

Increased viral suppression among people on first line antiretroviral treatment in Ethiopia: Meeting the third 90's

Minwuyelet Maru (✉ minwuyelet@yahoo.com)

Amhara public health institute

Daniel Dagne

Addisu Tesfie

Asefa Missaye

Gizachew Yismaw

Andargachew Mulu

Research

Keywords: Amhara region, ART failure, Dessie, Ethiopia, HIV, viral supression

Posted Date: January 9th, 2020

DOI: <https://doi.org/10.21203/rs.2.20431/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Antiretroviral treatment (ART) is aimed for complete suppression of viral replication but it fails for a variety of reasons. The aim of this study was to determine the prevalence and associated factors of treatment failure among people on first line ART in Amhara region, North east Ethiopia.

Methods A cross sectional study was conducted from March, 2018 to July, 2018. Questionnaire survey using a pre-structured questionnaire was taken focusing on demographic data and possible risk factors of antiretroviral treatment failure. Clinical history including baseline characteristics was extracted by reviewing medical records using data abstraction sheet and data was analyzed using STATA version 14.

Results A total of 640 clients of all age from 16 health facilities were enrolled in the study. The overall antiretroviral treatment failure was 16.45% from which clinical, immunologic and virologic failure were 0.47%, 13.59% and 3.13% respectively. The viral suppression was 91.09%, but more than half, 29 (50.88%) study participants with high first viral load (>1000 copies/ml) were defaulted and not tested for the 2 nd viral load testing. Binary and multivariable logistic regression analysis showed significance association of treatment failure with age at treatment initiation (OR, 1.029), duration on ART (OR, 0.87) and adherence (AOR, 4.22). High proportion of treatment failure was also found in females (62.75%) and in those below primary education (76.47%).

Conclusions In conclusion increased viral suppression is observed but the rate of default during 3 month of enhanced adherence counseling is high. The overall magnitude of treatment failure in Amhara region is 16.45%. Fair/poor adherence, older age at treatment initiation and shorter duration on ART are significantly independent factors of treatment failure. Therefore improving client follow up to adherence to treatment should be strengthened.

Introduction

Antiretroviral treatment is recommended for everyone with HIV to help people with HIV live longer, healthier life and to reduce the risk of HIV transmission. Ethiopia accepted the WHO recommendation to provide lifelong ART to all people living with HIV, including children, adolescents and adults, pregnant and breastfeeding women, regardless of clinical status or CD4 cell count. [1]. Antiretroviral treatment is aimed for complete suppression of viral replication. Once effective ART is started, it usually takes 3 to 6 months for a person's viral load to reach an undetectable level. Suppression of viral load to undetectable levels in people living with HIV (PLHIV) using antiretroviral therapy makes less prone to HIV-related illness. However according to a recent global report only 73% of PLHIV were virally suppressed worldwide [2] indicating the global target of 90% viral suppression is yet not being achieved and sub-Saharan Africa has a similar report [3].

Treatment failure (clinical failure, immunologic failure or virologic failure, or any combination of the three) is important indicator showing disease progression. Studies show that the magnitude of ART treatment failure in Ethiopia ranges from 4.1% [4] to 19.8% [5]. Antiretroviral treatment fails for a variety

of reasons most importantly non-adherence to antiretroviral treatment [6] which is higher in low and middle income countries [7]. Other factors that can contribute to treatment failure include antagonism between some drug combinations, degree of CD4 status before treatment initiation [8], presence of co-infection, type of treatment regimen, body mass index (BMI) [9], old age [10] and other socio economic factors. Therefore, describing the situation in the region may help to minimize unnecessary regimen switch, to improve current practices, thereby improving health outcomes and preventing emergence and transmission of drug resistant strains. Accordingly this study is aimed to assess the magnitude and associated factors related to treatment failure among people on first line ART in Amhara region, North east Ethiopia.

