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Body mass index variation over time and associated factors among HIV positive adults on second line ART in Northwest Ethiopia: A retrospective follow up study

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Abstract

Objectives: This study aimed to assess the evolution of Body Mass Index of HIV positive adults on second line ART over time and factors affecting it in Northwest Ethiopia.

Design: Institution based retrospective follow up study was conducted using data extracted from 1016 patient cards from February 2008 to February 2016.

Setting: Eight referral hospitals from Amhara region, Ethiopia were included

Participants: HIV patients who started second line antiretroviral therapy

Outcome measures: Change in BMI since starting second line antiretroviral therapy

Results: Five hundred thirty eight (52.95%) of participants were males and median age of participants was 33 (P25=28, P75=39). The median follow up time was 18 months (P25=5.2, P75, 32.2 months). The average change of BMI has showed a linear increase over time. The amount of BMI increment or decrement according to each variable was shown as β coefficients. Treatment duration (β=0.013, 95% CI (0.004, 0.022)), Isoniazid prophylaxis (β=0.87, 95% CI (0.32, 1.42)), Cotrimoxazole prophylaxis (β=0.63, 95% CI (0.08, 1.19)), ambulatory functional status(β=-1.16, 95% CI (-1.95, -1.31)), bedridden functional status(β= -1.83, 95% CI (-2.47, -1.21)), WHO stage III(β=-0.42, 95% CI (-0.65, -0.20)) WHO stage IV (β= -0.62, 95% CI (-1.02, -0.22)), CD4 count (β=0.001, 95% CI (0.0008, 0.0015)); and time interaction of variables like tertiary educational status(β=0.02, 95% CI (0.01, 0.04)), ambulatory functional status(β=0.03, 95% CI (0.01, 0.05)) and WHO stages III (β=0.01, 95% CI (0.007, 0.02)) were found to be significant predictors.

Conclusion: BMI of patients has shown a linear increment over the treatment time. Factors affecting it have been identified but its effect on Cardio-vascular disease needs further study.

Strengths and limitations of this study

- Being a retrospective study, this study shares the limitations of secondary data collection as a result we were unable to find some predictors like viral load, alcohol consumption, smoking and nutritional history.
- The study is not based only on patient cards that started the second line antiretroviral therapy at the same point in time and also the length of follow up period for each participant was not equal across all participants
- The most important strength of this study was the use of longitudinal data analysis. This ensures a valid estimate by handling data that is measured in different time period and has missing values.
- Besides we had a total of 5380 number of BMI measurements taken from 1016 participants with a median BMI of 20.52 Kg/m^2 (P25= 18.2, P75=23). Baseline BMI was calculated for all 1016 patients. These will again strength the precision of the estimates.

Background

Human Immunodeficiency Virus (HIV) has continued to be a major global public health problem, having killed more than 35 million lives so far. In 2017, 940 000 people died from HIV-related causes globally(1). According to the Ethiopia demographic and health survey of 2016 the adult prevalence of HIV in Ethiopia was 0.9%(2). Death due to HIV/AIDS has enormously decreased due to the introduction of anti retroviral therapy (ART) and millions of people are currently accessing it (3).

Body weight of HIV patients has been an important diagnostic and evaluation measure. Low BMI is recognised as one of the first criteria for the clinical definition of Acquired Immune Deficiency Syndrome (AIDS). The current World Health Organization (WHO) clinical staging of the disease also includes moderate unexplained weight loss (<10% presumed or measured body weight, stage 2), unexplained severe weight loss (>10% of body weight or BMI $\leq$ 18.5 kg/m^2, clinical stage 3) and HIV wasting syndrome (Unexplained severe wasting, clinical stage 4) as criteria to define advanced HIV infection(4).

The BMI of HIV patients is an important predictor of ART treatment outcome (5-8), including the prediction of the CD4 cells change (9) and death (10-12). Negative change in BMI of patients was also found to be an independent predictor of dropout from HIV care (13).

The BMI of HIV patients is affected by gender(14) duration of treatment (10, 15, 16), Isoniazid Prophylaxis Therapy (IPT) and Cotrimoxazole prophylaxis(CPT) (17, 18) WHO stage (14) and CD4 count (15, 19).

Even though BMI evolution is a very important and easily calculable tool that can predict treatment outcome, dropout from treatment, CD4 recovery and death literatures about its

evolution across treatment time and factors affecting it are limited. Therefore this study tried to fill this information gap by determining the BMI evolution over treatment time and identifying the key factors affecting it. Information generated by this study will contribute to monitor the response of patients for antiretroviral therapy.

Method and materials

Study design and period

An institution based retrospective follow up study was conducted among adults, age 24 and above who are started on second line ART from February 2008 to February 2016

Study area and population

The study was conducted in Amhara regional state which is one of the nine administrative regions and two city councils of Ethiopia. The region constitutes majority of ART users in the country. The study population was adult HIV infected patients on second line ART in all the nine referral hospitals of the region. The first-line treatment consists of a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) with one non-nucleoside reverse transcriptase inhibitor (NNRTI). Should failure of first-line treatment occur, a second-line treatment is implemented, using two NRTIs not previously used in first-line treatment, as well as one additional protease inhibitor (PI).

Sample size and sampling procedure

All HIV patients who initiated second line therapy (n=1233) between February 2008 and 2016 were included. But only 1016 patients who had two or more measurements of weight were included in the study.

Data collection procedures

Data extraction check list was prepared and the data were collected from HIV patient registration cards. Data about the baseline weight and height of patients and other factors like socio-demographic, clinical, and treatment related factors were also collected from each HIV patient registration cards. Adherence to ART was assessed by pill counts at visits and is recorded as 'GOOD' (≥95% adherence) or FAIR (80%–95%), while POOR adherence is less than 80% (20).

Data structure, compilation and analysis strategy

The data was cleansed and entered in to EPI info version 7 and analyzed using STATA version 14.0. Body Mass Index (BMI) of HIV patients was computed by dividing the weight of patients in kilogram (kg) that was recorded during each follow up visit, to their baseline height in meter squared. Exploratory data analysis for the weight of patients including individual profile plot, mean profile plot, descriptive and summary statistics were done. To determine the factors associated with BMI of patients univariate analysis for each independent variable was assessed and those found to be significant (p-value<0.25) were selected for the multivariate analysis. The need for random intercept and random slope was checked by likelihood ratio test. Finally a model that can handle repeated measurements that have between individual variation and within individual variation, that is linear mixed effect model with random intercept and random slop was fitted.

