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The effect of appointment spacing model of care on virological suppression and associated factors among HIV-positive individuals on antiretroviral therapy at public health facilities of Debre Markos town, Northwest Ethiopia: interrupted time series design

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Abstract

Introduction: Appointment spacing model (ASM) of care is crucial for human immunodeficiency viruses (HIV) patients receiving antiretroviral therapy in order to improve service quality and patient's clinical outcomes, including viral suppression. However, there is a paucity of information about the effectiveness of ASM on viral suppression. Therefore, this study aimed to assess the level and trends of virological suppression and associated factors among patients on antiretroviral therapy enrolled into ASM in Northwest Ethiopia.

Material and methods: An interrupted time series study design was conducted among 272 adult HIV-positive patients, who were stable and enrolled into ASM. They were selected by using a systematic random sampling technique. Data were collected from patients' charts, registration books, and computer databases using abstraction sheets. Regression coefficients with a 95% confidence interval (CI) computed, and variables having less than p-value = 0.05 in the segmented regression model were considered significant predictors of virological suppression.

Results: This study revealed that virological suppression was decreased from the baseline of 99.22% to 96% after the implementation of ASM. The trends of virological suppression were significantly decreased by 1.38 (95% CI: –2.2, –0.5%, p = 0.0007) after the implementation of ASM. Poor adherence was the most influential variable that caused level and trend decrements over time (p = 0.04).

Conclusions: The level of virological suppression was significantly reduced after the implementation of ASM. The most significant factor associated with decreased levels and trends over time was poor adherence. It would be beneficial to assess and maintain good adherence of patients on antiretroviral therapy throughout the clinical visit during the implementation of ASM.

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Introduction

Globally, human immunodeficiency virus (HIV) remains a major public health concern [1]. In 2019, approximately 38 million people were living with HIV, and about 25.4 million people were accessing antiretroviral therapy (ART) [1, 2]. Sub-Saharan Africa accounts for two-thirds of all new HIV infections worldwide [3].

According to the United Nation Programme 2019 report on HIV/AIDS (UNAIDS), Ethiopia is one of the 30 countries, which account for the highest number of newly HIV-infected people in the world [4]. In 2018, the national HIV prevalence rate in adults aged 15-49 years was 0.9%, with 1.2% for females and 0.6% for males [1]. According to the UNAIDS spectrum estimate, there were a total of 665,723 people living with HIV (PLHIV) in Ethiopia, of which 97.1% of adults were receiving ART and 87.6% had suppressed viral loads [5]. A fixed-dose combination of tenofovir (TDF) + lamivudine (3TC) + efavirenz (EFV), or TDF + 3TC + doultegravir (DTG) as a once-daily dose is the preferred first-line ART regimen for adult HIV-positive patients in Ethiopia [1]. Globally, the UNAIDS plan to achieve is 95% of people on HIV treatment with suppressed viral load by 2030, in order to assure global HIV epidemic control [4]. Despite this ambitious goal, a systematic review of HIV treatment cascades in 69 countries found that viral suppression ranged from 7% in China to 68% in Switzerland [6]. From the UNAIDS fact sheet report, from of all people accessing ART, only 88% were virally suppressed [7].

Approximately, 95% of HIV service delivery worldwide is facility-based and undifferentiated to individual needs [8]. This increases the challenges for HIV programs in managing diverse needs of patients and makes meeting the target difficult, even if different strategies are implemented to improve virological suppression for those on ART [8, 9]. Patient-centered HIV care aims to deliver all services closer to the individual. This reduces the difficulty, cost of travel, and shortens waiting time [9]. In many settings, lack of transportation and money as well as long waiting time in health facilities were the major barriers to access the services and retention in care, particularly in rural areas [10]. Therefore, to address the growing number of stable individuals on ART and to improve outcomes, the World Health Organization (WHO) endorsed and recommends the appointment spacing model of care (ASM) by the end of 2014 [11]. In the appointment spacing model of care, patients are expected to have a clinical visit in health facilities twice a year only. In the standard of care, patient is required to attend frequent clinical visit that are usually every three-month appointment period [1]. ASM provides safer, discreet, and more accessible healthcare options, implemented for stable patients on ART. This model of care provides clinical check-ups, laboratory monitoring, and antiretroviral drug refills every six months, which is very important to treat all and to improve quality of life with better treatment outcomes, including viral suppression [8, 12]. ASM is vital for relieving unnecessary burden on healthcare facilities and clinicians as well as meeting the needs of care recipients [9]. Ethiopia adopted ASM of service delivery by the end of 2017 as a continuum of care, and enrolled 69,074 patients [1, 13].

