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St. Paul's Hospital Millennium Medical College

Predictors of mortality among adult HIV infected patients on HAART at St. Paul's Hospital Millennium Medical College : Facility Based Case Control Study

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A Research thesis submitted to the Department of Internal Medicine for the partial fulfillment of the Requirements for completion of a Specialty training in internal medicine

August, 2019
Addis Ababa, Ethiopia

ABSTRACT

Back ground Although efforts have been made to reduce AIDS-related mortality by providing antiretroviral therapy services, still people are dying while they are on treatment due to several factors. This study aimed to investigate the predictors of mortality among adult antiretroviral therapy users in Saint Paul's Hospital Millennium Medical College.

Objective To assess predictors of mortality among adult HIV infected patients on HAART at Saint Paul's Hospital Millennium Medical College.

Method A hospital-based case control study was conducted from January 2013- December 2018 on adult HIV infected patients on HAART having follow up at ART clinic of Saint Paul' Hospital Millennium Medical College, Addis Ababa, Ethiopia. Cases were clients started ART and died during the period while controls were clients started ART and alive during the same period. Data were collected from 336 of ART clients. For cases, the first 84 dead clients were taken and a ratio of three controls to one case was taken using simple random sampling method. Data were entered, cleared and analysed using SPSS version 25. Frequencies and percentages were used to describe study subject's characteristics. Bivariable logistic regression was used to determine an association between categorical variables and multivariable logistic regression was used to identify factors associated with ART client's mortality.

Results of 336 study participants, 84 were cases and 252 were controls. More than half of cases 49 (58.3 %) were females. Similarly, more than half of controls 171 (68.4 %) were also females. Most of cases 37 (44%) were under age group of 35-44 in years while that of controls 107(42.8 %) predominantly under age group of 25-34 in years. Overall mortality rate was 5.7/100 persons years and pattern of death was decreasing over 5 years still ART clients with WHO stage III and IV, CD 4 count less than 350 cells/mm³, platelet counts less than 150 X 1000 cells/ μ L, TB coinfection, other opportunistic diseases, not being given CPT and poor adherence had higher odds of death compared to their respective counterparts.

Conclusion Overall mortality rate was high and the pattern of mortality was generally decreasing. Advanced WHO clinical stage, low CD 4 count, low platelet count, presence of TB and other opportunistic diseases at ART initiation, not being given CPT and poor adherence were factors associated with mortality among ART clients. Initiation of ART at early WHO clinical stage, prevention and control of TB and other opportunistic infections, early work up of underlying causes of low platelet and treatment and counseling and improving adherence are recommended interventions to health care workers.

ACKNOWLEDGEMENT

First, I would like to thank Saint Paul's Hospital Millennium Medical College department of Internal Medicine for giving this golden opportunity to practice research. Secondly, my gratitude went to my advisers and ART unit staffs who had given me a good deal of their skill in providing me guidance and advice to do this research.

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ACRONYMS

ABC	Abacavir
AZT/ZDV	Azidothymidine/zidovudine
DRV	Darunavir
DDI	Didanosine
DTG	Dolutegravir
EFV	Efavirenz
3TC	Lamuvudine
D4T	Stavudine
TDF	Tenofovir

ABBREVIATIONS

AIDS	Acquired Immuno Deficiency Syndrome
ART	Anti Retroviral Therapy
BMI	Body mass index
CD4	Cluster of Differentiation
CI	Confidence interval
MOH	Ethiopian Ministry of Health
HAART	Highly Active Anti Retroviral Therapy
HIV	Human Immunodeficiency Virus
OI	Opportunistic infections
PLWHA	People living with HIV/AIDS
SPHMMC	Saint Paul's Hospital Millennium Medical College
TB	Tubercle Bacilli
WHO	World Health Organization

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1. INTRODUCTION

1.1. Background

HIV/AIDS is a global pandemic. As of UNAIDS 2017 report it is affecting 36.7 million people worldwide of which 34.5 million are adults. Sub-Saharan Africa accounting for 69%, with nearly 1 in every 20 adults living with HIV; Around 1.7 million people died from AIDS related causes worldwide, 74% occurred in Sub-saharan Africa (1).

Ethiopia is one of the hardest hit sub-Saharan African countries by the HIV pandemic. According to the 2017 new spectrum estimate, 722,248 Ethiopians are currently living with human immunodeficiency virus (HIV) and all of them require ART. However, only 420,000 individuals are currently taking antiretroviral (ARV) drugs (2016 global AIDS monitoring report). Since HIV epidemic in Ethiopia was detected in 1984, HIV/AIDS has claimed the lives of millions and has left behind hundreds of thousands of orphans(2).

Antiretroviral therapy (ART) has drastically improved the survival of patients who suffer from HIV/AIDS (3). The primary goals of ART are as follows: maximal and durable suppression of viral replication, restoration of immunologic function, reduction of HIV-related morbidity and mortality, improvement of quality of life, and prolonging survival (4, 5).

Global commitment to scale up HIV treatment in resource limited settings is bearing fruit. The fast growth in ART coverage represents one of the great public health success stories in recent history of HIV care that lead to reduction of mortality and improvement of quality of life of people living with HIV/AIDS (PLWHA) (3, 5).

The government of Ethiopia has been working on the scaling up of ART for all people to reduce AIDS-related morbidity and mortality. Ethiopian Ministry of Health (MOH) introduced ART since 2003 on subsidized, fee-based scheme and has developed national guidelines on the use of ART. Since 2005, ART became freely available. Further, ART service was decentralized to health centers in 2006, which marked the rapid scale-up phase in the history of the Ethiopian ART program. In addition to adopting the World Health organization (WHO) recommended public health approach, Ethiopia used innovative models such as a nationwide campaign to achieve national targets both for ART and HIV testing and counseling (6-8).

Currently, ART in Ethiopia being used includes tenofovir(TDF),Lamivudine (3TC), Efavirenz (EFV),Nevirapine (NVP), Zidovudine (AZT), Abacavir(ABC), lopinavir (LPV/r), atazanavir(ATV/r) while some drugs like didanosine(DDI) and stavudine(D4T) are out of use.Dolutegravir (DTG), Darunavir (DRV), and Raltegravir (RAL) are also included in new 2018 ART national guideline (2).

Despite the scale-up of ART, early mortality is a major challenge. High rates of early mortality were reported from a number of Sub-Saharan African ART programs (9-11). Age, sex, marital status, educational status, place of residence, time of HIV diagnosis and ART initiation, adherence to ART, WHO clinical stage, CD4 count, Viral load, Hemoglobin level, nutritional status (BMI), functional status, socio-economic condition, substance use, TB co-infection and opportunistic infections have been associated with mortality among clients on ART (12-15).

1.2. Statement of the problem

Global trends in HIV infection demonstrate an overall increase in HIV prevalence and substantial declines in AIDS related deaths largely attributable to the survival benefits of antiretroviral treatment. Despite these benefits of ART, Sub-Saharan Africa still accounted for 74% of deaths from AIDS related illnesses (1).

Even though the benefit of ART for people living with HIV/AIDS in terms of improving quality of life and reducing morbidity and mortality is well established, early mortality is a major challenge even if there is a regional variation in the extent of its benefit(9-11).

