ORIGINAL RESEARCH

Determinants of Virologic Failure Among Adults on Second Line Antiretroviral Therapy in Wollo, Amhara Regional State, Northeast Ethiopia

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Background: Treatment failure among the population on second line antiretroviral therapy is a major public health threat. In Ethiopia there has been limited research done on second line treatment failure.

Objective: To identify determinants of virologic failure among adults on second line antiretroviral therapy in six public hospitals of Wollo, Amhara regional state, northeast Ethiopia.

Methods: An institution-based unmatched case–control study was conducted from February 1, 2020 to April 30, 2020 on a total of 377 clients in six public hospitals of Wollo, Amhara regional state, northeast Ethiopia. Clients whose viral load result >1,000 copies/mL in two consecutive results at least 3 month apart were cases, while ≤1,000 copies/mL were controls. The sample size was calculated by using Epi-Info version 7. Cases (94) and controls (283) were selected using a simple random sampling method in a ratio of cases-to-controls of 1:3. The model fitted and binary logistic assumptions were fulfilled with 95% confidence level and *P*-values<0.05 were taken as statistically significant.

Results: Virologic failure was predicted by poor adherence (AOR=6.060, 95% CI=2.837–12.944), not disclosing their HIV status (AOR=4.178, 95% CI=1.431–12.198), OI (AOR=4.11, 95% CI=1.827–9.246), CD4 count <100 cells/mm^3 (AOR=3.497, 95% CI=1.233–9.923) and 100–350 cells/mm^3 (AOR=5.442, 95% CI=2.191–13.513), low BMI <16 kg/m^2 (AOR=7.223, 95% CI=2.218–23.520), and young age 15–29 years (AOR=2.898, 95% CI=1.171–7.170).

Conclusion and Recommendations: Determinants of second line ART virologic failure were patients who had poor adherence to ART, not disclosed, opportunistic infection, low CD4 counts <350 cell/mm^3, low BMI (<16 kg/m^2), and young age 15–29 year patients. Social support, disclosing their HIV status, and getting early treatment for any opportunistic infection is crucial to patients.

Keywords: HIV, second line ART, virologic failure, case–control study, Wollo, northeast Ethiopia

Introduction

Second line antiretroviral therapy (ART) virologic failure is defined as patients who are on second-line regimen and have a high viral load level (>1,000 copies/mL) in two consecutive measurement after 6 months of treatment and repeat test after 3 months to decide second line treatment virologic failure.[1] It is well established that virological failure (the gold standard criteria) occurs earliest, followed by immunological failure, then clinical failure.[2]

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First line virologic failure is a viral load count of more than 1,000 copies/mL in two consecutive results at least 3 months apart after 6 months of switching to second line antiretroviral therapy.[1,3] Patients using the WHO recommended second-line of boosted atazanavir have comparable virologic suppression to those on boosted lopinavir.[4] Viral load monitoring has been recommended by the WHO for the identification of treatment failure and to prompt enhanced adherence support.[5]

Globally more than 36.9 million people were living with HIV by the end of 2017.[5] Sub-Saharan Africa carries the highest burden with an estimated 24.7 million people living with HIV, nearly 70% of the global total.[6] According to the 2014 UNAIDS report, around 1.7 million people died from AIDS related causes worldwide and 70% occurred in sub-Saharan Africa.[7] Ethiopia is one of the hardest hit sub-Saharan African countries by the HIV pandemic with an estimated death of 52,405 by 2014.[8]

According to the global estimate, about 5.5% of patients were receiving second-line treatment in 2016 worldwide. In sub-Saharan Africa, nearly two out of 100 HIV patients switched to second line ART every year. Patients on second-line treatment accounted for 1.5% of all patients on ART in Ethiopia.[9] In Amhara regional state the overall incidence of second-line treatment failure was 9.86 per 100 person-years.[10]

Studies from Asia reported that after 2 years on second-line ART, failure rates ranged between 8% and 41%, and studies from Africa reported that the rate was between 13% and 40%.[11] A higher rate of virological failure of 17.7% was reported in India among patients who were on second line ART beyond 1 year and a much higher rate of virological failure of 37% was also recently reported from Myanmar Asia among patients who were on second line ART.[12] In a resource limited setting the rates of second-line failure have been demonstrated to be as high as 38% by 36 months.[13]