Despite WHO's recommendation for innovative approaches, such as ASM, to address HIV/AIDS-related problems [14-17], different pieces of literature revealed that virological non-suppression is still high and remains a public health problem that leads to high number of AIDS-related morbidity, mortality, and increased number of new HIV infections. Monitoring and evaluating the model was an important part of the implementation of service. However, there is a paucity of information about the effectiveness of ASM on virological suppression in many resource-limited settings, including Ethiopia. Therefore, the purpose of this study was to assess the level and trends of viral suppression before and after ASM, which is vital to show the effect of ASM on virological suppression, and identify its' associated factors among patients enrolled into ASM in public health facilities of Debre Markos town. Therefore, this information can be helpful for healthcare professionals, policy-makers, and governmental and non-governmental organizations in enhancing the implementation of ASM and development of an evidence-based intervention to improve the survival of individuals on ART.

Material and methods

Study design and setting

An institution-based interrupted time series design was conducted at public health facilities in Debre Markos town from October to November, 30, 2020, including medical records until June, 2020. Debre Markos is capital town of the East Gojjam Zone, located 300 kilometers Northwest from Addis Ababa, the capital city of Ethiopia, and 265 kilometers from Bahir-Dar, the capital of the Amhara Regional State. The town has four public health facilities, which provide ART services for the town and catchment area population. Debre Markos Health Center and Debre Markos Referral Hospital started to implement ASM and viral load tests, whereas Wuseta and Hidase Health Centers do not provide ASM. According to health management information system (HMIS) reports, there were a total of 5,060 patients on ART in Debre Markos, out of which, 3,168 patients were enrolled into ASM until June, 2020.

Population and sample

All adult HIV patients, who were enrolled into ASM for HIV care and treatment, were the source population. Study population included those patients, who had at least two viral load measurements before, and two viral load measurements after ASM in the selected public health facilities. Patients who were lost to follow-up, discontinued ASM, died, and were transferred out of the catchment area were excluded, since all have a great impact on the outcomes' variables. Target sample size was calculated by considering a previous study report, where 68% of patients had virological suppression in the standard of care (three months follow-up) and 79% had viral suppression after being enrolled into ASM [18]. Using G-power version 3.1.9.4 software, and by assuming 5% margin of error, 95% level of confidence, and 80% power, the sample size to determine viral suppression was calculated using the following formula:

$n = (p1q1 + p2q2)\ (f(\alpha,\beta))\ /\ ((p1 - p2)^2$

The final sample size was 276 individuals after a 10% attrition rate. A simple random sampling technique with proportional allocations was applied to determine participants from each facility. There were 62 samples from Debre Markos Health Center (Ni(n/N) = 703; 276/3,168), and 214 from Debre Markos Referral Hospital (Ni(n/N) = 2,465; 276/ 3,168) because Wuseta and Hidase Health Centers do not provide ASM. Finally, 272 patients who met the inclusion criteria were included in the final analysis.

Study variables and operational definition

Dependent variable was virological suppression, whereas socio-demographic and clinical characteristics, such as age, sex, religion, marital status, educational level, occupation, residence disclosure status, treatment supporter, nutritional status, regimen type, adherence, isoniazid preventive therapy (IPT), cotrimoxazole preventive therapy (CPT), WHO clinical stages, TB co-infection, functional status, and opportunistic infections other than TB predictor variable, were all collected. Virological suppression was defined as viral load below the detected threshold using viral assay (< 1,000 copies of viral RNA/ml of blood) after taking plasma and separated from whole blood [1, 19]. Appointment spacing model included stable adult patients, who were offered the opportunity to provide six months of ART, with a clinical follow-up after each visit [20].