Methods

Study Area and Period

The study was conducted in 16 ART sites health facilities (11 health centers and 5 hospitals) from 6 zonal administrations of Amhara national regional State from March 1, 2018 to July 30, 2018. ART clients visiting the health facilities for receiving their first viral load result during the study period were recruited for the study.

Study Design

A cross-sectional study was conducted among all first line antiretroviral initiated clients who have one viral load measurement after at least 6 months of taking ART. Questionnaire survey using a pre-structured questionnaire was taken focusing on demographic data and possible risk factors of antiretroviral treatment failure. Clinical history including baseline characteristics and adherence status was extracted by reviewing medical records using data abstraction checklist. Those who have viral load result greater than 1000 copies/ml were appointed at 3 month for another viral load test to confirm virologic failure. Immunologic failure for adults and adolescents is assessed by comparing baseline and current CD4 cell count where <100 cells/ μ L, below baseline, or <50% of peak after taking ART for 6 months is considered as immunologic failure. For children younger than 5 years, persistent CD4 levels below 200 cells/mm or <10 % peak after 6 month of treatment or for children older than 5 years persistent CD4 levels below 100 cells/mm was considered as immunologic failure.

Sample Size Determination

Sample size was determined using the formula for single population proportion by taking 19.8% prevalence of treatment failure [5]. After considering 2.5 design effect and 7% non-response a total of 657 study subjects were proposed and 640 study subjects were consecutively recruited when they attend the clinics for their follow up to receive their first viral load result.

The data was analyzed by STATA version 14 (Statacorp, USA). Frequencies, proportion and summary statistics were used to describe the study population in relation to relevant variables. Odds ratio and P-

value were used to assess the presence and degree of association between treatment failure and possible risk factors and P value <0.05 was considered as presence of significant association.

Operational Definitions

- **Viral suppression:** a viral load of <1000copies/mL after 6 months of ART.
- **Viral re-suppression:**- a viral load of >1000 copies/mL after 6 months of ART and < 1000 copies/mL after 3 months of enhanced adherence and counseling.
- **Virologic failure:** a repeated viral load of >1000 copies/mL after 3 months of the first viral load.
- **Clinical failure:** new or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 conditions) after 6 months of ART for adults and for Children new or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of ART.
- **Treatment failure:**- Presence of immunologic, virologic or clinical failure or any combination of these.

Data Quality Control

Data collection was made by trained health professionals and standardized formats were used for data extraction from medical charts at each health facility. Data collection process was supervised by the investigators. Collected data was checked for completeness prior to data entry and data exploration on entered data was made to see unexpected values, outliers, and identify variables which need transformation.

Results

Socio-demographic and Clinical Characteristics

A total of 640 clients of all age were enrolled in the study from which 405 (63.28%) were females. The median age during anti-retroviral treatment (ART) initiation was 32 years (± 10.8) ranging from 1 to 70 year and the current median age was 38 years (± 11.3). Majority, 370 (57.81%) were between 20 to 35 years of age and 52 (8.1%) were below 19 years old which are not categorized under adults based on WHO age classification [1]. Five hundred one (78.29%) of the study participants were below primary education and 337 (52.66%) were married. The mean length of stay before treatment initiation was 8 month (± 19 month) ranging from < 1 to 120 months but from 124 participants who were tested after launching of test and treat strategy 84 (67.74%) study participants were initiated within 1 month of testing. The mean duration of stay on ART was 7.48 years (± 3.75) with minimum 1 and maximum 15 years. The mean baseline CD4 count was 282 cells/mm³

(± 238) and the current mean CD4 count was 515 cells/mm³ (± 246) which showed significance increment from the baseline ($p<0.001$) and the CD4 change in females was significantly higher than in males ($p<0.01$).

