index; CI, confidence interval; CPT, co-trimoxazole preventive therapy; HR, hazard ratio; INH, isoniazid; IQR, interquartile range; KM, Kaplan–Meier; PY, person-years; SD, standard deviation; TB, tuberculosis; WHO, World Health Organization.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in relation to this work.

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