Studies show that in developing countries Including Ethiopia, different factors including clinical, demographic, socio-economic and behavioral factors have been reported to be related to predictors of mortality of HIV-infected patients under ART(12-15).So, this affects one country in many aspects economically, socially and politically and there is no enough data at national level.

Coming to our hospital, the hospital is giving ART service for HIV infected patients since 1995 E.C. Since the start of ART service, ART clients are still dying while on ART and this is major public health problem. However, those factors which contribute to the deaths of HIV-infected patients while on ART are not explored particularly at SPHMMC which has burden of patients in Ethiopia. Therefore, this study will investigate the predictors of mortality among adult ART users in SPHMMC, Addis Ababa, Ethiopia.

1.3. Significance of the study

As HIV-infected persons on HAART are surviving and experiencing longer life expectancies, knowing factors that determine mortality predictors once patients started ART is important.

This study aims in assessing predictors of mortality among adult HIV infected patients who died while on HAART. So, the result will be useful for both health care planning and the development of strategies to improve survival of HIV patients on HAART.

Furthermore; there are no enough data on the predictors of mortality among adult HIV infected patients who were on HAART and died both at national level and in our institution, it can be a bench-mark for future studies.

So, this study will be important in giving emphasis on the management of identified factors that contribute for mortality among adult HIV infected patients on HAART. Furthermore; it will be helpful to take measures on those modifiable mortality predictors so that survival will be improved.

2. LITERATURE REVIEW

A retrospective cohort study done in the Far-western region, Nepal on Survival on antiretroviral treatment among adult HIV-infected patients showed that crude mortality rate was 6.3 (95% confidence interval (CI) 5.3-7.6) but more than three-times higher in first 3 months after ART initiation (21.9 (95% CI 16.6- 28.8)). The independent determinants of mortality were male sex, poor baseline performance scale, decrease in baseline bodyweight , and poor WHO clinical stage(16) .

Study done on Survival and causes of death among HIV-infected patients starting antiretroviral therapy in north-eastern Vietnam which is part of a randomized controlled trial showed mortality rate was 7.4/100 person-y and survival probability was 91% after 1 year. At baseline, the predictive factors for AIDS-related death were age <35 y, clinical stage 3 or 4, body mass index (BMI) <18 kg/m² , CD4 count <100 □ haemoglobin level <100 g/l and plasma viral load < 100,000 copies/ml. Tuberculosis (TB) was the most common cause of death (40%)(17).

A prospective cohort study done on mortality in an antiretroviral therapy programme in Jinja, south-east Uganda showed mortality rates (95% CI) per 100 person-years were 11.8 (10.1, 13.8) deaths in the first year and 2.4 (1.8, 3.2) deaths thereafter. The one, two and three year survival probabilities (95% CI) were 0.89 (0.87 - 0.91), 0.86 (0.84 - 0.88) and 0.85 (0.83 - 0.87) respectively. Low baseline CD4 count, low body weight, advanced clinical condition (WHO stages III and IV), not being on cotrimoxazole prophylaxis and male gender were associated independently with increased mortality. Tuberculosis, cryptococcal meningitis and diarrhoeal disease were estimated to be major causes of death(18).

Cohort study done on predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania estimated mortality was 19.2, 29.0 and 40.7% at 3, 12 and 36 months, respectively. Independent predictors of mortality were severe anemia (hemoglobin <8 g/dL; adjusted hazard ratio [AHR] 9.20; 95% CI 2.05–41.3), moderate anemia (hemoglobin 8–9.9 g/dL; AHR 7.50; 95% CI 1.77–31.9), thrombocytopenia (platelet count <150 × 10⁹/L; AHR 2.30; 95% CI 1.33–3.99) and severe malnutrition (body mass index <16 kg/m²; AHR 2.12; 95% CI 1.06–4.24). Estimated one year mortality was 55.2% in patients with severe anemia, compared to 3.7% in patients without anemia ($P < 0.001$)(13).

Aretrospective cohort study Mortality and its determinants among patients infected with HIV-1 on antiretroviral therapy in a referral centre in Yaounde, Cameroon showed mortality incidence rate was 16.3%) about (88.5%) during the first year of follow-up. Baseline predictors of mortality were male gender (adjusted HR 2.15 (95% CI 1.34 to 3.45)), active tuberculosis (2.35 (1.40 to 3.92)), WHO stages III–IV of the disease (3.63 (1.29 to 10.24)), low weight (1.03 (1.01 to 1.05)/kg), low CD4 count (1.04 (1.01 to 1.07)/ 10/mm³ lower CD4) and low haemoglobin levels (1.12 (1.00 to 1.26)/g/dL lower)(14).

Open cohort study on Rapid Scale-up of Antiretroviral Therapy at Primary Care Sites in Zambia showed early mortality rate 26 per 100 patient-years within first 3 months and 5.0 per 100 patient-years after 3 months of follow up. Mortality was strongly associated with CD4 cell count between 50/μL and 199/μL (adjusted hazard ratio [AHR], 1.4; 95% confidence interval [CI], 1.0-2.0), CD4 cell count less than 50/μL (AHR, 2.2; 95% CI, 1.5-3.1), WHO stage III disease (AHR, 1.8; 95% CI, 1.3-2.4), WHO stage IV disease (AHR, 2.9; 95% CI, 2.0-4.3), low body mass index (<16; AHR,2.4; 95% CI, 1.8-3.2), severe anemia (<8.0 g/dL; AHR, 3.1; 95% CI, 2.3-4.0) and poor adherence to therapy (AHR, 2.9; 95% CI, 2.2-3.9)(19).

A retrospective cohort study was conducted among HIV infected patients on ART in eastern Ethiopia in Hiwot Fana, Jugal and DilChora hospitals and overall mortality rate provides an incidence density of 2.03 deaths per 100 person years (95% CI 1.64 - 2.50). Out of a total of 86 deaths over 60 month period; 63 (73.3%) died during the first 12 months, 10 (11.6%) during the second year, and 10 (11.6%) in the third year of follow up. In multivariate analysis, the independent predictors for mortality were loss of more 10% weight loss, bedridden functional status at baseline, ≤ 200 CD4 cell count/ml, and advanced WHO stage patients (12).

Another retrospective cohort study on Survival and determinants of mortality in adult HIV/Aids patients initiating antiretroviral therapy in Somali Region, Eastern Ethiopia at Kharamara hospital showed that the estimated mortality was 8.4%, 9.8%, 11.3%, 12.7% and 14.1% at 6, 12, 24, 36 and 48 months respectively. The independent predictors of death were single marital status (AHR: 2.31; 95%CI: 1.18-4.50), a bedridden functional status (AHR: 5.91; 95%CI: 2.87-12.16), advanced WHO stage (AHR: 7.36; 95%CI: 3.17-17.12), BMI < 18.5 Kg/m² (AHR: 2.20; 95%CI: 1.18-4.09), CD4 count < 50 cells/BL (AHR: 2.70; 95%CI: 1.26-5.80), severe anemia (AHR: 4.57; 95%CI: 2.30-9.10), and TB co-infection (AHR: 2.30; 95%CI: 1.28-4.11)(20).