Stable patient was defined as an individual of > 15 years old and on ART for at least one year, no adverse drug reactions requiring regular monitoring, good understanding of life-long adherence, two consecutive viral load measurements < 1,000 copies/ml, with no acute illness, and not pregnant/breastfeeding [20]. Drug adherence was defined as the percentage of doses taken as prescribed, using a number of doses missed in the last one month; good if was equal to or greater than 95% adherence (i.e., missing only 1 out of 30 doses, or missing 2 out of 60 doses); fair if patient was taking 85-94% of the prescribed medications; and poor if there was less than 85% adherence [1]. However, drug non-adherence was defined if there was a history of at least one poor or fair drug adherence throughout the study period.

Data collection and quality control

Data were collected using an extraction checklist prepared in English and extracted from HMIS reports, patient medical charts, and computer databases. Four data collectors (two data clerks, and two monitoring and evaluation officers) and two supervisors, who were working at ART treatment initiation centers were recruited. Two days intensive training on objectives of the study, and how to review documents as well as confidentiality of information was provided to data collectors and supervisors. Before data collection, records (both baseline and follow-up) were reviewed and identified by medical registration.

Data management and analysis

Data were verified for completeness, then edited, coded, and entered using Epi-data version 3.1, and exported to STATA version 14 software for analysis. Descriptive statistics, including frequencies, proportions, and scatter plots to show the patterns and trends were computed to summarize the variables. For the goodness of fit of the model, R and adjusted R^2 were used. The presence of first-order autocorrelation was tested by using Durbin-Watson (DW) statistics and co-linearity as well as multi co-linearity between independent variables were assessed by a variance inflation factor (VIF) and tolerance test. A logistic segmented regression model was applied to estimate trend and level changes from pre-intervention to post-intervention.

Level and trend changes VL before and after ASM at public health facilities in Debre Markos town using a segmented regression model were estimated. The following multivariable regression model was specified to estimate the level and trend of virological suppression among patients enrolled into ASM: $Yt = \beta_0 + \beta_1 \text{time } t + \beta_2 \text{ intervention } t + \beta_3 \text{ time after intervention } t + \text{et.}$, where: Yt is the mean virological suppression per patient in a month; t time is a continuous variable indicated in months at time t from the start of the observation period; intervention is an indicator for time t occurring before (intervention = 0) or after (intervention = 1) ASM, which was implemented at month 30 in the series; and time after the intervention is a continuous variable containing the number of months after the intervention at time t coded as 0 before ASM and (time-24) after ASM. In this model, β_0 is the baseline levels of the outcome; mean virological suppression per patient per month, at time zero; β_1 is the change in the trend of virological suppression per patient for each observation; β_2 is the level change just after the intervention; and β_3 estimates the change in the trend of virological suppression per patient after the implementation of ASM, which compares the trend before ASM and after ASM. The sum of β_1 and β_3 is the post-intervention slope. To estimate the level and trend change associated with the intervention, controlling of baseline level and trends were applied. The error term (et) at time t represents random variability not explained by the model. Parameter estimates from the segmented regression model effects of ASM on virological suppression; adherence was included in the model since it was the most influential variable in this study.

Regression coefficients with a 95% confidence interval (CI) were used to determine the strength of the association between the dependent and independent variables. Variables with a p-value < 0.05 in the segmented regression

Table 1. Socio-demographic and clinical characteristics of patients on ART enrolled into ASM at public health facilities of Debre Markos town, Northwest Ethiopia, 2020 (*n* = 272)