Patient and Public Involvement

Since we have used secondary data/chart review, patients or the public were not involved during identifying the research question or design and conduct of the study.

Results

Patient characteristics

We had a total of 1016 adult patients who were taking second line ART. Among the total 538 (52.95%) were males. All participants were above or equal to the age of 24 with median age of 33 year (P25=28, P75=39). Large proportion of these patients 370 (37.1%) were unemployed and 371 (36.9%) have attended secondary school.

The median follow up time was 18 months (P25=5.2, P75, 32.2). There were a maximum of 12 and a minimum of 2 measurements of weight per patient. Almost all visits were not balanced in their time of measurements. The median time between each weight measurement was 6.7(P25=4.27, P75=10.03), 6.08(P25=4.14, P75=9), 6.13(P25=4.2, P75=8.9), 6.27(P25=4.53, P75=8.9), 5.9(P25=3.97, P75=7.79), 5.83(P25=3.7, P75=8.13), 5.45 (P25=3.37, P75=7.43), 4.86(P25=2.97, P75=6.2), 5.19(P25=3, P75=7.37), 5.97(P25=4.23, P75=7.04), 5.55(P25=2.83, P75=5.86) and 3(P25=0.9, P75=4.84) months from first to twelfth weight measurement respectively.

At the initiation of second line ART majority of participants, 393 (45.54%), were at WHO stage I and 324 (37.54%) were at WHO stage III. Large proportion of participants 871 (86%) had working functional status at base line, the rest 114 (11.25%) and 28 (2.75%) were ambulatory and bed ridden respectively. The median CD4 count was 253 (P25=147, P75=399). Isoniazid Prophylaxies Therapy and CPT were given for 247 (24.87%) and 256 (25.65%) of participants respectively (**Table 1**).

Exploratory data analysis

At baseline a total of 391(38.5%) had BMI of less than 18.5kg/m^2 whereas 549(54%), 64(6.3%) and 12(1.2%) had BMI 18.5-24.9 kg/m^2, 25-29.9 kg/m^2 and $\geq$30kg/m^2 respectively.

Individual Profile

The average BMI of patients at baseline was 19.03Kg/m^2 (SD=3.6 Kg/m^2). The minimum and maximum BMI was 8.33 Kg/m^2 and 33.59 Kg/m^2 respectively. Before proceeding to the formal statistical analysis we have described the data by exploring how individuals change in BMI over time. To make the individual profile plot more informative and understandable, we have prepared it for the first 100 individuals (**Figure 1**).

As we can see from this plot, the BMI status of patients has high variability within an individual over time and among individuals at baseline and also through time. Therefore to fit the data which has variability in the intercept and slope of trajectories very well, we have used a mixed model.

Exploring the mean profile

As stated above all measurements in the data have no similar time of measurements therefore we have used smoothing to determine BMI evolution over time (**Figure-2**).

As one can easily understand from the mean profile plot the BMI of these patients showed a linear increment over the treatment time.

Modeling the BMI

Correlation structure checking and model comparison

Comparing with AIC, the correlation structure with lowest AIC was chosen, in this case the unstructured correlation structure (**Table-2**).

The need for random slop and intercept was checked by likelihood ratio test of model without a random intercept, with only random intercept and a model with both random intercept and slop (**Table-3**).

So as we can see from the table-3 the inclusion of random intercept and random slop is reasonable so in the final model we have used both random intercept and random slop.

Factors affecting the BMI evolution over time

Based on the multi-variable output: time since the start of second line ART, IPT , CPT, Functional status, WHO stage of the disease; and time interaction of categorical variables like educational status, functional status and WHO stages were found to be significant predictors of the BMI evolution of HIV patients on second line ART.

Keeping all the other variables constant, for a one month increment in the treatment duration the BMI of patients' increases by 0.013 kg/m^2. But specifically individuals who have tertiary level of education, ambulatory functional status and who are at WHO stage III have additional 0.02 kg/m^2, 0.03 kg/m^2 and 0.01 kg/m^2 increment respectively in their BMI for a one month increment in the duration of treatment.

Taking IPT and CPT increases BMI by 0.87 kg/m^2 and 0.63 kg/m^2 respectively as compared to their counter parts. Nongovernmental organizations employment was associated with a 2.02 kg/m^2 increment when compared to government employment. Patients who are ambulatory and bedridden in their functional status have a 1.16 kg/m^2 and 1.83 kg/m^2 decrement in their BMI as compared to those who have working functional status. Patients who are at WHO stage III and WHO stage IV have decreased BMI by 0.42 kg/m^2 and 0.62 kg/m^2 when compared with those who are at WHO stage I. For a unit $cell/mm^3$ increase in the CD4 count of patients BMI was found to increase by a factor of 0.001 kg/m^2 (**Table-4**).

DISCUSSION

This study has found a linear increment in BMI of patients over treatment time. There were BMI differences between subjects at baseline and in their progress over time.

Factors found to have a significant effect on the evolution of BMI over treatment time at multivariable linear mixed effect model were second line treatment duration, IPT, CPT, employment status, functional status of the patient, WHO stage and CD4 count. Time interaction of educational status, functional status, and WHO stage.

For a one month increase in treatment duration the BMI of patients increases by 0.04, this finding is in line with studies in South Africa (21), India (10) and United states(22). The possible reasons for weight gain could be due to normal reversion of the weight loss associated with HIV or due to drug related metabolic changes which include hyperlipidemia, insulin resistance and diabetes(23).

Patients who took IPT and CPT have increased BMI when compared to their counter parts. This finding is supported by other studies like a study conducted in Abidjan (17) and multicenter controlled clinical trial in Africa (18). The main reason for this association could be the reduction of potentially disabling and wasting disease like tuberculosis and other opportunistic infections by these prophylactic drugs(24, 25). A highly increased appetite by the prophylaxis could also be possible explanation(26).

Being ambulatory and bedridden decreases BMI when compared to those who are working. Since these individuals are not working they may not access nutritious and balanced diet which affects their BMI. Another reason could be additional decreased immunity caused by physical inactivity which makes them more susceptible to minor infections leading to a higher calorie loss(27). These group of people are also at higher risk of diarrheal disease for they cannot take care of themselves which in turn causes weight loss(28).

