Determinants of First- Line Treatment Failure among HIV Infected Adults at Public Hospitals, Harar Town, Eastern Ethiopia

MPH THESIS

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BIOGRAPHICAL SKETCH

My name is Shumet Msganaw. I was born in 1992 G.C at Dessie town, southern Ethiopia. I completed my Elementary education at Genatit primary elementary school from 1998-2005, secondary, and preparatory Mekdela high school from 2006-2010.I have joined Haramaya University College of Computing and Informatics Science in Department of Statistics 20011. After graduation I was employed and served in Haramaya University, College of health and Medical Sciences and in September, 2017 I have joined Haramaya University Post Graduate Program Directorate as Self- sponsored student pursue his study in Master of Public Health in Epidemiology.

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Abbreviations and Acronyms

3TC	Lamivudine
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
CD4	Cluster Differentiation
D4T	Stavudine
DDI	Didanosine
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HFSUH	HiwotFana Specialized University Hospital
HU	Haramaya University
IF	Immunological Failure
JGH	JugulaGeneral Hospital
LV	Viral load
NVP	Nevirapine
TB	Tuberculosis
TDF	Tenofovir
TF	Treatment Failure
VF	Virological Failure
OI	Opportunistic Infection

SUMMERY

Background:-Treatment failure is the inability of antiretroviral therapy to control human immune deficiency virus infection and further mortality risk. The identification and management of first-line treatment failure is a key challenge for human immune deficiency virus programs. Identifying and managing determinants of first-line treatment failures are the main important to improve a high treatment success rate and develop the quality of life. However, there is limited evidence on the determinants of treatment failure among Human Immunodeficiency Virus-infected people on highly active antiretroviral treatment in Harar, eastern Ethiopia.

Objective: To identify determinants of first- line antiretroviral treatment failure at Hiwot Fana Specialized University Hospital & Jugula General Hospital from 12 March to 12 May 2019.

Methodology: Case- control study was conducted in selected public hospitals among adults on first-line antiretroviral therapy. In this study, 171 cases and 342 controls were collected from medical records of positive adults. Data were entering in to Epi data version 3.1 and has been exported to STATA version 14.2for analysis. The multivariate logistic regression model was used to identify determinants on first-line treatment failure. In bivariate analysis, were all variables of p-value <0.25 entered in to multivariate analysis. Adjusted odds Ratio with 95% confidence intervals were computed and statistical significance was declared with P-value <0.05.

Results: In this study, higher odds of first line antiretroviral treatment failure were observed on the patients with age ranges 15 to 30 years (Adjusted odd ratio (AOR) =2.95, 95% CI: 1.72-4.99)**,** low CD4 count <200 cell/mm3 at current (AOR=2.22, 95% CI: 1.30-4.17), WHO stage III or IV (AOR=3.21, 95% CI: 1.98-5.23), poor adherence to treatment (AOR= 2.98, 95% CI: 1.60-5.56) had had gastric problem (AOR=5.02, 95% CI: 2.73-9.23) and recent body mass index <= 16.5 kg/m2 (AOR=3.11, 95% CI: 1.69-5.71).

Conclusion: From this study, age 15 to 30 years, low cluster differentiation cell count at recent, treatment stage III and IV at baseline, low current body mass index at recent, poor adherence to treatment, and history of gastro intestinal problem were associated with first-line antiviral therapy failure. Health professionals should pay special attention to the risk group identified.

Keywords: antiretroviral therapy, case-control study, treatment, Immunological, virology failure

Introduction

1.1. Background

Globally, an estimated 36.7 million people were living with the Human Immunodeficiency Virus (HIV) in 2015. Additionally, there were about 1.8 million people became newly infected with HIV and 1.0 million people have been died from Acquired Immune Deficiency Syndrome (AIDS) related illnesses in the simultaneous year(WHO, 2017)

In sub-Saharan Africa, HIV has been a highly epidemic health problem, with nearly 25.5 million people living with HIV. In Ethiopia, AIDS has continued to be one of the top priorities of the health sector program. Ethiopia is the one among the countries most affected by the HIV epidemic, with 718,550 people living with HIV in 2017 and HIV/AIDS has become one of the top priorities of the health sector program of the Ethiopian government Central Statistics Agency(CSA, 2017).

According to the report of CAS in 2018 around 690,000 adults living with HIV, 45,000 were on treatment (Wubshet et al., 2012). Highly Active Antiretroviral Therapy (HAART) has gradually reduced the morbidity and mortality associated with Human Immunodeficiency Virus (HIV) infection, and has improved the prognosis of People Living with HIV/AIDS (PLWHA) (Bhaskaran et al., 2008). Treatment Failure is the inability of antiretroviral drugs (ARV) to control HIV infection and further its mortality of the infected clients. Antiretroviral treatment (ART) failure is associated with virologic failure, immunologic failure, and/or clinical failure. The goal of the treatment is to suppress virus replication for as long as possible, restore and/or preserve immune function, improve quality of life, and reduce HIV related morbidity and mortality (Hammer et al., 2013)

Treatment failure results in a number of challenges reduce both the duration and the chance of viral control due to cross- resistance between different alternative drugs and overlapping toxicities between and within a class of HAART. Subsequently, the likelihood that successful HAART will last life-long is poor. Besides, second-line ART is more expensive, more toxic and less efficacious than that of first-line HAART counter-parts (Orrell et al., 2007)

1.2. Statement of the Problem

Human immune deficiency virus attacks most of the economically productive ages in the world. This leads to the reduce work-force; limit the development of the country and ART outcomes continue to worse (Makunde et al., 2012).

The current status of antiretroviral therapy therefore enhance even though, the sign of problems the is remain until now; it is not devoid of unwanted secondary effects, poor absorption of anti-HIV medications, problems due to other illnesses or conditions, problems due to poor health before starting treatment, side effects of medications or interactions with other medications and substance abuse leading to poor treatment adherence and treatment failure (Harries et al., 2010).

Treatment failure, whether exposed to any type of failure, discontinuing ART, or loss to follow-up, has been shown to increase morbidity and mortality (Evangeli et al., 2014). HIV positive adults staying on a failing first-line therapy is lead to an increased mortality risk and result of treatment failure leads to the improvement of drug resistance limits the ability to construct new, potent, tolerable regimens in the future, distinguishing, the managing of first-line antiretroviral therapy (ART) failure has become a key problem(inadequate capacity and lack of laboratory facilities) for resource-limited settings (Rupérez et al., 2015).