As indicated in table 1, two hundred thirty one participants (36.09%) were categorized in WHO stage III at the start of antiretroviral treatment and only 223 (34.84%) were in WHO stage I. The current WHO stage indicated improvement of clinical status in which 590 (92.19%) were in WHO stage I. TDF-3TC-EFV combination was the most prescribed regimen during ART initiation which were 338 (52.81%) and it is still the most common in the current regimen comprising 59.08% of all other regimens. One hundred eighteen (18.44%) had history of regimen shift and 98 (15.31%) had history of TB treatment. Regarding their adherence 512 (80.25%) was reported to have good adherence.

Table 1: Baseline clinical characteristics of clients taking ART in Amhara region, 2018

Variable		Freq.	Percent
WHO clinical stage baseline	Stage I	223	34.84
	Stage II	155	24.22
	Stage III	231	36.09
	Stage IV	31	4.84
CD4 Baseline	≤100	126	19.69
	101-200	148	23.13
	201-350	201	31.41
	351-500	87	13.59
	501-750	54	8.44
	≥751	24	3.75
Regimen at start	d4t based	93	14.53
	AZT based	185	28.90
	TDF based	362	56.56
Stay after diagnosis to ART initiation	≤15 days	287	49.65
	between 15 to 30 days	78	13.49
	between 1 to 3 month	57	9.86
	between 3 to 6 month	28	4.84
	≥6 month	128	22.15
Body mass index(Kg/m²)	≤18.5	202	33.84
	≥18.6	395	66.16
Adherence	Good	512	80.25
	Fair/poor	126	19.74

Treatment Failure and its Associated Factors

The overall antiretroviral treatment failure was 16.45% from which clinical, immunologic and virologic failure contribute 3(0.47%), 87 (13.59%) and 20 (3.13%) respectively.

However, eight clients (1.2%) had both clinical and virologic or immunologic and virologic failure.

Table 2: Treatment status of clients taking ART in Amhara region, 2018

Variable	Freq.	Percent
Treatment failure (all types)		
Yes	102	16.45
No	518	83.55
Clinical failure		
Yes	3	0.47
No	637	99.53
Immunologic failure		
Yes	87	13.59
No	553	86.41
Virologic failure		
Yes	20	3.13
No	591	92.34
Unknown status	29	4.53
Viral suppression		
Suppressed	583	91.09
Not suppressed	57	8.91
Viral re-suppression		
Yes	8	14.04
No	20	35.09
No 2 nd viral load	29	50.88

As indicated in table 2, the viral suppression rate was 91.09%, but among 57 participants who had unsuppressed viral load (>1000copies/ml at 6 month), more than half, 29 (50.88%) study participants were defaulted from follow up during the 3 months of

enhanced adherence counseling and didn't come in the appointed date to test for the 2nd viral load. High proportion of treatment failure was found among 20-35 age groups during ART initiation (55.88%), in WHO clinical stage I during initiation (40.20%), in females (62.75%), in those below primary education (76.47%), those who were less than 2 years of stay on ART (47.52%) and in those having fair/poor adherence (28.07%).

Table 3: Factors associated with first line treatment failure in Amhara region, 2018

Variable	Category	Treatment failure		Crude Odds ratio (95% CI)
		Yes, n (%)	No, n (%)	
Sex	Male	38 (16.89%)	187 (83.11%)	1.05 (0.67, 1.63)
	Female	64 (16.20%)	331 (83.80%)	I
Education	No formal education	40 (15.87%)	212 (84.13%)	0.56 (0.24, 1.29)
	Primary school	38 (16.31%)	195 (83.69%)	0.58 (0.25, 1.34)
	Secondary school	15 (15.15%)	84 (84.85%)	0.53 (0.21, 1.36)
	College and above	9 (25.00%)	27 (75.00%)	I
Marital status	Married	47 (14.29%)	282 (85.71%)	0.68 (0.41, 1.14)
	Never married	22 (21.57%)	80 (78.43%)	1.13 (0.61, 2.11)
	Widowed	4 (10.00%)	36 (90.00%)	0.45 (.15, 1.39)
	Divorced	29 (19.46%)	120 (80.54%)	I
Drug interruption	Yes	12 (21.43%)	44 (78.57%)	1.43 (0.72, 2.82)
	No	90 (15.99%)	473 (84.01%)	I
Comorbidity encountered	Yes	29 (18.01%)	132 (81.99%)	1.17 (0.72, 1.88)

