

## Increased Viral Suppression Among People on First-Line Antiretroviral Treatment in Ethiopia: Meeting the Third 90's

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### Abstract

#### Background

Antiretroviral therapy (ART), which aims to completely suppress viral replication, fails for a variety of reasons. The aim of this study was to identify factors associated with prevalence and treatment failure in ART patients who received first-line treatment in the Amhara region of northeastern Ethiopia.

#### Methods

A cross-sectional study was conducted from March 2018 to July 2018. Survey using a pre-structured questionnaire focused on demographics and potential risk factors for antiretroviral treatment failure was used. Medical history, including baseline features, was extracted by reviewing medical records 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 treatment failure of first line antiretroviral drugs was 19.04% with clinical, immunologic and viral failure of 0.31%, 12.66% and 6.09% respectively. More than half of the 57 participants with an unsuppressed viral load (>1000 copies/ml at 6 months), 29 (50.88%) were dropped out from follow up. Females had a higher proportion of immunologic failure (13.09%), but males had a higher proportion of viral failure (8.09%). A high proportion of overall treatment failure (33.33%), immunologic failure (18.75%), as well as viral failure (14.58%), was observed in age groups under the age of 18 years. Multivariate logistic regression revealed clients with a CD4 baseline count of less than 250 and fair/poor adherence had higher odds of treatment failure.

#### Conclusions

In this study we conclude that antiretroviral treatment failure indicated by viral failure in Amhara region, Ethiopia is 6.09% which indicated increased viral suppression as compared to Ethiopia's national viral failure rate of 11%. Low CD4 baseline count and fair/poor adherence are significantly associated independent predictors of treatment failure. Therefore improving client follow up to adherence to treatment should be strengthened and ART program should focus on strengthening test and start strategy to enroll clients early before CD4 count declines. A higher proportion of viral failure in male and younger age suggests acquisition of resistant viral strain and indicate the need for a drug resistance survey

**Keywords:** Amhara Region, ART failure, Ethiopia, HIV, Viral suppression

### Introduction

Human immunodeficiency virus (HIV) is affecting more than 36.7 million people at the end of 2016 worldwide with 1.8 million people becoming newly infected globally in the same year and Africa is the most affected continent with 25.6 million people living with HIV which accounts for almost two-thirds of the global total of HIV infections [1]. In Ethiopia central statistical agency (CSA) in the 2016 Ethiopia demographic and health survey (EDHS) report-

ed the prevalence of HIV at 1.2% nationally ranging from 0.1% in Somali region to 4.8% in Gambella and 0.4% in rural areas versus 2.9% in urban areas that indicated urban areas are affected seven times higher than rural areas [2]. The estimated number of people living with HIV and needing ART in Ethiopia are 710,000 in which about 650,000 (91%) are adults and 62,000 (9%) are children under 15 years of age [3].

Antiretroviral therapy is recommended for all people living with HIV, helping people live longer, healthier lives and reducing the risk of HIV infection. Ethiopia has accepted WHO recommendations to provide lifelong ART for all people living with HIV, including children, adolescents, and adults, pregnant and lactating women, regardless of clinical status or CD4 count [4]. Antiretroviral therapy (ART), which aims to completely suppress viral replication, fails for a variety of reasons. Once effective ART is initiated, it usually takes 3-6 months for a person's viral load to reach undetectable levels which makes people living with HIV (PLHIV) 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]. The goal of UNAIDS 2020 is that 90% of people living with HIV know their status and 90% of people living with HIV (who know their HIV status is positive) are already on ART treatment and 90% of people on treatment are virally suppressed. The treatment success is confirmed by undetectable viral count in two consecutive viral load measurements after 6 months of treatment. However, according to a recent global report, only 73% of people living with HIV worldwide achieve successful viral suppression, and the global goal of 90% has not yet been met and Sub-Saharan Africa has a similar report. [3, 5].

Treatment failure (clinical failure, immunologic failure or viral failure, or any combination of the three) is a key indicator of disease progression. Although viral failure is considered an early indicator of treatment success, clinical and immunologic conditions need to be described for better outcomes. Studies in Ethiopia showed regional variations in the magnitude of all types of ART failure, ranging from 4.1% [6] to 19.8% [7] and Amhara region is one of the high HIV burden regions with growing concern to reach the 3rd 90 due to gaps in ART programs [8].

