Determinants of Virological Failure Among Adult Clients on First-Line Antiretroviral Therapy in Amhara Regional State, Northeast Ethiopia. A Case –Control Study

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Background: Virological failure is defined as having viral load measurement greater or equal to 1000 copies/mm³ after at least six-month exposure to antiretroviral therapy. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS-2018) report, globally nearly one in five patients on first-line antiretroviral therapy had experienced virological failure. In line with this, Ethiopia federal ministry of health also reported that one in four patients had experienced virological failure in the year 2016. To date, very little is known about the predictors of virological failure in the local context. Therefore, this study intended to address the determinants of virological failure among patients on a first-line antiretroviral regimen.

Methods: A case–control study was conducted among clients on first-line antiretroviral therapy in Amhara regional state, January 2019 with a sample of 257 clients; of these, 86 clients were cases. Data were collected via patient interview and chart extraction for clinical profiles using standardized tools. Binary logistic regression was computed to identify the determinants of virological failure using Stata version 14 and the result was displayed using adjusted odds ratio with a 95% confidence interval.

Results: Out of the proposed samples, 255 clients were considered for final analysis. The odds of virological failure are higher among poor medication adherence (AOR: 10.2; 95% CI [4.1–25.8]), age < 35 years (AOR: 3.07 95% CI 1.4–6.8), low baseline CD4 (AOR 3.9; 95% CI 1.6–9.6), and Khat chewers (AOR: 9.5; 95% CI 2.8–32.4) as compared with their counterparts.

Conclusion: Being a young age, poor immunity at the initiation of antiretroviral, Khat chewer, and poor medication adherence significantly associated with virological failure.

Keywords: HIV/AIDS, virological failure, highly active antiretroviral therapy, case–control study

Introduction

Virological failure (VF) diagnosed based on a single plasma viral load (VL) measurement of ≥ 1000 copies/mL at any time after 6 months or more on antiretroviral therapy (ART),¹ which is a more proximal informative to treatment failure, is a common problem that an HIV patient faces after starting treatment.² According to WHO and national consolidated guidelines, once the patient had commenced antiretroviral therapy, it is expected to have an undetectable viral load at sixth

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month.³ In line with this, United Nation AIDS president emergency plan for AIDS relief (PEPFAR) ambitious plan incorporates Viral suppression in three 90s strategy to end AIDs epidemics as a public health threat by 2030 through fast-tracking commitment to meet the three 90s by 2020.^{4,5}

Early Virological failure leads to a premature switch to second-line drugs, which is expensive and toxic as compared with the standard first-line regimens.^{6,7}

However, studies show that VF is much higher than expected, and viral replication continues to be a major challenge among adult people living with HIV. In Ethiopia federal ministry of health reported that one in four patients had experienced virological failure in the year of 2016⁸ and also Ethiopian population-based HIV impact assessment reported in December 2018 shows only 70.1% of Urban residence adults age between 15 and 64 able to suppress their viral load numbers.⁹

Even though there is viral load monitoring for every client since January 2016 and July 2016 at the national level and Dessie public health institute, respectively, the zonal health department report showed that more than 190 clients face virological failure within 6 months.^{8,10}

The predictors of this problem vary from person to person as well across settings, however very little is known about the predictors of first-line virological failure in the local setting and in many studies as well, the social and personal characteristics are not included. Hence, this study was intended to address the determinants of virological failure among patients on a first-line antiretroviral regimen.

Methods

Study Design and Setting

A case-control study conducted in Dessie City Public Facility which, is 401Km from Addis Ababa a capital city of Ethiopia. Antiretroviral treatment therapy started in 2003 and 2005 at the national level and in Dessie City, respectively. Whereas the national Antiretroviral Treatment Guideline was adopting for the first time in 2007¹¹ and then updated in 2014¹² and 2018.² According to the national health-care service delivery system, the differentiated service delivery modality allows every client to visit the health facility regularly every six, three, two, and a monthly basis based on the clients' health status and willingness.² Every client should be monitored at 6 months soon after initiation ART and then every year for their viral load status. According to Ethiopian Public Health Institute

Dessie branch the plasma viral load level less than 150 copies/mL is reported as an undetectable viral load level. There are five public facilities providing ART of which two of them are hospitals and the rest three are health centers. Overall, about 10, 378 people living with HIV/AIDS are on antiretroviral drug treatments in Dessie City of these 9914 are adults and the rest 464 are pediatrics.^{10,13}

Study Participant and Sample Size Determination

Adult PLHIV clients, active on first-line ART, who have a first viral load measurement between July 2018 to December 2018 with viral load result ≥ 1000 copies/mL and < 1000 copies/mL of their viral load monitoring at 6 months or more after ART initiation as a source population for cases and controls, respectively.