	No	69 (15.79%)	368 (84.21%)	I
WHO stage at baseline	Stage II	22 (14.5)	130(85.5)	0.72 (0.41, 1.27)
	Stage III	34 (15.25)	189 (84.75)	0.77 (0 .46, 1.27)
	Stage IV	5 (17.86)	23 (82.14)	0.93 (0.33, 2.60)
	Stage I	41 (18.89)	176 (81.11)	I
Substance abuse	No	85 (16.13%)	442 (83.87%)	0.85 (0 .48, 1.52)
	Yes	17 (18.28%)	76 (81.72%)	I
Adherence	Fair/poor	31 (27.43%)	82 (72.57%)	2.32 (1.43, 3.76)
	Good	71 (14.00%)	436 (86.00%)	I

Binary logistic regression analysis was conducted to explore factors associated with treatment failure and clients who had history of drug interruption had 1.43 times higher risk of treatment failure than their counter parts and those who had no substance abuse history (no history of regular chat chewing, smoking and drinking) were 0.85 times less likely to fail from their antiretroviral treatment. It is found that fair or poor treatment adherence had higher risk of treatment failure (OR, 2.32, 95% CI: 1.43, 3.76) as compared to those who had good adherence. Multivariable logistic regression showed age at treatment initiation, duration on ART and treatment adherence was found to have significant association. Older age during ART initiation had higher risk of treatment failure (AOR, 1.029, 95% CI: 1.001, 1.059), longer duration on ART had protective effect to

treatment failure (AOR, 0.87, 95% CI: 0.82, 0.93) and fair or poor treatment adherence had higher risk of treatment failure (AOR, 4.22, 95% CI: 2.20, 8.10).

Discussion

This study was designed to assess the magnitude and associated factors of treatment failure from 16 health facilities in Amhara region. The study found viral suppression of 91.09 after 6 months of ART and 92.34 treatment successes after 3 month of enhanced counseling of clients who had unsuppressed viral load ($>100\text{copies/ml}$) at 6 month of treatment. However high rate of clients, 50.88%, defaulted from enhanced adherence and counseling was observed in this study which will have great programmatic effect to achieve the third 90's goal. The overall first line antiretroviral treatment failure was 16.45% from which 0.47%, 13.59% and 3.13% were clinical, immunologic and virologic failures respectively. This finding is slightly lower than a study from Addis Ababa which reported 21% treatment failure of which 1.8%, 15.3% and 4.4% clinical, immunologic and virologic failures respectively [11], 21% immunologic failure was also reported from Debremarkos, Amhara region [12] and another study from Addis Ababa reported 19.8% treatment failure. However the virologic failure in the present study is higher than the study from Addis Ababa that reported 1.3% [5] which could be due to presence of different proportions of adherence status. The finding of the present study is much higher than studies in Gondar, Amhara region, 4.1%, treatment failure [4] and in Bale zone hospitals of Oromia region, 9.8% treatment failure [13]. The possible justification for this could be these studies were retrospective studies in which early detection might be missed that underestimate the findings.

The present study found older age at treatment start, short duration on ART and fair/poor adherence were significantly associated and independent predictors of treatment failure. Higher risk of treatment failure in older age was revealed in the present study in line with findings from Addis Ababa [5] and contrary to studies in Nigeria, Kenya and Thailand that report younger age during ART initiation as risk of treatment failure [14, 15] which might be justified as variations in circulating and acquisition of resistance viral strains. Adherence is an important factor for treatment failure as it is used as indicator of whether the treatment failure is due to improper medication or due to viral factors such as resistance mutations. In our finding clients with fair/poor adherence were found to be 4.22 times higher risk of treatment failure compared to clients with good adherence similar to findings in different parts of Ethiopia, Gondar and Bale [4, 13, 16] as well as studies in Kenya and Nigeria [17, 18]. In the present study clients data recorded by standard checklist assessment and self-report were used to describe adherence which might underestimate the actual scenario and the real situation may be high. On the contrary association of treatment failure in clients with short duration on ART and older age before treatment initiation suggests occurrence of acquired resistant viral strains as these clients are healthy looking and sexual experience which is supported by the finding from Jimma, Ethiopia in which 81.8% of study subjects with virologic failure showed viral mutations [19].