Retrospective Cohort Study done on predictors of Mortality among Adult Antiretroviral Therapy Users in Southeastern Ethiopia at Goba Hospital showed that overall mortality incidence rate was 20.3 deaths per 1000 person-years. Male, bedridden, overweight/obese, and HIV clients infected with TB and other infectious diseases had higher odds of death compared with their respective counterparts. On the other hand, ART clients with primary and secondary educational level and early and less advanced WHO clinical stage had lower odds of death compared to their counterparts (21).

A Hospital-Based Retrospective Cohort Study Determinants of Mortality among HIV Positives after Initiating Antiretroviral Therapy in Western Ethiopia at Nekemte Referral Hospital The estimated mortality was 4%, 5%, 6%, 7%, and 7% at 6, 12, 24, 36 and 48 months respectively with mortality incidence density of 1.89 deaths per 100-person years (95% CI 1.74, 3.62). Forty years and above AHR = 3.055 (95% CI 1.292, 7.223), low baseline hemoglobin level (AHR = 0.523 (95%CI .335, 0.816)), and poor ART adherence (AHR 27.848 (95% CI 8.928, 86.8)) were found to be an independent determinants of mortality(22).

A Retrospective Cohort Study on Predictors of Mortality among Patients Enrolled on Antiretroviral Therapy in Aksum Hospital, Northern Ethiopia showed an overall mortality rate of 3.2 per 100 person-years. The independent predictor of mortality identified for this cohort were haemoglobin level less than 11 mg/dl (Hazard Ratio (HR) = 1.9,95%-CI = 1.01, 3.52), CD4 cell counts lower than 50 cells/ml (HR = 2.1, 95%- CI = 1.13,3.89), Male gender (HR = 1.9, 95%-CI = 1.01,3.52), Weight less than 40 kg (HR = 2.3,95% CI = 1.24,4.55), primary level of education and lower (HR = 2.6, 95%- CI = 1.29,5.55)(23).

A retrospective cohort study on Predictors of Survival in HIV-Infected Patient after Initiation of HAART in Zewditu Memorial Hospital, Addis Ababa, Ethiopia showed the incidence of mortality was 3.8/100 person-years. Independent predictors of mortality were WHO clinical stages 3-4 (HR = 2.3at 95% CI (1.26, 5.31)), anemia (hemoglobin level <10 gm/dL (HR = 5.54at 95% CI (2.58, 11.86)) and TB coinfection (HR=4.13 at 95% CI (1.79, 9.51)(24).

3. OBJECTIVE

3.1. General Objective

- ✓ To assess predictors of mortality among adult HIV infected patients on HAART at SPHMMC, January 2013-December 2018.

3.2. Specific Objectives

- ✓ To estimate mortality rate among adult HIV infected patients on HAART at SPHMMC, January 2013-December 2018.
- ✓ To identify predictors associated with mortality among adult HIV infected patients on HAART at SPHMMC, January 2013-December 2018.

4. METHOD

4.1. Study Area and Period

The study was carried out in SPHMMC which is located at Gullele Sub city at Swaziland Street, Addis Ababa, Ethiopia. The hospital is one of the biggest referral hospital in the capital under the Federal Ministry of Health. The hospital has different units in it: internal medicine, pediatrics, gynecology/obstetrics, surgery, dentistry, psychiatry, ophthalmology, hospital pharmacy, dermatology. Under department of internal medicine, ART clinic is giving service for HIV infected patients daily including weekends and it has about 30 health care workers in it. The study was conducted within 7 months of period using data collected from ART clinic of SPHMMC from January 1, 2013 to December 31, 2018.

4.2. Study Design

A hospital-based case control study was conducted on HIV infected patients on HAART who were on follow up at SPHMMC ART clinic from January 1, 2013 to December 31, 2018. Cases were clients started HAART and died during the period while controls were clients started HAART and alive during the same period.

4.3. Source Population

All cases and controls at SPHMMC ART clinic from January 1, 2013 to December 31, 2018.

4.4. Study population

All cases and controls who fulfilled the inclusion criteria at SPHMMC ART clinic from January 1, 2013 to December 31, 2018.

4.4.1. Inclusion criteria

All HIV infected patients on HAART for more than 02 weeks and who were 15 years old and above for both cases and controls

4.4.2. Exclusion criteria

All cases died by accident

4.4.3 Non-response

All ART clients who were lost to follow-up, transferred out, started ART outside of SPHMMC and dropped out for both cases and controls while accidentally died were excluded for cases as well.

4.5 Sample Size Determination

Taking the study done in Zewditu Memorial Hospital, Addis Ababa, Ethiopia as a reference which had prevalence of exposure 3.8% with a two sided confidence interval of 95%, power of 80%, taking 4.13 odds ratio of TB coinfection and control to case ratio 3:1, the calculated sample size is totally 336 using online epi info. Accordingly, sample size for cases was 84 and sample size for controls was 252.

4.6 Sampling technique

For cases, the first available 84 samples were taken and for controls, a ratio of three controls to one case being 252 samples were taken using simple random sampling method from study populations. For every cases, controls those started ART within the same year as that of cases were taken.

4.7 Data collection

Data related to sociodemographic characteristics and predictors of mortality of adults on HAART were collected from the patient's chart & filled on a well-prepared checklist that is adopted from standard questionnaire by WHO. Four data collectors were recruited from medical personnel in the respective sites.

4.8 Data quality control

Supervisor trained data collectors ahead of data collection on how to fill the required data on the questionnaire and principal investigator checked for data completeness.

4.9 Description of Variables

4.9.1 Dependent variables

- ✓ Dead or Alive

4.9.2 Independent variables

- ✓ Age
- ✓ Gender
- ✓ Socioeconomic status
- ✓ Marital status
- ✓ Drug adherence
- ✓ CD4 Count at initiation of treatment
- ✓ Hemoglobin level at initiation of treatment
- ✓ Platelet count at initiation of treatment
- ✓ Functional status at initiation of treatment
- ✓ Prophylactic drug use

4.10 Operational Definition

Adherence- describes the degree to which a patient correctly follows medical advice.

According to the Ethiopian ART follow up form adherence taken from ART clients' follow up chart prepared by WHO is assessed objectively as follows:

	%	(of 30 doses)	(of 60 doses)
Good (G)	>95%	< or = 2 doses	< or = 3 doses
Fair (F)	85-94%	3-5 doses	3-9 doses
Poor (P)	,<85%	>or =6 doses	> 9 doses

Functional status - is an individual's ability to perform normal daily activities required to meet basic needs, fulfill usual roles, and maintain health and well-being.

W = Working (able to perform usual work in or out of the house)

A = Ambulatory (able to perform activities of daily living)

B = Bedridden (not able to perform activities of daily living)

Socioeconomic status: an economic and sociological combined total measure of a person's work experience and of an individual's or family's economic and social position in relation to others, based on income, education, and occupation.

4.11 Data processing and analysis

Data was arranged, cleared and analyzed. The collected data was entered into a computer using Statistical Package for Social Science (SPSS) window version 25. Demographic and baseline clinical and laboratory characteristics were summarized into frequencies and percentage using tables, pie charts, bar chart and graph. Bivariable logistic regression and multivariable logistic regression were utilized and wherever appropriate P-value <0.05 was considered as statistically significant.