The study was no more conducted to assess treatment failure and factors that are associated with it in the study setting. Since viral load determination is not used in the management of HIV, the lack of study will affect the effective follow-up and management of patients. With no routine viral load monitoring and unaware of factors that predict treatment failure early, health providers are forced to keep patients on a failing regimen for a longer duration, which leads to the development of drug-resistant HIV strains. Moreover, patients need more attention and advanced monitoring system due to uncertainty if viral load (VL) monitoring compared to clinical or immunological monitoring affects critical outcomes of First-line ART (Cozzi-Lepri et al., 2012)

This study was focusing on the determinants associated with first-line antiretroviral treatment failure and it would provide information for clinicians to use in the follow-up and management of patients.

1.3. Significance of the Study

The main aim of this study was to provide basic information on the determinant of first-line treatment failure to the physician and the concerned HIV infected adults on ART clinic of Hiwot Fana Specialized University Hospital (HFSUH) and Jugula general hospital (JGH). Public health professionals will use the information generated in the design of ART related programs, care, and support endeavors. At the same time, the finding of this study contribute to nongovernmental health organizations, and Harar regional health bureau program managers, designing planner to take public health intervention and used as the source of literature for further studies**.**

1.4. Objective of the Study

- To identify the determinant factors associated with first-line treatment failure among adults following ART at HFSUH and JGH from 12 March to 12 May2019.

` 2. LITERATURE REVIEW

2.1. Determinant Factors of First -Line Treatment Failure

Globally, there were several studies that have been conducted with different design to determine the determinant of initial treatment failure on HIV infected adults initiated on ART clinic. Monitoring the infected adults taking ART is necessary to ensure successful treatment, distinguishing adherence problems and determine regimen switch in case of treatment failure.

In Africa, according to case-control study which was conducted in Zvishavane District, Zimbabwe, 2014 indicated thatthe first-line treatment failure was observed among the infected adults who receiving ART; whose base-line CD4 count < 50 cells/mm3, Stage 3 or 4 ,drug stock out and poor ART adherence (Matare et al., 2015).

The institutional retrospective cohort study has been done in HIV-infected patients at Chiang Mai University Hospital, Thailand to determine the risk factors associated with treatment failure From January 2002 to December 2008, According to this finding poor adherence was the strongest predictor for virological failure. Among the total of 535 immunologically evaluable patients, 179 (33.5%) patients have developed immunological failure. In addition to poor adherence, low CD4 cell count at recent< 100 cells/mm3 and the increment of CD4 cell count of < 50 cell/mm3 after were the prominent predictors ART failure (Khienprasit et al., 2011).

In Ethiopia**,** case-control study which has been conducted at Addis Ababa public hospitals using record review on HIV infected adults from February 6 to March 6, 2012 to determine first-line treatment failure. The total sample size was 309 (103 cases and 206 controls). From the final result first-line treatment failure was observed on the treatment interruption, base-

line CD4 cell count <50 cells/μl, pulmonary Tuberculosis treatment (AOR 2.9, 95% CI 1.55 to 5.34) and history of gastric problem of the infected adults who have initiated ART clinics(Yimer and Yalew, 2015).

Based on case-control study which was conducted from May to June, 2015 at University of Gondar referral hospital showed that the higher odd of immunological failure is observed on age's ranges from 15 to 35 years old, low recent CD4 cell count, longer duration on treatment, and poor adherence to ARVtherapy.

According to a follow up study done between July 2010 and August 2012 at Jimma public hospital, Southwest Ethiopia; reported a virologic failure was observed among HIV positive adults (Abdissa A et al., 2014).

The case- control study which was conducted on HIV infected adults from 2004 to 2012 at Adama hospital in Oromiaya and Yirga Alem Hospital in southern nation nationalities and people showed that A total of 134 cases and 134 controls were included in the study. At baseline, the mean age ±1 SD of cases was 37.5±9.7 years whereas it was 36.9±9.2 years among controls. Old age group and higher educational status (P<0.001) were significant predictors of immunological treatment failure (Teshome and Assefa, 2014).

The case-control study was conducted from February to April 2015 using medical records in Oromiya Regional state to determine loss to follow-up in antiretroviral treatment for adult patients on ART clinic. From this finding high odds treatment failure was observed on the patient adults whose- age 15–24 years, day laborers, baseline CD4 cell count <= 350 cells/mL. Plus to these factors suboptimal was the main factor for increased risk of treatment fail (Megerso et al., 2016).

The case- control study conducted from November to December; 2014 at Woldiya Hospital, the northern part of Ethiopia to identify the determinant of first line treatment failure on ART initiated patient indicated that a total of 59 cases and 245 controls were included in the analysis. From this study, some factors were like high CD4 cell count and longer duration on ART, lead protective of treatment failure. In opposite side, high odds of first-line treatment failure was seen on the infected adults who take stavudine (D4t) based regimen, low current BMI, Unemployment, were independently significant predictors of treatment failure (Babo et al., 2017).

The study which has been done between January 01, 2007 and April 01, 2008 at Debremarkose hospital showed that, Recurrent pneumonia infection, inability to work due to health problem, From this study, baseline CD4 count ≤ 100 cells/ mm3, and change in to body weight, were significant predictors of first-line treatment failure(Melsew YA et al., 2013).

Identifying and managing determinants of first line treatment failures are the main important issue to improve a high treatment success rate, develop quality of life and safe life for long period of time. However, there was limited evidence on the determinants of treatment failure among HIV-infected people on HAART in Ethiopia and even more in the study area.

Thus, conducted this study essential to distinguishing factors on which first-line treatment failure was observed among the infected adults at HFSUH and JGH of ART clinics. This aims to provide basic relevant information for clinicians for appropriate decision and management of patients on antiretroviral treatment.

The objective of this study is to determine the determinant factors associated with first-line treatment failure among HIV-Infected Adults at HFSUH and JH, Harar town, Eastern Ethiopia.

2.2. Conceptual Framework

Figure 1: This conceptual frame work was just developed after reviewing different related literature.

