Magnitude of virologic failure and associated factors among adult patients on antiretroviral therapy at Debre Markos Referral Hospital, Northwest Ethiopia, 2018

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Abstract

Background : Viral load monitoring is used as an important marker for diagnosing early treatment failure in patients with HIV infection/AIDS. Ethiopia has started targeted viral load monitoring recently. However, factors leading to virological failure are not well understood. The aim of this study is to assess magnitude of virologic failure and associated factors among adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia.

Methods : Cross sectional study was conducted on 304 participants who had started first line HAAR. Data were collected from patients' chart starting from ART commencement and face to face interview using semi structured questionnaire. Viral load from separated plasma were analyzed according to protocols. The collected data were analyzed using SPSS version 20. Binary and multiple logistic regression models were fitted to identify factors associated with virological failure among adult patient on ART and to control confounding effect. The results were presented as odds ratio (OR) with 95% confidence intervals. Independent associations were considered with $p<0.05$.

Results: Magnitude of virological failure was 10.5%. Lower income, (AOR = 3.5, 95% CI = 1.2 - 10.5, P = 0.024), lack of social support (AOR = 2.9, 95% CI = 1.01 – 8.2, P = 0.024), Interruption of ART, (AOR = 3.5, 95% CI = 1.01 – 12.1, P = 0.046), drug adherence (AOR = 3.6, 95% CI = 1.1 – 11.3, P = 0.028), non-working functional status (AOR = 3.5, 95% CI = 1.2 – 9.7, P = 0.018), WHO stage III or IV (AOR = 2.9, 95% CI = 1.01 – 8.0, P = 0.040), CD4 count < 200 cells/ml (AOR = 3.0, 95% CI = 1.1 – 8.0, P = 0.031) and TB co-infection (AOR = 3.7, 95% CI = 1.2 – 11.3, P = 0.018) were significantly associated with virological failure.

Conclusions and recommendations : The prevalence of virologic failure was high. Lower income, lack of social support, interruption of ART, drug non-adherence, baseline non-working functional status, WHO stage, CD4 count < 200 cells/ml and TB co-infection Conducting faith healing, TB co infection, WHO stage III and IV, adherence, and income were determinants of virologic failure. Therefore early identification of associated factors and monitoring of virologic failure has to be strengthened to benefit patients to prevent from further complication. Keywords : HIV, virological failure, ART, Ethiopia

Background

Human immunodeficiency virus(HIV) is responsible for a worldwide pandemic, and it is the cause of acquired immune deficiency syndrome (AIDS)[1]. Antiretroviral (ARV) drugs refer to the medicines used to treat HIV whereas antiretroviral therapy (ART) refers to the use of a combination of three or more ARV drugs for treating HIV infection synonym with Higlhy active antiretroviral therapy (HAART) [2]. High viral load (virological failure) is defined by a persistently detectable viral load more than 1000 copies/ml after at least 6 months of ART initiation[3].

Clinical failure is defined as any WHO stage III or IV illness in the past 12 months. Immunological failure is defined as current CD4 cell count less than CD4 cell count at time of ART initiation or Persistent CD4 levels below 100 cells/mm3

Treatment failure is when an antiretroviral regimen is unable to control HIV infection. which can be clinical failure, immunologic failure, virologic failure, or any combination of the three[4].

In 2013 the WHO recommended routine annual viral load monitoring (VLM) for all patients on ART, as the most accurate measure of treatment response. An elevated VL (> 1000 copies/ml) in a patient who has been on ART for at least six months can indicate either therapeutic failure due to antiretroviral resistance, and / or poor adherence to treatment[3, 5].According to the viral load testing principle in Ethiopia, the three main reasons for viral load testing are: 1) routine testing; 2) suspected failure testing, and 3) repeat viral load testing after suspected treatment failure for patients who were virologically non-suppressed on first time testing and underwent enhanced adherence support for 3 months and then repeat three to 6 months before switching to second line drug[6].

Since the introduction of combination drug regimens to treat human immunodeficiency virus infection, known as highly active antiretroviral therapy (HAART), the rates of HIV-related morbidity and mortality have been markedly reduced[7].However, the presence of antiretroviral drug resistance mutations in the infecting viruses may decrease the effectiveness of antiretroviral treatment because the mutations reduce the chances of full viral suppression[8]. Antiretroviral therapy began in Ethiopia in 2003 and free ART was launched in 2005An estimated 769,500 Ethiopians are currently living with HIV, of whom all require ART and 392 086 are currently taking the treatment. To address this problem, the Government of Ethiopia issued the first ART guidelines in 2003, revised in 2005 and 2008 to facilitate a rapid scale up of the service. The need for universal access to care and treatment is the global and national agenda. In view of this adopting the new recommendation of test and start and differentiated care model (appointment spacing model)[9] .

There is indisputable success over the past twenty years in reducing HIV associated morbidity, mortality, transmission, stigma and improving the quality of life of people living with HIV[8]. But still investing and ensuring the sustainability of a viral load monitoring model must be a priority to detect early treatment failure[10]. Priority setting and health system reforms to manage HIV as a chronic disease must be upheld in government agenda[5]. The World Health Organization (WHO) cites poor access to services, complex drug regimens, pregnancy, mental health disorders, substance abuse, weak social support as major barriers to adherence [3].

The latest UNAIDS data, covering 160 countries, shows the last two years the number of people living with HIV on antiretroviral therapy has increased by about a third, reaching 17.0 million people, since the first global treatment target was set in 2003, annual AIDS-related deaths have decreased by 43%. In the world's most affected region Africa, the number of people on treatment has more than doubled since 2010. AIDS related deaths in the region have decreased by 36% since 2010[11]. In 2015 there were 2.1 million new HIV infections worldwide, adding up to a total of 36.7 million people living with HIV. Number of people living with HIV on antiretroviral therapy, global, 7.5 million in 2010, 9.1 million in2011, 10.9 million2012, 12.9 million2013, 15.0 million in 2014, and 17.0 million in2015 shows ladder fashion increasing globally putting global burden in the world particularly in eastern Africa according to UNAIDS 2016 estimates.

In 2014, the Joint United Nations Program on HIV/AIDS (UNAIDS) and partners launched the3 90–90–90 targets; the aim was to diagnose 90% of all HIV-positive persons, provide antiretroviral therapy for 90% of those diagnosed, and achieve viral suppression for 90% of those treated by 2020[8]. In 2014/2015, of the 36.9 million

of people with HIV globally, only 54% were diagnosed, 41% were on ART and 32% were virally suppressed i.e. virological failure 68 percent, demonstrating that we are still very far from achieving the three 90–90–90 targets[12]. The lowest achievement rates were in low income and middle income countries [5].This is estimated to result in 73% of people with HIV achieving viral suppression, a crucial step in ending the AIDS epidemic by 2030. However, 36.9 million people are living with HIV today and about 2.1 million new infections were recorded in 2015. Early placement of patients on combined ART and achievement of viral load suppression reduces mortality and HIV transmission and improves quality of life[13].