The three 90 treatment target sets the goal by 2020: 90% of people living with HIV knowing their HIV status, 90% of people who know their HIV-positive status accessing treatment, and 90% of people on treatment having suppressed viral loads.[14] Identifying factors contributing to viremia and virologic failure is key to achieving the third of the 90 targets.[15]

Treatment failure among the population on second line ART becomes a major public health threat. Its magnitude and factors leading to it are poorly defined.[16] Patients who switch to second line ART factors leading to virologic failure are not well understood or well-studied.[17] However, in Ethiopia there is much research conducted on first line antiretroviral treatment failure, but there is limited research conducted on second line treatment failure. This study tried to identify determinants of second line antiretroviral therapy virologic failure in six public hospitals of Wollo Amhara regional state, northeast Ethiopia.

This study finding is crucial to people living with HIV staying healthy, improving their life expectancy and quality-of-life, decreasing their HIV associated morbidity and mortality, and preventing drug toxicity and others. In addition, the clinicians and healthcare workers will benefit from this study to assist and focus on monitoring treatment for susceptible patients, achieving viral suppression, and preventing second line treatment failure by addressing the determinants identified. It is also crucial for local and health facility managers to develop operational planning and avail third line antiretroviral therapy in the health facilities.

Methods and Materials
Study Area, Period, and Design

The study was conducted in six public hospitals of Wollo (Lalibela general, Woldia zonal, Dessie referral, Borumeda general, Mekaneselam primary and Hidar 11 general hospitals) of Amhara regional state, northeast Ethiopia. The total number of health workers was 1,691, 23 adherence counselors, and 17 case managers were working at ART clinics of the above hospitals. Generally in all study public hospitals 12,589 adults and 1,011 children were on first line ART, 1,301 adults were on second line ART, and 97 adults on second line ART were virologic results not suppressed. At the time of data collection there were 27 clients switched to third line ART at Dessie referral and Woldia zonal hospitals. Both hospitals started third line ART treatment at the end of February 2020.[18] The study was conducted from February 1, 2020 to April 30, 2020. A facility-based unmatched case–control study design was conducted.

Population

All HIV positive adults ≥15years after 6 months switched to second line ART in a study of hospitals in Wollo, Amhara regional state, northeast Ethiopia. HIV positive adults ≥15years old, 6 months after switching to second line ART whose plasma viral load was >1,000 copies/mL

in two subsequent viral load measurements at least 3 months apart were cases (virologic failure), while study participants with a viral load level of ≤1,000 copies/mL were controls (virologic suppression).

Eligibility Criteria

HIV positive adults ≥15years old, 6 months after switching to second line ART who had >1,000 copies/mL in two subsequent viral load results at least 3 months apart for the cases and who had suppressed viral load results were included. But those who were referred from other treatment centers with incomplete information (baseline C.D.4 count, baseline WHO stage, baseline BMI of patients in kg/m², and opportunistic infection) and transferred out to other health facilities were excluded.

Sample Size and Sampling Technique

The sample size was calculated by using Epi-Info version 7 by taken the key predictors of virologic failure from a previous study. The following assumptions were considered during sample size determination, from the study 95% confidence level, Odds ratio=3.4, power=80%, and a ratio of controls to cases of 3:1 was used. Therefore, the largest calculated sample size were 343 and, by adding a 10% non-response rate the total sample size was 377 clients (94 cases and 283 controls). All six public hospitals found in Wollo, Amhara regional state, northeast Ethiopia were included. The list of clients whose viral load results were available up to January 30, 2020 were extracted from a database computer in each ART clinic of study facilities. Then 94 cases whose viral load results were >1,000 copies/mL in two subsequent viral load measurements and 283 controls whose viral load results were suppressed were selected based on proportional allocation by using a computer generated simple random sampling method in the ratio of controls to cases of 3:1.

Data Quality Control

The data collection tool was an interview administered structured questionnaire for primary data and checklist for document review. It was adapted from other similar studies and the Federal Ministry of health Ethiopian ART national guidelines, register, intake and follow-up form of the patient. The questionnaire was originally developed in English and used as if for secondary data collection and translated to Amharic for primary data collection. Pretest was done in 5% of the patient at Dessie referral hospital before actual data collection. Data was collected by trained data collectors. Two days training was given to data collectors. Seven ART trained health professionals (five BSc and two clinical nurses) working at ART clinic in the study hospitals participated in the data collection. Supervision and on spot checking of the data collection procedure was made. Those who had no volunteer to participate in the study returned the questionnaires.