When compared with patients who are at WHO stage I, those who are at WHO stage III and WHO stage IV have decreased BMI. This finding is in line with a multicenter study in resource

limited settings which shows individuals who had high clinical status (WHO stage III and WHO stage IV) had poorer weight gain when compared to weight change in patients at lower WHO stage(14). The possible reason can be unexplained chronic diarrhea and HIV enteropathy in these patients and the associated malabsorption (4) or it could be due to pyrexia of unknown origin in the late stage of the disease which results an increased calori loss and wasting(29).

The BMI of patients was also found to increase with the increment in their CD4 count. This positive association is supported by evidence from a study conducted in Boston (15) and Tanzania (19). This increment can be explained by association of increment of CD4 count with good clinical changes like viral suppression, improved immunity and appetite leading to increment in the BMI of patients (13).

Being a retrospective study, this study shares the limitations of secondary data collection as a result we were unable to find some predictors like viral load, alcohol and smoking marital status and nutritional history.

CONCLUSION

In this study we have found a linear increment in the BMI of HIV patients on second line ART. There was a significant variation of BMI of patients at baseline and through ART treatment time. Duration of treatment, IPT, CPT, functional status, WHO stage of the disease, CD4 count; and time interaction of categorical variables like educational status, functional status and WHO stages were found to be significant predictors. The positive change in the BMI of patients shows an encouraging trend for we know this has a positive impact on the CD4 recovery, decrease lost to follow up and death. Clinicians also must consider the identified risk factors when they provide service for these patients.

ABBREVIATIONS

AIC, Akaike's Information Criterion; AIDS, Acquired Immunodeficiency Virus; ART, Anti-Retroviral Therapy; BIC, Bayesian information criterion; BMI, Body Mass Index; CI, Confidence Interval; CPT, Co-trimoxazole preventive therapy; HIV, Human Immuno Deficiency Virus; IPT, Isoniazid Prophylaxis Therapy; Kg, Kilogram; NGO, Non Governmental Organizations; WHO, World Health Organization.

Declarations

Ethical consideration

Ethical clearance was obtained from Institutional Review Board of Institute of Public Health, University of Gondar. Names and unique ART numbers of patients was not collected to keep the privacy of patients during the data collection.

Availability of data and materials

The data upon which the result based could be accessed by a reasonable request made to the corresponding author.

Funding

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Consent for publication

Not applicable

Competing interest

Authors declare that they have no any conflict of interest

Authors' contribution

AGB, LDG, EGZ, TAA, ATT have actively participated during Conception and design, acquisition of data, analysis and interpretation of data. All authors have read and approved the final version of the manuscript.

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Authors' information

Adhanom Gebreegziabher, has BSc degree in Public health as a background and second degree in Epidemiology and Biostatistics; now teaching Epidemiology, Research methodology and communicable disease control courses in the University of Gondar, Ethiopia

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Figures Legend

Figure 1: Individual profile plot of BMI over time for the first 100 individuals at second line ART in Amhara region, 2008-2016

Figure 2: Time plot of BMI versus treatment time in months with lowess smoothed curve superimposed for HIV patients on second line ART in Amhara region 2008-2016

Tables

Table 1 Baseline socio-demographic and baseline characterstics of adults HIV patients on second line ART in Amhara region, 2008 to 2016

Variables	Number	Percentage
Age		
25-34	547	53.89
35-44	333	32.81
45-54	104	10.25
55-64	26	2.56
≥ 65	6	0.59
Sex		
Female	478	47.05
Male	538	52.95
Educational status		
Illiterates	315	31.34
Primary education	201	20.00
Secondary education	371	36.92
Tertiary education	118	11.74
Missing	11	0.01
Occupation		
Unemployed	370	36.42
Governmental	286	28.15
Non-Governmental	21	2.06
Private	66	6.50
Daily laborers	254	25.00
Missing	19	1.87
WHO stages		
Stage I	393	45.54
Stage II	66	7.65
Stage III	324	37.54
Stage IV	80	9.27
Functional status		
Working	871	86
Ambulatory	114	11.25
Bed ridden	28	2.75
CPT given		
No	742	74.35
Yes	256	25.65
INH given		
No	746	75.13
Yes	247	24.87

CPT= Cotrimoxazole Prophylaxis Therapy

INH= Isoniazide

Table 2: Correlation structure checking and model comparison

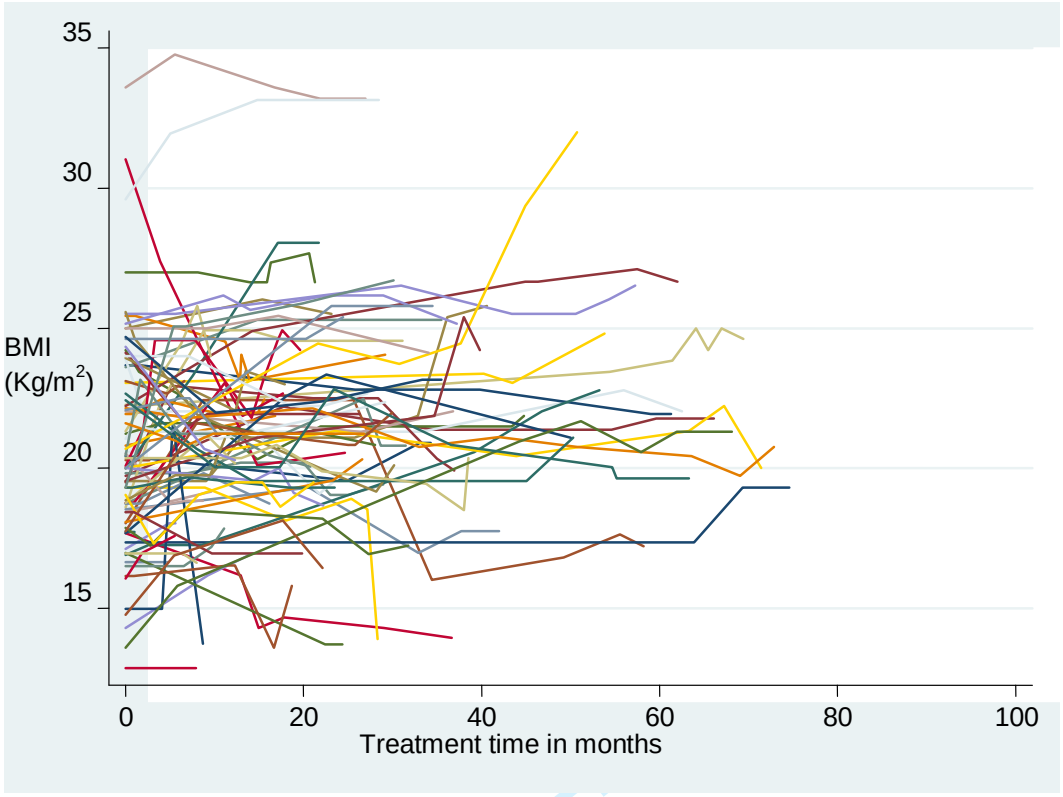
	Unstructured	Identity	Exchangeable
AIC	14337.93	17775.34	17666.17
BIC	14531.08	17956.02	17853.09

