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Determinants of First Line Antiretroviral Treatment Failure in Public Hospitals of Addis Ababa, Ethiopia: Unmatched Case Control Study

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Abstract
Background: The identification and management of first-line antiretroviral therapy failure is a key challenge for human immune deficiency virus programs in resource-limited settings. Ethiopia being one of the resource-limited countries has limited resources available for diagnosing treatment failure and monitoring patient response with viral load, which is the gold standard, is not feasible in this limited setting. Patients initiate treatment with very advanced disease. However, factors lead to treatment failure is not well understood and well-studied. **Objective:** To identify determinants of first line antiretroviral treatment failure in public hospitals of Addis Ababa **Methods:** An unmatched case control study was conducted at Addis Ababa public hospitals using record review. Total sample size was 309 (103 cases and 206 controls). Bivariate analysis was done and all explanatory variables associated with first line treatment failure with $P<.05$ were entered in to multivariable logistic regression analysis using back ward stepwise likely hood ratio method to identify independent predictors. **Result:** One hundred three cases and two hundred six controls were included in the study. Treatment interruption (Adjusted odds ratio 5.4, 95% confidence interval 2.33 to 12.13), base line clusters of differentiation cell count <50 cells/µl (Adjusted odds ratio 2.7, 95% confidence interval 1.24 to 5.64), pulmonary Tuberculosis treatment (Adjusted odds ratio 2.9, 95% confidence interval 1.55 to 5.34) and history of gastric problem (Adjusted odds ratio 6.6, 95% confidence interval 2.33 to 18.87) were all independently associated with first line antiretroviral treatment failure. **Conclusion and Recommendation:** Base line lower clusters of differentiation cell count <50 cell/µl, treatment interruption, history of pulmonary Tuberculosis treatment during follow up time and chronic gastric problem were the independent predictors of first line antiretroviral treatment failure. There for Health professionals should pay special attention for the risk group identified.
Keywords: antiretroviral therapy, case control study, treatment failure, highly active

1. INTRODUCTION

About 34 million people were living with human immune deficiency virus/acquired immune deficiency syndrome (HIV/AIDS) in 2010 (estimates range from 30.9 to 36.9 million, 0.5% of the world population). Annually 58.5 million healthy life-years lost, 1.8 million Deaths per year, US$ 52.3 billion, or 0.086% of global gross domestic product (GDP) in damages per year and most of these (68%) lives in sub-Saharan African countries. Human immune deficiency virus affects mostly people in the economically productive age range, reducing the work-force and, in doing so, constraining development [1, 2].

The overall growth of the global AIDS epidemic appears to have stabilized. The annual number of new HIV infections has been steadily declining since the late 1990s and there are fewer AIDS-related deaths due to the significant scale up of antiretroviral therapy over the past few years [4]. But significant challenges remain and treatment outcomes continue to be substantially worse. Treatment failure, whether attributable to any type of failure, discontinuing ART, or loss to follow-up, has been shown to increase morbidity and mortality [19].

However, the identification and management of first-line antiretroviral therapy (ART) failure is a key challenge for HIV programs in resource-limited settings [6]. Staying on a failing first-line therapy is associated with an increased mortality risk & consequences of early treatment failure can be significant (development of drug resistance limits the ability to construct new, potent and tolerable regimens in the future) [7].

Ethiopia has the fifth largest population of HIV infected individuals living in Africa, which accounts to approximately 4% of the world's HIV/AIDS cases [9]. Adult HIV prevalence in 2010 was 2.4% (7.7% urban and 0.9% rural) with male female ratio of 1.9% and 2.9% respectively. According to federal ministry of health of Ethiopia (FMOH) report, there were 1.2 million people live with HIV, and 397,818 are estimated to be in need of antiretroviral treatment in 2010 [10]. According to 2011 Addis Ababa health bureau, estimated HIV prevalence in Addis Ababa was 8.5% and 258,238 people living with HIV/AIDS (PLWHA), ever started 250,285, 76,421 ART service users and 55,136 currently on ART [11].

The current status of antiretroviral therapy is therefore encouraging, but significant problems remain; 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 [12,].

Patients failed for first line drug are 46% more likely to fail again for 2nd line drug & attributed to the higher number of side effects, have greater likelihood of experiencing drug resistance and treatment fatigue as a result of being on treatment longer [13]. 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 [14] because of the association with earlier and more frequent switching to second-line regimens than the use of clinical/immunological monitoring strategies [15].

However, data from ART program and global procurement systems also suggests that treatment switching has occurred at lower than expected rates in resource-limited settings due to low access to second-line drugs (due to expensiveness), difficulties in defining treatment failure in an adherent patient with no other reasons for an elevated VL & the development of drug resistance limits the ability to construct new, potent and tolerable regimens in the future. Thus; the identification and management of first-line antiretroviral therapy failure is a key challenge for HIV programs in resource-limited settings [3, 5, 16].