Adequately highlighted the gap in HIV diagnosis and provision of ART, which may be unattainable under the ambitious, UNAIDS 90–90–90 targets given the current trends[12]. Achieving the United Nations Program on HIV/AIDS (UNAIDS) 90–90–90 targets will require a viral load-informed care to ensure optimal HIV clinical follow-up and resistance systematic analysis of national HIV treatment cascades from 69 countries shows none of the countries had met the 3,90targets[14]. They found that diagnosis 90% of all HIV-positive people diagnosed ranged from 87% (the Netherlands) to 11% (Yemen). Treatment coverage 81% of all HIV-positive people on ART) ranged from 71% (Switzerland) to 3% (Afghanistan). Viral suppression 73% of all HIV-positive people virally suppressed was between 68% (Switzerland) and 7% (China)[13] .In 2014/2015, of the 36.9 million of people with HIV globally, only 54% were diagnosed, 41% were on ART and 32% were virally suppressed, demonstrating that we are still very far from achieving the 90–90–90 targets. The lowest achievement rates were in low income and middle income countries [13]

Early detection of treatment failure, adherence counseling and appropriate switching to second-line therapy are key strengths of a viral load monitored model[15].

Identified gaps: Viral load monitoring has become the standard of care for monitoring the success of treatment and diagnosing early treatment failure of ART and has been explicitly recommended, when available, by the WHO since 2010.But in our settings in which there is no access to viral load testing, clinical monitoring alone or a combination of clinical and immunologic monitoring is used to assess response to ART and determine treatment failure which is late after many complication occur. The development of drug-resistant virus strains can be another threat if this virus starts to transmit in the population. Early detection of treatment failure is crucial to sustain the effectiveness of the first-line therapy by doing as recommended by WHO. But still there is no study is conducted in the study area by testing clients VL to identify between the two factors. Because these technologies are expensive and introduced to our country recently so determining their VL after 6 month of ART initiation, proper initiation will show virologic failure and these study will identify factors associated with virologic failure.

Methods

Study area, setting and period

The study was conducted at Debre Markos Referral Hospital which is located 300 km and 265 km away from the capital city of Ethiopia: Addis Ababa and the Amhara regional city; Bihar Dar respectively. The major Health services provided in the hospital are outpatient, Inpatient and Emergency service. And in outpatient department services such as antiretroviral treatment, voluntary counseling and testing, mental health service, dental health service, radiology health service, laboratory service, emergency service, pharmacy service, cervical cancer

screening, reproductive health training, There are five Inpatient wards (Gynecological &Obstetric, Surgical, Medical, Pediatric and Eye unit) with 189 Hospital beds. There are 9 senior physicians, 24 general practitioners, 222 BSC and clinical nurses and other different professionals. The laboratory staffs are 31(technicians, technologist and MSC in microbiology and parasitology) are highly qualified and the hospitals are well equipped with modern laboratory machine like viral load machine and FMOH select DMRH as one of the 20 viral load monitoring site which is expected to serve as referring site to determine viral load for all ART site in east Gojjam zone and partial west Gojjam .The study was conducted from February 8-May07/05/2018.

Study Design and population

Facility based cross sectional study design was conducted from February8-May07/2018. The source population was all adult PLHIV on Highly Active Antiretroviral Treatment registered and following their treatment in Debre Markos referral Hospital (DMRH) whilst the study population was adult PLHIV ≥ 15 years old who are taking HAART for ≥ 6 month in DMRH who have follow up during study period that can fulfill the inclusion criteria

Sample size determination and sampling technique

The sample size is determined p = prevalence from previous studies of virologic failure,10.7% in Feleg Hiwot referral hospital(30) and immunologic failure in DMRH is 21%,by taking virologic failure 10.7%(0.017) giving any particular out come to be with 5% marginal error and 95% confidence interval of certainty (alpha = 0.05). The sample size will be estimated based on single population proportion (p). The formula:

$n = (Z\alpha/2)^2 P(1-P)$

$(d)^2$

Where: n = Sample size z = critical value 1.96, p = prevalence of virologic failure rate 10% d = precision (marginal error) = 0.05 Thus the sample size is n = (1.96)2 × 0.1(1-0.1) 0.0025 = 152 ,15.4 + 152 With 10% non response rate the total sample size will be 167.

All adult client age 15 years and over, HIV infected, continuing on ART for more than 6 month, and returning to clinic for a regular follow-up visit during study period. Simple random sampling method was used with lottery method from appointment registration book. Interview for most of the data and document review for clinical characteristics of patient and blood sample was drawn to determine VL in ART clinic before medication refill by having consent from client (Table 1).

Table 1

Sample size determination for the study of magnitude of virological failure and associated factors among adults on antiretroviral therapy in Debre Markos referral hospital, northwest, Ethiopia, in 2018

S.no.	Major significant Predictor	CI	Power	Proportion of VF among exposed	Proportion of VF Non exposed	Control to case ratio	OR	None response rate	Sample size required
1	functional status	95%	80%	24.7%	5.1%	1:1	6.1%	10%	187
2	Faith healing	95%	80%	28.7%	5.5%	1:1	6.9	10%	108
3	Base line CD4 count	95%	80%	19.6%	7.4%	1:1	3.05	10%	304
4	Medication dosage	95%	80%	23.8%	7.2%	1:1	4.02	10%	189

Operational definition

High viral load: HIV RNA > 1000 copies/ml. Alcoholism: is defined as drinking more than five alcoholic beverages on at least one occasion within the past 30 days. Substance use: is defined as persons reporting smoking, chat chewing and shisha in the last 30 day. Lack of social support: is lack of social support during illness to take to health facility. Lack of disclosure: is defined as lack of telling to people due to fear of negative consequences. ART interruption:' is defined as a treatment interruption for at least 1 week during the previous 6 months. Adult: Those patients with age 15 or more. Missed dose: missing one or more doses in the previous month.

Data Collection Tools

An adapted semi structured questionnaire was prepared in English and translated into Amharic, which is taken from federal MOH adherence assessment tool and viral load extraction tool from other published research [22].

Interviews were conducted from client coming to follow up in a private setting at the ART clinic before medication refill. In the survey, an interviewer-administrated questionnaire was conducted to collect demographic data, substance use and psychosocial factors. socio economic and behavioral factors, drug related characteristics of clients but Clinical characteristics of HIV patient data were collected from patient chart adherences was assessed by patient self report based on pills count as good if take > 95%,poor if < 95% taken. After completing the questionnaire, patients underwent routine follow-up and blood work with the addition of a single viral load test 5 ml of whole blood was drawn and preserved in an EDTA tube, stored at appropriate temperatures for processing and tested for viral load by molecular machine(rochi).