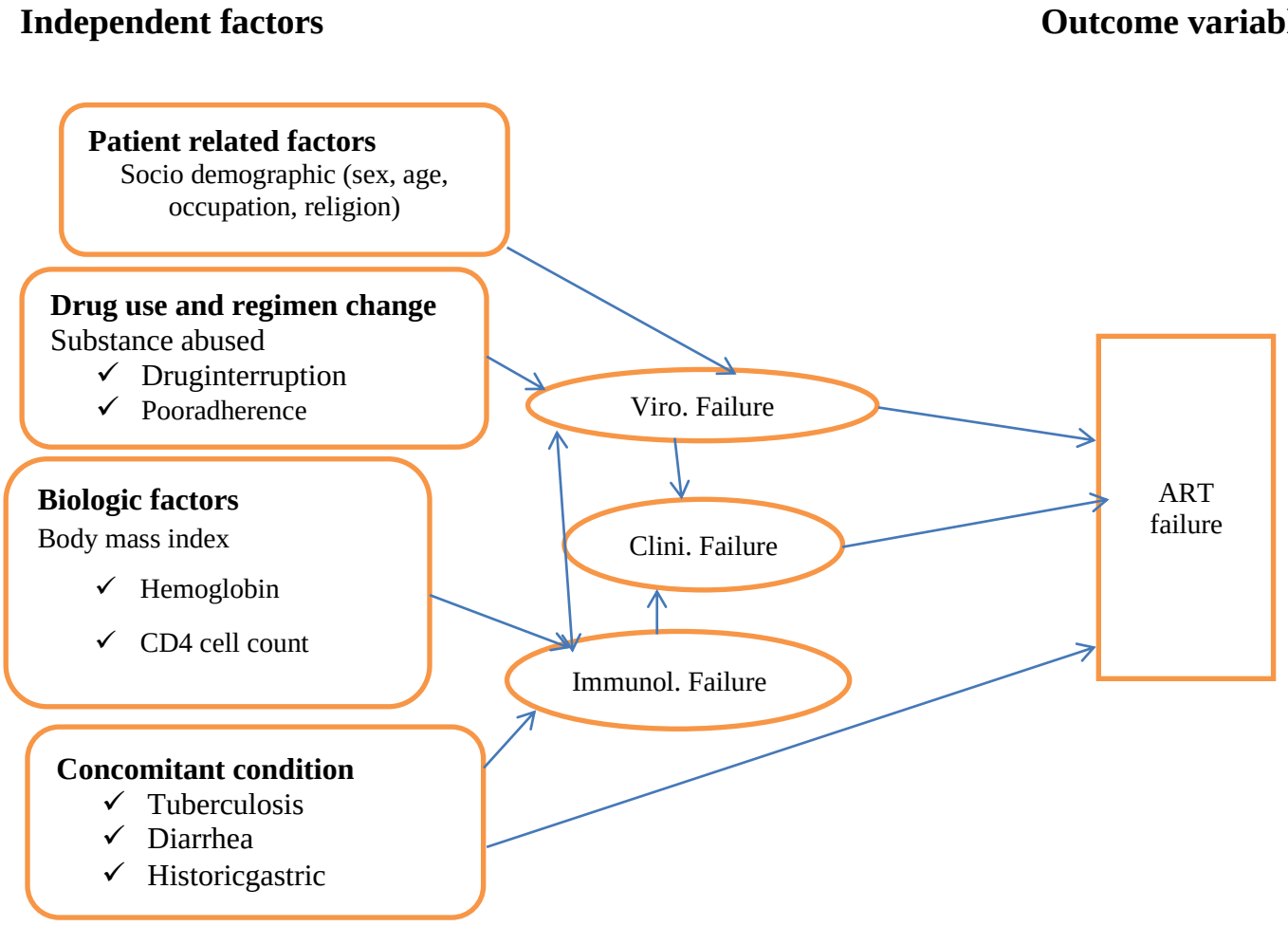

Figure 1: Conceptual frame- work for the determinant of first- line treatment failure (developed from different related literature)

3. METHODS AND MATERIALS

3.1. Study Area and Study period

This study was conducted in Hiwot Fana Specialized University Hospital (HFSUH) and Jugula General Hospital (JGH), which are found in Harar town, eastern Ethiopia. HFSUH and JGH bring health care to much of Harar town and its surrounds. In Harar, there are a total of 7 hospitals: 2 governmental hospitals, 2 private hospitals and 1 Fistula hospital established by NGO and 7 Health centers, 29 private clinic and 26 Health posts. HFSUH and JH are located in Eastern Ethiopia, 526 km away from Addis Ababa. HFSUH and JH are both of governmental Hospitals. It serves as the Referral Hospital of the Harare regional State and surrounding districts. It has four main departments; Gynecology/Obstetrics, Internal Medicine, Surgery, and Pediatric with 41, 48, 50 and 60 beds respectively. The hospitals have two major operation theatres with full equipment and share the same operation theatres with gynecology/obstetrics and surgery department. It also has library with internet service. ART was started in 2005, and there are 5000 clients on ART Harar regional health Beroue annual report(HHB, 2009). The data has been collected from March 12-May 12, 2019.

3.2. Study Design

A hospital-based case-control study has been conducted at Hiwot Fana Specialized University Hospital and Jugula General Hospital.

3.3. Source population

All HIV- infected clients taking first- line treatment failure at ART clinics in Hiwot Fana Specialized University Hospital and Jugula General Hospital.

3.5. Study population

All HIV- infected adults whose aged were ≥ 15 years old on first-line treatment users and fail it from Sep 1, 2010 to March 30, 2018 were included in the study population for controls and cases.

3.6. Inclusion Criteria

- HIV positive adults on follow up in the ART clinic.
- Adult patients change their regimen due to first-line treatment failure.
- Adult patients who have full information on their medical records.

3.7. Exclusion Criteria

- All HIV infected adults whose laboratory measures less than for six consecutive months
- Transferred in-patient for less than six months.

3.8. Sample size determination and sampling technique

The sample size was calculated from the key determinants of treatment failure from previous study using Epi info, v.7 software from the proportion of CD4 count≤ 350 cells/mm3 (78% in cases and 65% in controls) (Megerso et al., 2016)

$$n1 = \frac{Z\alpha/2\sqrt{[1 + 1/r]\, p\,(1-p)} + Z\beta\sqrt{p1\,(1-p1) + p2\,(1-p2)/r}}{(p1 - p2)2}$$

Where; n1 = the required sample size for the cases n2 = the required sample size for the controls n1:n2 =1:2=r

p1= Proportion of exposure in case

p2= Proportion of exposure in controls

$$P = \frac{p_1 + rp_2}{1+r}$$

Zα/2= Critical value at 95% level of confidence

Zβ = standard normal distribution value corresponding to power.

There for, taking the largest calculated sample size study will be 465 (155 cases and 310 controls) taken and add 10% for incomplete data from medical review gives to 513 (171 cases and 342 controls)

3.9. Sampling procedure and technique

All cases fulfilling the inclusion criteria and baseline information were included in the study from these two purposively selected hospitals. To all controls, simple random sample has been applied from the list of clients on ART for the past eight years (Sep 2010 to march 2018) of the two hospitals. The duration of ART for cases and controls comparable controls will selected from those who started ART on the nearly time as cases.