Variables	Frequency	Percentage
Sex		
Female	153	56.25
Male	119	43.75
Residence		
Urban	254	93.38
Rural	18	6.62
Catchment		
Within the catchment area	197	72.43
Out of the catchment area	75	27.57
Religion		
Orthodox	260	96.00
Muslim	11	4.00
Protestant	1	0.40
Marital status		
Single	128	47.06
Divorced	65	23.90
Widowed	53	19.49
Married	26	6.56
TB co-infection		
Yes	3	1.10
No	269	98.90
Treatment supporter		
Yes	255	93.75
No	17	6.25
Disclosure status		
Disclosed	255	93.75
Not disclosed	17	6.25
Adherence		
Good	246	90.44
Fair	3	1.10
Poor	23	8.46
INH status		
Completed	215	79.04
Discontinued	52	18.75
On treatment	6	2.21
CPT status		
Completed	216	79.41
Discontinued	45	16.54
On treatment	11	4.04

CPT – cotrimoxazole prophylactic therapy, INH – isoniazid

model were considered as statistically significant predictors of virological suppression.

Ethical consideration

This study was conducted in accordance with the Declaration of Helsinki. Ethical clearance was obtained from the Ethical Review Committee of Debre Markos University College of Health Science. A permission letter was obtained from the Zonal Health Office of Debre Markos town, and oral permission was also obtained from the respective health facility local person to use the data for the purpose of this study. Since retrospective data were used, the need of informed consent was waived by Ethical Review Committee of Debre Markos University College of Health Science. Moreover, name or any other identifying information was not recorded on the questionnaire, and all information taken from medical charts were kept securely in locked cabinets.

Results

Socio-demographic and clinical characteristics

A total of two hundred seventy-two adults on ART and enrolled into ASM were included in the analysis, which gives a response rate of 98.60%. More than half (56.25%) of the patients were females, and majority (95.59%) of the participants were Orthodox Christian followers. Nearly half (47%) of the individuals were never married, and majority (93.68%) were urban dwellers. Most of the respondents (90.44%) had good adherence, and 71.58% of the patients were within the catchment areas. More than three-fourth (79.65%) of the cases completed CPT, and majority (93.75%) of the participants disclosed their HIV status and had treatment supporter (Table 1).

Level and trends of virological suppressions

All participants were suppressed when enrolled into ASM, while 90% of them remained virologically suppressed by the end of the study. With the baselines, there was also an abrupt drop in changes from segment-to-segment in the series (Figure 1).

Two years of virological measurements in the standard treatment (every three months), and two years of virological measurements after the implementation of ASM were taken into account. Since virological measurements were done every six months, four virological measurements before the implementation of ASM and four measurements after the start of ASM were considered. From this observation, the proportion of viral load was decreased from 97% to 85.33% (Table 2).

Estimating change in the level and trend through segmented regression

Results from this study indicate that the change (slope) in VS was positive, estimated as a 0.6 percentage point increase per time segment (*p*-value for baseline trend = 0.06). Right after ASM, VS dropped abruptly by 3.2, with a significant change in VS after ASM (p-value for trend change = 0.001). After step-wise elimination of none of the significant terms, the most parsimonious model contained trend and level changes (Table 3).

Virological suppression related to associated factors

The regression coefficient for VL suppression related to adherence problem β_2 was –1.5, which was statistically significant ($p < 0.004$). This showed that there was a decreased level of VL associated with the adherence problems of patients after enrolling into ASM. The trend of VL was decreasing, and β_3 (–0.36) was statistically significant ($p = 0.003$), which revealed there was a decrease in the trends of VL suppression rate after the implementation of ASM. Patients enrolled into ASM with history of poor/fair adherence had a decrease in the level and trend of VL suppression rate. The trend after the implementation was decreased by 1.38, which was significant ($p = 0.007$, 95% CI: –2.2 to –0.5%); there was a gradual decline in virological suppression. We found that the trend and level change were significantly associated with adherence 1.5 ($p = 0.004$; 95% CI: 1.1-6.05%) (Table 4).