The sample size was calculated using Epi Info™ 7.2 StatCalc by taking key predictor variables sex with odds ratio 2.5 for odds of VF in male¹³ with the power of 80%, 95% confidence level, and two to one ratio of controls to cases.

By adding a 10% contingency, the total sample size was 257 (86 cases and 171 controls). Samples were recruited using simple random sampling techniques after randomly allocating participants using lottery methods from routine viral load register.

Operational Definition

Virological failure is diagnosed based on a single plasma viral load (VL) measurement of ≥ 1000 copies/mL at any time after 6 months or more on antiretroviral therapy.¹

Treatment interruption means the patient misses his/her appointment schedule for a month or more.¹⁴

Adherence defines treatment adherence as the extent to which a person's behavior of taking medications, corresponds with agreed recommendations from a health-care provider more than 95% as good adherence and poor adherence for less than 95% of their dose of drugs.²

Data Collection Tools and Procedures

The data were collected using a structured questionnaire through an exit interview and chart extraction about the sociodemographic, baseline and recent clinical profiles and personal and social behaviors for clients, who have viral load test results between July 2018 to December 2018. The data collection tools were developed from ART national guideline, registers and ART follow-up forms. The quality

Table 1 The Socio-Demographic Characteristics of Adult First-Line ART Clients in Dessie, Amhara Region Northeast Ethiopia Jan 2019

Variables		Frequency	Cases (n=85)	Controls (n=170)
Sex	Male	110 (43.1%)	45 (52.9%)	65 (38.2%)
	Female	145 (56.9%)	40 (47.1%)	105 (61.8%)
Residence	Urban	214 (83.9%)	68 (80%)	146 (85.9%)
	Rural	41 (16.9%)	17 (20%)	24 (14.1%)
Educational status	Unable to read and write	73 (28.6%)	31 (36.5%)	42 (24.7%)
	Able read and write	20 (7.8%)	5 (5.9%)	15 (8.8%)
	Primary school	81 (31.8%)	23 (27.1%)	58 (34.1%)
	From 9 to 10+3	65 (25.5%)	20 (23.5%)	45 (26.5%)
	First degree and above	16 (6.3%)	6 (7.1%)	10 (5.9%)
Occupation	Government employed	32 (12.5%)	8 (9.4%)	24 (14.1%)
	Self employed	92 (36.1%)	27 (31.8%)	65 (38.2%)
	Private Employed	24 (9.4%)	12 (14.1%)	12 (7.1%)
	Unemployed	12 (4.7%)	4 (4.7%)	8 (4.7%)
	Daily laborer	54 (21.2%)	20 (23.5%)	34 (20.0%)
	House Wife	36 (14.1%)	12 (14.1%)	24 (14.1%)
	Others ^a	5 (2.0%)	2 (2.4%)	3 (1.8%)
Marital status	Single	33 (12.9%)	15 (17.6%)	18 (10.6%)
	Married	137 (53.7%)	44 (53%)	92 (54.1%)
	Widowed	34 (13.3%)	7 (8.2%)	27 (15.9%)
	Divorced	51 (20.0%)	18 (21.2%)	33 (19.4%)

Note: ^aStudents.

of the data had tried to ensure through training of the data collectors, conducting pre-testing the tool and supervision during data collection.

Data Management and Analysis

The data were checked for completeness and entered into Epi-data version 3.1 then exported to Stata version 14. The data were managed by running frequencies, sorting, and listing variables and then descriptive statistics like frequencies and percentages were calculated to see the overall distribution of the study subjects with regard to the variables under the study. The binary logistic regression model was computed to identify determinants of VF by considering the Hosmer–Lemeshow goodness-of-fit test, which was non-significant (0.72).