3.10. Data Collection Methods

Data collection format that have been used to extract all the necessary information with regard to the variables of interest was prepared by the principal investigator. The data were important to this study collected by four ART nurses and one supervisor for 30 days in the two purposively selected hospitals. Those recruited data collectors and supervisors for their two hospitals have been given trained for two days about the objective of the study, and on how to collect data from the patients' medical records. The process of data collected in the right way has been monitored through supervisor and principal investigator through daily. The identification of cases was by the principal investigator through the help of the ART registers and patient medical charts and controls have been selected with a ratio of one- to-two.

3.11. Study Variables

3.11.1. Dependent Variable

- First-line treatment failure

3.11.2. Independent Variables

- (Age, sex, religion, occupation, marital status)
- Historic gastric problem while on ART
- Baseline and current CD4 cell count
- Baseline and current body mass index,
- Baseline and current hemoglobin
- Adherence to ART
- Functional status,
- History of TB, diarrhea while on ART
- ARV regimen,
- Baseline and current WHO stages.

3.12. Operational Definition

First-line ART: - the initial treatment of patients fulfills national clinical and laboratory criteria for starting ART.

- First-line treatment failure: - not fulfilling WHO 2016 guidelines.
- Clinical failure when there is a new or recurrent WHO stage 3 or4.
- Immunological failure: - occur when CD4 falls to the pre-therapy baseline (or below) or there is a 50% fall from the on-treatment peak value (if known) or CD4 levels are persistently < 200cells/mm3.
- Virological failure: - occur when plasma VL greater than 1000 copies/ml. Therefore, in this study

treatment failure is occurred when at least one of the above criteria is fulfilled, first-line regimen is changed to second-line regimen

- Co morbidity: is the occurrence of additional disease.

Adherence;- Good Adherence the patients used:> 95% of doses is used fair Adherence: 85 – 94% of doses are used and Poor Adherence: <85% of doses are taken (UNID, 2017)

3.13. Data quality control

The quality of data has been assessed before, during and after data entry. Every filled data collection was n checked for completeness and consistency at the data collection point by the supervisor and before entry by the principal investigator. Quality of data also ensured through collection, entry & analysis. Trained have been given for data collectors and close follow up of data collectors by supervisors and the principal investigator including observation of how they properly collected the recorded data.

3.14. Data Analysis

Data were entered using Epidata version 3.1 and exported to STATA version 14.2 for analysis. Data have been cleaned and edited by running simple frequencies and cross-tabulation before analysis. Descriptive statistics applied to summarize social characteristics of patient in their medical records. The multivariate logistic model has been used to identify the determinant of first-line treatment failure. Independent variables with p <0.25 in the bivariate analysis will be included in the multivariable analysis. Covariates in the final model will be selected by backward step-wise selection procedure. The goodness of the model was checked by Hosmer and Lemeshow goodness of fit test. Adjusted Odds Ratio with 95% confidence intervals was compute and statistical significance has been conducted considered with P-value <0.05.

3.15. Ethical considerations

The proposed proposal was approved by the Institutional Health Research Ethics Review Committee (IHRERC) of College of Health and Medical Science of Haramaya University for this medical chart review, as all the data were identified. The selected hospitals were informed about the objective of the study through a supporting letter from school of public health. Informed, voluntary written and signed consent was also obtained from head of public hospitals. Since the study was conducted through review of medical records, there was no harm done to the individual patients. In order to maintain confidentiality, patients' information was collected from patient charts and ART registers by ART nurses of two hospitals and there was no direct contact of principal investigator with patients. In addition, no information that identifies individual patients was filling in the data collection format. Moreover, the collected data was kept safe throughout the whole process of the research work.

3.16. Dissemination of Results

The finding of this study was disseminated to the Hospitals where the study has been done. The result of study finding was presented at graduate studies of public health, and other interested eastern Harar of both governmental and non-governmental health organizations. Finally, I will publish in scientific journal and online dissemination will be considered.

4. RESULTS

4.1. Socio-demographic Characteristics

From this particular study, the mean age of participants while starting antiretroviral therapy for case and controls was 37± 11 and 33± 10 years respectively. In relation to sex; 94 (52.29 %) of the cases were females while 176 (51.31%) of controls were male. Among the total of cases and controls, eighty-three (48.5 %) cases and one hundred twenty (35.1%) controls were Muslim religion followers respectively. In this study, 94 (55.29 %) of cases and 137 (40.1 %) of controls were unemployed. Regarding the marital status, the majority of cases 58 (34.12%) and 88 (25.66 %) controls were divorced (Table 2).

Table 2: Socio-demographic characteristics of HIV positive adults at Harar public hospitals; 2010-18

Variables	Treatment failure test	
	Cases (%)	Controls (%)
Age, year		
15-30	98(57.31)	80 (23.39)
31-44	54 (31.59)	108 (31.57)
>= 45	19 (11.1)	154 (45.04)
Sex		
Male	76 (44.71)	176 (51.31)
Female	94 (55.29)	167 (48.69)
Religion		
Orthodox	50 (29.41)	121 (35.28)
Muslim	83 (48.82)	120 (34.99)
Catholic	8 (4.71)	36 (10.5)
Protestant	29 (17.06)	65 (18.95)
Occupation		
Gov.t employed	17 (10.00)	66 (19.24)
Self employed	30 (17.79)	91 (26.53)
Unemployed	94 (55.29)	137 (39.94)
Other	29 (17.06)	49 (14.29)
Marital Status		
Single	28 (16.47)	72 (20.99)
Married	52 (30.59)	105 (30.61)
Divorce	58 (34.12)	88 (25.66)
Widowed	30 (17.65)	59 (17.20)

4.1.2. Clinical and Other health-problem related Characteristics

Regarding, Body Mass Index (BMI) at recent (during the time of data collection) 107 (62.94%) of cases and 172 (50.29%) of controls had BMI below 16.5 Kg/m2. When we see recent hemoglobin level, 95 (55.88%) of cases were observed at most12 g/dl and223 (65.78%) of controls were above 12 g/dl. In relation to functional status in these two hospitals, about 78 (45.88 %) of cases were on working status at baseline and 27.06 % (59) of them were bedridden while 20 %(34) of cases were ambulatory. According to this study, higher proportion, 35.57 %(122), controls had different infection opportunities at baseline while64.43 %(221) of them had not opportunistic infection.

Ninety two (54.12 %) of cases were attacked with tuberculosis and176 (51.31%) of controls had similar opportunistic diseases. With regarding history of chronic diarrhea and gastric, about 52.06 % and 72.94 % of cases were exposed diarrhea and gastric respectively. In spite of this, around 39.65 % of controls and 58.02 % of controls infected adults were developed diarrhea and gastric respectively.