Data Quality Assurance

The validity of the questionnaires was assured by proper designing and also pre-testing the questionnaire in 5% (15) of respondents other than those involved in the actual study in Debre markos health center. One days

training was given to data collectors and supervisors at Debre Markos referal hospital. Questionnaire was checked for completeness on a daily basis by immediate supervisors. After checking all questionnaires for consistency and completeness the supervisors were submit the filled questionnaire to the principal investigator. Data collection and supervision was carried out by qualified personnel, four nurses who were not working in the study site were recruited and trained for data collection and they had at least diploma in status and the supervisors was BSC holder in health .

Data processing, analysis and interpretation

All responses to the survey questionnaires or collected data was retranslated against the original English version and entered into Epi Data version 3.1 and analyzed by SPSS version 20. Data cleaning were made manually by removing missing/conflicting ideas and responses to questions about relevant information. Recoding and re-categorizing was made for relevant variables. Frequencies and summary statistics were used to describe the study population in relation to socio-demographic and other relevant variables. The strength of association between dependent and independent variables was assessed using adjusted odds ratio with 95% confidence interval. Bivariate and multivariate logistic regressions was performed to assess statistical association between dependent and independent variable.. Then, variables, which showed statistical association with p-value of less than 0.25 on bivariate analysis, were candidates for the multivariate logistic regression model. In the multiple logistic regression models significant association was declared at p-value < 0.05. Finally data was interpreted with the existed data by referring to literature reviews.

Result

1.1
Socio-demographic characteristics

A total of 304 study participants were included in the study which give a response rate of 100.0%. At baseline, the mean age of the study subjects was 37.3 years ± SD, (SD = 10.6). The age was ranged from 16 to 72 years. One hundred seventy three 179 (58.9%) were females. Regarding educational status 103 (33.9%) of the respondents completed college and above while 70 (23.0%) were not attended formal education. Majority, 243 (79.9%), of the respondents reside in rural residential area. Larger proportion of the respondents 100(32.9%) earn a monthly income of 1,500–3,199 ETB followed by 29.6% and 20.5% earning monthly income of ≥ 3200 ETB and < 1000 ETB respectively. These and the rest socio-economic and demographic characteristics of the respondents have been presented in Table 2.

Table 2
Socio-demographic characteristics of adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018

Variable	No	%
Age (year)		
15–29	67	22.0
30–35	77	25.3
36–41	79	26.0
≥ 42	81	26.6
Sex		
Male	125	41.1
Female	179	58.9
Marital status		
Single	48	15.8
Married	154	50.7
Divorced	63	20.7
Widowed and separated	39	12.8
Educational status		
No formal education	70	23.0
Literate	234	77.0
Occupation		
House wife	83	27.3
Government employee	75	24.7
Daily laborer	46	15.1
Driver	32	10.5
Others	68	22.4
Residence		
Rural	61	20.1
Urban	243	79.9
Distance from home to clinic (in Km)		

Variable	No	%
< 10 Km	181	59.5
≥ 10 Km	123	40.5
Monthly income		
< 1500 ETB	114	37.5
≥ 1500 ETB	190	62.5

1.2

Psycho-social related characteristics

Majority, 217 (71.4%), of study participants live with their own family whereas 61 (20.1%) and 26(8.6%) live alone and with their parents. One hundred thirty seven (45.1%) of the study participant's regular sexual partners were HIV positive, 46(15.1%) of the participants were discordant in their HIV status with their regular sexual partners and the rest had sexual partners with unknown HIV status. Ninety six (31.6%) of the study participants disclosed their status to their family, while 21(6.9%) respondent's families were non-supportive or kept him/her from taking ARTs. Lack of food was a problem for 58 (19.1%) of the respondents which hinder them to take ART dose. Eighteen (5.9%) of participant did not belief on the efficacy of the drug they have taken. From the total study participants 79(26.0%) experienced discrimination, 83(27.3%) lack social support and 55(18.1%) lack emotional support (Table 3).

Table 3
Psycho-social and substance use related characteristics of adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018

Variable	No	%
Live with		
Alone	61	20.1
Family	217	71.4
Parents	26	8.6
HIV status of regular sex partner		
Negative	46	15.1
Positive	137	45.1
Unknown	121	39.8
Disclosing HIV status to family		
Yes	96	31.6
No	208	68.4
Belief in efficiency of medication		
Yes	286	94.1
No	18	5.9
Discrimination		
Yes	79	26.0
No	225	74.0
Lack of social support		
Yes	83	27.3
No	221	72.7
Emotional support		
Yes	249	81.9
No	55	18.1
Family been non-supportive or kept him/her from taking ART		
Yes	21	6.9
No	283	93.1
Lack of food ever been a problem for taking ART		

Variable	No	%
Yes	58	19.1
No	246	80.9
Felt sad or hopelessness for 2 weeks		
Yes	26	8.6
No	278	91.4
Presence of loss of interest for 2 months		
Yes	26	8.6
No	278	91.4
History of substance use		
Yes	28	9.2
No	276	90.8

Twenty eight (9.2%) of the respondents had taken at least one type of substance (drunk alcohol, chewed khat or smoked tobacco) in the last one month; 28(9.2%), 15 (4.9%) and 5(1.6%) were drank alcohol, chewed khat and smoked tobacco in the last month respectively. Moreover, All of the participants reported substance use drank alcohol, 13 (46.4%) of them drink alcohol and chewed khat and 3 (10.7%) of them used khat, tobacco and alcohol.

1.3
Drug related characteristics of adult patient on antiretroviral therapy

More than half (54.6%) of the study participants were on 1E (TDF + 3TC + EFV) at baseline. 1C (AZT + 3TC + NVP). 1D (AZT + 3TC + EFV) and 1B (d4T + 3TC + EFV) were the initial ART regimens for 53(17.4%) 44(14.5%) and 34(11.2%) of the respondents respectively. Most of the participants, 214(70.4%), taken ART for more than 36 months; the median duration of treatment was 42.0 months (interquartile range [IQR], 18.0– 60.2).These and the rest drug related characteristics of the respondents have been detailed in Table 5.

Table 5
Medication related behavioral characteristics of adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018

Variable	No	%
Time on ART (in months)		
< 36 Months	90	29.6
36–72 Months	74	24.3
> 72 Months	140	46.1
Interrupted care follow up/medication refill since started ART		
Yes	56	18.4
No	248	81.6
Discontinued ART to take other traditional herbal medicine, holy water		
Yes	64	21.1
No	240	78.9
Missed ART doses in the past since started		
Yes	77	25.3
No	227	74.7
Forgetting to take ART doses at scheduled time		
Yes	73	24.0
No	231	76.0
Drug adherence		
Good	139	45.7
Poor	165	54.3

1.4
Medication related behavioral characteristics

Fifty six (18.4%) of the respondents had discontinued their interrupted care follow up/medication refill since started ART. About 197(64.8%) of the respondents missed their ART dose indeed in the past since started and about 24% experienced forgetting to take ART doses at scheduled time. Furthermore, 64(21.1%) of the study participants discontinued ART drugs to take other traditional herbal medicine and holy water About 45.4% of the respondents had good adherence (taken > 95% of drugs) to their treatment; while 95(23.4%) respondents had poor adherence (Table 4).