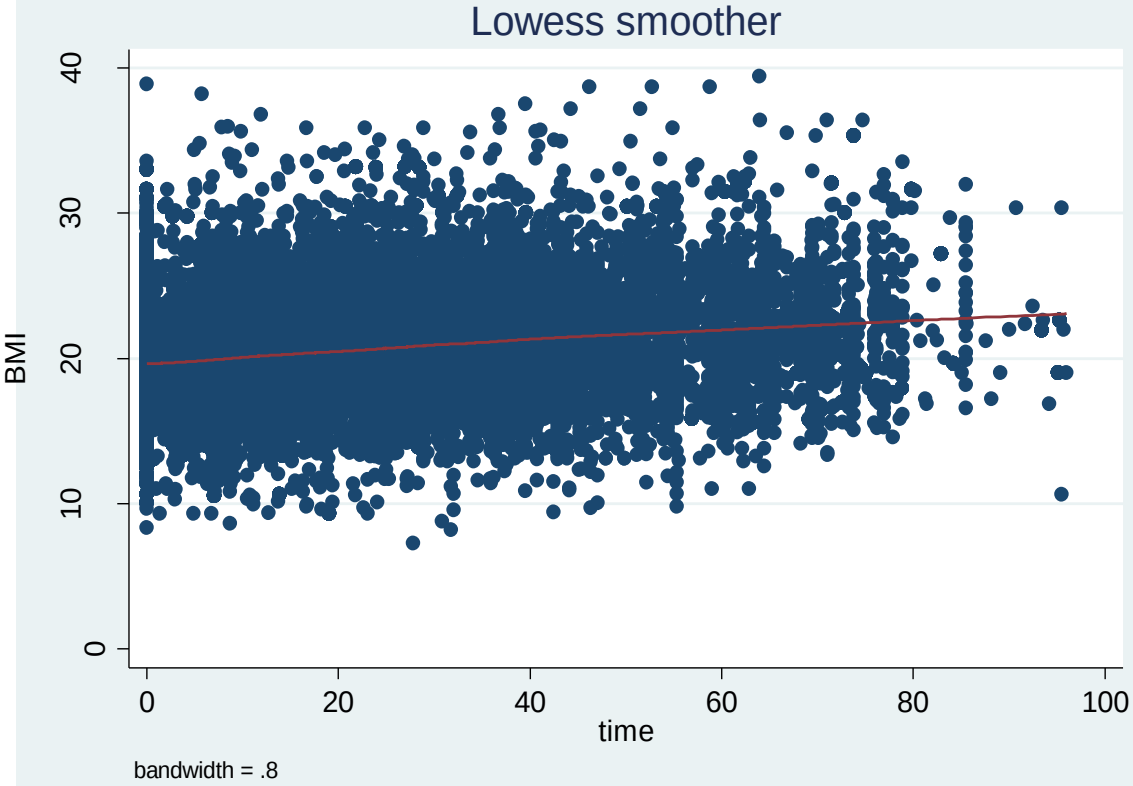
Table 3: Random Effects Models comparison

Random effects	LR X^2	P value
Model1 intercept	5625.28	**0.0000**
Model2 intercept, time	297.13	**0.0000**

Table 5 Parameter estimates for full linear mixed effect model

Characteristics	Co-efficient	Confidence interval		P value
		Lower	Upper	
Intercept	19.03	18.11	19.95	0.000
Sex				
Female	0.00			
Male	-0.01	-0.51	0.48	0.956
Adherence				
Poor	0.00			
Fair	0.43	-0.24	1.10	0.207
Good	0.48	-0.06	1.02	0.080
INH prophylaxis given				
No	0.00			
Yes	0.87	0.32	1.42	0.002
CPT prophylaxis given				
No	0.00			
Yes	0.63	0.08	1.19	0.025
Educational status				
Illiterate	0.00			
Primary	-0.03	-0.72	0.66	0.924
Secondary	0.47	-0.21	1.14	0.176
Tertiary	0.94	-0.01	1.89	0.051
Functional status				
Working	0.00			
Ambulatory	-1.16	-1.95	-1.31	0.000
Bedridden	-1.83	-2.47	-1.21	0.000
WHO stage				
Stage I	0.00			
Stage II	-0.06	-0.45	0.33	0.760
Stage III	-0.42	-0.65	-0.20	0.000
Stage IV	-0.62	-1.02	-0.22	0.002
CD4 count	0.001	0.0008	0.0015	0.000
Time on treatment	0.013	0.004	0.022	0.005
Education status x time				
Illiterate x time	0.00			
Primary x time	0.002	-0.01	0.015	0.801
Secondary x time	0.01	-0.003	0.019	0.162
Tertiary x time	0.02	0.01	0.04	0.009
Functional status x time				
Working x time	0.00			
Ambulatory x time	0.03	0.01	0.05	0.000
Bedridden x time	-0.01	-0.05	0.02	0.49
WHO stage x time				
Stage I x time	0.00			
Stage II x time	0.004	-0.008	0.166	0.522
Stage III x time	0.01	0.007	0.020	0.000
Stage IV x time	-0.0003	-0.016	0.016	0.969





STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	--
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10 - 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Body mass index variation over time and associated factors among HIV positive adults on second-line ART in Northwest Ethiopia: A retrospective follow up study

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Body mass index variation over time and associated factors among HIV positive adults on Second-line ART in Northwest Ethiopia: A retrospective follow up study

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Abstract

Objectives: This study aimed to assess the evolution of Body Mass Index of HIV positive adults on second line ART over time and factors affecting it in Northwest Ethiopia.