In this study, 107 (62.96%) of the cases and 201 (59.29%) of the controls had <200 cells/mm3 CD4 count at baseline, while 100 (58.82%) of the cases and 134 (39.07%) of the controls had CD4 count <200 cells/mm3 at current or data collection time.

With regard to substance use, the number of people who are using substance in both cases and controls is almost the same among the total cases, 134 (78.82 %) of them has interrupt drug prescribed by the physician's while 244 (71.14) of the controls has a similar their drugs. In relation to first-line regimen, among the total cases, sixty- seven cases were taken D4t based regimen and 135 of controls were AZT based regimen.

With regard to regimen based medication, 74 (43.53%) of cases and 146 (42.57 %) of the controls were classified as WHO Stage I and II at baseline, while 46 (27.06 %) of cases and 198 (57.73 %) the controls laid on stage III and IV during data collection time. Sixty-seven (39.64 %) of cases and 150 (43.86 %) of controls had HIV duration >= 48 months. Regarding treatment adherence in the two public hospitals, 35 (20.59%) cases had good adherence and 91 (53.53 %) had poor adherence (Table3).

Table 3. Behavioral and clinical-related information among HIV-positive adults who have had a follow-up at Harar public hospitals: 2010–2018

Variables	Treatment failure test	
	Case (%)	Controls (%)
Current body mass index, Kg/m2		
<16.5	107 (62.94)	172 (50.29)
16.5-18.49	35 (20.59)	32 (9.36)
≥ 18.5	28 (16.47)	138 (40.35)
Current hemoglobin g/dl		
<12	75 (44.12)	223 (65.78)
>=12	95 (55.88)	116 (34.22)
Functional status		
Working	78 (45.88)	136 (39.65
Ambulatory	34 (20.00)	81 (23.62)
Bedridden	46 (27.06)	101 (63.13)
Not recorded	12 (7.06)	25 (7.29)
History of opportunities infection		
Yes	92 (54.12)	122 (35.57)
No	78 (45.88)	221 (64.43)
History of TB		
Yes	92 (54.12)	176 (51.31)
No	78 (45.88)	167 (48.69)
History of chronic diarrhea		
Yes	97 (52.06)	207 (60.35)
No	73 (42.94)	136 (39.65)
History of gastric		
Yes	124 (72.94)	144 (41.98)
No	46 (27.06)	199 (58.02)
CD4 , cell/m3 at baseline		
≤ 200	107 (62.96)	201 (59.29)
>200	63 (37.06)	138 (40.71)
CD4 ,cell/mm3 at current		
< 200	100 (58.82)	134 (39.07)
Treatment interruption		
Yes	134 (78.82)	244 (71.14)
No	36 (21.18)	99 (28.28)-
First line regimen used		
TDF based	55 (34.81)	104 (29.38)
AZT based	36 (22.78)	130 (36.72)

D4t based	67 (42.41)	120 (33.9)
Duration on ART, month		
6-24	48 (28.40)	78 (22.81)
25-47	54 (31.95)	114 (33.33)
>=48	67 (39.64)	150 (43.86)
Baseline clinical stage		
Stage I and II	74 (43.53)	146 (42.57)
Stage III and IV	96 (56.47)	197 (57.43)
Treatment stages at recent		
Stage I and II	46 (27.06)	198 (57.73)
Stage III and IV	124 (72.94)	145 (42.27)
Adherence to treatment		
Good	35 (20.59)	158 (46.06)
Fair	44 (25.88)	65 (18.98)
Poor	91 (53.53)	120 (34.39)

4.2. Bivariate Analysis

4.1.1. Bivariate analysis of Socio-demographic characteristics

According to the bivariate analysis on socio-demographic characteristics, age between 15 and 35 less than35 years (COR 2.10, 95% CI 1.18 -2.48), was associated with first-line ART failure (Table 4).

Table 4. Bivariate analysis result of socio-demographic characteristics with first-line ART failure in public hospital; 2010-2018

Variables	Treatment failure test		COR (95% CI)	P-value
	Cases (%)	Controls (%)		
Age, year				
15-30	83 (48.54)	112(32.75)	2.92 (1.65-4.87)	<0.0001
31-44	54 (31.58)	96 (28.07)	1.32 (0.87-2.43)	0.769
>= 45	34 (19.88)	134 (39.18)	1.00	
Sex				
Male	76 (30.59)	176 (69.41)	1.00	
Female	94 (35.03)	167 (64.97)	0.82 (0.53-1.11)	0.229
Occupation				
Gov.t employed	17 (20.48)	66 (79.52)	1.00	
Self employed	30 (24.79)	91 (75.21)	0.78 (0.40-1.53)	0.473
Unemployed	94 (40.69)	137 (59.31)	0.38 (0.21-0.88)	0.031
Other	29 (37.18)	49 (62.82)	0.44 (0.23-0.68)	0.020
Marital status				
Single	28 (28.00)	72 (72.00)	1.00	
Married	52 (33.12)	105 (66.88)	0.78 (0.45-1.36)	0.388
Divorce	58 (35.29)	88 (64.07)	0.69 (0.40-1.19)	0.183
Widowed	30 (33.71)	59 (66.29)	0.85 (0.41-1.42)	0.396

4.2.2. Bivariate analysis of Clinical and other health-problem related characteristics

Among variables related to clinical and other health problem; that are clinically important in HIV treatment program, low CD4 cell count <200 cell/mm3 at recent was (COR 2.23, 95% CI 1.53-3.24) while WHO clinical stage during data collection time (III&IV COR=3.68, 95 % CI 2.47-5.49), recent BMI (<16.5 kg/m2, COR 3.11, 95% CI 1.98-4.88). HIV positive adults who had history of opportunities infection (COR 2.14, 95% 1.47-3.11) and those who had a history of gastric (COR 3.73, 95% CI 2.50-5.56), were significantly associated with antiretroviral treatment failure according to a bivariate analysis (Table 5).