Table 4
Drug related characteristics of adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018

Variable	No	%
First line drug regimen		
1A (d4T + 3TC + NVP)	3	1.0
1B (d4T + 3TC + EFV)	34	11.2
1C (AZT + 3TC + NVP)	53	17.4
1D (AZT + 3TC + EFV)	44	14.5
1E (TDF + 3TC + EFV)	166	54.6
1F (TDF + 3TC + NVP)	4	1.3
Time on ART (in months)		
< 36 Months	90	29.6
36–72 Months	74	24.3
> 72 Months	140	46.1
ART doses taken per day		
Once	197	64.8
Twice	107	35.2
Presence of reported side effects		
Yes	77	25.3
No	227	74.7
Regimen change		
Yes	94	30.9
No	210	69.1
Regimen stopped		
Yes	20	6.6
No	284	93.4

1.5
Clinical characteristics of adult patient on antiretroviral therapy

Among the participants, 196 (64.5) were classified as working and the rest were ambulatory and bed reddened in accordance their magnitude at baseline which summed to give the proportion of non-working participants (35.5%) (Fig. 4).

Nearly two third, 196 (64.5%), of the participants started treatment at stage 1 and 2 of WHO disease classification; the rest 51 (16.8%) and 56 (18.4%) were suffered WHO stages 3 and 4 conditions respectively at the time of ART initiation (Fig. 5).

The median baseline CD4 cell count was 344.5 cells/ml (IQR = 582 − 213); the proportions of participants with baseline CD4 count of < 200 cells/ml, 200–500 cells/ml > 500 cells/ml were 23.7%, 42.4% and 33.9%, respectively. Moreover, 69 (22.7%) of the study participants had TB co-infection at the initiation of ART, while 45(14.8%) of the participants acquired TB after enrollment in ART. In addition 165(54.5%) of the respondents had opportunistic infection at the time of their ART initiation; 79(52.1%) of these had more than one opportunistic infection (Table 6).

Table 6
Baseline clinical characteristics of adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018

Variable	No	%
CD4 count cells/ml		
< 200	72	23.7
200–500	129	42.4
> 500	103	33.9
TB co-infection at initiation of ART		
Yes	69	22.7
No	235	77.3
TB development after ART initiation		
Yes	45	14.8
No	259	85.2
Opportunistic infection other than TB at initiation of ART		
Yes	165	54.3
No	139	45.7
No of opportunistic infection (n = 165)		
One OI	86	52.1
More than one OIs	79	47.9

Candidiasis, herpes zoster, recurrent pneumonia and diarrhea (> 1 month) were the four most frequent opportunistic infections developed by 54(32.7%), 49(29.7%), 48(29.1%) and 36(21.8%) of the respondents who had opportunistic infection respectively (Fig. 6)

The median viral load was 57.5 (IQR: 127.8–43.0). Majority of the study participants, 272(89.5%), had viral load of < 1000 RNA copies/ml and the rest 32 had viral load of ≥ 1000 RNA copies/ml indicating the magnitude of virological failure to be 10.5% (Fig. 7).

1.6
Determinant factors of virologic failure among of adult patient on ART

The bivariate logistic regression modeling result revealed that sex, educational status and average monthly income of the respondents were socio-demographic factors that had statistically significant (p-value less than 0.05) association with antiretroviral virological failure. The bivariate logistic regression modeling result also showed that, lack of social support, discrimination, feeling sad or hopelessness, loss of interest in most things like hobbies, work, or activates that usually give pleasure, family been non-supportive taking ARTs and substance use were psycho-social related factors significantly associated with virological failure. The result showed that none of the drug related factors had statistically significant relationship with virological failure. From medication related behavioral factors of the respondent's discontinuation /interruption of care follow up/medication, presence of missed ART doses in the past 30 day and discontinuation /interruption of ART to take other traditional herbal medicine, holy water and drug adherence were significantly associated with the dependent variable. Significant associations were also found between virological failure and baseline clinical characteristics of the respondents, namely: baseline functional status, baseline WHO clinical stage, baseline CD4 count and baseline TB co-infection (Anex-4 No 2).

As summarized in the following table (Table 7), multivariate logistic regression model was fitted to assess the independent effect of each of the factor found to be associated in the bivariate analysis. Average monthly income, lack of social support, discontinuation /interruption of ART to take other traditional herbal medicine, holy water etc…, drug adherence, baseline functional status, baseline WHO clinical stage, baseline CD4 count and baseline TB co-infection were remained to be independent determinant factors for virologic failure among adult patient on ART.

Table 7

Factors associated with virologic failure among of adult patient on antiretroviral therapy at Debre Markos Referral Hospital, North West Ethiopia, 2018

Variables	Virologic failure				COR (95% CI)	AOR (95% CI)
	Yes		No			
	No	%	No	%		
Monthly income (ETB)						
< 1500 ETB	12	18.5	53	81.5	3.8 (1.5–6.7)*	3.5 (1.2–10.5)*
≥ 1500 and above ETB	5	5.6	85	94.4	1	1
Lack of social support						
Yes	16	19.3	67	80.7	3.1 (1.5–6.5)*	2.9 (1.01–8.2)*
No	16	7.2	205	92.8	1	1
Discontinued ARVs to take other traditional herbal medicine, holy water						
Yes	18	28.1	46	71.9	6.3 (2.9–13.6)**	3.5 (1.01–12.1)*
No	14	5.8	226	94.2	1	1
Drug adherence						
Good	9	6.5	130	93.5	1	1
Poor	23	13.9	142	86.1	2.3 (1.01–5.2)*	3.6 (1.1–11.3)*
Baseline functional status						
Working	16	8.2	180	91.8	1	1
Non-working	16	14.8	92	85.2	2.0 (1.01–4.1)*	3.5 (1.2–9.7)*
WHO stage at baseline						
Stage1/2	12	6.1	184	93.9	1	1

* Association is significant at the 0.05 level. ** Association is significant at less than 0.001 level

Variables	Virologic failure				COR (95% CI)	AOR (95% CI)
	Yes		No			
	No	%	No	%		
Stage 3/4	20	18.5	88	81.5	3.5 (1.6–7.5)*	2.9 (1.01–7.9)*
CD4 count						
< 200	17	23.6	55	76.4	4.5 (2.1–9.5)**	3.0 (1.1-8.0)*
≥ 200	15	6.5	217	93.5	1	1
TB co-infection at initiation of ART						
Yes	16	23.2	53	76.8	4.1 (1.9–8.9)**	3.7 (1.2–11.3)*
No	16	6.8	219	93.2	1	1
* Association is significant at the 0.05 level. ** Association is significant at less than 0.001 level						

The multivariate logistic modeling result showed that monthly income was a strong determinant factor for virologic failure; those adult patients on ART who earned a monthly income of less than 1500 ETB were 3.5 times more likely to experience virologic failure as compared with those adult patients that earned a monthly income of 1500 ETB and above (AOR = 3.5, 95% CI = 1.2–10.5, P = 0.024). Lack of social support was another important determinant of virologic failure. Patients lacked social support were more likely to experience virologic failure (AOR = 2.9, 95% CI = 1.01–8.2, P = 0.024) than their counterparts.