Antiretroviral therapy fails for a variety of reasons, the most important reason being non-adherence to antiretroviral therapy which is high in low- and middle-income countries [9, 10]. Other factors that may contribute to treatment failure are antagonism between some drug combinations and the level of CD4 status before treatment initiation [11]. Co-infection, type of regimen, body mass index (BMI), age, and other socioeconomic factors also impact [12, 13]. Thus, describing the situation in the region may help minimize unnecessary regimen changes, and improve current practices, thereby improving health conditions and preventing the emergence and spread of drug resistant strains. Also, while prevention of treatment failure by identifying and minimizing patient-related factors is relatively straightforward, it has a significant impact on combating the disease. In this regard, insufficient information is found locally, and therefore, this study aims to assess the extent and related factors associated with treatment failure among people on first-line ART in the Amhara region of northeastern Ethiopia.

## Material and Methods

### Study Area and Period

The study was conducted in the Amhara region, Ethiopia which consists 15 zonal administrative units with a 2017 estimated population of 21.1 million [14]. According to the regional health bureau number of PLHIV was about 208,000 and the region has more than 300 ART site health facilities and 5 viral load monitoring laboratories. However, about 40% of PLHIV were found in 32 priority towns and we randomly selected 16 ART site health facilities (11 health centers and 5 hospitals) from 6 zonal administrations in the eastern part of the region were studied from March to October-2018.

### Study Design

A facility-based cross-sectional study was conducted among first-line antiretroviral-initiated clients. A questionnaire survey was taken using a structured questionnaire focused on demographics and possible risk factors for antiretroviral treatment failure. Clinical histories, including baseline features and adherence status, were extracted by reviewing medical records using a data abstraction checklist. Viral load test was done using automated real time HIV-1 viral load sp2000extraction and m2000detection system (Abbott Laboratories, IL, USA) having a detection limit of 50 copies/ml. Adults with viral load results >1000 copies/mL were appointed for another viral load test after 3 months to confirm viral failure. Immunologic failure is assessed by comparing baseline and current CD4 cell counts, where <100 cells/ $\mu$ L, below baseline, or <50% of peak after taking ART for 6 months is considered as immunologic failure. In children <5 years of age, persistent CD4 levels <200 cells/mm or <10% peak after 6 months of treatment is considered an immunologic failure. In children >5 years of age, persistent CD4 levels below 100 cells/mm was considered an immunologic failure.

### Sample Size and Sampling Technique

The sample size was determined using the single population proportion formula, assuming a prevalence of treatment failure of 19.8% [7]. After considering a design effect of 2.5 and a non-response of 5%, a total of 640 subjects were proposed and recruited sequentially when they visited the clinic for initial viral load follow-up.

### Operational Definitions

- Viral suppression: <1000copies/mL on 6 months of ART.
- Viral re-suppression:- >1000 copies/mL on 6 months of ART and <1000 copies/mL after 3 months of enhanced adherence and counseling.
- Viral failure: >1000 copies/mL after 3 months of the initial viral load.
- Clinical failure:
  - Adults: New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 conditions) 6 months after ART
  - Children: New or recurrent clinical events (WHO clinical stages 3 and 4) suggestive of progressive or severe clinical immunodeficiency

ciency, excluding tuberculosis 6 months after ART.

- Immunologic failure:
  - Adults older than 19 years:- CD4 cell count of <100 cells/ $\mu$ L, below baseline, or <50% of peak 6 months after ART.
  - Children older than 5 years:- Persistent CD4 levels below 100 cells/mm
  - Children younger than 5 years: - Persistent CD4 levels below 200cells/mm or <10 %.
- Treatment failure:- Presence of immunologic, viral or clinical failure or any combination of the three.

### Data Quality Assurance and Analysis

Data collection and laboratory tests were performed by trained health professionals, and standardized formats were used for data extraction from each health facility’s medical records. The data collection process was supervised by investigators. Collected data was checked for completeness before data entry, data exploration was performed on the entered data to detect unexpected values and outliers, and variables that needed transformation were identified.