4.12 Ethical Consideration

Letter of support was obtained from department of internal medicine, SPHMMC. Ethical approval was obtained from the Saint Paul's Millennium Medical College institutional review board (IRB) and confidentiality of the study subjects was ensured.

4.13 Dissemination of results

The results of the study will be communicated to the ART Clinic and the department of internal medicine. It is also presented in the Annual research conference and at relevant scientific conferences. It will be sent to local journals for possible publication.

5. RESULT

5.1 Socio-Demographic Characteristics

A total of 84 cases and 250 controls were included in this case control study. More than half of cases 49 (58.3 %) were females. Similarly, more than half of controls 172 (68.4 %) were also females. The study subjects were divided in to four age groups, namely, Group I, II, III and IV aged from 15-24, 25-34, 35-44 and above 45 in years respectively for both cases and controls. Most of the patients were in age group II and III for cases 21 (25%) and 37(44 %) respectively while for controls age group II 107 (42.8 %) and group III 88 (35.2 %).

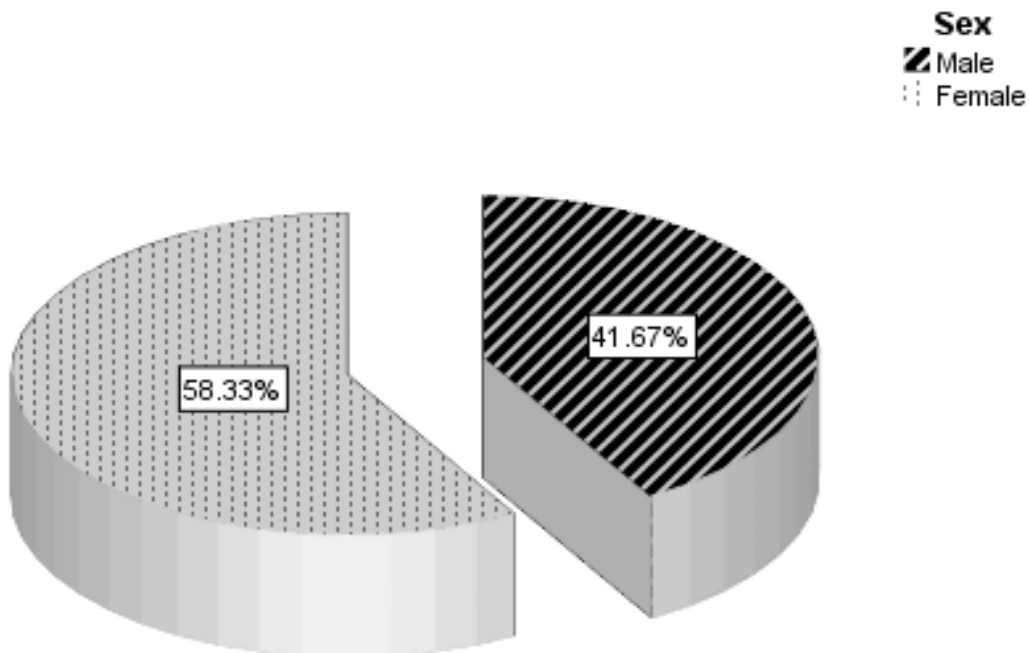


Figure 1: Pie-chart showing percentage of female and male of ART clients of cases.

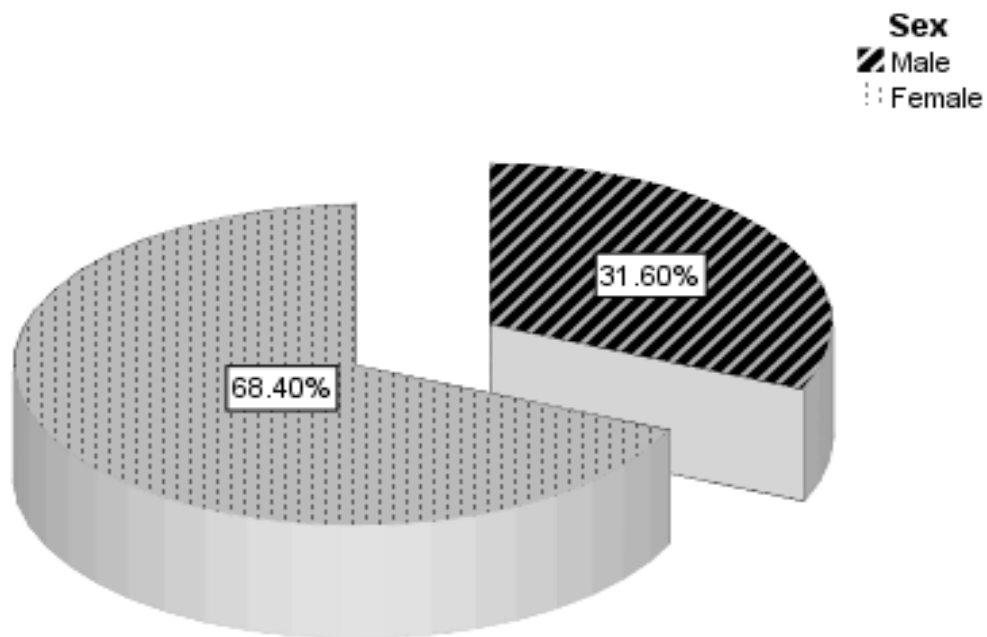


Figure 2: Pie-chart showing percentage of female and male ART clients of controls.