Data Management and Analysis

First data were checked for completeness. After being coded it was entered into EPI-data version 3.1, then it was checked for accuracy, consistency, and missing values through tabulation and frequency. Then it was transferred to Statistical Package for Social Science (SPSS) version 21 for analysis. The model fitness was checked by using Hosmer and Lemeshow goodness of test. Logistic regression assumption checked for filling of the assumption by using VIF<10, tolerance test>0.1, and standard error<2. All fulfilled the assumptions. Then bivariable logistic regression was run and variables with a *P*-value of less than 0.25 were entered into a multivariable binary logistic regression model for further analysis. Data were interpreted by using odds ratios with 95% confidence level and a *P*-value<0.05 was taken as statistically significant.

Operational Definitions
Second Line ART Virologic Failure
Viral load result >1,000 copies/mL after 6 months were switched to second line ART in two subsequent measurements at least 3 months apart.[1]

Cases
All HIV positive adults ≥15 years old whose plasma viral load result was >1,000 copies/mL in two subsequent viral load measurements at least 3 months apart after 6 months of being switched to second line ART were cases (virologic failure).[1]

Controls
All HIV positive adults ≥15 years old whose plasma viral load was ≤1,000 copies/mL after 6 months of switching to second line ART were controls (virologic suppression).[1]

Adherence
Assessed by patients self-report about missed doses within a month, missing more than three doses from BID doses and missing more than one dose from daily doses was considered as poor adherence.[1]

Opportunistic Infections

Infections that develop as a result of HIV-inflicted damage to the immune system (TB, PCP, gastrointestinal OI, herpes simplex, herpes zoster, fungal infection) and other national ART guidelines define opportunistic infection.[1]

Lost to Follow-Up

Patient's with three or more consecutive missed clinic appointments in medical record.[1]

Defaulter

Patient's with less than three consecutive missed clinic appointments.[1]

Results

Socio-Demographic Characteristics

From the total of 377 patients on second line ART in six public hospitals of Wollo, 363 (87 cases and 276 controls) participated in this study, which accounts for a response rate of 96.2%. Among the participants, 201 (55.4%) were females and 251 (69.1%) respondents were urban residents. From the respondents, 136 (37.5%) are ≥40years, 93 (25.6%) 15–29years, and 134 (36.9%) were 30–39 years. Among respondents, 282 (77.7%) had full or part time work (Table 1).

Behavioral and Other Characteristics

From the study participants, 46 (52.9%) of the cases and 36 (13%) of the controls had poor adherence to ART medication. Among the participants, 32 (36.8%) cases and 16 (5.8%) controls did not disclose their HIV status. From the respondents, 21 (5.8%), 12 (3.3%), and 68 (18.7%) had a history of alcohol use, cigarette smoking, and chat chewing, respectively. Most of the clients (239, 65.8%) were not correctly or consistently useing a condom, and 34 (9.4%) had a history of default or missed less than three consecutive clinic appointments.

The majority of study participants (300, 82.6%) used a wall chart or mobile alarm ARV reminder to take their medication and the rest used family or friend, TV or radio. One hundred and eighty (49.6%) of the clients travelled more than 10 km from their home to get the service. Of those, 322 (88.7%) had a caretaker and 331 (91.2%) of participants had no fear of stigma due to HIV/AIDS or use of ART medication. Finally, among the study participants, 311 (85.6%) did not not manifest depression in the last 2 weeks during the data collection period.

Clinical and Related Characteristics

Since the study participants started ART medication, 309 (85.1%) clients were more than 36months on first line ART, 228 (62.8%) were on second line ART for less than 2 years, and 343 (94.5%) had a less than 12months delay before switching to second line ART.