Design: Institution based retrospective follow up study was conducted using data extracted from 1016 patient cards from February 2008 to February 2016.

Setting: Eight referral hospitals from Amhara region, Ethiopia were included

Participants: HIV patients who started second-line antiretroviral therapy

Outcome measures: Change in BMI since starting second-line antiretroviral therapy

Results: Five hundred thirty eight (52.95%) of participants were males and median age of participants was 33 (IQR: 28; 39). The median follow up time was 18 months (IQR: 5.2; 32.2). The average change of BMI has showed a linear increase over time. The amount of BMI increment or decrement according to each variable was shown as β coefficients. Treatment duration (β=0.013, 95% CI (0.004, 0.022)), Isoniazid prophylaxis (β=0.87, 95% CI (0.32, 1.42)), Cotrimoxazole prophylaxis (β=0.63, 95% CI (0.08, 1.19)), ambulatory functional status (β= -1.16, 95% CI (-1.95, -1.31)), bedridden functional status(β= -1.83, 95% CI (-2.47, -1.21)), WHO stage III (β=-0.42, 95% CI (-0.65, -0.20)) WHO stage IV (β= -0.62, 95% CI (-1.02, -0.22)), CD4 count (β=0.001, 95% CI (0.0008, 0.0015)); and time interaction of variables like tertiary educational status (β=0.02, 95% CI (0.01, 0.04)), ambulatory functional status (β=0.03, 95% CI (0.01, 0.05)) and WHO stages III (β=0.01, 95% CI (0.007, 0.02)) were found to be significant predictors.

Conclusion: BMI of patients has shown a linear increment over the treatment time. Factors affecting it have been identified but its effect on Cardio-vascular disease needs further study.

Strengths and limitations of this study

- Being a retrospective study, this study shares the limitations of secondary data collection, as a result, we were unable to find some predictors like viral load, alcohol consumption, smoking, and nutritional history.
- The study is not based only on patient cards that started the second-line antiretroviral therapy at the same point in time and also the length of follow up period for each participant was not equal across all participants
- The most important strength of this study was the use of longitudinal data analysis. This ensures a valid estimate by handling data that is measured in different time periods and has missing values.
- Besides we had a total of 5380 number of BMI measurements taken from 1016 participants with a median BMI of 20.52 Kg/m^2 (IQR: 18.2; 23). Baseline BMI was calculated for all 1016 patients. These will again strength the precision of the estimates.

Background

Human Immunodeficiency Virus (HIV) has continued to be a major global public health problem, having killed more than 35 million lives so far. In 2017, 940 000 people died from HIV-related causes globally(1). According to the Ethiopia demographic and health survey of 2016, the adult prevalence of HIV in Ethiopia was 0.9%(2). Death due to HIV/AIDS has enormously decreased due to the introduction of antiretroviral therapy (ART) and millions of people are currently accessing it (3).

Body weight of HIV patients has been an important diagnostic and evaluation measure. Low BMI is recognized as one of the first criteria for the clinical definition of Acquired Immune Deficiency Syndrome (AIDS). The current World Health Organization (WHO) clinical staging of the disease also includes moderate unexplained weight loss (<10% presumed or measured body weight, stage 2), unexplained severe weight loss (>10% of body weight or BMI $\leq$ 18.5 kg/m^2, clinical stage 3) and HIV wasting syndrome (Unexplained severe wasting, clinical stage 4) as criteria to define advanced HIV infection(4).

The BMI of HIV patients is an important predictor of ART outcome (5-8), including the prediction of the CD4 cells change (9) and death (10-12). A negative change in BMI of patients was also found to be an independent predictor of dropout from HIV care (13).

The BMI of HIV patients is affected by gender(14) duration of treatment (10, 15, 16), Isoniazid Prophylaxis Therapy (IPT) and Cotrimoxazole prophylaxis(CPT) (17, 18) WHO stage (14) and CD4 count (15, 19).

This study focused on patients mainly because there is no much option for physicians to choose from if therapy failed. BMI evolution is a very important and easily calculable tool that can predict treatment outcome, dropout from treatment, CD4 recovery, and death, but literatures about its evolution across treatment time and factors affecting it are limited. Therefore this study tried to fill this information gap by determining the BMI evolution over treatment time and identifying the key factors affecting it. The information generated by this study will contribute to monitoring the response of patients for antiretroviral therapy.

Method and materials

Study design and period

An institution based retrospective follow up study was conducted among adults, age 24 and above who are started on second-line ART from February 2008 to February 2016

Study area and population

The study was conducted in Amhara regional state which is one of the nine administrative regions and two city councils of Ethiopia. The region constitutes majority of ART users in the country. The study population was adult HIV infected patients on second-line ART in all the nine referral hospitals of the region. The first-line treatment consists of a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) with one non-nucleoside reverse transcriptase inhibitor (NNRTI). Should failure of first-line treatment occur, a second-line treatment is implemented, using two NRTIs not previously used in first-line treatment, as well as one additional protease inhibitor (PI).

Sample size and sampling procedure

All HIV patients who initiated second-line therapy (n=1233) between February 2008 and 2016 were included. But only 1016 patients who had two or more measurements of weight were included in the study.

Data collection procedures

Data extraction checklist was prepared and the data were collected from HIV patient registration cards. Data about the baseline weight and height of patients and other factors like socio-demographic, clinical, and treatment related factors were also collected from each HIV patient registration card. Adherence to ART was assessed by pill counts at visits and is recorded as 'GOOD' (≥95% adherence) or FAIR (80%–95%), while POOR adherence is less than 80% (20).

The data structure, compilation and analysis strategy

The data was cleaned and entered in to EPI info version 7 and analyzed using STATA version 14.0. Body Mass Index (BMI) of HIV patients was computed by dividing the weight of patients in kilograms (kg) that was recorded during each follow-up visit, to their baseline height in meter squared. Exploratory data analysis for the weight of patients including individual profile plot, mean profile plot, descriptive and summary statistics were done. To determine the factors associated with BMI of patients bi-variable analysis for each independent variable was assessed and those found to be significant (p-value<0.25) were selected for the multivariable analysis. The need for random intercept and random slope was checked by likelihood ratio test. Since we cannot ignore the repeated measurements that have between individual variation and within individual variation(21), linear mixed effect model with random intercept and random slope was fitted.