In resource limiting setting since there is limited availability of second line ART, switching is often not done & incomplete formularies limit options. Often there is no CD4 or viral load monitoring. Current 2nd line regimens are complex, and have difficult drug interaction especially with rifampicin impacting on the management of tuberculosis (TB) co-infection. Furthermore cost is an important barrier; the cost for 2nd line in 2006 was 2% of total cost. This condition makes difficulty in HIV treatment program especially in resource limiting countries like Ethiopia [7, 17, and 18].

Ethiopia being one of the resource-limited countries, has limited resources available for diagnosing treatment failure and monitoring patient response with viral load which is the gold standard, is not feasible, patients initiate treatment with very advanced disease [3]. However, factors lead to treatment failure is not well understood and well-studied especially in Ethiopia.

Therefore the rationale of the study is identifying those risk factors for first line ART failure (that will help to define early predictors of treatment efficacy that permit better use of these potent drugs, avoid unnecessary side effects of second line drug, prevent drug resistance & decrease economic burden especially in resource limiting setting like Ethiopia due to the expensiveness of second line drug). It will also help as a guide for health professionals and higher officials to alleviate the problem & will help to Patients to develop strategies allowing them to take their treatment correctly.

2. MATERIAL AND METHODS

The study was conducted in Addis Ababa public hospitals at chronic HIV care. Addis Ababa has an area of 540 square kilometer with an estimated population of 3,038,096 people (52.36% female, 47.67% male). The structures of organ power of the city consists of city government,10 sub cities and 116 districts with 38 hospitals (10 public hospitals, 2 nongovernmental (NGO), 3 defense and police ,23 private) and 27 health centers.

ART service is being given at 55 sites (10 public hospitals, 15 private hospitals, 25 health centers & 5 NGO clinics) [11]. Of these sites, 9 public hospitals treating about 44,309 adult HIV infected patients were included in the study. The study was conducted from February 6 to March 6, 2012.

Unmatched case control study was conducted based on medical records of patients getting ART service at HAART clinics in Addis Ababa public hospitals. Patients greater than or equal to 15 year old who are on second line drug due to treatment failure and first line drug users from Sep 2005 to Sep 2011 for cases and controls respectively were the study population for the study. All patients started ART in other ART site (lacks full information in their records), and patients with incomplete base line records were excluded in the study.

Sample size determination and Sampling technique

Sample size was calculated using epi info version 3.5.1 software using proportion of nevirapine based first line regimen among cases and controls 48.18% and 31.1% respectively [29] using 80% power with 95% CI and case to control ratio of 1:2. Total sample size was 309 (206 control and 103 cases). All public hospitals in Addis Ababa except ALERT hospital were included for the study (because private hospitals started ART service recently). List of patients from each hospital on ART for the past six years (Sep 2005 to Sep 2011) were generated from the ART dispensing tool & merged. Then sample frame for cases & controls separately was prepared by the principal investigator. Sampled cases & controls were selected by simple random sampling technique & the selected cases and controls were distributed to each hospital based on their unique ART registration number.

A. Selection of cases

List of patients for cases based on their unique ART registration number from nine hospitals were generated for the past six years from the ART dispensing tool which is electronic software used for dispensing ARVs but is able to generate reports. Then sampled cases were taken using simple random sampling technique.

B. Selection of controls

List of patients for controls from nine hospitals were generated for the past six years from the ART dispensing tool which is electronic software used for dispensing ARVs but is able to generate reports. Finally Simple

random sampling technique was used to select controls.

Data collection instruments and techniques

The patient information collecting sheet was prepared in English. It was adapted from federal ministry of health of Ethiopia ART guide line and ART follow up form and data were collected by record review. The collected data were checked by supervisors and principal investigator. Data collectors and supervisors were trained for two days about the objectives of the study, contents of tools and how to collect the data before the data collection. Data were collected by 9 trained data collectors (ART trained nurse). The principal investigator and three other ART trained health officers (HOs) supervised the data collection process.

Data processing, analysis and presentation

Data were first checked manually for completeness and consistency by supervisors & principal investigator during the time of data collection and rechecked again at office before data entry. Data were entered and cleaned using epi info version 3.5.3. Then exported to SPSS version 16.0 for analysis & descriptive statistics were done to summarize the data. Then bivariate analysis was done to see the association between outcome variable & independent variable. All explanatory variables associated with first line antiretroviral treatment failure with $P<.05$ were entered in to multivariable logistic regression analysis. However scientifically intuitive and clinically important variables were included in multivariable analyses though $P>.05$. Backward stepwise likely hood ratio logistic regression was used in multivariable analysis.

Multi-collinearity test was done to check whether there are correlated independent variables or not by examining the values of variance inflation factor (VIF); there were no seriously correlated variables. $P<.05$ in multivariable analysis was used to declare association between independent predictors and the outcome variable. Finally conclusion and recommendation were made based on the findings of the study.