Conclusions

In this study we conclude that the observed increased viral suppression showed Ethiopia is on track to meet the third 90 of WHO target. The rate of default during 3 month of enhanced adherence counseling is high and the overall magnitude of treatment failure in Amhara region is 16.45% which is significantly associated with fair/poor adherence. Therefore improving client follow up to adherence to treatment should be strengthened and ART program should focus on increasing adherence for clients who had high viral count at 6 month. Older age at treatment initiation and shorter duration on ART are also significantly associated independent factors of treatment failure that indicate urgent need of drug resistance survey in the study area as these suggest acquisition of resistant viral strain. High proportion of treatment failure was also found in females and in those below primary education suggesting ART program should focus on these groups.

Abbreviations

3TC
Lamivudine
ART
Anti-Retroviral Treatment
AZT
Zidovudine
D4t
Savudine
EFV
Efavirenz
HIV
Human Immunodeficiency Virus
PLHIV
People Living with HIV
TB
Tuberculosis
TDF
Tenofovir
WHO
World Health Organization

Declarations

Ethical approval

The study has got approval from Amhara Public Health Institute ethical review board. All study subjects during the study period was informed the purpose of the study and their consent was sought in written.

Consent for publication

The authors declare that there is no conflict of interests regarding the publication of this paper

Availability of data

The dataset used to support the findings of this study are available from the corresponding author upon request (minwuyelet@yahoo.com).

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by funds from the Amhara Public Health Institute core budget.

Author's contribution

Minwuyelet M.: designed the study, analyzed and interpreted the data, Daniel D.: analyzed the data, Addisu T.: initiated and drafted the manuscript, Asefa M.: revised the manuscript, Gizachew Yismaw: revised the manuscript, Andargachew M. revised the manuscript

Acknowledgement

The authors thank Amhara Public Health Institute for funding this work. Our special gratitude goes to staffs of health facilities that participate in the study and all study participants

References

1. WHO, *Consolidated Guidelines On The Use Of Antiretroviral Drugs For Treating And Preventing HIV Infection* 2016: Geneva.
2. UNAIDS. *HIV and AIDS estimates Country Factsheet Ethiopia 2016*. 2016; Available from: <http://www.unaids.org/en/regionscountries/countries/ethiopia>.
3. Taieb, A., *Choice of initial antiretroviral drugs and treatment outcomes among HIV-infected patients in sub-Saharan Africa: systematic review and meta-analysis of observational studies*. BioMed Central, 2017. **4**(173): p. 1-14.
4. Mohammed Biset, D.K., Assefa Belay, Samson Getu, Derso Teju, Desalegn Endale, Yemisirach Tsegaye, Zebiba Wale, *First-line antiretroviral treatment failure and associated factors in HIV patients at the University of Gondar Teaching Hospital, Gondar,North west Ethiopia*. HIV/AIDS - Research and Palliative Care, 2016. **8**: p. 141-146.
5. Teshome Yimer Y, Y.A., *Magnitude and Predictors of Anti-Retroviral Treatment (ART) Failure in Private Health Facilities in Addis Ababa, Ethiopia*. . PLoS ONE 2015. **10**(15): p. 1-17.