Table 5.Bivariate analysis of Clinical and other health problem of infected adult's Harar public hospitals: 2010-2018

Variables	Treatment failure test		COR (95% CI)	P-value
	Cases (%)	Controls (%)		
CD4 , cell/m3 at baseline				
≤ 200	107 (34.74)	201 (65.26)	1.17 (0.78-1.70)	0.427
>200	63 (31.34)	138 (68.66)	1.00	
CD4 ,cell/mm3 at recent				
< 200	100 (42.74)	134 (57.26)	2.23 (1.53-3.24)	< 0.001
≥ 200	70 (25.09)	209 (74.91)	1.00	
WHO Stages at baseline				
Stage I and II	74 (33.64)	146 (66.36)	1.00	
Stage III and IV	96 (32.76)	197 (67.24)	0.96 (0.66-1.39)	0.836
WHO Stages at recent				
Stage I and II	46 (18.85)	198 (81.15)	1.00	
Stage III and IV	124 (46.10)	145 (53.90)	3.68 (2.47-5.49)	< 0.001
Recent body mass index, Kg/m2				
<16.5	102 (39.69)	155 (60.31)	3.11 (1.98-4.88)	0.000
16.5-18.49	35 (53.03)	31 (46.97)	1.00 (0.49-1.41)	0.430
≥ 18.5	33 (17.67)	156 (80.33)	1.00	
Recent hemoglobin level, g/dl				
<12	75 (25.17)	223 (74.83)	1.19 (0.82-1.72)	0.362
>=12	95 (45.02)	116 (54.98)	1.00	
History of opportunities infection				
Yes	92 (42.99)	122 (57.01)	2.14 (1.47-3.11)	0.000
No	78 (26.0.9)	221 (73.91)	1.00	

History of TB				
Yes	92 (31.84)	176 (68.16)	1.12 (0.77-1.62)	0.549
No	78 (24.33)	167 (65.67)	1.00	
History of chronic diarrhea				
Yes	97 (31.91)	207 (68.09)	0.87 (0.60-1.23)	0.475
No	73 (34.93)	136 (65.07)	1.00	
History of gastric				
Yes	124 (46.27)	144 (53.73)	3.73 (2.50-5.56)	0.000*
No	46 (18.78)	199 (81.22)	1.00	
Substance used				
Yes	84 (49.41)	170 (49.56)	0.99 (0.69-1.44)	0.974
No	86 (50.59)	173 (50.44)	1.00	
Functional status				
Working	78 (36.45)	136 (63.55)	1.00	
Ambulatory	34 (29.57)	81 (70.43)	0.73 (0.67-1.23)	0.210
Bedridden	46 (31.29)	101 (68.71)	0.79 (0.81-1.97)	0.311
Not recorded	12 (32.43)	25 (67.57)	0.83 (0.57-2.51)	0.638

4.2.3. Bivariate analysis of antiretroviral medication-related information

Among variables related to anti-retroviral medication, first line regimen D4t based (COR =1.06, 95% CI 1.01-2.12), poor adherence (COR 3.22, 95% CI: 2.17-5.40) were significantly associated with first line antiretroviral treatment failure in a bivariate analysis (Table 6).

Table 6. Antiretroviral medication-related information among HIV-positive adults who have had follow-up at Harar public hospitals: 2010-2018

Variables	Treatment failure test		COR (95% CI)	P-value
	Cases (%)	Controls (%)		
Treatment interruption				
Yes	134 (35.45)	244 (64.55)	1.51 (0.97-2.33)	0.064
No	36 (26.67)	99 (73.33)	1.00	
First line regimen used				
TDF based	55 (34.59)	104 (65.41)	1.00	
AZT based	36 (26.47)	130 (73.53)	0.52 (0.345-1.23)	0.059
D4t based	67 (35.83)	120 (64.17)	1.06 (1.01-2.12)	0.045
Duration on ART, month				
6-24	48 (38.10)	78 (61..90)	1.00	
25-47	54 (32.14)	114 (67.86)	1.3 (0.80-2.11)	0.289
>=48	67 (30.88)	150 (69.12)	1.38 (0.87-2.18)	0.173
Adherence to treatment				
Good	35 (18.13)	158 (81.87)	1.00	
Fair	44 (40.37)	65 (59.63)	1.12 (0.70-1.79)	0.636
Poor	91 (43.13)	120 (56.87)	3.22 (2.17-5.40)	0.000

4.3. Multivariate Analysis

When all variables that were associated with first-line ART failure at p-value less than 0.25 in the bivariate logistic regression analysis were entered into multivariate logistic regression analysis to controlling the confounding finally baseline age of HIV positive adults, low CD4 cell count at recent, recent body mass index, base-line WHO staging, having gastric problem and poor adherence to ART treatment were the determinant of first line ART failure at p-value less than 0.05.

In this particular study, the odds of developing first-line ART failure among HIV positive adults whose baseline age is under 15 to 30 years was 2.5 times (AOR 2.95, (95% CI:1.52-4.23) higher than those whose age is above 45 years.

With regard to recentCD4 cell count, patients with low recent CD4 cell count below 200 cells/mm3 failed for first-line antiretroviral drug 2.2 times (AOR2.32, 95% CI: 1.60-5.56) higher than their counter-parts. The likely hood of developing first-line ART failure among HIV positive adults of poor adherence to treatment was 2.98 times more as compared to good adherence(AOR 2.98, 95%CI: 1.60-5.56).

The likelihood of developing first-line ART failure among infected adults with baseline WHO stage (III & IV) was 3.22 times higher as compared to baseline stage (I & II) (AOR 3.21, 95% CI: 1.98-5.23).Those patients having history of gastric problems during HAART follow up time were failed 5.0times more than those who have no history of gastric problems with (AOR 5.0, 95% CI:2.73-9.23). The odds of developing first-line ART failure among patient with recent body mass index <16.5 kg/m2 was 3.11 times high as compared to those with recent body mass index >= 18 kg/m2 with 95% CI: 1.69-5.71.(Table 7)

Table7. Determinants of ART failure among HIV-positive adults who had follow-up atHarar public Hospital: 2010–2018