Patient and Public Involvement

Since we have used secondary data/chart review, patients or the public were not involved during identifying the research question or design and conduct of the study.

Results

Patient characteristics

We had a total of 1016 adult patients who were taking second-line ART. Among the total 538 (52.95%) were males. All participants were above or equal to the age of 24 with a median age of 33 years (IQR: 28; 39). A large proportion of these patients 370 (37.1%) were unemployed and 371 (36.9%) have attended secondary school.

The median follow up time was 18 months (IQR: 5.2; 32.2). There were a maximum of 12 and a minimum of 2 measurements of weight per patient. Almost all visits were not balanced in their time of measurements. The median time between each weight measurement is reported as median (inter-quartile range) as follows: 6.7(4.27, 10.03), 6.08(4.14, 9), 6.13(4.2, 8.9), 6.27(4.53, 8.9), 5.9(3.97, 7.79), 5.83(3.7, 8.13), 5.45 (3.37, 7.43), 4.86(2.97, 6.2), 5.19(3, 7.37), 5.97(4.23, 7.04), 5.55(2.83, 5.86) and 3(0.9, 4.84) months from first to twelfth weight measurement respectively.

At the initiation of second-line ART majority of participants, 393 (45.54%), were at WHO stage I and 324 (37.54%) were at WHO stage III. A large proportion of participants 871 (86%) had working functional status at baseline, the rest 114 (11.25%) and 28 (2.75%) were ambulatory and bedridden respectively. The median CD4 count was 253 (IQR: 147; 399). Isoniazid Prophylaxis Therapy and CPT were given for 247 (24.87%) and 256 (25.65%) of participants respectively (**Table 1**).

Table-1: Baseline socio-demographic and baseline characteristics of adult HIV patients on ART in Amhara region, 2008 to 2016

Variables	Frequency	Percentage
Age		
25-34	547	53.89
35-44	333	32.81
45-54	104	10.25
55-64	26	2.56
≥ 65	6	0.59
Sex		
Female	478	47.05
Male	538	52.95
Educational status		
No education	315	31.34
Primary education	201	20.00
Secondary education	371	36.92
Tertiary education	118	11.74
Missing	11	0.01
Occupation		
Unemployed	370	36.42
Governmental	286	28.15
Non-Governmental	21	2.06
Private	66	6.50
Daily laborers	254	25.00
Missing	19	1.87
WHO stages		
Stage I	393	45.54
Stage II	66	7.65
Stage III	324	37.54
Stage IV	80	9.27
Functional status		
Working	871	86
Ambulatory	114	11.25
Bedridden	28	2.75
CPT given		
No	742	74.35
Yes	256	25.65
INH given		
No	746	75.13
Yes	247	24.87

CPT= Cotrimoxazole Prophylaxis Therapy

INH= Isoniazid

Exploratory data analysis

At baseline a total of 391(38.5%) had BMI of less than 18.5kg/m^2 whereas 549(54%), 64(6.3%) and 12(1.2%) had BMI 18.5-24.9 kg/m^2, 25-29.9 kg/m^2 and $\geq$30 kg/m^2 respectively.

Individual Profile

The average BMI of patients at baseline was 19.03Kg/m^2 (SD=3.6 Kg/m^2). The minimum and maximum BMI was 8.33 Kg/m^2 and 33.59 Kg/m^2 respectively. Before proceeding to the formal statistical analysis we have described the data by exploring how individuals change in BMI over time. To make the individual profile plot more informative and understandable, we have prepared it for the first 100 individuals (**Figure 1**).

As we can see from this plot, the BMI status of patients has high variability within an individual over time and among individuals at baseline and also through time. Therefore to fit the data which has variability in the intercept and slope of trajectories very well, we have used a mixed model.

Exploring the mean profile

As stated above all measurements in the data have no similar time of measurements, therefore, we have used smoothing to determine BMI evolution over time (**Figure-2**).

As one can easily understand from the mean profile plot the BMI of these patients showed a linear increment over the treatment time.

Modeling the BMI

Correlation structure checking and model comparison

Comparing with AIC, the correlation structure with the lowest AIC was chosen, in this case the unstructured correlation structure (**Table-2**).

Table 2: Correlation structure checking and model comparison

	Unstructured	Identity	Exchangeable
AIC	14337.93	17775.34	17666.17
BIC	14531.08	17956.02	17853.09

The need for random slope and intercept was checked by the likelihood ratio test of model without a random intercept, with only random intercept and a model with both random intercept and slope (**Table-3**).

Table 3: Random Effects Models comparison

Random effects	LR X^2	P value
Model-1 intercept	5625.28	0.0000
Model2 intercept, time	297.13	0.0000

So as we can see from the table-3 the inclusion of random intercept and random slope is reasonable so in the final model, we have used both random intercept and random slope.

Factors affecting BMI evolution over time

Based on the multi-variable output: time since the start of second-line ART, IPT, CPT, Functional status, WHO stage of the disease; and time interaction of categorical variables like educational status, functional status and WHO stages were found to be significant predictors of the BMI evolution of HIV patients on second-line ART.

Keeping all the other variables constant, for a one month increment in the treatment duration the BMI of a patient increases by 0.013 kg/m^2. But specifically individuals who have tertiary level of education, ambulatory functional status and who are at WHO stage III have additional 0.02 kg/m^2, 0.03 kg/m^2 and 0.01 kg/m^2 increment respectively in their BMI for a one month increment in the duration of treatment.

Taking IPT and CPT increases BMI by 0.87 kg/m^2 and 0.63 kg/m^2 respectively as compared to their counterparts. Nongovernmental organization employment was associated with a 2.02 kg/m^2 increment when compared to government employment. Patients who are ambulatory and bedridden in their functional status have a 1.16 kg/m^2 and 1.83 kg/m^2 decrement in their BMI as compared to those who have working functional status. Patients who are at WHO stage III and WHO stage IV have decreased BMI by 0.42 kg/m^2 and 0.62 kg/m^2 when compared with those who are at WHO stage I. For a unit cell/mm^3 increase in the CD4 count of patients BMI was found to increase by a factor of 0.001 kg/m^2 (**Table-4**).