Discontinuation /interruption of ART to take other traditional herbal medicine, holy water etc… and drug adherence were found to be the other statistically significant determinant factors of virologic failure. Compared to those patients who did not interrupted their treatment /ART/, patients who had interrupted ART to take other traditional herbal medicine, holy water etc had 3.5 times higher probability of having virological failure (AOR = 3.5, 95% CI = 1.01–12.1, P = 0.046). Similarly patients who had not good drug adherence were 3.6 times more likely to experience virological failure than their counterparts (AOR = 3.6, 95% CI = 1.1–11.3, P = 0.028).

Baseline clinical characteristics of the patients; functioning status, WHO stage, CD4 count and TB co-infection were also strong predictors of virological failure. When compared to working patients at the initiation of ART, the probability of virological failure was 3.5 times higher for patients who were not working due to health problem at the time of ART initiation of (AOR = 3.5, 95% CI = 1.2–9.7, P = 0.018). Similarly, those patients who started ART at WHO stage 3 or 4 had a 2.9 times higher probability of experiencing virological failure when compared to those who patients started at WHO stage 1 or 2 (AOR = 2.9, 95% CI = 1.01–8.0, P = 0.040). Regarding the baseline CD4 cell count, those patients with baseline CD4 count < 200 cells/ml were 3.0 times more likely to have virological failure compared to those patients with CD4 count ≥ 200 cells/ml (AOR = 3.0,

95% CI = 1.1–8.0, P = 0.031). Compared with baseline HIV mono-infected patients, HIV/TB co-infected patients at the initiation of ART had remarkably higher odds of experiencing virologic failure (AOR = 3.7, 95% CI = 1.2–11.3, P = 0.018) (Table 7).

Discussion

The finding of this study showed that the magnitude of virological failure (viral load ≥ 1000 copies/ml) was 10.5%. This finding was comparable with studies conducted in Uganda 11% [26], and it was also in line with studies done in Ethiopia; Tigray (11.5%) [35], Gondar (11.8%) [32] and Bahir Dar Feleg Hiwot (10.7%) [30]. However, the result of the current study, higher virological failure was reported studies done in Kenya 23.7% [22] and Cameron (23.2%) [23], 20.6% [37] and Swaziland 16% [28]. This difference may be due to differences in definition of virological failure, where plasma viral load 400 copies/ml was used as cut-off point for virological failure [22, 23, 37]. Differences in the inclusion criteria used might also be another possible explanation, i.e., the study participants included in those studies were clinically or immunologically failed and had lower median age (9.5 years old) [37, 38]. On the other hand, the finding of the current study was higher than studies in Bale (9.3%) [29], Gondar (4.1%) [24], Addis Ababa (1.3%) [41] and Jimma (5.3%) [36]. It was also lower than a meta-analysis done in Ethiopia that reported overall virological failure of 5.6 [42]. The possible explanation might be due to difference in interventions for optimization of patient's adherence, better treatment outcome and type of regimen given. For instance, nutritional support was given for the study participants [36] which were different from the current study setting. Furthermore, the differences might also be due to the study areas where the residents of these areas can also be with different socio-economic status.

In the current study virological failure was varied by monthly income of the respondents, patients who had had low monthly income were more likely to experience virological failure. In agreement with this finding there is good reason to expect that socio-economic variables should be associated with antiretroviral adherence and living conditions including availability of food which in turn can impact HIV disease activity (including viral replication) [38, 39]. For instance, a study done in Jimma, Ethiopia [36] reported that patients with average family income of middle and highest were more likely to have an overall adherence and ART outcome than the lowest average family income. Likewise a study from India [39] reported that having the economic ability to fulfil their basic needs and to receive their medication had a positive significant association with both ART drug adherence and treatment outcomes [39].

The finding of the current study showed that social support was another determinant factor for virological failure; Patients lacking psychosocial support from family and others exhibited poor virological suppression. This implies that consistent psycho-social support have a positive impact on ART outcomes. In line with this studies done in Uganda [26], Swaziland [38] reported positive social support was associated with relatively good treatment adherence and in turn better viral load reduction. Moreover, WHO's ART guideline recommend behavioral intervention (social support, avoidance of discrimination, depression) to prevent treatment interruption and to control HIV activities/replication and bring better treatment success [3]. Social support, such as someone to help with the tasks of starting to rebuild a life, assistance with cooking and assistance to grow crops, all encouraged ART adherence, prevention of opportunistic infections and reduction of viral replication and finally better treatment outcome [33, 34, 39]. Similarly, it has been reported in other study [40] as social

support was a constant predictor of could virological suppression because it help to avoid risky daily behaviors and activities of the patient.

Interruption medication, specifically interruption of treatment to take other traditional herbal medicine, holy water etc…, was a strong determinant factor of virological failure. In agreement with previous studies conducted in Ethiopia [32, 33, 34], this study identified that those patients who had interrupted their ART medication and use traditional herbal medicine or faith heal (like Holy water) were at a higher risk to developing virological failure than their counterparts. This fining was supported and evidenced by results of the above mentioned studies conducted in Ethiopia. A study done in Gondar [32] showed that individuals who missed 3 doses of ART per month were associated with an increased risk of drug resistance and reduced immunity, this in turn resulted in the loss of the opportunity to suppress viral replication and leads to virological failure.

Poor ART adherence found to have a great impact on the occurrence of HIV treatment failure [3]. It is widely agreed that once treatment is initiated, it should not be interrupted [3, 9, 38, 44]. Despite this fact, in the current study the magnitude of poor adherence was about 23.3% and this poor adherence to ART was found to be an important determinant of virological failure. Patients with poor medication adherence were 3.5 times as likely to develop virological failure as patients with good adherence. This is because low level of antiretroviral in the body owing to the non-adherence is not sufficient to suppress viral replication, hence leads to detection of HIV RNA level in the blood [3, 44]. Even though, there was differences in adherence measurement, this finding was comparable with findings of studies conducted in Uganda [26], Kenya [22], Swaziland [38], Tigray [35], Gondar [32] and Jimma [36] where poor medication adherence was the main risk factor for virological failure. For example the study done in Gondar reported that patients with poor medication adherence were 16 times more likely to develop virological failure compared with patients with good adherence [32]. In order to explain the effect of adherence on ART viral suppression studies suggested that around 70% of patients on first-line ART who had a first high viral load will re-suppress following an adherence intervention [44], indicating non-adherence as the reason for the high viral load in the majority of cases.