Discussion

The interrupted time series (ITS) study is a valuable and strong quasi-experimental approach for evaluating the longitudinal effects of a population-level health intervention that has been implemented [21]. In this study, the baseline trend of viral load suppression was not significant, which showed that there were no significant changes in the trends as compared with pre-enrollment into ASM. However, there were noticeable changes in the baseline level, which indicated that there was a significant level change from segment-to-segment in the series, both before and after enrollment into ASM. The study also found that there were significant changes in virological suppression trends after enrolling into ASM HIV care, as shown by the overall segmented regression model, compared with before patients' enrollment into ASM care and baseline trends. The trend after the implementation was decreased by 1.38, and there was a gradual decline in virological suppression. The current study also re-

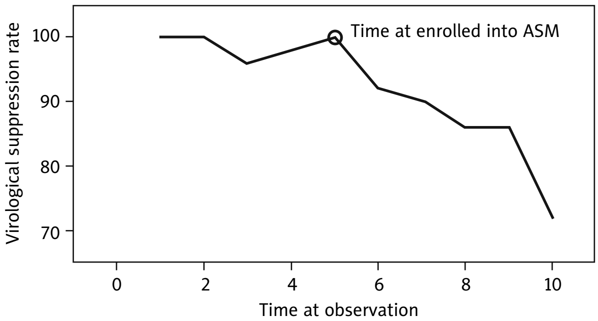

Figure 1. Trends and levels of virological suppression among HIV patients on ART before and after enrollment into ASM at public health facilities of Debre Markos town, Northwest Ethiopia, from 2016-2020

Table 2. Virological suppression of HIV-positive patients on ART before and after enrollment into ASM in public health facilities of Debre Markos town

Variable	Number of observations	Proportion	Standard deviation	Minimum	Maximum	95% CI
Virological suppression before ASM	4	97.00	3.829	92	100	81.6-110.3%
Virological suppression after ASM	4	85.33	10.172	70	100	67.3-96.7%

ASM – appointment spacing model.

Table 3. Parameter estimates, standard errors, and p-values from the full and most parsimonious segmented regression models predicting mean virological suppression per patient per month in public health facilities of Debre Markos town over time

Parameter	Coefficient	Standard error	t-statistics	p-value	95% CI
Full segmented regression model					
Intercept β_0	99.22	2.258	43.94	< 0.001	86.7-105.3%
Baseline trend β_1	0.605	0.264	2.29	0.06	–0.04-1.2%
Level change after ASM β_2	–3.2	3.821	25.12	< 0.001	93.7-104.8%
Trend change after ASM β_3	–0.771	0.124	–6.21	0.001	–1.08 - –0.5%
Most parsimonious segmented regression model					
Level β_2	–3.238	4.439	0.73	0.04	–7.6 - –4.09%
Trend change after ASM β_3	–1.376	0.340	4.04	0.007	–2.2 - –0.5%

Table 4. Virological suppression and adherence

Variables	Coefficient	Standard error	*p*-value	95% CI
VL associated with adherence	–2.13	0.24	0.007	–11.30-5.1%
β_0 (slop before ASM)	99.5	22.4	> 0.001	57.7-132.9%
β_1 (trend before ASM)	98.0	6.5	> 0.0001	51.32-115.0%
β_2 (slop change after ASM)	–1.5	1.10	0.004	1.1-6.0%
β_3 (trend change after ASM)	–0.36	0.49	0.003	–2.11-3.55%

vealed that the mean virological suppression was 97% before the implementation of ASM and was 85% after ASM, with the overall mean virological suppression of 90%. Changes in trend and level of VS were found significantly associated with adherence, but no other variables were noted to be significantly related to changes in trend and level of VS.