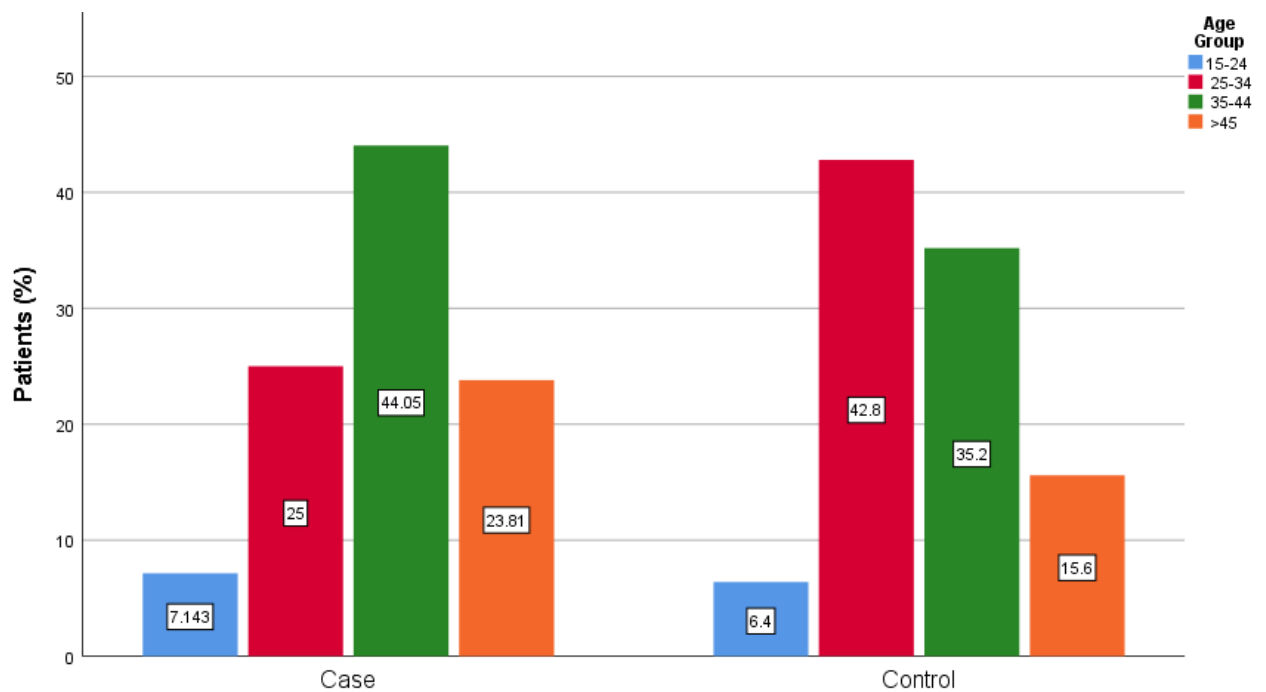


Figure 3: Bar chart showing Case-control percentage of ART clients in all age groups

The majority of study subjects 45 (53.6 %) of the cases and 131 (52.4%) of controls were married being followed by never married 24 (28.6%), divorced 8 (9.5%), separated 4 (4.8%) and widowed 3 (3.6%) in cases and in controls never married 61 (24%), divorced 34 (13.6%), widowed 21 (8%) and separated 5 (2%). Regarding religion majority of study subjects 63 (75%) of cases and 200 (80 %) of controls were followers of orthodox Christianity followed by Muslims 19 (22.6%) of cases and 28 (11.2 %) of controls.

In terms of educational status, most of both cases and controls had primary and secondary educational status, 33 (39.3%) and 34 (40.5%) of cases respectively and of controls primary 81 (32.4%) and secondary 87 (34.8%). Those had no formal education of cases were 5 (6%) and of controls were 39 (15.2%) while those had tertiary level of education of cases were 12 (14.3%) and of controls were 45 (17.6%).

Regarding occupation of study subjects, majority of both cases 48 (57.1 %) and controls 104 (41.6 %) were unemployed but some were merchant and the others were housewives in both cases and controls. 26 (31 %) of cases and 81 (32.4%) of controls were employed. Some were employed at government institutions while the others at private institutions in both cases and controls. In addition, 6 (2.4 %) of controls were drivers and students.

Table 1: Sociodemographic characteristics of cases and controls, SPHMMC, January, 2013 - December, 2018.

Sociodemographic variables		Cases n(%)	Controls n (%)
Sex	Male	35 (41.7)	80 (31.7)
	Female	49 (58.3)	172 (68.3)
Age(yrs)	15-24	6 (7.1)	17 (6.4)
	25-34	21 (25.0)	107 (42.8)
	35-44	37 (44.0)	88 (35.2)
	>45	20 (23.8)	40 (15.6)
Marital status	Never married	24 (28.6)	61 (24.2)
	Married	45 (53.6)	131 (52.0)
	Divorced	8 (9.5)	34 (13.5)
	Widowed	3 (3.6)	21 (8.3)
	Separated	4 (4.8)	5 (2.0)
Educational status	No education	5 (6.0)	39 (15.5)
	Primary	33 (39.3)	81 (32.1)
	Secondary	34 (40.5)	87 (34.5)
	Tertiary	12 (14.3)	45 (17.8)
Religion	Muslim	19 (22.6)	28 (11.2)
	Orthodox	63 (75.0)	200 (80.0)
	Protestant	2 (2.4)	22 (8.4)
	Catholic	0 (0.0)	0 (0.0)
	Others	0 (0.0)	2 (0.4)
Occupation	Employed	26 (31.0)	81 (32.1)
	Unemployed	48 (57.1)	104 (41.3)
	Unknown	10 (11.9)	60 (23.8)
	Others	0 (0.0)	7 (2.8)

5.2 Baseline Clinical characteristics

Majority of the cases 36 (42.9%) were ambulatory at initiation of ART followed by working 31 (36.9%) and bedridden only 17(20.2 %). Majority of controls 212 (84.8%) were working at initiation of ART followed by ambulatory 32 (12.4 %) and bedridden only 8 (2.8 %).

WHO stage was categorized into four according to its standard staging. Majority of cases were stage III and IV, 31 (36.9%) and 30 (35.7 %) respectively while of controls majority were stage I and II, 130 (52%) and 57 (22.8%) respectively. Regarding baseline CD 4count, majority of cases had less than 200 cells/mm³accounting 48 (57.1%). In contrary of cases, majority of controls had CD 4 count more than 350 cells/mm³accounting 104 (41.2%).

Nutritional status of study subjects by BMI, majority were in 18.6-24.9 Kg/m² in both cases 43 (51.2%) and controls 202 (80.8 %). More than half of cases had baseline hemoglobin level above 10 g/dl. The same is true for controls having baseline hemoglobin level above 10 g/dl 211 (84 %). Regarding baseline platelet count, cases had 65 (77.4 %) for platelet count above 150 X 1000 cells/ μ L and controls 239 (94 %) had platelet count above 150 X 1000 cells/ μ L.

Regarding TB coinfection at initiation of ART, cases had been coinfectd 32 (38.1%) either by pulmonary tuberculosis or extrapulmonary tuberculosis while controls coinfectd 27(10.4%) by either of TB forms.

Less than half of cases had different types of opportunistic diseases 41 (48.8%). These opportunistic diseases include oral candidiasis 10 (24.4 %), esophageal candidiasis 8 (19.5%), PCP 7 (17.1%), Cryptococcal disease (meningioencephalitis) 7 (17.1%), CNS toxoplasmosis 2 (4.9%) and others 7 (17.1%) including herpes zoster and malignancy (lymphoma and cervical CA). But controls, only 63 (24.4%) had these opportunistic diseases. Of these, oral candidiasis account 32(50.8%), esophageal candidiasis 8 (12.7%), PCP 4(6.3%), CNS toxoplasmosis 3 (4.8%) and others 16 (25.4%) all had herpes zoster and no malignancy.

Coming to the given prophylaxis, more than half of cases took CPT 64 (76.2%) while controls took it similarly more than half 148 (58.8%). However, none of cases took IPT while controls 44 (17.2%) were given.

Majority of cases had good adherence 55 (65.5%) followed by poor adherence 16 (19 %) and fair adherence 13 (15.5%). Similarly, majority of controls had good adherence 242 (96.4%) followed by fair adherence 7 (2.4%) and poor 3 (1.2%) adherence.

Started ART regimen for cases, 1e accounts 60 (71.4 %) followed by 1c, 1d and others 3 (3.6%), 4 (4.8%) and 3 (3.6%) respectively. But later on, for 14 (16.7%) of cases first line ART regimen changed to second line ART regimen. For controls, 1e accounts 222 (88.4%) followed by 1c, 1d and others 3 (1.2%), 3 (0.8 %) and 12 (4.8 %) respectively. Later on, for controls 12 (4.8 %) first line ART regimen changed to second line ART regimen.

Table 2: Clinical characteristics of cases and controls, SPHMMC, January, 2013 - December, 2018.