From the study participants 184 (50.7%) were on TDF +3TC+ATV/r, 70 (19.3%) on AZT+3TC+ATV/r, 69 (19%) on ABC+3TC+ATV/r, and the rest were on other ART regimens (TDF+3TC+LPV/r, AZT+3TC+LPV/r) and, based on the doses, 193 (53.2%) clients were taking one dose, whereas 170 (46.8%) were taking two or more doses per day. From the total study participants, 315 (86.8%) and 292 (80.4%) used INH and CPT, respectively. Related to opportunistic and other infections, 321 (88.4%) had no history of TB, 350 (96.4%) had no chronic diarrhea, 337 (92.8%) had no anemia, and 354 (97.5%) had no adverse drug reaction. Finally, among the respondents, 296 (81.5%) received three or more sessions of enhanced adherence counseling (Table 2).

Determinants of Virologic Failure

In bi-variable logistic regression from a total of 41 variables the following: sex, age, marital status, educational status, employment status, smoking, adherence, disclosure status of HIV, HIV status of spouse, condom use, history of default, ARV reminder use, type of health facility use ART, home-to-health facility distance, depression, functional status, opportunistic infection, body mass index, base line CD4 count, WHO T-stage, duration on first line ART, ART regimen, duration on second line ART, INH use, history of TB, anemia, diarrhea, and EAC session received passed the screening criteria (*P*-value<0.25) for further multivariable binary regression (Table 3).

In multivariable binary logistic regression the likelihood of developing virologic failure among patients with poor adherence to ART medication was 6-times (AOR=6.060, 95% CI=2.837–12.944) more likely as compared to those patients who had good adherence. Among study participants those patients who did not disclose their HIV status or use of ART medication were 4-times (AOR=4.178, 95% CI=1.431–12.198) more likely to develop virologic failure as compared to those patients who disclosed their HIV status or use of ART medication to current parent or close relatives but in contrast to this those patients disclosed their HIV status or use of ART medication to friends or colleagues were 76.8%

Table 1 Socio-Demographic Characteristics of Patients on Second Line Anti-Retroviral Therapy After 6 Months of Switched in Six Public Hospitals in Wollo, Amhara Regional State, Northeast Ethiopia in 2020

Variable		Virologic Failure		Total (363) No. (%)
		Cases (N=87) No. (%)	Controls (N=276) No. (%)	
Sex	Male	47 (54)	115 (41.7	162 (44.6)
	Female	40 (46)	161 (58.3)	201 (55.4)
Age	≥40 years	23 (26.4)	113 (40.9)	136 (37.5)
	15–29 years	40 (46)	53 (19.2)	93 (25.6)
	30–39 years	24 (27.6)	110 (39.9)	134 (36.9)
Residence	Urban	64 (73.6)	187 (67.8)	251 (69.1)
	Rural	23 (26.4)	69 (32.2)	112 (30.9)
Marital status	Single	26 (29.9)	56 (20.3)	82 (22.6)
	Married	28 (32.2)	141 (51.1)	169 (46.6)
	Divorced	24 (27.6)	53 (19.2)	77 (21.2)
	Widowed	9 (10.3)	26 (9.4)	35 (9.6)
Educational status	Illiterate	8 (9.2)	58 (21)	66 (18.2)
	Read and write	8 (9.2)	46 (16.7)	54 (14.9)
	Elementary	29 (33.3)	95 (34.4)	124 (34.2)
	Secondary and above	42 (48.3)	77 (27.9)	119 (32.8)
Employment status	Full or partial time work	59 (67.8)	223 (80.8)	282 (77.7)
	Unemployed	28 (32.2)	53 (19.2)	81 (22.3)
Monthly income	>5,000 birr	3 (3.4)	10 (3.6)	13 (3.6)
	≤1,000 birr	60 (69)	197 (71.4)	257 (70.8)
	1,001–2,500 birr	17 (19.5)	55 (19.9)	72 (19.8)
	2,501–5,000 birr	7 (8)	14 (5.1)	21 (5.8)

(AOR=0.232, 95% CI= 0.095–0.566) less likely to develop virologic failure as compared to those who disclosed their HIV status or use of ART medication to parents or close relatives.

Those patients who had opportunistic infection in their medical record were 4-times (AOR=4.11, 95% CI=1.827–9.246) more likely to develop virologic failure as compared to those who had no opportunistic infection. Among the respondents those patients who had a CD4 count <100 cells/mm^3 were 3.4-times (AOR=3.497, 95% CI=1.233–9.923) and those who had CD4 count of 100–350 cells/mm^3 were 5.4-times (AOR=5.442, 95% CI=2.191–13.513) more likely to develop virologic failure as compared to those who had a CD4 count ≥350 cells/mm^3.