First, bi-variable analysis of binary logistic regression was conducted and those variables with a p-value of less than 0.2 were included into multi-variable analysis. In multivariable binary logistic regression variables having a p-value less than 0.05 considered as the determinant of VF at the level of significance of 0.05.

Ethical Consideration

A written ethical clearance letter was obtained from the Ethical Review Committee (ERC) of Wollo University College of medicine and health sciences. The respondents were informed about the purpose of the study and written consent was obtained. The data were collected in accordance with Helsinki Declaration and the information provided by each respondent was kept strictly confidential.

Result

A total of 255 adults ART first-line users were involved in the study with a response rate of 85 (98.8%) and 170 (99.4%) among cases and controls, respectively.

Socio-Demographic Characteristics

The median age of the respondents was 32 and 38 years with an inter-quartile range (IQR) of 9 and 12 years for cases and controls, respectively. Female respondents contribute 40 (47%) of cases and 105 (61.8%) of controls (Table 1). Among urban dwellers 68 (80%) were cases and 146 (85.9%) were controls. Of the total 255 respondents, 81 (31.8%) were primary school among these 23

Table 2 The Baseline Clinical Characteristics of Adult First-Line ART Clients in Dessie, Amhara Region Northeast Ethiopia Jan 2019

Variables		Frequency	Cases (n=85)	Controls (n=170)
Baseline WHO stage	Stage I	58 (22.7%)	14 (16.5%)	44 (25.9%)
	Stage II	67 (26.3%)	20 (23.5%)	47 (27.6%)
	Stage III	112 (43.9%)	43 (50.6%)	69 (40.6%)
	Stage IV	18 (7.1%)	8 (9.4%)	10 (5.9%)
Baseline Regimen	TDF 3TC EFV	101 (39.6%)	39 (45.9%)	62 (36.5%)
	TDF 3TC NVP	19 (7.5%)	8 (9.4%)	11 (6.5%)
	AZT 3TC NVP	48 (18.8%)	15 (17.6%)	33 (19.4%)
	AZT 3TC EFV	22 (8.6%)	6 (7.1%)	16 (9.4%)
	OTHERS ^Δ	65 (25.5%)	17 (20.0%)	48 (28.2%)

Note: ^Δ(d4T+3TC+NVP), (d4T+3TC+EFV).

(27.1%) of them were cases (Table 1). Concerning respondent's occupation and marital status, 92 (36.1%) and 136 (53.3%) were self-employed and married, respectively (Table 1).

Baseline Clinical Characteristics

The median CD4 cell counts were 119.5 and 179 cells/ μ L with an inter-quartile range of 158 and 170.5 cells/ mm^3 among cases and controls, respectively. The minimum baseline CD4 cells were 4 and 9 cells/ mm^3 and the maximum was 707 and 1326 cells/ μ L for cases and controls, respectively. The median baseline BMI of the respondents (IQR) was 17.9 (2.6) kg/m^2 with a minimum of 14.8 kg/m^2 and a maximum of 34.3 kg/m^2 in case groups. From the baseline characteristics of the respondents, 43 (50.6%) and 69 (40.6%) were at WHO stage III among cases and

controls, respectively (Table 2). From the baseline regimen 39 (45.9%) cases and 62 (36.5%) controls were taking TDF 3TC EFV Table 2.

Recent Clinical Characteristics

The median recent CD4 counts (IQR) were 272 (296) cells/ μ L 1454 (327) cells/ μ L for cases and controls, respectively. The median BMI of the respondents (IQR) was 18.3 (2.7) kg/m^2 , among cases and also 20.25 (4.8) kg/m^2 for controls. Almost all 243 (95.3%) of the respondents were in stage one during the clinical assessment of their viral load schedule.

Out of the total 255 respondents, 68 (26.7%) were having a history of OI since ART initiation. Almost 240 (94.1%) of the respondents were working functional status and only a few 6 (2.4%) were having chronic co-morbid diseases (Table 3).