Data Quality control

To keep the quality of the study, information collecting sheet was prepared based on federal ministry of health of Ethiopia standard ART guide line and ART follow up form. Data collectors and supervisors were ART trained. Moreover, data quality also ensured during collection, entry & analysis. Training was given for data collectors and supervisors before data collection and there was close follow up of data collectors by supervisors and the principal investigator including observation of how they were collecting the recorded data.

Strength

The study was conducted in a context where HAART had been started for the last 6 years (Sep 2005 to Sep 2011) to minimize poorly record data and to include all public hospitals in the study (ART service was started in all public hospital level 6 years back in Ethiopia).

Being case control study is the strength of this study. Since antiretroviral treatment failure is a rare occurrence but had a serious impact globally and challenge HIV prevention and control program, case control study is a best study design for this situation and the design enabled to see multiple exposure unlike other study designs.

Limitation

This study has limitation due to the method of data collection technique used; using secondary data like relaying on past information which can be changed subsequently. This study didn't assess those predictors of treatment failure from the patient directly which limit to see whether the patients were taking the drug properly or not, had got shortage of drug or not and had got adequate information about the treatment from the service provider. Although there is a standard treatment guide line which works for all health institutions giving ART service, there might be a difference in quality of care & quality of service in each hospital. However, this study didn't assess it.

3. RESULTS AND DISCUSSION

3.1. Socio-demographic characteristics of study population

A total of 103 cases and 206 controls were included in the study. From these 93 (90.3%) of cases & 190 (92.2%) of controls were alive, 8 (7.8%) of cases & 9 (4.4%) of controls were died and 2 (1.9%) of cases &7 (3.4%) of controls were defaulters. The mean age at starting treatment was 37 and 36 with a standard deviation of 9 year for cases & controls respectively. Majorities, 55 (53.4%) of cases and 123 (59.7%) of controls were females. Most, 75 (72.8%) of cases and 165 (80.1%) of controls were orthodox Christian followers. Regarding to marital status, 44 (42.7%) of cases and 98 (47.6%) controls were married and 27 (36%) of cases and 39 (26%) of controls had HIV positive partner; 22 of 27 (81.2%) and 21 of 39 (53.8%) were on ART while 30 (29.1%) of cases and 65 (31.6%) of controls had unknown HIV status. About 32 (32%) of cases and 114 (53%) of controls were full time employed while 39 (37.9 %) of cases and 32 (15.5%) of controls were not working/due to ill health & majorities, 40 (38.8%) of cases and 79 (38.3%) of controls had finished their secondary education at the time of HAART initiation (Table 1).

Table 1 Socio-demographic characteristics of study population in public hospitals of Addis Ababa, 2012

Socio-demographic variables	Controls=206		Cases=103	
	n	%	n	%
Age(year)				
14-24	8	3.9	5	4.9
25-39	140	68	61	59.2
>=40	58	28.2	37	35.9
Sex				
Male	83	40.3	48	46.6
Female	123	59.7	55	53.4
Religion				
Orthodox	165	80.1	75	72.8
Muslim	16	7.8	18	17.5
Protestant	23	11.2	8	7.8
Other	2	0.9	2	1.9
Education				
No education	15	7.3	13	12.6
Primary	70	34	35	34
Secondary	79	38.3	40	38.8
tertiary	42	20.4	15	14.6
MS				
Never married	56	27.2	28	27.2
Married	98	47.6	44	42.7
Separated	6	2.9	6	5.8
Divorced	20	9.7	10	9.7
Widowed	26	12.6	15	14.6
HSP				
HIV positive partner	39	26	27	36
HIV negative partner	46	30.7	18	24
Partner unknown HIV status	65	43.3	30	40
Partner taking ART				
Yes	21	53.8	22	81.2
No	18	46.2	5	18.8
Employment status				
Working full time	114	55.3	33	32
Working part time	5	2.4	1	1
Unemployed	55	26.7	30	29.1
Not working/due to ill health	32	15.5	39	37.9

MS-marital status, HSP-HIV status of partner

3.2. Base line laboratory measures

Among cases and controls respectively; the median (interquartile range) baseline (at HAART initiation) CD4 count was 74 cells/µl (1–436) and 140 cells/µl (1-667). The mean (SD) white blood cell (WBC) count among cases was 5157 (2332) cells/mm3, while in controls was 5629 (2698) cells/mm3. The mean lymphocyte count in cases and controls was 25% and 31% while the mean neutrophil count among cases and controls was 38% and 42% with mean hemoglobin level 12.3g/dl and 13.1g/dl respectively (Table 2).