Data were analyzed with STATA Version 14 (Statacorp, USA). Frequency, proportion, and summary statistics were used to describe the study population in terms of relevant variables. Odds ratios and P-values were used to assess the presence and degree of association between treatment failure and possible risk factors. Variables with p-value <0.20 in binary logistic regression were recruited to multivariable regression and a P-value <0.05 was considered to indicate the presence of a significant association.

## Results

### Socio-demographic and Clinical Features

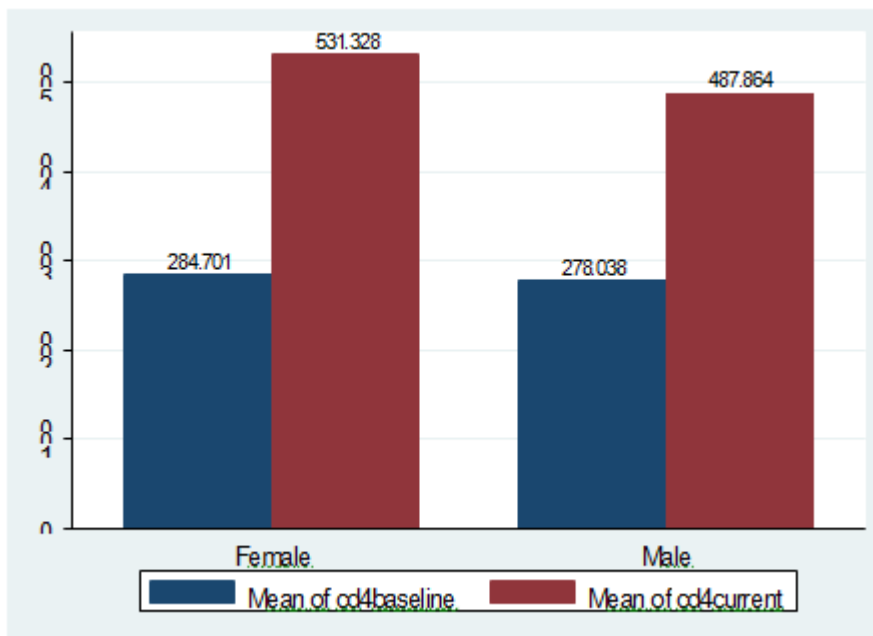
A total of 640 clients of all ages were enrolled in this study, of whom 405 (63.28%) were women. The median age was 38 years ( $\pm$ SD=11.3 years). More than half of the study participants, 374 (58.44%) were between 19 to 35 years of age and 172 (26.88%) were between 36 to 49 years old. Among the survey participants, 501 (78.29%) had no primary education and 337 (52.66%) were married (Table 1).

**Table 1. Socio demographic characteristics of clients on first line ART, Amhara region, Ethiopia, 2018**

Characteristics	Frequency	Percent
Age		
≤ 18 years	48	7.50
19-35 years	374	58.44
36-49 years	172	26.87
≥ 50 years	46	7.19
Education		
No formal education	260	40.63
Primary school	241	37.66
Secondary school	102	15.93
College and above	37	5.78
Sex		
Male	235	36.72
Female	405	63.28
Marital status		
Married	337	52.66
Never Married	106	16.56
Divorced	155	24.22
Widowed	42	6.56

The mean length of stay before treatment initiation was 8 months (+ SD=19 months) and ranged from < 1 month to 120 months. However, of the 124 study participants tested after the implementation of the national testing and treatment strategy, 84 (67.74%) started treatment within 1 month of testing. The mean baseline

CD4 count was 282 cells/mm<sup>3</sup> ( $\pm$ 238), and the current mean CD4 count was 515 cells/mm<sup>3</sup> ( $\pm$ 246), indicating a significant increase from the baseline (p<0.001), and the CD4 increase in females was significantly greater than males (p<0.01) (Figure 1).