Table 3 The Recent Clinical Characteristics of Adult First-Line ART Clients in Dessie, Amhara Region Northeast Ethiopia Jan 2019

Variables		Frequency	Cases (85)	Controls (n=170)
Current Regimen	TDF 3TC EFV	121 (47.5%)	42 (49.4%)	79 (46.5%)
	TDF 3TC NVP	32 (12.5%)	8 (9.4%)	24 (14.1%)
	AZT 3TC NVP	64 (25.1%)	24 (28.2%)	40 (23.5%)
	AZT 3TC EFV	38 (14.7%)	11 (13%)	27 (16.1%)
Current T stage	Stage I	243 (95.3%)	76 (89.4%)	167 (98.2%)
	Stage II	7 (2.7%)	4 (4.7%)	3 (1.8%)
	Stage III	5 (2.0%)	5 (5.9%)	0 (0.0%)
Current functional status of the patient	Working	240 (94.1%)	77 (90.6%)	163 (95.9%)
	Ambulatory	15 (5.9%)	8 (9.4%)	7 (4.1%)
History of Opportunistic Infection	Yes	68 (26.7%)	39 (45.9%)	29 (17.1%)
	No	187 (73.3%)	46 (54.1%)	141 (82.9%)
Non communicable disease	Yes	6 (2.4%)	2 (2.4%)	4 (2.4%)
	No	249 (97.6%)	83 (97.6%)	166 (97.6%)

Table 4 The Social and Personal Characteristics of Adult First-Line ART Clients in Dessie, Amhara Region Northeast Ethiopia Jan 2019

Variables		Frequency	Cases (n=85)	Controls (170)
Adherence to ARV	Good	198 (77.6%)	39 (45.9%)	159 (93.5%)
	Poor	57 (22.4%)	46 (54.1%)	11 (6.5%)
Treatment interruption	Yes	37 (14.5%)	27 (31.8%)	10 (5.9%)
	No	218 (85.5%)	58 (68.2%)	160 (94.1%)
Reason for treatment interruption	Side effect	2 (5.1%)	1 (4.36%)	1 (6.25%)
	Illness	9 (23.1%)	6 (26.08%)	3 (18.75%)
	Social Problem	8 (20.5%)	6 (26.08%)	2 (12.5%)
	Hopelessness	12 (30.8%)	6 (26.08%)	6 (37.5%)
	Use of traditional medicine	8 (20.5%)	4 (17.4%)	4 (25%)
Duration of interruption	Less than one Month	11 (29.7%)	5 (18.5%)	6 (60.0%)
	For one month	10 (27.0%)	7 (25.9%)	3 (30.0%)
	For two months	3 (8.1%)	3 (11.1%)	0 (0.0%)
	3 months and above	13 (35.1%)	12 (44.4%)	1 (10.0%)
Disclosing HIV status	Yes	199 (78.0%)	54 (63.5%)	145 (85.3%)
	No	56 (22.0%)	31 (36.5%)	25 (14.7%)

Social and Personal Characteristics

Most of the respondents 198 (77.6%) were with good adherence among those 39 (45.9%) were cases and 159 (93.5%) of them were controls (Table 4). Regarding to treatment interruption 58 (68.2%) of the respondents, who were never interrupted, were cases and among those, who interrupt 13 (35.1%) were interrupted for 3 months and more. Among the respondents who were disclosed their HIV status 54 (63.5%) were cases and 145 (85.3%) of them were Controls (Table 4).

Behavioral Characteristics

Most respondents 221 (86.7%) had no multiple sexual partners and 64 (75.3%) of them were cases and 124 (48.6%) of cases use condom consistently from those 31 (36.5%) were cases and 93 (54.7%) were controls (Table 5).

Out of the total 255 respondents 231 (90.6%), 216 (84.7%), 251 (98.4%) of the respondents were never taken any alcohol, khat, and smoking within 1 year Prior to viral load test (Table 5).