Table 4: Parameter estimates for full linear mixed effect model

Characteristics	Co-efficient	Confidence interval		P value
		Lower	Upper	
Intercept	19.03	18.11	19.95	0.000
Sex				
Female	0.00			
Male	-0.01	-0.51	0.48	0.956
Adherence				
Poor	0.00			
Fair	0.43	-0.24	1.10	0.207
Good	0.48	-0.06	1.02	0.080
INH prophylaxis given				
No	0.00			
Yes	0.87	0.32	1.42	0.002
CPT prophylaxis given				
No	0.00			
Yes	0.63	0.08	1.19	0.025
Educational status				
Illiterate	0.00			
Primary	-0.03	-0.72	0.66	0.924
Secondary	0.47	-0.21	1.14	0.176
Tertiary	0.94	-0.01	1.89	0.051
Functional status				
Working	0.00			
Ambulatory	-1.16	-1.95	-1.31	0.000
Bedridden	-1.83	-2.47	-1.21	0.000
WHO stage				
Stage I	0.00			
Stage II	-0.06	-0.45	0.33	0.760
Stage III	-0.42	-0.65	-0.20	0.000
Stage IV	-0.62	-1.02	-0.22	0.002
CD4 count	0.001	0.0008	0.0015	0.000
Time on treatment	0.013	0.004	0.022	0.005
Education status x time				
Illiterate x time	0.00			
Primary x time	0.002	-0.01	0.015	0.801
Secondary x time	0.01	-0.003	0.019	0.162
Tertiary x time	0.02	0.01	0.04	0.009
Functional status x time				
Working x time	0.00			
Ambulatory x time	0.03	0.01	0.05	0.000
Bedridden x time	-0.01	-0.05	0.02	0.49
WHO stage x time				
Stage I x time	0.00			
Stage II x time	0.004	-0.008	0.166	0.522
Stage III x time	0.01	0.007	0.020	0.000
Stage IV x time	-0.0003	-0.016	0.016	0.969

DISCUSSION

This study has found a linear increment in BMI of patients over the treatment time. There were BMI differences between subjects at baseline and in their progress over time.

Factors found to have a significant effect on the evolution of BMI over treatment time at a multivariable linear mixed effect model were, second-line treatment duration, IPT, CPT, employment status, functional status of the patient, WHO stage, and CD4 count. Time interaction of educational status, functional status, and WHO stage were also significant predictors of BMI evolution.

For a one month increase in treatment duration the BMI of patients increases by 0.04 kg/m^2, this finding is in line with studies in South Africa (22), India (10) and United States(23). The possible reasons for weight gain could be due to normal reversion of the weight loss associated with HIV or due to drug related metabolic changes which include hyperlipidemia, insulin resistance and diabetes(24).

Patients who took IPT and CPT have increased BMI when compared to their respective counterparts. This finding is supported by other studies like a study conducted in Abidjan (17) and multicenter controlled clinical trial in Africa (18). The main reason for this association could be the reduction of potentially disabling and wasting diseases like tuberculosis and other opportunistic infections by these prophylactic drugs(25, 26). A highly increased appetite by the prophylaxis could also be possible explanation(27).

Being ambulatory and bedridden decreases BMI when compared to those who are working. Since these individuals are not working they may not access a nutritious and balanced diet which affects their BMI. Another reason could be additionally decreased immunity caused by physical inactivity which makes them more susceptible to minor infections leading to a higher calorie

loss(28). These groups of people are also at higher risk of diarrheal disease for they cannot take care of themselves which in turn causes weight loss(29).

When compared with patients who are at WHO stage I, those who are at WHO stage III and WHO stage IV have decreased BMI. This finding is in line with a multicenter study in resource limited settings which shows individuals who had high clinical status (WHO stage III and WHO stage IV) had poorer weight gain when compared to weight change in patients at lower WHO stage(14). The possible reason can be unexplained chronic diarrhea and HIV enteropathy in these patients and the associated malabsorption (4) or it could be due to pyrexia of unknown origin in the late stage of the disease which results an increased calorie loss and wasting(30).

The BMI of patients was also found to increase with the increment in their CD4 count. This positive association is supported by evidence from a study conducted in Boston (15) and Tanzania (19). This increment can be explained by the association of increment of CD4 count with good clinical changes like viral suppression, improved immunity, and appetite leading to increment in the BMI of patients (13).

Being a retrospective study, this study shares the limitations of secondary data collection, as a result, we were unable to find some predictors like viral load, alcohol consumption, smoking, marital status, and nutritional history. The data may also have errors in documenting weight among some measurements.

CONCLUSION

In this study, we have found a linear increment in the BMI of HIV patients on second line ART. There was a significant variation of BMI of patients at baseline and through ART treatment time. Duration of treatment, IPT, CPT, functional status, WHO stage of the disease, CD4 count; and time interaction of categorical variables like educational status, functional status and WHO

stages were found to be significant predictors. The positive change in the BMI of patients shows an encouraging trend for we know this has a positive impact on the CD4 recovery, decrease lost to follow up and death. Clinicians also must consider the identified risk factors when they provide service for these patients.

ABBREVIATIONS

AIC, Akaike's Information Criterion; AIDS, Acquired Immunodeficiency Virus; ART, Anti-Retroviral Therapy; BIC, Bayesian information criterion; BMI, Body Mass Index; CI, Confidence Interval; CPT, Co-trimoxazole preventive therapy; HIV, Human Immuno Deficiency Virus; IPT, Isoniazid Prophylaxis Therapy; Kg, Kilogram; NGO, Non Governmental Organizations; WHO, World Health Organization.

Declarations

Ethical consideration

Ethical clearance was obtained from the Institutional Review Board of Institute of Public Health, University of Gondar. Names and unique ART numbers of patients were not collected to keep the privacy of patients during the data collection.

Availability of data and materials

The data upon which the result based could be accessed by a reasonable request made to the corresponding author.

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Consent for publication

Not applicable

Competing interest

Authors declare that they have no conflict of interest

Authors' contribution

AGB, LDG, EGZ, TAA, ATT have actively participated during Conception and design, acquisition of data, analysis, and interpretation of data. All authors have read and approved the final version of the manuscript.