In addition, those patients who had low BMI<16kg/m^2 were 7.2-times (AOR=7.223, 95% CI=2.218–23.520) more likely to develop virologic failure as compared to those with normal BMI (≥18.5kg/m^2). Finally, patients whose age group was 15–29years were 2.8-times (AOR=2.898, 95% CI=1.171–7.170) more likely to

develop virologic failure as compared to those ≥40 years age.

Discussion

The objective of this study was to identify determinants of virologic failure among adults' ≥15 years old on second line anti-retroviral therapy in six public hospitals of Wollo, Amhara regional state, northeast Ethiopia by 2020. The study identified that poor adherence to ART medication, those who did not disclose their HIV status, those with a history of opportunistic infection, a CD4 count less than 350 cells/mm^3 when switched to second line ART treatment, low BMI (<16 kg/m^2), and a young age group 15–29 years were associated with second line ART virologic failure.

The study identified poor adherence to ART medication was more likely to develop virologic failure as compared with good adherence. This is line with a study conducted in south Africa and Northwestern Tanzania which shows poor adherence was a strong predictor of second-line ART failure.[12,19] In Rwanda and Kenya,

Table 2 Clinical and Related Characteristic of Patients on Second Line Anti-Retroviral Therapy After 6 Months of Switched in Six Public Hospitals of Wollo, Amhara Regional State, Northeast Ethiopia in 2020

Variable		Virologic Failure		Total (363) No. (%)
		Cases (N=87) No. (%)	Controls (N=276) No. (%)	
Functional status	Working	81 (93.1)	274 (99.3)	355 (97.8)
	Ambulatory	6 (6.9)	2 (0.7)	8 (2.2)
ADR in medical history	Yes	3 (3.4)	6 (2.2)	9 (2.5)
	No	84 (96.6)	270 (97.8)	354 (97.5)
Opportunistic infection	Yes	42 (48.3)	33 (12)	75 (20.7)
	No	45 (51.7)	243 (88)	288 (79.3)
CD4 at switching 2nd line ART	≥350 cells/μul	34 (39.1)	223 (80.8)	257 (70.8)
	100–350 cells/μl	27 (31)	31 (11.2)	58 (16)
	<100 cells/μl	26 (29.8)	22 (7.9)	48 (13.2)
WHO stage	Stage I	46 (52.9)	240 (87)	286 (78.8)
	Stage II	14 (16.1)	24 (8.7)	38 (10.5)
	Stage III	22 (25.3)	8 (2.9)	30 (8.3)
	Stage IV	5 (5.7)	4 (1.4)	9 (2.5)
BMI in kg/m2	≥18.5 kg/m^2	46 (52.9)	236 (85.5)	282 (77.7)
	16–18.49 k/m^2	17 (19.5)	28 (10.1)	45 (12.4)
	<16 kg/m^2	24 (27.6)	12 (4.3)	36 (9.9)
Duration in first line ART in month	>36 months	65 (74.7)	244 (88.4)	309 (85.1)
	≤36 months	22 (25.3)	32 (11.6)	54 (14.9)
Duration on second line ART in months	≥2 years	24 (27.6)	111 (40.2)	135 (37.2)
	<2 years	63 (72.4)	165 (59.8)	228 (62.8)
2nd line regimen change	Yes	5 (5.7)	15 (5.4)	20 (5.5)
	No	82 (94.3)	261 (94.6)	343 (94.5)
INH used	Yes	71 (81.6)	244 (88.4)	315 (86.8)
	No	16 (18.4)	32 (11.6)	48 (13.2)
History of TB treatment	Yes	19 (21.8)	23 (8.3)	42 (11.6)
	No	68 (78.2)	253 (91.7)	321 (88.4)
Lost follow-up in medical record	Yes	4 (4.6)	7 (2.5)	11 (3)
	No	83 (95.4)	269 (97.5)	352 (97)
CPT used	Yes	72 (82.8)	220 (79.7)	292 (80.4)
	No	15 (17.2)	56 (20.3)	71 (19.6)
Anemia in medical records	Yes	14 (16.1)	12 (4.3)	26 (7.2)
	No	73 (83.9)	264 (95.7)	337 (92.8)

patients who were on second line ART with good adherence to ART were also significantly associated with viral suppression.[20,21] It is evident that individuals missing more than three doses from BID dose or more than one dose from daily dose of ART per month are associated with an increased risk of virological failure, leading to reduced immunity. This may result in them being exposed for opportunistic and other infections.