Table 5 The Behavioral Characteristics of Adult First-Line ART Clients in Dessie, Amhara Region Northeast Ethiopia Jan 2019

Variables		Frequency	Cases (n=85)	Controls (n=170)
Multiple Sexual partners	Yes	34 (13.3%)	21 (24.7%)	13 (7.6%)
	No	221 (86.7%)	64 (75.3%)	157 (92.4%)
Consistent Use of condoms	Yes	124 (48.6%)	31 (36.5%)	93 (54.7%)
	No	98 (38.4%)	50 (58.8%)	48 (28.2%)
Alcohol consumption status	Never	231 (90.6%)	71 (83.5%)	160 (94.1%)
	Sometimes	21 (8.2%)	12 (14.1%)	9 (5.3%)
	Always	3 (1.2%)	2 (2.4%)	1 (0.6%)
Chewing Khat status	Never	216 (84.7%)	53 (62.4%)	163 (95.9%)
	Sometimes	32 (12.5%)	25 (29.4%)	7 (4.1%)
	Always	7 (2.7%)	7 (8.2%)	0 (0.0%)
Smoking cigarette status	Never	251 (98.4%)	83 (97.6%)	168 (98.8%)
	Sometimes	2 (0.8%)	1 (1.2%)	1 (0.6%)
	Always	2 (0.8%)	1 (1.2%)	1 (0.6%)

Table 6 Determinants of Virological Failure Among Adult First-Line HAART Clients in Dessie, Amhara Region Northeast Ethiopia Jan 2019 (N=255)

Variables		Cases (n=85)	Controls (170)	COR (95% CI)	AOR (95% CI)
Sex	Male	45 (52.9%)	65 (38.2%)	1.82 (1.07–3.08)	1.29 (0.55–2.98)
	Female	40 (47.1%)	105 (61.8%)	1	1
Age	<35 years	61 (71.8%)	64 (37.6%)	4.2 (2.29–7.4)	3.07 (1.4–6.8)*
	≥35 years	24 (28.2%)	106 (62.4%)	1	1
Baseline WHO stage	Advanced Stage ^a	51 (60%)	79 (46.5%)	1.73 (1.02–2.93)	1.73 (0.76–3.93)
	Early stage ^b	34 (40%)	91 (53.5%)	1	1
History of OI	Yes	39 (45.9%)	29 (17.1%)	4.122 (2.29–7.4)	3.6 (0.47–8.7)
	No	46 (54.1%)	141 (82.9%)	1	1
Baseline CD4	< 200cells/μL	62 (72.9%)	99 (58.2%)	1.93 (1.1–3.41)	3.9 (1.57–9.66)*
	≥200 cells/μL	23 (27.1%)	71 (41.8%)	1	1
Recent CD4	<200 cells/μL	24 (28.2%)	15 (8.8%)	4.066 (2.0–8.27)	1.46 (0.34–4.6)
	≥200 cells/μL	61 (71.8%)	155 (91.2%)	1	1
Baseline BMI	Low baseline BMI ^c	59 (69.4%)	79 (46.5%)	2.6 (1.51–4.54)	1.03 (0.39–2.85)
	Normal ^d	26 (30.6%)	91 (53.5%)	1	1
Recent BMI	Low ^c	49 (57.6%)	37 (21.8%)	4.89 (2.78–8.60)	3.4 (0.55–7.7)
	Normal ^d	36 (42.4%)	133 (78.2%)	1	1
Adherence Status	Poor ^e	46 (54.1%)	11 (6.5%)	17.05 (8.1–35.9)	10.23 (4.1–25.8)*
	Good ^f	39 (45.9%)	159 (93.5%)	1	1
Treatment interruption	Yes	27 (31.8%)	10 (5.9%)	7.45 (3.4–16.3)	7.05 (0.26–22.2)
	No	58 (68.2%)	160 (94.1%)	1	1
Care givers HIV status	HIV negative	51 (60%)	73 (42.9%)	1.99 (1.21–3.6)	0.61 (0.25–1.47)
	HIV positive	34 (40%)	97 (57.1%)	1	1
Disclosure status	Yes	31 (36.5%)	25 (14.7%)	1	1
	No	54 (63.5%)	145 (85.3%)	3.3 (1.8–6.14)	1.82 (0.7–4.9)
Multiple Sexual Partners	Yes	21 (24.7%)	13 (7.6%)	3.96 (1.87–8.39)	2.82 (0.94–8.47)
	No	64 (75.3%)	157 (92.4%)	1	1
Alcohol Consumption	Yes	14 (16.5%)	10 (5.9%)	3.16 (1.34–7.44)	1.6 (0.37–6.8)
	Never	71 (83.5%)	160 (94.1%)	1	1
Khat Chewing	Yes	32 (37.6%)	7 (4.1%)	14.1 (5.9–33.7)	9.54 (2.8–32.4)*
	Never	53 (62.4%)	163 (95.9%)	1	1