Table 2 Base line laboratory measures of study population in public hospitals of Addis Ababa, 2012

Base line laboratory measures	Controls=206			Cases=103		
	mean	SD	median	mean	SD	median
CD4 count(cell/micro liter)	145	99	140	98	89	74
WBC count(cell/mm^3)	5629	2698	5350	5157	2332	4500
Lymphocyte count (%)	31	12	30	25	11	22
Neutrophil count (%)	42	18	42	38	21	33
Hg(g/dl)	13.1	2.5	13	12.3	2.1	12

SD-standard deviation, WBC-white blood cell count

3.3. ARV drug related variables

The most frequent starting regimens for cases were AZT 3TC NVP (32%), d4t 3TC NVP (26.2%), AZT 3TC EFV (17.5%), and d4t 3TC EFV (12.6%). Similarly d4t 3TC NVP (28.2%), AZT 3TC EFV (27.7%), AZT 3TC NVP (20.4%) and d4t 3TC EFV (13.1%) were the most frequent starting regimens among controls. For the 55

female cases and 123 female controls for whom PMTCT exposure could be determined, 8 of 55 (14.5%) and 4 (3.3%) had received PMTCT interventions respectively (Table 3).

Table 3 ARV drug related variables of study population in public hospitals of Addis Ababa, 2012

ARV drug related variables	Controls=206		Cases=103	
	n	%	n	%
Base line first line drug				
AZT 3TC NVP	42	20.4	33	32
d4t 3TC NVP	58	28.2	27	26.2
AZT 3TC EFV	57	27.7	18	17.5
d4t 3TC EFV	27	13	13	12.6
TDF 3TC NVP	7	3.4	7	6.8
TDF 3TC EFV	15	7.3	5	4.9
Previous PMTC exposure				
Yes	4	3.3	8	14.5
No	119	96.7	47	85.5

ARV-anti retro viral, AZT-zidovudine, 3TC-lamividine, EFV-efaverenz, NVP-nevirapine, TDF-tenofovir, d4t-stavudine, PMTCT-prevention of mother to child transmission of HIV

3.4. Adherence related variables

Majority of cases, 58 (56.3%) and 66 (32%) controls were not consistently adhered during HAART follow up. On the other hand, 37 (35.9%) of cases & 9 (4.4%) of controls interrupted (defaulted) HARRT. Most of the cases, 73 (70.9%) and 158 (76.7%) controls disclosed their HIV sero-positive status during HAART initiation. The median (interquartile range) duration of treatment for case & controls with first line drug was 41 and 53 months respectively; 82 (79.6 %) of cases and 185 (89.8 %) of controls were treated for more than 24 months. Majority of cases, 65 (63.1%) and 154 (74.8%) of controls were not using any of the substance. However 8 (7.8%) of cases and 15 (7.3%) of controls used alcohol, 5 (4.9%) of cases & 1 (0.5%) of controls were smokers, 3 (2.9%) of cases and 7 (3.4%) of controls used soft and hard drugs, while 22 (21.4%) of cases and 29 (14.1%) of controls used two or more substances during the time of HAART initiation (Table 4).

Table 4 Adherence related variables of study population in public hospitals of Addis Ababa, 2012

Adherence related variables	Controls=206		Cases=103	
	n	%	n	%
Consistency of adherence				
Consistently adhered	140	68	45	43.7
Inconsistently adhered	66	32	58	56.3
Treatment interruption				
No	195	94.7	66	64.1
Yes/defaulted	9	4.3	21	20.4
Yes/other	2	1	16	15.5
Disclosed HIV sero-status				
Yes	158	76.7	73	70.9
No	48	23.3	30	29.1
Duration on first line drug treatment				
<24 month	21	10.2	21	20.4
>=24 month	185	89.8	82	79.6
substance use				
No	154	74.8	65	63
Alcohol	15	7.3	8	7.8
Tobacco	1	0.5	5	4.9
Soft and hard drugs	7	3.4	3	2.9
Use 2 or more of the above substance	29	14	22	21.4

Soft drug ("Kat", shisha, pills), hard drugs (cocaine, morphine, IV drug use)

3.5. Base line nutritional status (BMI)

About 48 (46.6%) of cases' and 143 (69.4%) of controls' body mass index (BMI) laid in the category >=18.5 kg/m2 while 32 (31.1%) of cases' and 45 (21.8%) of controls' BMI laid between 16-18.4 kg/m2. The remained 23 (22.3%) of cases' and 18 (8.7%) of controls' BMI laid under the category of <16kg/m2 (Table 5).

Table 5 Base line BMI of study population in public hospitals of Addis Ababa, 2012

Base line BMI	Controls=206		Cases=103	
	n	%	n	%
>=18.5kg/m^2	143	69.4	48	46.6
16-18.4kg/m^2	45	21.8	32	31.1
<16kg/m^2	18	8.7	23	22.3

BMI-body mass index

3.6. Other health problems and clinical disease mechanism related variables

Regarding to history of opportunistic infection and other medical health problems about 39 (37.9%) of cases and 30 (14.6%) of controls had history of opportunistic infection. About 58 (56.4%) of cases & 47 (22.8%) of controls had history of TB treatment; pulmonary TB treatment accounted for 91.4% and 76.5% among cases and controls respectively. Majority of cases, 61 (59.2%) & 66 (32%) of controls took additional medication other than HAART. About One fourth of the cases, 26 (25.2%) & 7 (3.4%) of controls had history of chronic diarrhea while 30 (29.1%) of cases & 6 (2.9%) of controls had history of chronic gastric problem.