The study identified that those patients who did not disclose their HIV status were more likely to develop virologic failure as compared to those who disclosed to parents or close relatives, and those who disclosed their HIV status to friends or colleagues were less likely to develop virologic failure as compared to those who disclosed to parents or close relatives. In contrast to this study finding, a study conducted in South Africa shows those

Table 3 Determinant Factors of Virology Failure Among Patients on Second Line Anti-Retroviral Therapy After 6 Months of Switched in Six Public Hospitals of Wollo, Amhara Regional State, Northeast Ethiopia in 2020

Independent Variable	Virologic Failure		COR (95% CI)	AOR (95% CI)
	Yes	No		
Age				
≥40 years	23	113	1	1
15–29 years	40	53	3.708 (2.019–6.810)*	2.898 (1.171–7.170)*
30–39 years	24	110	1.072 (0.571–2.011)	0.508 (0.204–1.262)
Adherence				
Good (≥95%)	41	240	1	1
Poor (<95%)	46	36	7.480 (4.326–12.934)*	6.060 (2.837–12.944)***
Disclosure status				
Current parent/close relatives	43	107	1	1
Friends or colleague	12	153	0.195 (0.098–0.388)	0.232 (0.095–0.566)**
Not disclosed	32	16	4.977 (2.480–9.989)*	4.178 (1.431–12.198)**
Condom use				
Yes	17	107	1	1
No	70	169	2.607 (1.456–4.669)*	1.469 (0.565–3.821)
Default treatment				
Yes	19	15	4.862 (2.348–10.065)*	1.249 (0.321–4.860)
No	68	261	1	1
Opportunistic infection				
Yes	42	33	6.873 (3.942–11.983)*	4.110 (1.827–9.246)**
No	45	243	1	1
CD4 count				
>350 cells/mm^3	34	223	1	1
100–350 cells/mm^3	27	31	5.713 (3.044–10.722)*	5.442 (2.191–13.513)***
<100 cells/mm^3	26	22	7.751 (3.956–15.189)*	3.497 (1.233,9.923)*
BMI in kg/m2				
≥18.5 kg/m^2	46	236	1	1
16–18.49 kg/m^2	17	28	3.115 (1.577–6.151)*	2.001 (0.771–5.194)
<16 kg/m^2	24	12	10.261 (4.791–21.975)*	7.223 (2.218–23.520)**
Duration on second line ART in months				
≥2 years	24	111	1	1
<2 years	63	165	1.766 (1.041–2.995)*	1.873 (0.805–4.355)

Notes: *Pvalue<0.05, **P-value<0.01, ***P-value<0.001.

who disclosed only to friends or work colleagues were 3.4-times more likely to experience virologic failure compared to those who disclosed to a partner or close relative.[20] Therefore, not disclosing their HIV status may be due to HIV-related stigma or discrimination, which could affect patients' abilities to access social support (sexual partnerships and supportive care) as well as economic well-being (employability and food security).

The other findings were patients who had opportunistic infection in their medical record were 4-times more likely to develop virologic failure as compared to those patients who had opportunistic infection. The results were consistent with a study conducted in South India where the odds of developing treatment failure among patients who had opportunistic infection both prior to and after initiation of ART were strongly associated with virologic failure. Also those patients experience diarrhea found to be significantly associated with treatment failure.[22] A study done in south Africa shows a patient who had no history of TB had lower risk of developing virologic failure.[23]

Opportunistic infections are the predominant causes of morbidity and mortality among HIV-infected patients. This may result in more rapid progression of HIV disease. On the other hand, rapid progression of HIV increases the susceptibility to be infected by different opportunistic infections, increased viral replication, reduced immunity, and finally clinically deterioration of the patient.