Notes: ^aStage I and II, ^bStage III and IV, ^cBMI<18.5, ^dBMI≥18.5, ^eARV drug Adherence≥95%, ^fARV drug adherence<95%, *Significantly associated variables.

Determinant Factors for VF

During multi-variable backward logistic regression analysis age less than 35 years, low baseline CD4 counts (<200cell/mL), poor adherence and, Khat chewing practice are significantly associated with virological failure [Table 6](#).

The likelihood of developing VF in clients with poor adherence to antiretroviral treatment is 10 times as compared with good adherence. The risk of developing

virological failure among clients in a younger age group (age less than 35 years) is increased 3 times as compared with an older age group (age greater than 35 years). Those clients with baseline CD4 count less than 200 cells/μL increase the likelihood of developing VF 4 times as compared with baseline CD4 count greater than 200cells/mm³. Clients on first-line adult ART users, who were “Khat” chewers, are 9.5 times more likely to develop VF as compared with not Khat chewing group [Table 6](#).

Discussion

In this study, the determinants of virological failure in adult antiretroviral therapy users reveal that age less than 35 years, presence Low baseline CD4 (below 200cell/mL), Khat chewing, and poor adherence to antiretroviral drugs were found to have increased odds of virological failure.

Poor adherence to ART drugs is one of the predictors of VF. The finding of this study is consistent with a study conducted in Gondar, Mekele, and Uganda, where poor adherence was the main risk factor for virological failure. Missing one or more drugs, within 7-days dose leads to high viral replication, which leads to VF.^{15–17} Therefore, poor adherence has a proxy indicator for Virological failure, poor immunological and Clinical outcomes, and also has its own public health implication on having a spread of HIV infection and drug resistance.

The younger age groups of antiretroviral therapy users are prone to virological failure. In line with these various studies have revealed that younger age groups were at increased risk of VF.^{15,18} The possible reason may be due to fear of disclosure to their family and relatives.¹⁹ So that different study shows that younger age groups are not disclosing their HIV status and disclosure is one of the predictor variable for Virological failure.^{20,21} Therefore, health-care providers better provide a patient-centered approach to younger age groups in order to reduce mortality in earlier ages of ART clients and increase productivity at individual and national levels.

A low baseline CD4 count is considered as the determinant of VF in this study. Different studies have shown that low baseline CD4 count was significant predictors of VF explained by the frequent occurrence of opportunistic infections that leads to disease progression subsequently increased risk of virological failure.^{22,23} Hence, strengthen test and Treat-all approach in clients with low baseline CD4 cell counts, commence appropriate prophylaxis, and provide intensive counseling on drug adherence.

Even though there is limited scientific paper investigating the association between “Khat” Chewing practice and Virological response on HIV/AIDS patients, in this study “Khat” is one of the predictor variables which is significantly associated to VF this may be due to the prevalence of “Khat” chewing high in the area.^{24,25} “Khat” chewing reduces nutritional and drug absorption, which leads to immune suppression as well “Khat” chewing leads to the use of other substances that may interact with the antiretroviral drugs, this leads to poor response to antiretroviral drug, then finally develop virological failure.²⁴ So, Khat chewing increases the

risky sexual behavior which in turn increases the spread of HIV infection from high viral load clients.²⁶

Conclusion

Among the socio-demographic characteristics, age is negatively associated with the development of virological failure, as well in baseline clinical characteristics baseline CD4 cell count is also shows a negatively associated with the development of virological failure.

From personal and behavioral characteristics poor adherence to antiretroviral treatment and Khat chewing are the main predictor variables for virological failure. Prepare a list in the care plan for clients with poor adherence, discuss with them to resolve the root cause of adherence problem and to avoid their risky behaviors.

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Author Contributions

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

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