Variables	First line Treatment failure		COR (95% CI)	AOR (95%CI)	P-value
	Case (%)	Controls (%)			
Age, year					
15-30	83	112	2.92 (1.65-4.87)	2.95 (1.72-4.99)	< 0.001
31-44	54	96	1.32 (0.87-2.33)	1.32 (0.87-2.55)	0.057
>=45	34	134	1.00		
Marital status					
Single	28	72	1.00	1.00	
Married	52	105	0.78 (.045-1.36)	1.09(0.53-2.22)	0.822
Divorce	58	88	0.69 (0.40-1.19)	0.63 (0.31-1.26)	0.187
Widowed	30	59	0.85 (0.41-1.42)	1.01 (0.45-2.25)	0.973
Occupation					
Gov.t employed	17	66	1.00	1.00	
Self employed	30	91	0.78 (0.40-1.53)	0.65 (0.40-1.52)	0.530
Unemployed	94	137	0.38 (0.21-0.88)	0.63 (0.21-1.20)	0.520
Other	29	49	0.44 (0.23-0.68)	0.52 (0.49-1.56)	0.733
CD4 at recent, cells/mm3					
<200	35	158	2.22 (1.53-3.25)	2.33 (1.30-4.17)	0.004
>=200	24	75	1.00	1.00	
Clinical stage at baseline					
Stage I & II	46	198	1.00	1.00	
Stage III & IV	124	145	3.68 (2.47-5.23)	3.22 (1.98-5.23)	< 0.001
Duration on ART, month					
6-24	48	78	1.00	1.00	
25-47	54	114	1.34 (0.80-2.11)	1.27 (0.67-2.42)	0.460
>=48	67	150	1.38 (0.87-2.18)	1.69 (0.89-3.18)	0.108
Adherence to treatment					
Good	35	158	1.00		
Fair	24	75	0.27 (0.70-1.79)	0.82 (0.41-1.64)	0.572
Poor	91	120	3.42 (2.16-5.40)	2.98 (1.60-5.56)	0.001
Opportunistic infection					
Yes	92	122	2.14 (1.47-3.11)	0.68 (0.36-1.27)	0.221
No	78	221	1.00	1.00	
First line regimen					
TDF based	55	104	1.00	1.00	
AZT based	36	130	0.52 (0.34-1.23)	0.67 (0.98-1.43)	0.453
D4t based	67	120	1.06 (1.01-2.12)	1.09 (0.97-3.45)	0.632
Chronic gastric					
Yes	124	144	3.73 (2.50-5.56)	5.02 (2.73-9.23)	<0.001
No	46	199	1.00	1.00	

Treatment interruption					
Yes	134	244		1.61 (0.89-3.10)	0.537
No	36	99	1.00	1.00	
BMI at recent,kg/m2					
<16.5	107	172	3.10 (1.98-4.88)	3.11(1.69-5.71)	0.001
16.5 to 18.49	35	32	0.58 (0.34-1.02)	0.53 (0.25-1.00)	0.053
>=18.5	28	138	1.00	1.00	

Note: -Hosmerand Lemeshow p-value=0.1217COR= curd odd ratio, AOR= adjusted odd ratio, CI =confidence interval.

5. DISCUSSION

There are various exposure factors of first-line antiretroviral treatment failure which has been identified from HIV-positive adults who had followed up at Harar public hospitals. These were patients whose age 15 to 30 years, low recent CD4 cell count<200 cells/mm3,low recent body mass index <16.5 Kg/m2, treatment stage (III & IV), poor adherence and patients who have gastric problem were identified to have encouraged the odds of first-line treatment failure.

In relation to the age of patients, the odds of developing first line ART failure among HIV positive adults whose ages15 to 30 years was 2.95times higher than their counterparts. This finding was supported by studies conducted in Cameroon(Meriki et al., 2014), China (Zuo Z et al., 2016)and Gondar, northern Ethiopia(Bayu et al., 2017). This might be HIV positive adults have different living standards and easily vulnerable to harm full addiction. It also HIV positive adults separate them self's from society due afraid. Moreover this may lead social stigma, discrimination, and exposed to different diseases. This might be improved depression, anxiety, and unhealthy situations.

The likeli-hood of getting first-line antiretroviral treatment failure among patients with low recent CD4 cell count (<= 200 cell/mm3) was 2.3 times more than their counterparts. This report was consistent with other studies done in Northwestern Uganda (Izudi et al., 2016), Woldiya, southern Ethiopia (Bayou et al., 2015), and Gondar, northern Ethiopia (Bayu et al., 2017). CD4 T-cell count has negative relationship to viral duplications in the HIV positive people and increases its load. If the patients' immune status going to decrease in blood of HIV positive people leads to increases rate of viral replication as compared to immune-competent of their counterparts. Therefore, the immune status in the blood loses its power to resist adverse diseases. Similarly people with HIV virus infected are more vulnerable to various opportunistic infections. Finally the immune system of infected clients is not able to resist concomitant risks(AIDSinfo, 2016).

Patients with treatment stages III and IV were 3.22 times more likely to develop first-line ART failure among patients than those with stages I and II. This finding is consistent with the study done in Zimbabwe (Matare et al., 2015). HIV positive people with poor treatment adherence were 2.98 times more likely to develop first-line ART failure as compared to infected clients with good adherence. This finding was supported by the studies which were conducted in Mozambique(Rupérez et al., 2015),Woldiya, southern Ethiopia(Babo et al., 2017), Gonder, northern Ethiopia(Bayu et al., 2017). It is true that HIV positive missing 3 doses of ART per month by default and other reasons have high risk of developing drug resistance and reduced human immunity in body that able resist different opportunistic infections (WHO,

2017). Therefore, this leads rapid viral duplication, minimizes CD4 cell count in the lymphocyte blood and leads to first-line ART failures (Leng et al., 2014).

HIV positive clients with gastro intestinal problems were5.0 times more likely to develop first-line ART failure compared with clients with no gastric problems. This result is consistent with a study done in Addis Ababa (Yimer and Yalew, 2015). If HIV positive people laid on gastro-intestinal problems yields in adequate caloric intake, mal-absorption of nutrients from the gastrointestinal tract, increased metabolic rates, and other direct effects of HIV infection. Therefore, healthy gastro-intestinal tract is necessary for proper absorption of medications and essential for controlling nausea and diarrhea will improve the quality of life and helps to adhere to medications, causing better long-term treatment outcomes.

The odds of developing first-line ART failure among patient with low (< 16 kg/m2) recent body mass index was3 times more than those who had current BMI of >18.5 kg/m2. This finding is supported by a study conducted Northwestern Uganda (Izudi et al., 2016)and Woldiya, southern Ethiopia(Babo et al., 2017), Gonder, northern Ethiopia(Bayu et al., 2017).Low body mass index is correlated with decreasing CD4 cell count in the blood that able resist variety disease. Low body mass results from malnutrition and leads to an infected individuals exposed to various disease progression. It also increase viral load by progressing in to the advantage stages of the diseases and by patients not taking drug properly(Duggal et al., 2012).

6. CONCLUSION AND RECOMMENDATION

6.1. Conclusions

This finding revealed that; age 15 to 30 years, low recent CD4 cell count, treatment stage III and IV, low recent body mass index, poor adherence to treatment, and history of gastro intestinal were positively and significantly associated with first-line antiviral therapy failure. Therefore, the effort goes to improve adherence to ART, which aims to encourage immunity and suppress viral replication and load. Moreover, more attention should be given to younger patients who have taken ART.

6.2. Recommendations

From this finding; the following recommendation is forwarded for the concerned bodies. Health professionals should give special attention to monitoring HIV positive adults whose ages range from 15 to 35 years, with low CD4 cell count, patients laid on clinically stage III and IV from start to the end. Additionally, deliberate efforts are highly essential for HIV care by concerned bodies like ART managers, adherence counselors in the hospitals on patients with low body mass index (by improving their nutritional status by giving nutritional counseling and support), and improving poor adherence to ART treatment by strengthening encourage adherence counseling. HIV positive patients on HAART should be treated for all gastro intestinal problems and should be treated through time.