**Figure 1:** Baseline and current CD4 count among females and males on first line ART in Amhara region, Ethiopia, 2018

As shown in Table 2, only 223 (34.84%) study participants were in WHO stage I at the start of antiretroviral treatment while 231 (36.09%) were in WHO stage III. The WHO staging based on current clinical status indicated clinical improvement, with 590 (92.19%) clients on 6-month ART in WHO stage I. About half of the study participants 287 (49.65%) stay less than 15 days to initiate ART after diagnosis. The combination of TDF-3TC-EFV was the most commonly prescribed regimen during ART initiation, at 338

(52.81%), and remains the most common in the current regimen, which comprises 378 (59.08%) of all other regimens. One hundred and eighteen (18.44%) had a history of change in treatment regimen and 98 (15.31%) had a history of TB treatment. Regarding their adherence, as measured by pill count and retrieved from their medical records, 513 (80.16%) were reported to have good adherence and nutritional status using body mass index (BMI) revealed that 237 (37.03%) were underweight, with BMI < 18.5.

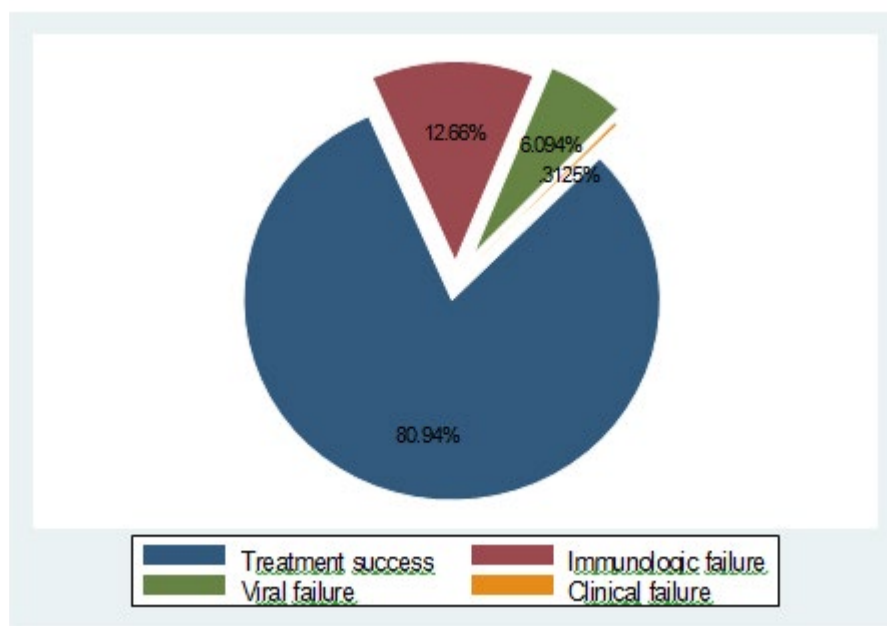
**Table 2. Baseline clinical characteristics of clients on first-line ART, Amhara region, Ethiopia, 2018**

Characteristics	Freq.	Percent
WHO clinical stage		
Stage I	223	34.84
Stage II	155	24.23
Stage III	231	36.09
Stage IV	31	4.84
CD4 Baseline		
≤100	126	19.69
101-200	148	23.12
201-350	201	31.41
351-500	87	13.59
>500	78	12.19
History of TB Treatment		
Yes	98	15.31
No	542	84.69
Body Mass index(Kg/m <sup>2</sup> )		
≤ 18.5	237	37.03
≥ 18.6	403	62.97

Adherence		
Good	513	80.16
Fair/poor	127	19.84
Total	640	100

### Treatment failure and its Associated Factors

The overall treatment failure of first-line antiretroviral drugs was 19.04% with clinical, immunologic and viral failure of 0.31%, 12.66%, and 6.09% respectively and the treatment success was 80.94% (Figure 2). The viral suppression rate was 91.09% and re-suppression was achieved for 8 out of 28 (27.58%) study participants tested during the three months of enhanced adherence counseling follow-up. More than half of the 57 participants with an unsuppressed viral load (>1000 copies/ml at 6 months), 29 (50.88%) were dropped out from follow-up.