In agreement with previous studies [32, 35–42], the current study found baseline non-working functional status, low CD4 cell count, advanced WHO clinical stage, and presence of opportunistic infections leads to ART virological failure. Despite this fact, these risk factors are highly interconnected, CD4 cell count is the backbone of immunity construction that helps the human body to protect from the disease and can prevent HIV replication [44]. As patients' immune status becomes compromised, the rate of viral replication increase and the chance of acquiring opportunistic infections is high which leads to advanced stage of the disease. Consequently, the patient gives more emphasis to the current problem than the chronic HIV, stop taking drugs and interrupt follow-up (poor adherence) which cause HIV treatment failure/virological failure.

Baseline working status of the patents was one of the determinant factor of virologic failure; this study found that the patients who were not able to work (initial non-working functional status, i.e. ambulatory/bedridden) due to health problem had 3.5 times more risk of developing virological failure than patients who were able to work (initial working functional status). This finding was concordant with study done in Ethiopia [35, 41, 43]. This might be due to the fact that those worker patients may have better income that in turn creates opportunity to get better care and support. This finding could also be explained as patients who were unable to work might be in their advanced WHO stage of the disease aggravated from greater immunosuppression (low CD4 count)

[5, 13, 44] or they might be depressed, feel hopelessness which might in turn lead to poor drug adherence then virological or in general treatment failure [37–40]. .

Patients with baseline low CD4 count were more likely to develop virological failure as those with higher CD4 count (> 200 cells/mm3). The finding was consistent with those of studies conducted in Uganda [16], Kenya [28], Vietnam [28] and India [28]. It had been evidenced that CD4 count has an inverse relationship with viral replication and load. That is, as patients' immune status becomes compromised (low CD4 count), the rate of viral replication increases compared to their immune-competent counterparts [3, 40, 44]. Furthermore, clients with compromised immunity are more vulnerable to different opportunistic infections that sustain the vicious cycle of immunity and viral replication [44]. On the other hand, low CD4 count might reflect viral replication due to treatment interruption (poor adherence) or resistance [7, 18].

In this study TB co-infection at start of ART was founded to be a strong determinant factor of virologic failure. This finding was in line with study conducted in Haiti [19], Cameroon [23] and Uganda [26]. One of the possible explanation for this result might be the fact that the intimate linkage between HIV and Tb might compress the immunity of the patient (including decrease in count of CD4 cells) and enables the progression of HIV disease to advanced stage rapidly and disallowing patients from regular treatment intake and hence lead to virological failure [31, 34].

Even though statistically significant association between virological failure and age, educational status, substance use, duration of ART (time on ART) and presence of other opportunistic infections was reported by a lot of previous studies [19, 23, 29, 38], the result of the current study did not suggest an association between these factors and ART virological failure. The differences in study designs, where some of the previous studies were case-control and cohort study designs; study population (patients in more than one health facility, different sample size, different aged /some include children); and study areas might be possible explanation for the difference between the results of the current and previous studies.

Conclusions

The magnitude of virological failure among adult HIV patients on ART was high, it was higher than most the findings of studies in the country and even in the region.

Having lower monthly income, lack of social support, interruption of ART to take traditional herbal medicine/Holy water, baseline non-working functional status, baseline advanced (III and IV) WHO stage, baseline CD4 count < 200 cells/ml and baseline TB co-infection were predictors of ART virologic failure among adult HIV patients on ART.

Abbreviations

AIDS Acquired Immuno Deficiency Syndrome

ART Ante Retroviral Therapy

DMRH Debre Markos Referral Hospital

HAART Highly Active Antiretroviral Therapy

HIV Human Immunodeficiency Virus

MOH Ministry of Health

PLWHIV People Living With HIV

PMTCT Prevention of Mother-to-Child Transmission of HIV

VL Viral Load

VLM Viral Load Monitoring

VF Virologic Failure

WHO World Health Organization

Declarations

Ethics approval and consent to participate

Ethical clearance was obtained from the ethical review committee of Debremarkos University, College of Health Sciences but the committee's reference number and human participant consent not applicable.

Consent for publication

The information requested does not applicable

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Debre Markos University contributed all financial need for the research.

Ethical consideration and consent

Ethical approval and clearance was obtained from Debre Markos University health Science College. Formal letter was received from hospital to review patients' medical charts for data collection. Prior to the interview Verbal consent was obtained from the study participants and parents of age 15-17years old. No identifiers were collected from the clients to ensure their confidentiality.

Author's contributions

The authors' responsibilities were as follows: ***A.A*** *participated in the design of the study, performed the data collection and the statistical analysis and served as the lead author of the manuscript.* ***M.T and G.A*** *supervised the study, and ensured quality of the data.* ***TB and SB*** *were involved in writing the manuscript. All authors also highly participated in preparing and revising this final manuscript and approved the final manuscript.*