Baseline Characteristics		Cases n (%)	Controls n(%)
Functional status	Working	31 (36.9)	212 (84.1)
	Ambulatory	36 (42.9)	32 (12.6)
	Bedridden	17 (20.2)	8 (3.2)
WHO stage at ART initiation	Stage I	13 (15.5)	130 (51.6)
	Stage II	10 (11.9)	57 (22.6)
	Stage III	31 (36.9)	43 (17.0)
	Stage IV	30 (35.7)	22 (8.7)
BaselineCD4 (cells/mm3)	< 200	48 (57.1)	95 (37.7)
	201-350	19 (22.6)	53 (21.0)
	>350	17 (20.2)	104 (41.3)
BMI (Kg/m2)	<18.5	33 (39.3)	37 (14.7)
	18.6-24.9	43 (51.2)	202 (80.2)
	>25	8(9.5)	13 (5.2)
Hemoglobin level (g/dl)	<7	13 (15.5)	9 (3.6)
	7.1-10	16 (19.0)	32 (12.7)
	>10.1	55 (65.5)	211 (83.7)
Platelets count (cells/ μ L)	<150 X 1000	19 (22.6)	13 (5.2)
	>150 X 1000	65 (77.4)	239 (94.8)
TB coinfection	Yes	33 (39.3)	27 (10.7)
	No	51 (60.7)	225 (89.3)

Table 2: continued

Other opportunistic diseases	Yes	41 (48.8)	63 (25.0)
	No	43 (51.2)	189 (75.0)
Types opportunistic diseases	Oral candidiasis	10 (24.4)	32 (50.8)
	Esophageal candidiasis	8 (19.5)	8 (12.7)
	PCP	7 (17.1)	4 (6.3)
	Cryptococcal disease	7 (17.1)	0 (0.0)
	CNS toxoplasmosis	2 (4.9)	3 (4.8)
	Others	7 (17.1)	16 (25.4)
CPT	Given	64 (76.2)	148 (58.7)
	Not Given	20 (23.8)	104 (41.3)
IPT	Given	0 (0.0)	44 (17.5)
	Not Given	84 (100.0)	208 (82.5)
ART adherence	Good	55 (65.5)	242 (96.0)
	Fair	13 (15.5)	7 (2.8)
	Poor	16 (19.0)	3 (1.2)
ART regimen	1c	3 (3.6)	3 (1.2)
	1d	4 (4.8)	3 (1.2)
	1e	60 (71.4)	222 (88.1)
	Others	3 (3.6)	12 (4.8)
	2f	7 (8.3)	7 (2.8)
	2h	5 (6)	4 (1.6)
	2e	2 (2.4)	1 (0.4)

5.3 Pattern of Death

The number of patient's dead were 34, 23, 15, 8 and 4 for the first, second, third, fourth and fifth year and decreased by 13.08%, 9.54%, 8.34%, 4.76% respectively. The maximum death reported was 34 in the first year. The minimum was 4 in the fifth year. There were 84 deaths in 1467-person years with overall mortality rate of 5.7/100 persons years.

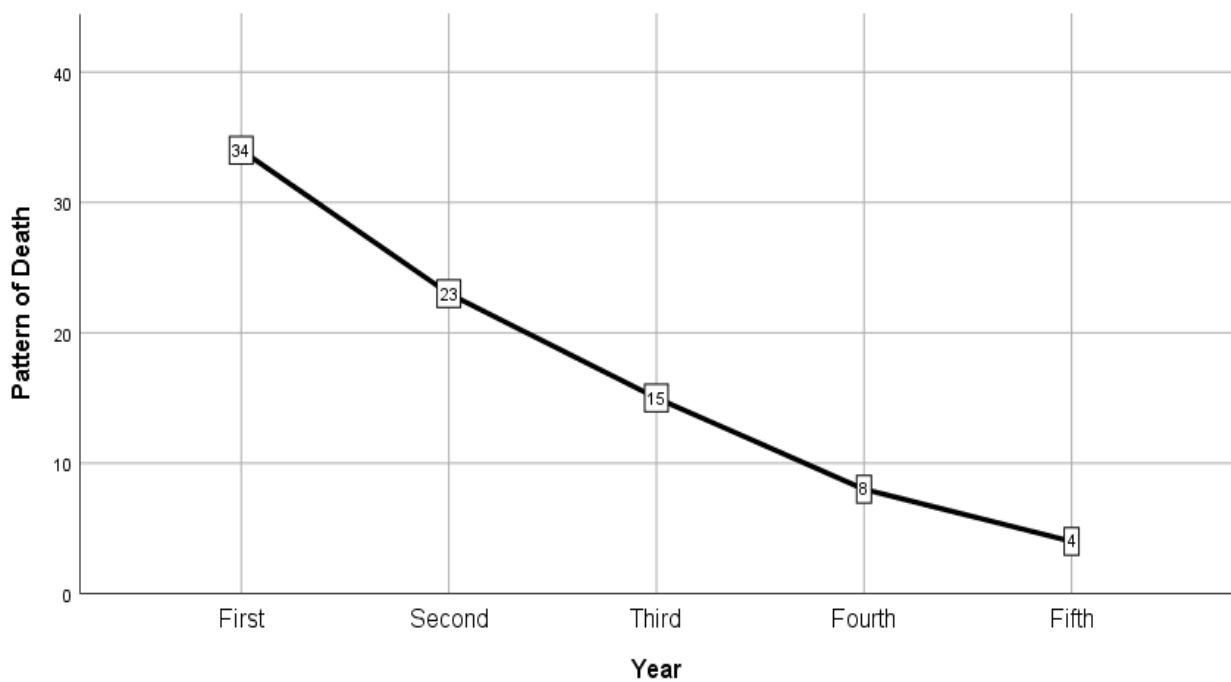


Figure 4: The pattern of death reported for five years.

5.4 Predictors of Mortality: Bivariable Logistic regression

Bivariable logistic regression was used to determine an association between categorical variables. Accordingly, ART clients with ambulatory (COR = 7.942; 95% CI: 4.313-14.623) and Bedridden (COR =16.608; 95% CI:6.375-43.267),WHO stage III (COR =7.381 ; 95% CI:3.539-15.395), WHO stage IV (COR =14.286 ; 95% CI: 6.435-31.714) and CD 4 less than 200 cells/mm³ (COR =3.094; 95% CI:1.665 -5.750) and CD 4 count between 201-350 cells/mm³ (COR = 2.172; 95% CI:1.043 -4.523) were associated with mortality.

BMI less than 18.5 Kg/m²(COR = 4.306; 95% CI:2.421-7.658), BMI greater than 25kg/m² (COR =3.132 ; 95% CI:1.207-8.124), hemoglobin level less than 7 g/dl (COR = 6.205; 95% CI:2.449 -15.716), platelet count less than 150 X 1000 cells/ μ L(COR =5.409 ; 95% CI: 2.480 - 11.796), TB coinfection (COR = 5.575; 95% CI: 3.068-10.129), other opportunistic diseases(COR =2.939; 95% CI:1.754 - 4.924), ART clients who did not take CPT (COR =4.46; 95% CI:2.54-7.82), fair (COR =9.494; 95% CI:3.455-26.085) and poor (COR =23.370; 95% CI:6.580- 83.002) adherence were also associated with mortality.