6. Ziad El-Khatib, et al., *Adherence to Drug-Refill Is a Useful Early Warning Indicator of Virologic and Immunologic Failure among HIV Patients on First-Line ART in South Africa*. PLoS ONE, 2011. **6**(3): p. e17518.
7. Jean B. Nachega, Edward J. Mills, and Mauro Schechter, *Antiretroviral therapy adherence and retention in care in middle-income and low-income countries: current status of knowledge and research priorities*. Current Opinion in HIV and AIDS, 2010. **5**: p. 70-77.
8. Charles F. Gilks, et al., *A Single CD4 Test with 250 Cells/Mm Threshold Predicts Viral Suppression in HIV-Infected Adults Failing First-Line Therapy by Clinical Criteria*. PLoS ONE. **8**(2): p. e57580.
9. Yohannes Demissie Babo, Getahun Asres Alemie, and Fasil Walelign Fentaye, *Predictors of first-line antiretroviral therapy failure amongst HIV-infected adult clients at Woldia Hospital, Northeast Ethiopia*. PLoS ONE, 2017. **12**(11).
10. Ronald J. Bosch, et al., *Pretreatment Factors Associated With 3-Year (144-Week) Virologic and Immunologic Responses to Potent Antiretroviral Therapy*. Acquir Immune Defic Syndr, 2007. **44**(3): p. 268-277.
11. Sisay C, B.A., Sisay A, Mekonen H, Terfa K, , *Incidence and Predictors of Anti-Retroviral Treatment (ART) Failure among Adults Receiving HIV Care at Zewditu Memorial Hospital, Addis Ababa, Ethiopia*. J AIDS Clin Res, 2017. **8**(749).
12. Melsew YA, T.M., Tessema GA, Ayele TA, *Rate of Immunological Failure and its Predictors among Patients on Highly Active Antiretroviral Therapy at Debremarkos Hospital, Northwest Ethiopia: A Retrospective Follow up Study*. J AIDS Clin Res 2013.
13. Haile D., T.A., Gashaw K., Demelash H., Nigatu D., *Predictors of Treatment Failure among Adult Antiretroviral Treatment (ART) Clients in Bale Zone Hospitals, South Eastern Ethiopia*. PLoS ONE 2016. **11**(10): p. 1-14.
14. Khienprasit, N.C., R. Sirisanthana, T. Supparatpinyo, K., *Incidence and risk factors of antiretroviral treatment failure in treatment-naive HIV-infected patients at Chiang Mai University Hospital, Thailand*. AIDS Res Ther, 2011. **8**(1): p. 42.
15. Hassan, A.S., et al., *HIV-1 virologic failure and acquired drug resistance among first-line antiretroviral experienced adults at a rural HIV clinic in coastal Kenya: a cross-sectional study*. AIDS Res Ther, 2014. **11**(1): p. 9.
16. Bayu, B.e.a., *Determinants of virological failure among patients on highly active antiretroviral therapy in University of Gondar Referral Hospital, Northwest Ethiopia: a case- control study*. HIV/AIDS- Research and Palliative Care, 2017. **9**: p. 153-159.
17. Charles M. Kwobah, A.W.M., Julius K. Koech, Gilbert N. Simiyu, Abraham M. Siika1,, *Factors Associated with First-Line Antiretroviral Therapy Failure amongst HIV-Infected African Patients: A Case-Control Study**. World Journal of AIDS, 2012. **2**: p. 271-278.
18. Chuka J Anude, E.E., Henry C Onyegbutulem, Man Charurat, Mary-Ann Etiebet, Samuel Ajayi, Patrick Dakum, Oluyemisi Akinwande, Chris Beyrer, Alash'le Abimiku and William Blattner, *Immuno-virologic*

outcomes and immuno-virologic discordance among adults alive and on anti-retroviral therapy at 12 months in Nigeria. BMC Infectious Diseases, 2013. **13**(113).

19. Abdissa, A., et al., *Drug resistance in HIV patients with virological failure or slow virological response to antiretroviral therapy in Ethiopia.* BMC Infectious Diseases, 2014. **14**(1): p. 181.