6.3. Limitation of study

The main limitation of the study is recall bias, missing data, misclassification information and diagnosed bias because of method of data collection technique used using secondary data depending on the past information. In addition, this study did not measure the determinants of treatment failure clearly among HIV positive people on HAART directly to see whether they taking the drug properly or not prescribed by physician. Even if there was a standard national treatment guide line which works for all health institutions in the country for ART service, there might be a difference in quality of care and quality of service in each hospital. However, this study did not measure it.

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APPENDIX

Annex I: Information sheet and informed voluntary consent form for health facility head)

My name is_____. I am working as a data collector for the study being conducted in this institution. SHUMET MISGANAW who is studying his Master's degree at Haramaya University College of Health and Medical Sciences in public health.

I kindly request you to lend me your attention to explain you (data clerk) about the study and your institution is being selected as the study setting.

1. **Study title**

   Determinates of first line treatment failure among HIV infected adults on HAART at HFSUH and JH

2. **Purpose of the study**

   The finding of this study can be importance for the health institution to plan strategies that can address preventive message towards prevention and control of low change of regimens. Moreover, the aim of this study is to write a thesis as a partial requirement for the fulfillment of a Master's Program in Public Health Epidemiology.

3. **Procedure and duration**

   I will collect the data from the records that are help full for the study. This check list has parts and about 25 that I am going to collect and it will take about 30 minutes to complete each from the records.

4. **Risks and benefits**

   The risk of being participating in this study is very minimal, but only taking your time. There would not be any direct payment for participating in this study. But the findings from this research may reveal important information for the local health planners.

5. **Confidentiality**

   The information you will provide us will be confidential. There will be no information that will identify you in particular. The findings of the study will be general for the study community and will not reflect anything particular about individual persons.

6. Rights

Participation in this study is fully voluntary. The institution has the right to declare to participate or not in this study and has the right to withdraw from the study at any time and this will not label the institution for any loss of benefits which it otherwise is entitled.

7. Contact address

If there are any questions or enquires any time about the study or the procedures, you can contact by using the following addresses.

Principalinvestigator Address

Name:ShumetMsganaw Tel. 0254662011, HaramayaUniversity

Address:Mekdela P.O.Box: 235, Harar,Ethiopia CHMS Mobile phone:0941806151

E-mail: Shumet25000@gmail.com

8. Declaration of informed voluntaryconsent

I have read the participant information sheet. I have clearly understood the purpose of the research, the procedures, the risks and benefits, issues of confidentiality, the rights of participating and the contact address for any queries. I have been given the opportunity to ask questions about things that may have been unclear. I will be informed that I have the right to withdraw from the study at any time or not to answer any question that I do not want. Therefore, I declare my voluntary consenton behaveof __ hospital health manager to allow this study to be conducted in health office with my initials(signature).

Name ofhospitalhead:_____Signature_____Date_____

Name ofdatacollector:_____Signature_____Date_____

Medical record review of HIV care intake form and follow up form

No.	Required variables	Filling from medical records
	Socio-demographic Characteristics	
1.	Sex	1.Male 2.Female
2.	Age of HIV infected adults during ART initiation	
3.	What was the religion of patient?	1. Orthodox 2. Muslim 3. Catholic 4. Protestant 5. Other specify---
4.	Marital status of patient?	1. Single 2. Married 3. Divorced 4. Widowed
5.	What occupation of patient?	1.Government employed 2.Self employed 3. Unemployed 4. Other……
6.	History of substance used	1. No 2. Yes
7.	Date first-line ART started (dd/mm/yyyy) in EC	
8.	Unique ART number	
	Clinical characteristics of HIV infected adults on ART	
9.	1. Clinical stage at baseline	**…….**
	2. Clinical stage at 6 months	**……**
	3. Clinical sage at 12 months	**…….**
	4. Clinical stage at 24 months	**……**
	5. Clinical stage at recent	**……**
10.	Weight of HIV infected adults at baseline (Kg)	……
	Weight of HIV infected adults at recent (Kg)	…..
11.	Body mass index of HIV infected adults at baseline	……

	Body mass index of HIV infected adults at recent	……
12.	Hemoglobin of infected adults at baseline	…….
	Hemoglobin of HIV infected adults at recent	……
13.	Opportunistic infections of infected adults	1. Yes 2. NO
14.	History of Tuberculosis	1. Yes 2. NO
15.	History of chronic gastric	1. Yes 2. No
16.	History of chronic diaharria	1. Yes 2. NO
17.	drug interruption	1. Yes 2. No
18.	Duration on ART, months	…….
19.	Adherence to treatment	1. Good 2. Moderate/Fair 3. Poor
20.	Diagnosis of recurrent greater than 2 episode	1. Yes 2. No
21.	First-line ART regimen	1. TDF+3TC+NVP 2. TDF+3TC+EVP 3. D4t+3TC+NVP 4. D4t+3TC+EVP 5. AZT+3TC+NVP 6. AZT+3TC+EVP 7. Other specify…
22.	Substitute of ARV regimen	1. None 2. Once 3. Two and more
23.	Reason of drug substitution	0. No reason 1. Side effect 2. Pregnancy 3. Due new TB 4. New drug Available 5. Drug stock out
24.	First line treatment failure test	0. Failed (Case) 1. Not failed (Control)
25.	CD4 cell count of the HIV infected adults at baseline	….
26.	CD4 cell count of the HIV infected adults at 6 month	….
27.	CD4 cell count of the HIV infected adults at 12 month	….

28.	CD4 cell count of the HIV infected adults at 24 month	….
29.	CD4 cell count of the HIV infected adults at recent	….

Name and signature of data collector…

Annex II Curriculum vitae (CV) of the investigator

Personal details:

Name: Shumet Msganaw

Place of birth: Mekdella, Masha

Date of birth: 15, May, 1993

Sex: Male

Marital status: Single

Nationality: Ethiopian

Contact address: E-mail: shumet25000@gmail.com

Phone: +251941806151

Educational background:

Elementary: Genatit school (1-8)

Secondary and preparatory: Mekedela High School (9-12)

Educational qualification - Graduated from Haramaya University with BSc in Statitistics.

Four year work experience

Institution of data base manager position

Language skill

Language	Level	
	Communication	Writing
English	Excellent	Excellent
Amharic	Excellent	Excellent
Affan Oromo	Some what	Some what