**Figure 2:** Antiretroviral treatment response of clients on first line ART in Amhara region, Ethiopia, 2018

A high proportion of overall treatment failure (33.33%), immunologic failure (18.75%), as well as viral failure (14.58%), was observed in age groups under the age of 18 years. As shown in table 4, the odds of treatment failure were 2.12, 1.16, and 1.20 times higher in the age groups <18 years, 19 to 35, and 36 to 49 respectively as compared to the age group >50 years and above respectively. Females had a higher proportion of immunologic failure (13.09%), but males had a higher proportion of viral failure (8.09%) (Table 3). For each predictor variable, binary logistic regression was performed, and those with p values less than 0.20 (adherence, age, and baseline CD4 count) were included in multivariable logistic regression analysis to investigate factors associated with treatment failure, which revealed that baseline CD4 and adherence had a significant association.

**Table 3: Proportion of first line treatment response in Amhara region, Ethiopia, 2018**

Characteristics	Clinical failure N (%)	Immunologic failure N (%)	Viral failure N (%)	Overall treatment failure N (%)	Treatment success N (%)
Age					
≤ 18 years	0 (0.00) 2	9 (18.75)	7 (14.58)	16 (33.33) 69	32 (66.67)
19-35 years	(0.53) 0	46 (12.30)	21 (5.61)	(18.45)	305 (81.55)
36-49 years	(0.00) 0	21(12.21)	9 (5.23) 2	30 (17.44)	142 (82.56)
≥ 50 years	(0.00)	5 (10.87)	(4.35)	7 (15.22)	39(84.78)
Sex					
Male	1 (0.43)	28 (11.91)	19(8.09)	48 (20.43)	187 (79.57)
Female	1 (0.25)	53 (13.09)	20(4.94)	74 (18.27)	331 (81.73)

Comorbidity					
Yes	0 (0.00)	23 (13.69)	13 (7.74)	36 (21.43)	132 (78.57)
No	2 (0.42)	58 (12.29)	26 (5.51)	86 (18.22)	386 (81.78)
Body mass index (Kg/m <sup>2</sup> )					
≤ 18	1 (0.42)	29 (12.24)	15 (6.33)	45 (18.99)	192 (81.01)
>18	1 (0.25)	52 (12.90)	24 (5.96)	77 (19.11)	326 (80.89)

Clients with a CD4 baseline count of less than 250 had 2.16 higher odds of treatment failure than their counterparts. It was found that those with fair/poor adherence had 3.41 times the odds of treatment failure as those with good adherence (Table 4).

**Table 4: Factors associated with treatment failure among people on first line ART in Amhara Region, Ethiopia, 2018**

Characteristics	Treatment failure		COR (95%CI)	AOR (95%CI)	p-value
	YesN (%)	No N (%)			
Age					
<18 years	16 (33.33)	32 (66.67)	2.78 (1.02-7.60)	2.12 (0.74-6.01)	P=0.157
19-35 years	69 (18.45)	305 (81.55)	1.26 (0.54-2.93)	1.16 (0.48-2.78)	P=0.731
36-49 years	30 (17.44)	142 (82.56)	1.17 (0.48-2.88)	1.20 (0.47-3.03)	P=0.691
>=50 years	7 (15.22)	39 (84.78)	1	1	
Baseline CD4 count					
<=250	74 (24.34)	230 (75.66)	1.93	2.16 (1.41-3.30)	P<0.001
>250	48 (14.29)	288 (85.71)	1	1	
Adherence					
Fair/poor	45 (35.43)	82(64.57)	3.10 (2.00-4.81)	3.41 (2.16-5.38)	P<0.001
Good	77 (15.01)	436 (84.99)	1	1	

## Discussion

The purpose of this study was to assess the magnitude and associated factors of treatment failure in 16 health facilities in the Amhara region. The study discovered that overall 19.04% of first-line antiretroviral treatment failure. Immunologic failure (12.66%) was the most common, followed by viral failure (6.09%), and clinical failure (0.31%). Clients with baseline severe immunosuppression, on the other hand, often take a long time to recover, even if viral suppression occurs, and immune reconstitution inflammatory syndrome (IRIS) may be the reason that new or recurring opportunistic conditions occur for clinical failure despite virologic responses to ART [15]. As a result, for such clients, the indication of treatment failure is suggested to be indicated by viral failure.