Table 3: Bivariable Logistic regression ,sociodemographic and clinical factors associated with mortality.

Variables		Cases n(%)	Controls n(%)	P-value	COR (%)
Sex	Male	35 (41.7)	80 (31.7)	0.093	1.546 (0.929-2.573)
	Female	49 (58.3)	172 (68.3)		1
Age(yrs)	15-24	6 (7.1)	17 (6.4)		1
	25-34	21 (25.0)	107 (42.8)	0.226	0.523 (0.183-1.493)
	35-44	37 (44.0)	88 (35.2)	0.825	1.121(0.407-3.090)
	>45	20 (23.8)	40 (15.6)	0.571	1.368 (0.463-4.035)
Educational Status	No education	5 (6.0)	39 (15.5)	0.206	0.482 (0.156-1.493)
	Primary	33 (39.3)	81 (32.1)	0.298	1.494 (0.702-3.181)
	Secondary	34 (40.5)	87 (34.5)	0.348	1.433 (0.676-3.038)
	Tertiary	12 (14.3)	45 (17.9)		1
Functional status	Working	31 (36.9)	212 (84.1)		1
	Ambulatory	36 (42.9)	32 (12.6)	<0.001*	7.942 (4.313-14.623) *
	Bedridden	17 (20.2)	8 (3.2)	<0.001*	16.608(6.375-43.267) *
WHO stage at ART initiation	StageI	13 (15.5)	130 (51.6)		1
	StageII	10 (11.9)	57 (22.6)	0.211	1.754 (0.727- 4.235)
	StageIII	31 (36.9)	43 (17.0)	<0.001*	7.381 (3.539-15.395) *
	StageIV	30 (35.7)	22 (8.7)	<0.001*	14.286 (6.435-31.714) *
CD4 (cells/mm3)	< 200	48 (57.1)	95 (37.7)	<0.001*	3.094 (1.665 -5.750) *
	201-350	19 (22.6)	53 (21.0)	0.038*	2.172 (1.043 -4.523) *
	>350	17 (20.2)	104 (41.3)		1
BMI (Kg/m2)	<18.5	33 (39.3)	37 (14.7)	<0.001*	4.306 (2.421-7.658) *
	18.6-24.9	43 (51.2)	202 (80.1)		1
	>25	8 (9.5)	13 (5.2)	0.019*	3.132 (1.207-8.124) *

Table 3: Continued

Hemoglobin level(g/dl)	<7	13 (15.5)	9 (3.6)	<0.001*	6.205 (2.449 -15.716)*
	7.1-10	16 (19.0)	32 (12.7)	0.058	1.909 (0.977-3.729)
	>10.1	55 (65.5)	211 (83.7)		1
Platelets count (cells/ μ L)	<150 X 1000	19 (22.6)	13 (5.2)	<0.001*	5.373(2.480 -11.796) *
	>150 X 1000	65 (77.4)	239 (94.8)		1
TB coinfection	Yes	33 (39.3)	27 (10.7)	<0.001*	5.392 (3.068-10.129) *
	No	51 (60.7)	225 (89.3)		1
Other opportunistic diseases	Yes	41 (48.8)	63 (25.0)	<0.001*	2.860 (1.754 - 4.924) *
	No	43 (51.2)	189 (75.0)		1
CPT	Given	64 (76.2)	148 (58.7)		1
	Not Given	20 (23.8)	104 (41.3)	0.005*	4.46 (2.54-7.82) *
IPT	Given	0 (0.0)	44 (17.5)		1
	Not Given	84 (100.0)	208 (82.5)	0.997	0.0001 (0.0001-0.002)
ART adherence	Good	55 (65.5)	242 (96.0)		1
	Fair	13 (15.5)	7 (2.8)	<0.001*	9.494(3.455-26.085)*
	Poor	16 (19.0)	3 (1.2)	<0.001*	23.370 (6.580 -83.002) *

* Remained statistically significant at $P < 0.05$

5.5 Predictors of Mortality : Multivariable Logistic regression

Multivariable logistic regression was used to identify factors associated with mortality. Accordingly, ART clients with ambulatory (AOR = 3.170; 95% CI:1.519-6.616) functional status had higher risk of death compared to Working functional status. However, for bedridden, association was not significant after adjusting for possible confounders.

ART clients with WHO stage III (AOR =6.376; 95% CI: 2.133-19.063) and WHO stage IV (AOR =5.139; 95% CI:1.519 - 17.390) had higher risk of death compared to WHO stage I and stage II. ART clients with CD 4 less than 200 cells/mm³ (AOR =2.892; 95% CI: 0.799-10.469) and CD 4 count 201-350 cells/mm³ (AOR =1.053; 95% CI:0.293 -3.778) had higher risk of death compared to CD 4 count above 350 cells/mm³. ART clients with platelet count less than 150 X 1000 cells/ μ L, (AOR =1.828; 95% CI:0.638 -5.237) had higher risk of death compared to those with platelet counts above 150 X 1000 cells/ μ L.

ART clients with TB coinfection (AOR =2.460; 95% CI:1.057-5.729) had higher risk of death compared to those without TB coinfection. Similarly, ART clients with other opportunistic diseases (AOR =1.438; 95% CI: 0.656-3.155) had higher risk of death compared to those without other opportunistic diseases.

ART clients who did not take CPT (AOR =1.758; 95% CI:0.602 -5.133) had higher risk of death compared to those who took it. ART clients with fair (AOR =6.672; 95% CI:2.151-20.693) and poor (AOR = 6.843; 95% CI:1.5980-29.301) adherence had higher risk of death compared to good adherence.

Even if, Bedridden, BMI less 18.5 Kg/m² and greater than 25 kg/m² and hemoglobin level less than 7g/dl had significant association by bivariable logistic regression, they did not show significant association by multivariable logistic regression.

Finally, Sex, age of study subjects, educational status and IPT did not show significant association with mortality by both bivariable and multivariable logistic regression.

Table 4: Multivariable logistic regression, factors associated with mortality.

Variables		Cases n(%)	Controls n(%)	P-value	AOR (95%)
Functional status	Working	31 (36.9)	212 (84.1)		1
	Ambulatory	36 (42.9)	32 (12.6)	0.002*	3.170(1.519-6.616)*
	Bedridden	17 (20.2)	8 (3.2)	0.051	3.485(0.995-12.209)
WHO stage at ART initiation	Stage I	13 (15.5)	130 (52.6)		1
	Stage II	10 (11.9)	57 (22.6)	0.842	0.896(0.306 - 2.627)
	Stage III	31 (36.9)	43 (17.0)	0.001*	6.376(2.133-19.063)*
	Stage IV	30 (35.7)	22 (8.7)	0.008*	5.139 (1.519 - 17.390)*
CD4 (cells/mm ³)	< 200	48 (57.1)	95 (37.7)	0.002*	2.892 (0.799-10.469)*
	201-350	19 (22.6)	53 (21.0)	0.039*	1.053 (0.293 -3.778)*
	>350	17 (20.2)	104 (41.3)		1
Platelets count(cells/ μ L)	<150 X 1000	19 (22.6)	13(5.2)	0.023*	1.828 (0.638 - 5.237)*
	>150 X 1000	65 (77.4)	239 (94.8)		1
TB Coinfection	Yes	33 (39.3)	27 (10.7)	0.037*	2.460 (1.057-5.729)*
	No	51 (60.7)	225 (89.3)		1
Other opportunistic Diseases	Yes	41 (48.8)	63 (25.0)	0.0364*	1.438 (0.656-3.155) *
	No	43 (51.2)	189 (75.0)		1
CPT	Given	64 (76.2)	148 (58.7)		1
	Not Given	20 (23.8)	104 (41.3)	0.0302*	1.758(0.602 - 5.133) *
ART adherence	Good	55 (65.5)	242 (96.0)		1
	Fair	13 (15.5)	7 (2.8)	0.001*	6.672 (2.151-20.693)*
	Poor	16 (19.0)	3 (1.2)	0.010*	6.843 (1.5980-29.301)*