More than half of the cases, 57 (55.3%) & 161 (78.2%) of controls were workable in their functional status during the time of HAART initiation. While only 8 (3.9%) of cases & 16 (15.5%) of controls were bedridden at the time of HAART initiation. About 39 (37.9%) of cases & 95 (46.1%) of controls were clinically WHO stage III while 35 (34%) of cases & 37 (18%) of controls were WHO stage IV (Table 6).

Table 6 Other health problems and clinical disease mechanism of study population in public hospitals of Addis Ababa, 2012

variables	Controls=206		Cases=103	
	n	%	n	%
History of OI				
No	176	85.4	64	62.1
Yes	30	14.6	39	37.9
History of TB treatment				
No	159	77.2	45	43.7
Yes/pulmonary	36	17.5	53	51.5
Yes/extra pulmonary	11	5.3	5	4.9
Taking additional medication				
No	140	68	42	40.8
Yes	66	32	61	59.2
History of chronic diarrhea				
No	199	96.6	77	74.8
yes	7	3.4	26	25.2
History of chronic gastric problem				
No	200	97.1	73	70.9
Yes	6	2.9	30	29.1
Base line functional status				
Work	161	78.2	57	55.3
Ambulatory	37	18	30	29.1
Bed ridden	8	3.9	16	15.5
Base line WHO stage				
Stage I	26	12.6	9	8.7
Stage II	48	23.3	20	19.4
Stage III	95	46.1	39	37.9
Stage IV	37	18	35	34

OI- opportunistic infection, TB-tuberculosis, WHO-world health organization

3. 7. Bivariate analyses

3.7.1. Bivariate analysis of Socio demographic characteristics

In a bivariate analysis of socio-demographic characteristics, none of them were associated with first line antiretroviral treatment failure except being Muslim in religion (Table 7).

Table 7 Association of Socio-demographic characteristics with first line antiretroviral treatment failure in public hospitals of Addis Ababa, 2012

variables	Controls=206		Cases=103				
	n	%	n	%	OR	95% CI	P
Age/continuous					1.010	0.984 to 1.036	0.46
Age(years)							
14-24	8	4.9	5	3.9	1.00		
25-39	140	59.2	61	68	0.69	o.21 to 2.21	0.541
>=40	58	35.9	37	28.2	1.02	0.31 to 3.35	0.973
Sex							
Male	83	46.6	48	40.3	1.29	0.80 to 1.24	0.29
Female	123	53.4	55	59.7	1.00		
Religion							0.063
Orthodox	165	80.1	75	72.8	1.00		
Muslim	16	7.8	18	17.5	2.47	1.19 to 5.11	0.015*
Protestant	23	11.2	8	7.8	0.76	0.32 to 1.78	0.537
Other	2	0.9	2	1.9	2.2	0.30 to 15.91	0.435
Base line MS							
Never married	56	27.2	28	27.2	1.00		
Married	98	47.6	44	42.7	0.898	0.50 to 1.59	0.714
Separated	6	5.8	6	2.9	2.00	0.59 to 6.76	0.265
Divorced	20	9.7	10	9.7	1.00	0.41 to 2.42	1.000
Widowed	26	14.6	15	12.6	1.154	0.52 to 2.51	0.719
Education							
No education	15	12.6	13	7.3	2.42	0.94 to 6.26	0.067
Primary	70	34	35	34	1.40	0.68 to 2.86	0.357
Secondary	79	38.8	40	38.3	1.41	0.70 to 2.85	0.330
tertiary	42	14.6	15	20.4	1.00		

* Significantly associated

3.7.2. Bivariate analyses of base line laboratory measures

Among variables related to base line laboratory measures that are clinically important in HIV treatment program, base line CD4 count <50 cell/µl and base line hemoglobin level were significantly associated with treatment failure in a bivariate analysis ((COR 5.20, 95% CI 2.74 to 9.880 (COR 0.48, 95% CI 0.28 to 0.83)) respectively (Table 8).