The current study's finding of viral failure (6.09%) is slightly higher than a study from Addis Ababa, Ethiopia, which reported 4.4% viral failure [16], and another Ethiopian study, which reported 1.3% viral failure [7], which could be due to a genuine difference in the local setting due to the presence of different adherence status. The finding, however, is significantly lower than Ethiopia's national viral failure rate of 11%, indicating increased viral suppression in the study area [17]. Moreover, the re-suppression rate for clients who had an unsuppressed viral load at 6 months was 27.58%, which was lower than the Ethiopian national figure of 35.3% [17]. On the contrary, the 50.88% dropout rate from en-

hanced adherence and counseling is higher than the 19% dropout rate reported in the Ethiopia national study, and will have a significant programmatic impact in achieving the third 90's goal.

Adherence is a critical factor in treatment failure because it can indicate whether the failure is due to ineffective medication or viral factors such as resistance mutations. According to the findings of this study, adherence was a significant and independent predictor of treatment failure, and those with fair/poor adherence are at a higher risk of treatment failure found to be 3.41 times more likely to fail treatment than clients with good adherence, which is consistent with findings in different parts of Ethiopia [17, 18] as well as studies in Kenya and Nigeria [21, 22].

According to our findings, immunologic failure indicated by baseline CD4 count is also a significant and independent predictor of treatment failure. In line with other Ethiopian findings, those with a CD4 baseline count of < 250 faces 2.16 higher odds of treatment failure. The proportion of immunologic failure was higher in females than males, whereas the proportion of viral failure was roughly double higher in males than females (8.09 versus 4.94). This could be due to the fact that many women living with HIV in developing countries have limited access to health services, resulting in late initiation of antiretroviral treatment. On the other hand, men had 1.71 (95% CI: 0.85-3.44) higher odds of viral failure than

women, which was consistent with studies in Uganda, Zimbabwe, and Burkina Faso [23], which could be explained in part by adherence status or the acquisition of resistant strains due to the mobile nature of this group [23].

Although not statistically significant, this study found that 33.33% of overall treatment failure occurred in the age group under 18 years, followed by 19-35 years. Several studies in other parts of the country, as well as studies from Kenya, Nigeria, and Cameroon, have found that younger age groups are more likely to fail treatment due to the acquisition of drug resistance strains as they are sexually active [18, 24].

### Conclusions

In this study we conclude that antiretroviral treatment failure indicated by viral failure in Amhara region, Ethiopia is 6.09% which indicated increased viral suppression as compared to Ethiopia's national viral failure rate of 11%. The overall treatment failure is 19.04% and the rate of default during three months of enhanced adherence counseling is high. Low CD4 baseline count and fair/poor adherence are significantly associated independent predictors of treatment failure. Therefore, improving client follow-up to adherence to treatment should be strengthened and ART programs should focus on strengthening test and start strategies to enroll clients early before the CD4 count declines. A higher proportion of viral failure in male and younger age suggests the acquisition of resistant viral strain and indicate the need for a drug resistance survey in the study area. The high proportion of treatment failure indicated by immunologic failure was found in females suggesting ART programs should focus on these groups.

### Limitation of the study

The findings of this study have to be seen in light of some limitations. The use of adherence measurement based self-report didn't adequately detect poor adherence which might underestimate the actual scenario. In addition, impact of primary ART resistance to treatment failure and baseline viral load is not known as the test is not routinely available in health facilities, thus, we suggest further large scale study.

### Abbreviations

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

### Data availability

The dataset used to support the findings of this study are available from the corresponding author upon reasonable request.

### Ethical approval

The study has got approval from Amhara Public Health Institute ethical review board ref. number 04/018/2010. All study subjects during the study period have been informed the purpose of the

study and their consent was sought in written.

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### Authors' contribution

Minwuyelet Maru.: Designed the study, analyzed and interpreted the data, Initiated and drafted the manuscript, Daniel Dagne: Analyzed the data, Addisu Tesfie: Involved in proposal write up and data collection, Asefa Missaye: revised the manuscript, Gizachew Yismaw: Revised the manuscript, Andargachew Mulu: Revised the manuscript

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### Disclosure

The authors declare that they have no competing interests.

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