*Remained statistically significant at $P < 0.05$

6. DISCUSSION

This 5-year retrospective chart review case control study of HIV infected patients on ART gives an insight into determinants of mortality in a hospital setting in SPHMMC. There were 84 deaths in 1467-person years with overall mortality rate of 5.7/100 persons years.

This finding is higher than the finding from Southeastern Ethiopia at Goba Hospital showed that overall mortality rate was 20.3 deaths per 1000 person-years (21) and eastern Ethiopia in Hiwot Fana, Jugal and DilChora hospitals showed overall mortality rate 2.03 deaths per 100-personyears (12). Similarly, it is higher than study done Northern Ethiopia, Aksum Hospital (23) and Zewditu Memorial Hospital, Addis Ababa, Ethiopia (24) showed an overall mortality rate of 3.2/100 and 3.8/100 person-years respectively but, lower than finding from north-eastern Vietnam reported mortality rate 7.4/100 person-year.

Regarding the factors associated with mortality, this study showed that of ART clients with WHO clinical stages III and IV were associated with higher odds of death as compared to clients with WHO clinical stage I and II. This indicated that advanced baseline WHO clinical stage was statistically significant clinical predictor of mortality as comparably documented by different studies from Africa and Ethiopia (12, 14, 16, 17, 18, 19, 20, 21, 24). This has implication that while the ultimate goal should be to treat patients before they progress to such advanced stages, careful documentation of the patient's disease stage will be helpful in identifying patients who need more intense follow-up. Improving the counseling and testing practices should be viewed as a more sustainable strategy.

This study showed that CD4 count less than 200 cells/mm³ and CD 4 count 201-350 cells/mm³ also associated with higher odds of death as compared to ART clients with CD4 above 350 cells/mm³. Different studies again from Africa and Ethiopia were in line with this study (12, 14, 17, 18, 19, 20, 23). This shows more immune depression increases risk of death. So, early diagnosis and treatment with ART decrease mortality.

In this study, ART clients with lower platelet count were more likely to die compared to those with normal platelet counts. In this regard, study from rural hospital in Tanzania reported supporting evidence that lower platelet count was one of predictors of mortality (13)

In the same way, this study also showed that TB coinfection at ART initiation was significantly associated with higher odds of mortality among ART clients as analogously reported by various studies (14, 17, 18, 20, 21, 24). It is believed that the delay in diagnosis and

treatment and not giving TB prophylaxis contributed to the higher mortality. In this study, all cases did not take TB prophylaxis while some of controls took it. This could be one of the reason that resulted in higher odds of ratio.

Likewise, this study also showed that ART clients with other opportunistic diseases were more likely to die as compared to those without other opportunistic diseases. Study done on mortality in an antiretroviral therapy programme in Jinja, south-east Uganda showed that cryptococcal meningitis was estimated to be major cause of death supporting this study as one of opportunistic diseases found in the study group (cases) was cryptococcal meningitis (18).

This study also showed ART clients not on CPT had higher odds of mortality compared to those received it. Study done on mortality in an antiretroviral therapy programme in Jinja, south-east Uganda also supported showing that ART clients not being on cotrimoxazole prophylaxis were associated independently with increased mortality (18).

In addition, this study showed that ART clients with fair and poor adherence had higher odds of mortality compared to those with good adherence. Supportive study done in Zambia and Western Ethiopia at Nekemte Referral Hospital showed poor adherence was independent determinant of mortality (19, 22).

Although different studies documented that male gender (14, 16, 17, 18, 24), old age (17,22), educational status (21, 23), BMI status (12, 13, 14, 17, 18, 19, 20, 23), anemia (13, 14, 17, 19, 20, 22, 23, 24) and bedridden (12, 16, 20) were reported significant predictors of mortality of ART clients, this study did not find statistically significant association between these variables and mortality.

7. STRENGTH AND LIMITATION OF THE STUDY

This study should be interpreted in light of its strengths and limitations. As strength, it was the first study done at SPHMMC with this topic in adult population. As limitation, since data is secondary, few variables were not used because not documented on chart and further studies will be needed.

8. CONCLUSION

This study showed that overall mortality rate was 5.7/100 persons years and pattern of mortality was generally decreasing. Advanced WHO clinical stage, low CD 4 count, low platelet count, presence of TB and other opportunistic diseases at ART initiation, not being given CPT and poor adherence were factors associated with mortality among ART clients.

9. RECOMMENDATION

Based on finding of this study, the following recommendations are forwarded to health care workers:

- Initiation of ART at early WHO clinical stage.
- Prevention and control of TB and other opportunistic infections.
- Early work up of underlying causes of low platelet and treatment.
- Counseling and improving adherence.

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ANNEX

Part one: socio demographic characteristics

1. Sex 1. male 2. female
2. Ages(yrs) 1. 15 -24 2. 25 - 34 3. 35-44 4. > 45
3. Marital status 1.never married 2. married 3. divorced 4. widowed 5.separated
4. Educational status 1. no education 2. primary 3. secondary 4. tertiary
5. Religion 1.Muslim 2.Orthodox 3.protestant 4. Catholic 5.Others
6. Occupation 1.Farmer 2. Merchant 3.Government Employee
 4. Day laborer 5.Housewife 6.others

Part two: Baseline clinical and laboratory information

1. Baseline functional status 1. Working 2. Ambulatory 3. Bedridden
2. WHO stage at ART initiation 1. stage I 2. stage II 3. stage III 4. stage IV
3. Baseline CD4 count(cells/mm³) 1. <200 2. 201-350 3. >350
4. Baseline BMI (Kg/m²) 1. <18.5 2. 18.5–24.9 3. >25.0
5. Baseline Hemoglobin level(g/dl) 1. <7 2. 7.1-10 3. >10
6. Baseline Platelet count (cells/ μ L) 1. < 150 × 1000 2. > 150 × 1000
7. TB co infection 1. yes 2. no
8. other Opportunistic diseases 1. yes 2. no
9. If yes for no.8 specify the disease
10. CPT 1. given 2. not given
11. IPT 1. given 2. not given
12. ART regimen 1. 1st line (1c,1d,1e, others) 2. 2nd line(2f,2h,2e)
13. ART adherence 1. good 2. fair 3. poor
14. Patient outcome 1. Died 2. Alive