Table 8 Distribution and association of base line laboratory measures with first line ARV treatment failure in public hospitals of Addis Ababa, 2012

variables	Controls=206		Cases=103				
	n	%	n	%	OR	95% CI	P
Base line CD4 count*							0.000
>150 cell/ µl	93	45.1	24	23.3	1.00		
50- 150 cell/ µl	81	39.3	43	41.7	1.72	0.94 to 3.12	0.074
<50 cell/µl	32	15.5	30	29.1	5.20	2.74 to 9.88	0.000
Base line Hg*							
>=11g/dl	40	19.4	34	33	1.00		
<11g/dl	166	80.6	69	67	0.48	0.28 to 0.83	0.009

*significantly associated variables with treatment failure, Hg- hemoglobin

3.7.3. Bivariate analysis of ARV drug related Variables

Among variables related to anti-retroviral drug, duration on HAART (COR 2.25, 95% CI 1.16 to 4.36), base line first line drug regimen (COR 1.79, 95% CI 1.10 to 2.93) and previous ART exposure (COR4.25, 95% CI 1.25 to 14.47) were significantly associated with first line antiretroviral treatment failure in a bivariate analysis (Table 9).

Table 9 Association of ARV drug related Variables with first line ARV treatment failure in public hospitals of Addis Ababa, 2012

variables	Controls=206		Cases=103				
	n	%	n	%	OR	95 % CI	P
Duration on first line ART*							
<24 month	21	20.4	21	10.2	2.25	1.16 to 4.36	0.015
>=24 month	185	79.6	82	89.8	1.00	———	—
NNRTI*							
EFV based	99	48.1	41	39.8	1.00		
NVP based	107	51.9	62	60.2	1.79	1.10 to 2.93	0.019
Previous ART exposure*							
No	202	98.1	95	92.2	1.00		
Yes	4	1.9	8	7.8	4.25	1.25 to 14.47	0.021

*significantly associated variables with treatment failure, PMTCT, prevention of mother to child transmission of HIV,NVP- nevirapin, ART, antiretroviral treatment; NNRTI, non-nucleoside reverse transcriptase inhibitors

3.7.4. Bivariate analysis of adherence related Variables

In a bivariate analysis of adherence related variables and substance use; substance use (COR 1.73, 95% CI 1.04 to 2.88), consistency of adherence (COR 2.73, 95% CI 1.68 to 4.45) and treatment interruption (COR 9.93, 95% CI 4.79 to 20.59) were significantly associated with first line treatment failure (Table 10).

Table 10 Association of adherence related Variables with first line ARV treatment failure in public hospitals of Addis Ababa, 2012

variables	Controls=206		Case=103				
	n	%	n	%	OR	95 %CI	P
Adherence*							
Consistently adhered	140	43.7	45	68	1.00		
Inconsistently adhered	66	56.3	58	32	2.73	1.68 to 4.45	0.000
Substance use*							
No	154	74.8	65	63.1	1.00		
Yes	52	25.2	38	36.9	1.73	1.04 to 2.88	0.035
Disclosed							
Yes	158	76.7	73	70.9	0.73	0.43 to 1.26	0.267
No	48	23.3	30	29.1	1.00	—	—
Treatment interruption*							
None	195	94.7	66	64.1	1.00		
Yes	11	5.3	37	35.9	9.93	4.79 to 20.59	0.000

*significantly associated; MS, marital status

3.7.5 Bivariate analyses of base line BMI

Regarding to base line BMI, base line BMI <16kg/m2 & 16-18.4 kg/m2 were significantly associated with first line antiretroviral treatment failure in a bivariate analysis ((COR 3.8, 95% CI 1.89 to 7.65) & (COR 2.11, 95% CI 1.21 to 3.70)) respectively (Table 11).

Table 11 Association of base line BMI with first line ARV treatment failure in public hospitals of Addis Ababa, 2012

variable	Controls=206		Cases=103				
	n	%	n	%	OR	95 %CI	P
Base line BMI*							
>=18.5kg/m^2	143	69.4	48	46.6	1.00		
16-18.4kg/m^2	45	21.8	32	31.1	2.11	1.21 to 3.70	0.008
<16kg/m^2	18	8.7	23	22.3	3.80	1.89 to 7.65	0.000

* Significantly associated; BMI, body mass index

3.7.6. Bivariate analyses of clinical disease mechanism and other health problems related variables

From all variables related to clinical disease mechanism & other health problems, WHO stage IV (COR 2.73, 95% CI 1.12 to 6.64), bed ridden in functional status (COR 5.65, 95% CI 2.29 to 13.90), ambulatory in functional status (COR 2.29, 95% CI 1.29 to 4.04), history of OI (COR 3.57, 95% CI 2.05 to 6.23), history of pulmonary TB treatment (COR 4.36, 95% CI 2.62 to 7.24), history of chronic gastric problem (COR 13.66,CI

5.47 to 34.25), history of chronic diarrhea (COR 9.59, 95% CI 4.00 to 23.02) & taking other medication (COR 3.08, 95% CI 1.88 to 5.02) were significantly associated with first line antiretroviral treatment failure in a bivariate analysis (Table 12).