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Figures

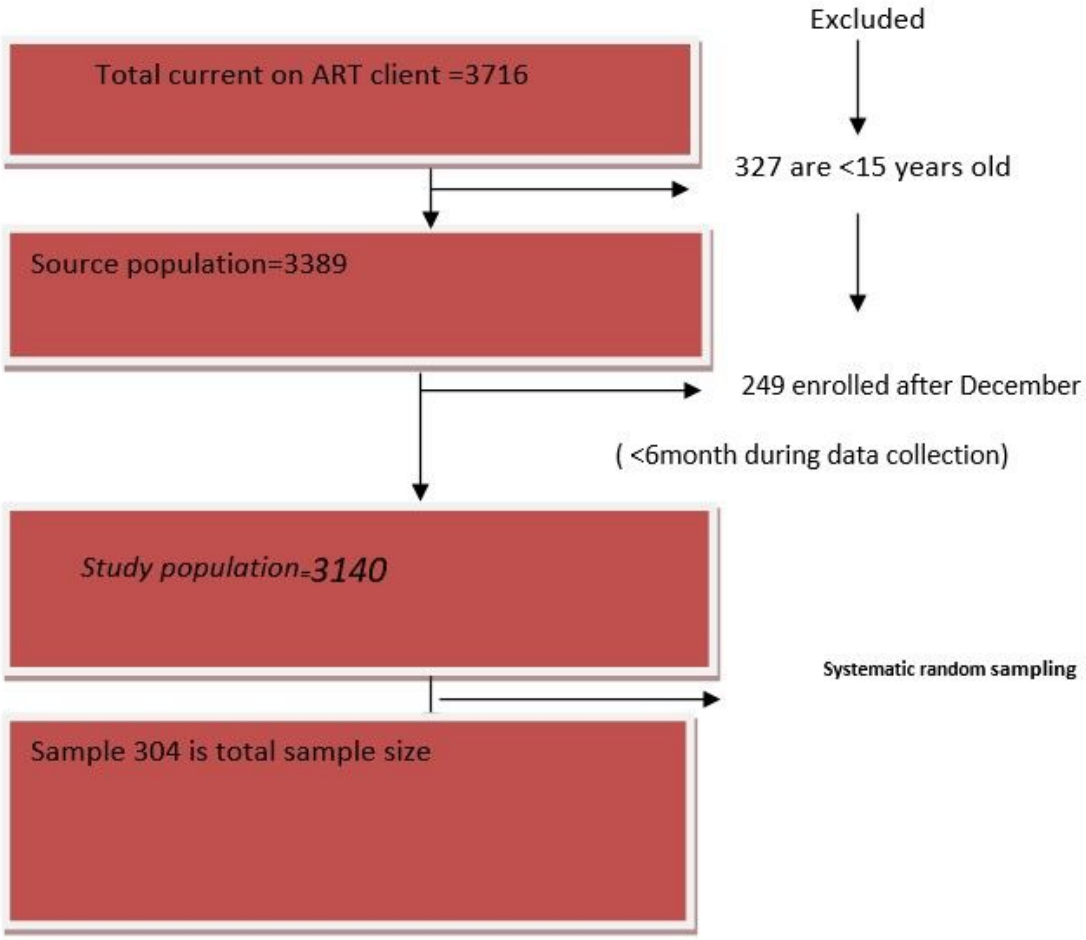


Figure 1

Schematic diagram that shows sampling procedure for the study of magnitude of virological failure and associated factors among adults on antiretroviral therapy in Debre Markos referral hospital, northwest, Ethiopia, in 2018.

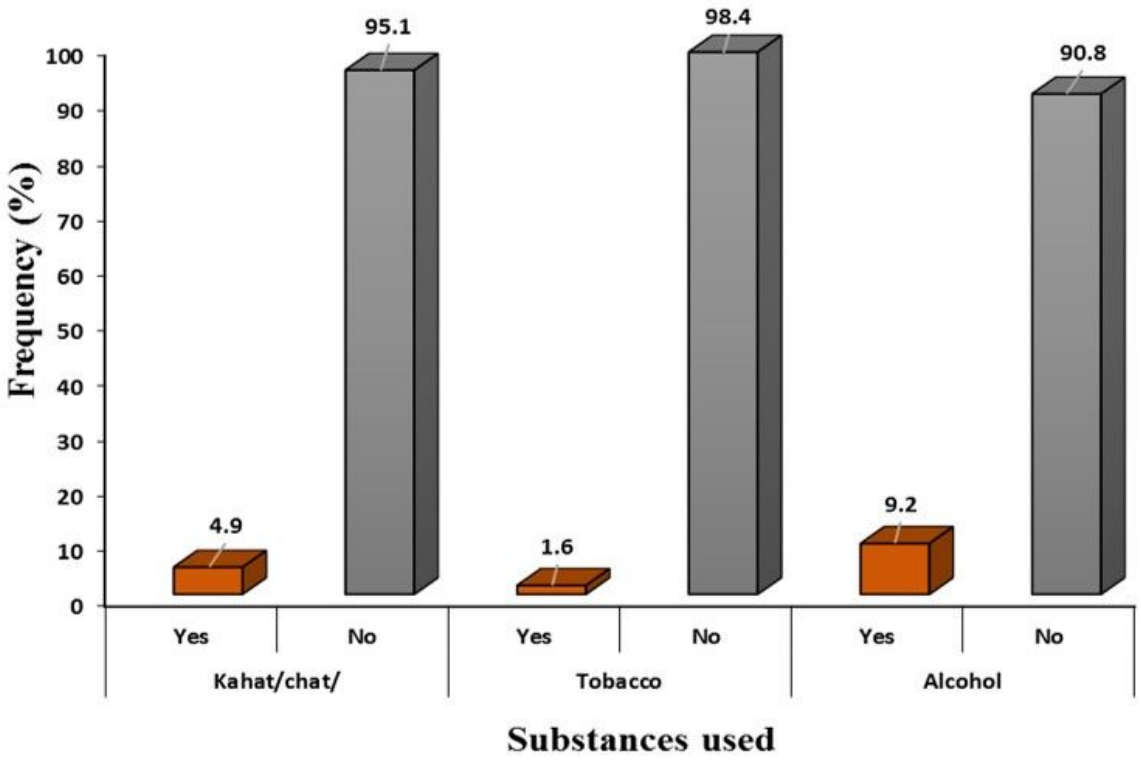


Figure 2

Distribution of substances used among adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018

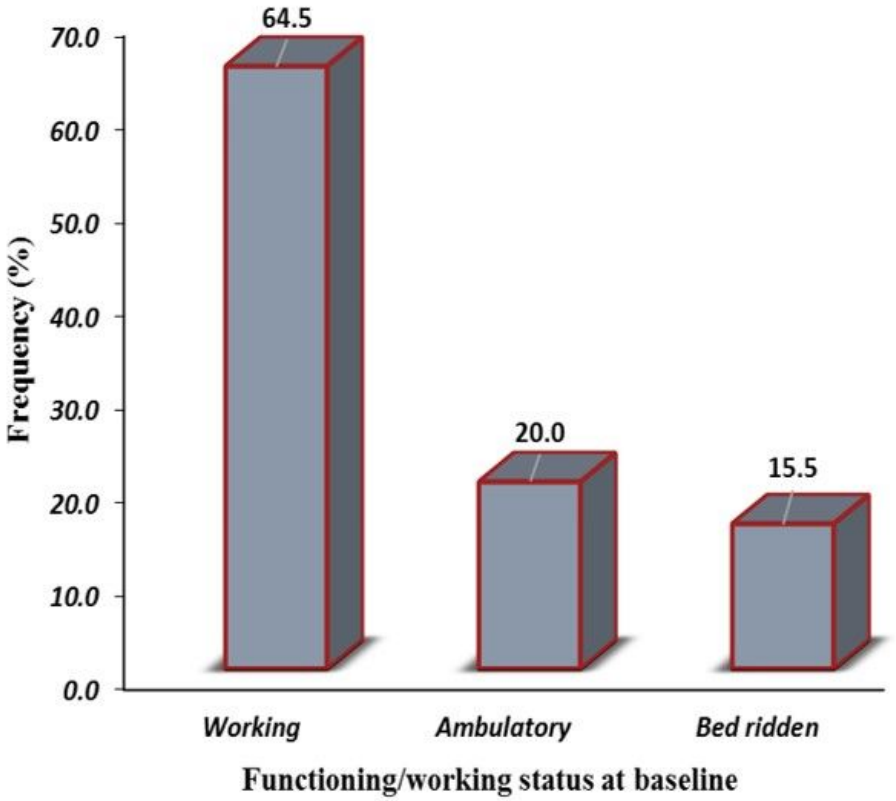


Figure 3

Baseline functioning/working status of adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018