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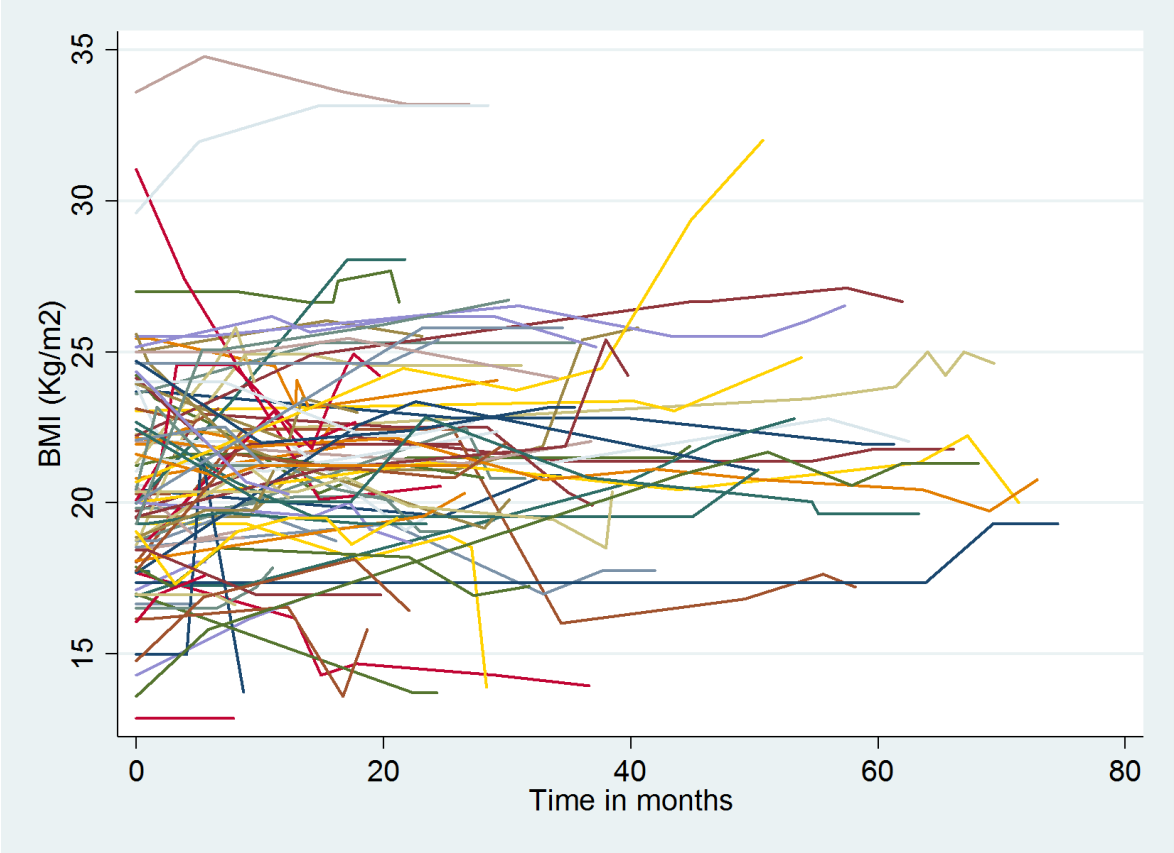
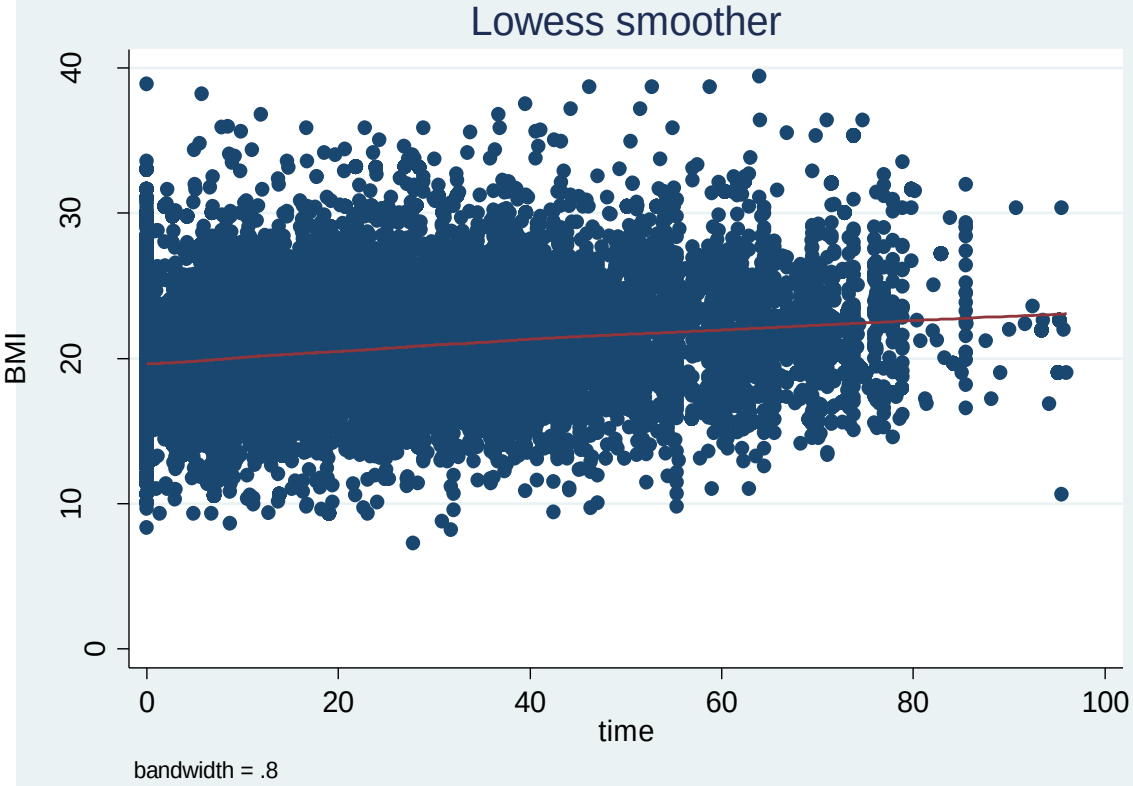
Figures Legend

Figure 1: Individual profile plot of BMI overtime for the first 100 individuals at second-line ART in Amhara region, 2008-2016

Figure 2: Time plot of BMI versus treatment time in months with lowess smoothed curve superimposed for HIV patients on second-line ART in Amhara region 2008-2016





STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	--
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10 - 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.