Table 12 Association of clinical disease mechanisms, and other health problems related variables with first line ARV treatment failure in public hospitals of Addis Ababa, 2012

variables	Controls=206		Cases=103				
	n	%	n	%	OR	95% CI	P
WHO stage*							0.021
Stage I	26	12.6	9	8.7	1.00	__	__
Stage II	48	23.3	20	19.4	1.20	0.48 to 3.02	0.693
Stage III	95	46.1	39	37.9	1.18	0.51 to 2.76	0.692
Stage IV	37	18	35	34	2.73	1.12 to 6.64	0.026
Functional status*							
Work	161	78.2	57	55.3	1.00	__	__
Ambulatory	37	18	30	29.1	2.29	1.29 to 4.04	0.004
Bed ridden	8	3.9	16	15.5	5.64	2.29 to 13.90	0.000
History of OI*							
No	176	85.4	64	62.1	1.00	__	___
Yes	30	14.6	39	37.9	3.57	2.05 to 6.23	0.000
TB treatment*							0.000
No	159	77.2	45	43.7	1.00	__	__
Yes/pulmonary	36	17.5	53	51.5	5.2	3.04 to 8.90	0.000
No/extra pulmonary	11	5.3	5	4.9	1.6	0.53 to 4.86	0.42
Chronic gastric problem*							
Yes	6	2.9	30	29.1	13.69	5.47 to 34.25	0.000
No	200	97.1	73	70.9	1.00	____	___
Chronic diarrhea*							
Yes	7	3.4	26	25.2	9.59	4.00 to 23.02	0.000
No	199	96.6	77	74.8	1.00	____	___
Taking other medication*							
Yes	66	32	61	59.2	3.08	1.88 to 5.02	0.000
No	140	68	42	40.8	1.00	____	___

*significantly associated; OI, opportunistic infection; TB, tuberculosis, OR-odds ratio

5.8. Multivariable analyses

All variables associated with first line treatment failure in the bivariate analysis with *P* value <.05 were entered in a multivariable logistic regression analysis. Finally, baseline CD4 count <50 cell/µl, treatment interruption, history of pulmonary TB treatment during HAART follow up time, and history of chronic gastric problem were independently associated with first line antiretroviral treatment failure.

Patients with base line CD4 count below 50cell/µl failed for first line antiretroviral drug 2.7 times than that of with >150 cell/microliter with 95% CI 1.24 to 5.64.

Patients who interrupted treatment through defaulting or other reason were failed for first line antiretroviral drug 5.4 times than that of not interrupted patients with 95% CI 2.33 to 12.13. While patients having history of pulmonary TB treatment during HAART follow up were failed almost 3 times than that of without history with 95% CI 1.55 to 5.34. Similarly, those patients having history of gastric problem during HAART follow up time were failed 6.6 times than that of with no history of gastric problem with 95% CI 2.33 to 18.87 (Table 13).

Table 13 Independent predictors of first line ARV treatment failure in public hospitals of Addis Ababa, 2012

Exposure variables	AOR	95% CI	P
ART interruption			0.000
No	1.00		
Yes	5.36	2.33 to 12.13	
TB treatment			0.004
No	1.00		
Yes/pulmonary	2.88	1.55 to 5.34	
Yes/extra pulmonary	1.35	0.41 to 4.48	
Base line CD4 count			0.033
More than 150 cell/microliter	1.00		
50-150 cell/microliter	1.83	0.95 to 3.55	
Less than 50 cell/microliter	2.65	1.24 to 5.64	
Gastric problem			0.000
No	1.00		
Yes	6.63	2.33 to 18.87	

AOR (adjusted odds ratio) adjusted for all other variables.CI, confidence interval; ART, antiretroviral treatment; TB, tuberculosis

Discussion

The study has provided an opportunity to find out determinants of first line antiretroviral treatment failure in what is globally a very serious challenge for antiretroviral treatment program. In the study, several risk factors of first line antiretroviral treatment failure were investigated in adult HIV-infected population in Addis Ababa public hospitals. Among base line laboratory measures, base line CD4 count <50 cell/µl was significantly associated with first line antiretroviral treatment failure. Patients with base line CD4 count below 50cell/µl failed 2.7 times than that of with >150 cell/µl with 95% CI 1.24 to 5.64. The result is consistent with other study done in South Africa; a baseline CD4 count less than 50 cells per microliter increased the odds of failure more than 5 folds [29]. Similarly, a study done by Euro SIDA study group had reported the association between lower base line CD4 count and treatment outcome or disease progression; despite immunological failure, patients with higher pre-HAART CD4+ cell counts would be at less immediate risk of disease progression [5].

Patients who interrupted treatment through defaulting or other reason were failed 5.4 times than not interrupted with 95% CI 2.33 to 12.13. The result is comparable with a study done in South Africa; the odds of treatment failure were more than 8 folds for Patients who interrupted treatment through defaulting or non-adherence [30]. The very high risk of first line antiretroviral treatment failure in the study in patients with unplanned interruptions to therapy raises a concern that the failure to stagger ART cessation may be contributing to subsequent treatment failure which is consistent with several previous reports [29, 32].