After ASM implementation, the proportion of patients with less than 1,000 copies of viral load per milliliter of blood was 96%, which was higher than in previous studies conducted in other parts of Ethiopia, Amhara Regional Referral Hospitals (91.3%) [22], Tigray Region (91%) [23], Uganda (89%) [24], Botswana (70.2%) [25], South Carolina (82.00%) [26], and Latin America (92.2%) [27]. Our study's higher proportion of viral suppression could be attributed to differences in study participants and ART regimens. Accordingly, the majority of our study participants had good adherence and they were from urban residences, and they might have access to healthcare facilities that did not require walking long distances to obtain HIV care services. This could make them to take their medication on time, which would have an impact on control of viral replication and improvement of immunological status [28, 29]. Previous studies have demonstrated that those patients, who live far from healthcare facilities with services offered, had delayed healthcare-seeking behavior, which in turn leads to virologic-non suppression [30, 31]. The other possible explanation could be that most of our study participants disclosed their HIV status and had treatment supporters, which could be a factor contributing to their effective intake of medication; a study showed that the role of treatment supporter is far more significant, and beyond monitoring the daily intake of drugs [32]. Poor ART adherence was shown to be associated with a lack of family support and not disclosure of HIV status, and resulted in poor immunological and virological treatment outcomes [33, 34]. It can also be due to the recent implementation of ASM in the study area. A previous study revealed that disparities in engagement in care had an impact on viral suppression [35]. Another difference could be that patients enrolled in ASM, who take their medication at six-month intervals, might place their medications in inappropriate places at home. This could have an impact on drug safety due to inconvenient location of the drug storage at home for a long time, which could reduce the effectiveness of drugs [36].

In the present study, there was a significant decrement in the level and trend of virological suppression for individuals enrolled into ASM HIV care, which was significantly affected by poor adherence. Adherence was identified as a potential associated factor for virological suppression in the current study, both before and after enrolling into ASM. This study finding was supported by previous studies conducted in Northern Ethiopia [14, 37], United States [38], South Carolina [39], Uganda [24], Mozambique [40], France [41], China [42], and sub-Saharan Africa [43]. Poor adherence results in a loss of the opportunity to suppress viral replication, and eventually leads to virological failure [44]. This is because, as the drug concentration decreases in the blood, the viral load might not be suppressed, which in turn leads to an increase in the viral load. Findings from systematic review and meta-analysis showed that improved adherence results in an increased likelihood of achieving viral suppression [45]. This suggests that an effort should be made to strengthen adherence counseling at the facility and community levels [46], and careful assessment of adherence for the day preceding the visit may provide an efficient and reliable adherence measure for ART patients [47]. This study has implications for clinicians, public health experts, and patients at large. In order to successfully implement the new ASM, efforts should be made to improve the adherence of patients. Global recommendations, such as SMS or telephone call reminders as well as patient-managed community adherence and support groups, should be practiced in the study setting. That could play an active role in supporting adherence to treatment.

Limitations

There were several limitations to this study. First, this study was based on secondary data obtained from patients' medical records and registers. As a result, potentially important variables, such as a lack of laboratory results, including CD4+ count, hemoglobin tests, and organ function tests to determine their relationship with the level and trend changes of virological suppression, were not assessed. It was also difficult to quantify the reasons for VL documentation problems. Second, the implementation of ASM is continuous and semi-annual, which restricts us to collect monthly data, not showing the month-to-month trend and level changes. Moreover, interrupted time series design cannot exclude confounding due to co-interventions or other events occurring around the time of the intervention. Finally, with the adoption of the new model of care within the study settings, the sample size and number of years of data were small, and a longer follow-up as well as a large sample size would be required to assess long-term trends of ASM.

Conclusions

This study showed that individuals on ART and enrolled into ASM had shown decreased trends and levels of virological suppression, especially those patients, who had adherence problems were at the greatest risk of decreased levels and trends in virological suppression. Overall, the findings showed that the new ASM implemented in August 2018, could not be a successful public health intervention, unless the adherence of patients on ART throughout the clinical visit is maintained. This suggests that efforts should be made to improve the adherence of individuals, and to maintain the trend and level of changes in a positive way. Healthcare providers, case managers, and treatment supporters should provide continuous counselling on the importance of life-long adherence to treatment outcomes, including virological suppression. In addition, supportive supervision with the capacity of building for care providers by offering special training on adherence and ASM should be given. Further study with large number of health facilities is also recommended to measure the effectiveness of ASM in the overall VL suppression at the population level.

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Conflict of interest

The authors declare no conflict of interest.

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