The study also identified that those patients who had a CD4 count <350 cells/mm^3 were more likely to develop virologic failure as compared to those patients who had a CD4 count ≥350cells/mm^3. This is in line with the studies conducted in Henan province of China; Cambodia, Rwanda, and Northwestern Tanzania, which show virologic failure was more common in patients CD4 cell counts less than 350cells/mm^3 at switch to second line ART were associated with virologic treatment as compared to ≥350cells/mm$^{3.12,20,24,25}$ This may be because a patient's immune status becomes compromised, and the rate of viral replication increases compared to their immune-competent counterparts. Furthermore, clients with compromised immunity are more vulnerable to different opportunistic infections that sustain the vicious cycle of immunity and viral replication increased.

In addition, the study identified that those patients who had low BMI<16 kg/m^2 were more likely to develop virologic failure as compared to those patients who had normal BMI (≥18.5 kg/m^2). This result is in line with a study conducted in South Africa indicating having a low BMI <16 kg/m^2 was associated with virologic failure as compared to normal BMI (16–18 kg/m^2) patients.[19] In addition, a study done in northwest Ethiopia with low BMI <16 kg/m^2 has been linked with HIV associated morbidity and mortality.[26] This is due to low BMI patients compromising their immunity result in exposed for opportunistic and other comorbid disease so their bodies immune system could not control the viral multiplication.

The study identified that patients of a younger age (15–29 years) were more likely to develop virologic failure as compared to those patients who were ≥40 years of age. Similar findings were reported from Rwanda, Malawi, and Zimbabwe, where the odds of develop virologic failure on second line ART adult patients in the age category of 15–29years were associated with virologic failure.[27–29] In northern Tanzania the odds of virologic failure among younger age less than 30 years were more likely associated with second line ART virologic failure.[15] In general, younger age is usually associated with virologic failure due to a number of unique behavioral and psychosocial factors like anxiety, stigma, and lack of disclosure, low social economic status, and poor adherence to ART medication. This finding highlights the value of focusing on the special needs of the younger age group HIV patients on second line ART to achieve the third 90 target.

Limitations of the Study
Recall bias for some variables may have occured.

Conclusion
The study identified that determinants of virologic failure on second line ART who had poor adherence to ART medication, had not disclosed their HIV status, opportunistic infection, Low CD4 counts less than 350cell/mm^3 at switchto second line ART, low BMI (<16 kg/m^2), and young age group (15–29 years old) patients were significantly associated with second line ART virologic failure.

Recommendations
For Patients
Do not miss their medication for any reasons, they get social supports and other benefits by disclosing their HIV status and get early treatment for any opportunistic infection without delay.

For Healthcare Providers
The healthcare providers should aim for early identification of patients during follow-up visit who had poor adherence, opportunistic infection, low CD4 count, malnourished patients, younger age group, and non-disclosed patients who will need closer clinical follow-up.

For Hospital Managers
Avail the third line ART medication for those who failed for second line ART if possible or link to other facilities with referral and also avail therapeutic food for malnutrition patients.

For Researchers
Researchers do further investigation by using other study designs like cohort and qualitative to explore cultural taboos and more determinants.

Abbreviations
AIDS, acquired immune deficiency syndrome, ART, antiretroviral therapy; BMI, body mass index; CD4, cluster of differentiation four; CEO, chief finance office; CI,

confidence interval; EAC, enhancing adherence counseling; FMOH, Federal Ministry of Health; HIV, human immunodeficiency virus; MDT, multi-disciplinary team; NNRTI, non-nucleotide reverse transcriptase inhibitors; OI, opportunistic infection; OR, odds ratio; PLHIV, people living with HIV; RLS, resource limited setting; TB, tuberculosis; UNAIDS, United Nation Joint HIV/Aids Program; VF, virologic failure; VL, viral load; WHO, World Health Organization.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to lack of databases in our institution, but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participants

Ethical approval was obtained from the ethical review board of Wollo University, College of Medicine and Health Sciences, School of public health. Permission was obtained from each hospitals CEO, Medical Director, and other concerned bodies working at the ART clinic. Each study participant had the objective of the study clearly explained to them in order to obtain their verbal consent, including their full right to withdraw or refuse to participate. Privacy and confidentiality of information taken from each client and their medical chart were kept properly and names were not recorded. The informed verbal consent process was approved by the ethical review board of Wollo University, and all participants or the parents/legal guardians of patients under the age of 18 provided informed verbal consent to take part in this study. The study also complies with the full filed ethical principles of Helsinki Declaration in research.

Author Contributions

All authors contributed to the conceptualization, data analysis, drafting or revising of the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest for this work.

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