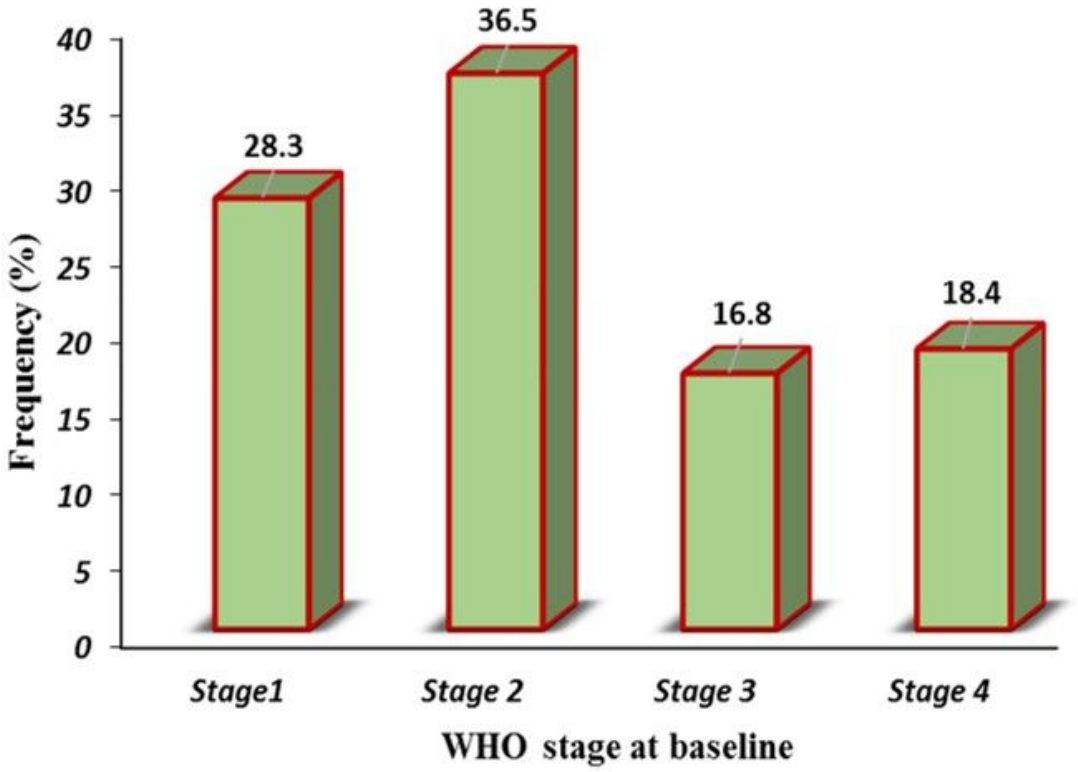
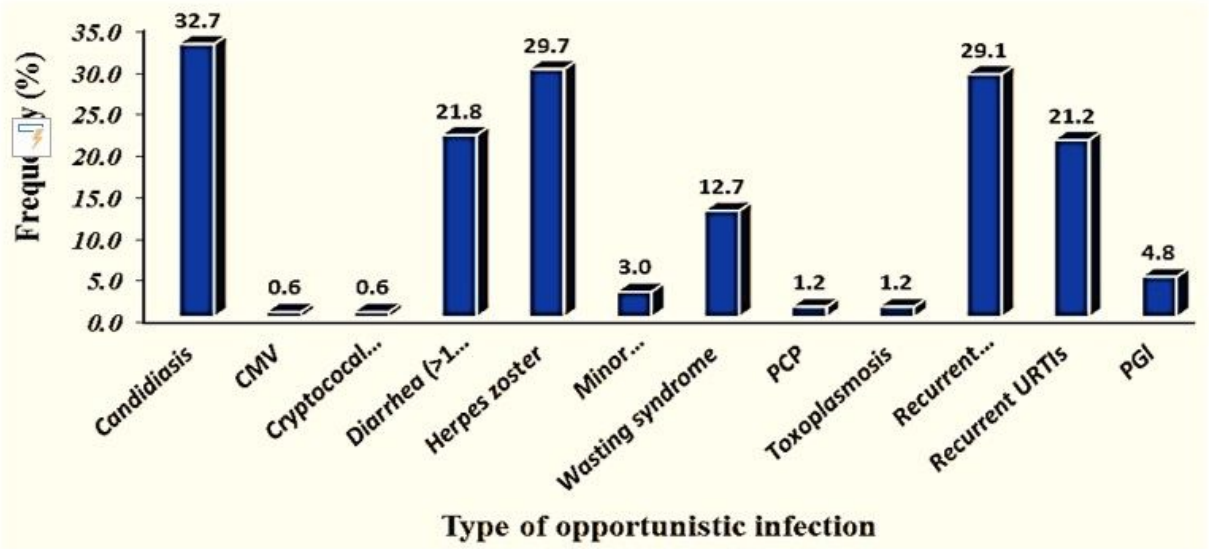


Figure 4

Baseline WHO stage of adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018



Foot note: *Because of the possibility of infection by multiple (more than one) opportunistic infections, the percentage exceeded 100%.*

Figure 5

Distribution of opportunistic infections among adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018

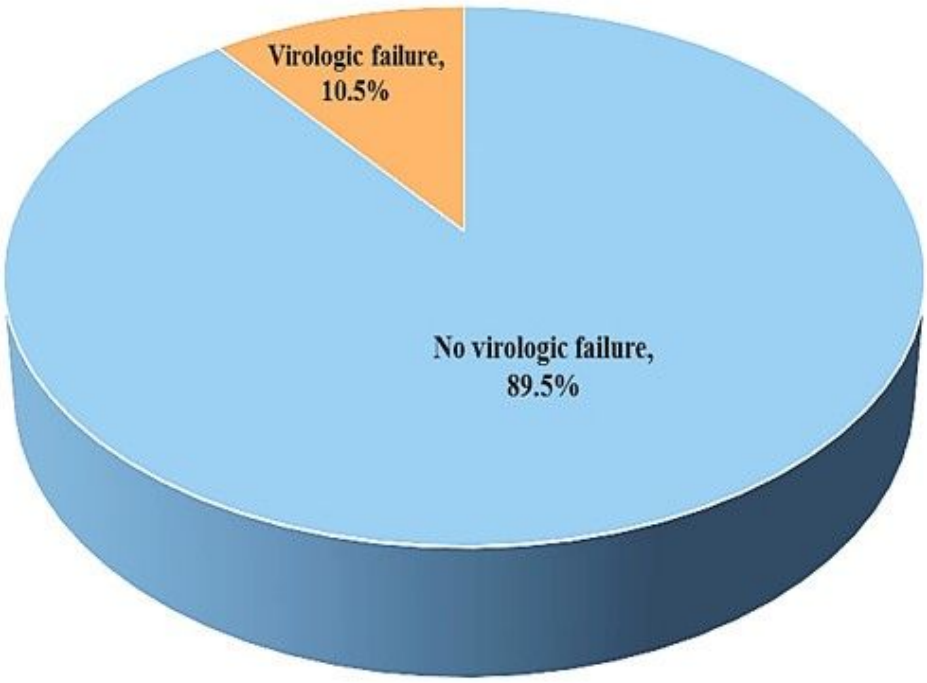


Figure 6

Magnitude of virologic failure among adult patient on ART at Debre Markos Referral Hospital, North West Ethiopia, 2018

Supplementary Files

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- Laboratoryrequisitionandreportform.docx