However the finding of this study is inconsistent with a study done in Kampala, Uganda; history of unplanned treatment interruption was negatively associated with virologic treatment failure (odds ratio, 0.2; 95% confidence interval, 0.1–0.6) [35]. This variation might be due to the difference in study design. Other reason might be the difference of the stages of failure seen in this study and a study in Uganda; this study includes all stages of treatment failure while the Ugandan study was specific to virulogic failure. The effect could be potential use of treatment interruptions as a strategy in heavily pretreated patients (e.g., to permit reemergence of drug-susceptible virus as a dominant strain), which is not advisable to be considered as a viable option in patients with advanced immune suppression at the time of virologic failure [34].

Chronic gastric problem and pulmonary TB treatment during HAART follow up were significantly associated with first line antiretroviral treatment failure in this study. Several studies have shown that other health problems other than HIV/AIDS are a strong risk factor for occurrence of first line antiretroviral treatment failure or poor treatment success. A comparative study done between low and high income countries showed that those patients with comorbidities are at a higher risk of mortality and poor treatment outcome; Eligibility for antiretroviral treatment and the need for treatment of tuberculosis should be determined earlier and HAART should be started before serious comorbidities develop [42].

Patients having history of pulmonary TB treatment during HAART follow up failed almost 3 times than that of without history with 95% CI 1.55 to 5.34. This finding is inconsistent with a study done in South Africa; pulmonary TB treatment was not associated with first line antiretroviral treatment failure [30]. The discrepancy might be due to the lower immune status related to poor nutritional status & low socio economic back ground of patients in Ethiopia as compared to South Africa. The other reason to be inconsistent between this study and a study done in South Africa might be due to the initiation of HAART after serious comorbidities and advanced stage of disease had occurred among patients in Ethiopia because of late HIV test and late initiation of HAART. There might be also a difference due to sample size variation in this study and South African study. In addition

to these, the study done in South Africa is specific to virulogic failure (early stage of treatment failure) though this study includes all stages (immunological, clinical or virulogical) failure in defining cases. 40
Similarly, those patients having history of chronic gastric problem failed 6.6 times than that of with no history of gastric problem with 95% CI 2.33 to 18.87. The result is consistent with a study done on gastro intestinal problems & HIV on treatment success which showed that gastro intestinal problem was a strong predictor for a better treatment outcome; a healthy GI tract is necessary for proper absorption of medications. And controlling symptoms like nausea and diarrhea will improve your quality of life and help you adhere to your medications, causing better long-term treatment outcomes [42].

4. CONCLUSION

Majorities, 55 (53.4%) of cases and 123 (59.7%) of controls were females. Most, 75 (72.8%) of cases and 165 (80.1%) of controls were orthodox Christian followers. regarding to marital status, 44 (42.7%) of cases and 98 (47.6%) controls were married. Among cases and controls respectively; the median (interquartile range) baseline (at HAART initiation) cd4 count was 74 cells/µl (1–436) and 140 cells/µl (1-667).the independent predictors for first line antiretroviral treatment failure were;base line cd4 count lower than 50 cell/µl, unplanned anti-retroviral treatment interruption, history of pulmonary treatment during HAART follow up and, history of chronic gastric problem were the independent predictors for first line antiretroviral treatment failure. Based on the findings of the study the following recommendation is forwarded. health professionals should pay attention not to delay to start art for patients having lower cd4 count, close follow up to all patients on art to avoid unplanned treatment interruption & consequent problems, patients on pulmonary TB treatment and/or history of TB treatment during HAART follow up need further investigation and all HIV infected patients on HAART should be examined for all gastro intestinal problems & should be treated subsequently. Finally, further study with regards to quality of care given in health institutionswhich are supposed to give ART service, care provider aspect & directly from patients' side should be done in the future.

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AUTHORS' CONTRIBUTIONS

Author A designed the study, performed the statistical analysis, wrote the protocol, and wrote the draft of the manuscript. 'Author B' and 'Author C' gave comments. All authors read and approved the final manuscript.

ETHICAL APPROVAL

Ethical approval to carry out the study was sought from Jimma University health research & post graduate coordinating office of college of public health and medical science. Formal letter was taken from JU and Permission was obtained from FMOH and AAHB. Formal letter was taken to each hospital and Permission obtained from each hospital. The study was done with a care not to interfere with the normal management of the patients. Since the data were collected using only patients' unique ART registration number confidentiality of the data were fully guaranteed and the collected data were used only for research purpose.

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Definition for the term

Virulogic failure-When Plasma viral load is above 5000 copies/ml it is virulogical failure [19].

Immunological failure- When CD4 count falls to the base line (below or 50%) from on treatment peak value or persistent CD4 level below100 cell/mm3 without concomitant infection to cause transient CD4 cell decreasement [19].

Clinical failure- New or recurrent WHO stage 4 conditions occurred and certain WHO stage 3 conditions (pulmonary TB and recurrent bacterial infections) [19].

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