

Prevalence and Factors Associated with Delayed Initiation of Antiretroviral Therapy Among People Living with HIV in Nekemte Referral Hospital, Western Ethiopia

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Background: Ethiopia has adopted the “Universal Test and Treat” strategy to its national policy in 2016 to put all people living with HIV/AIDS (PLHIV) on antiretroviral therapy (ART) regardless of their World Health Organization (WHO) clinical stage or CD4 cell count level. A significant percentage of PLHIV start therapy has been delayed despite the availability of ART, which results in poor treatment outcomes including HIV-related morbidity and mortality, and continued HIV transmission.

Methods: This cross-sectional study was conducted to determine the magnitude and associated factors of delayed ART initiation among PLHIV at ART Clinic, Nekemte Referral hospital, Western Ethiopia between January 1, 2020 and March 31, 2020 for the time period of January 1, 2016 to December 31, 2019. A consecutive sampling method was used to recruit 417 study subjects. The collected data were entered into Epi data version 3.1 and exported to STATA version 14 for statistical analysis. Logistic regression analysis was used to identify associated factors with delayed ART initiation among PLHIV. *P*-values<0.05 were used to declare significant association.

Results: A total of 417 PLHIV were included in the study. The mean age of study subjects was 33.49 (SD±9.81) years. The majority of participants attended formal education (77%) and were urban dwellers (82%). One-third (34%) of them initiated ART delayed, beyond 7 days of confirmed HIV diagnosis. Subjects with normal nutritional status (BMI=18.5–24.9kg/m²) (AOR=3.12, 95% CI=1.29–7.57; *P*=0.012), CD4 count ≥351cells/mm³ (AOR=2.89, 95% CI=1.27–6.58; *P*=0.011), tuberculosis (TBC) co-infection (AOR=2.76, 95% CI=1.13–6.70; *P*=0.025), use of traditional treatment (AOR=4.03, 95% CI=2.03–8.00; *P*<0.001) and did not know other ART user(s) (AOR=2.86, 95% CI=1.52–5.37; *P*=0.001) were significantly associated with delayed ART initiation.

Conclusion: Early HIV testing mechanisms and timely linkage to HIV care by advocating “Test-and-Treat” should be strengthened.

Keywords: PLHIV, antiretroviral therapy, Western Ethiopia

Background

By the end of 2019, there were 37.9 million people living with HIV infections worldwide, two-thirds of them in sub-Saharan Africa. Two million people were newly infected with HIV and 770,000 people died of AIDS-related causes. Two-thirds of eligible individuals accessed antiretroviral therapy worldwide. In 2018,

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more than half a million people were estimated to be living with HIV/AIDS in Ethiopia. Two-thirds of eligible individuals were put on ART.^{1,2}

In 2015, the joint United Nations Program on HIV/AIDS set the Fast-Track target to reduce new HIV infections and HIV-related deaths to fewer than 500,000 in 2020 and end the HIV epidemic worldwide by 2030. The Fast-Track targets include the 90-90-90 strategy: 90% of people living with HIV know their status, 90% who know their HIV status access ART, and 90% of people receiving ART have suppressed viral loads. Since then, the World Health Organization has declared the “Universal Test and Treat” by endorsing initiation of ART within 7 days of confirmed HIV diagnosis. Ethiopia initiated “Test and Treat” in 2016 and committed to reducing new adult HIV infections by 50% by 2020 and to ending AIDS as a public health threat by 2030. Despite ART benefit in “treat all” policy, challenges remain in PLHIV to ensure timely access to HIV care from resource poor settings.^{3–9}

Challenges to HIV care in PLHIV include, but are not restricted to, individual-level, clinical, and health facility-related factors. Individual-level factors contributing to delayed ART initiation included low literacy status, poor economic status, and rural residence. Working functional status, TBC co-infection, and high baseline CD4 count were among a few clinical predictors of delayed ART initiation. As well, health facility type, distance from ART center, perceived confidentiality of HIV records, and perceived home-based care affected timing of ART initiation.^{14–28}

This study is the first of its kind at national-level to determine the magnitude and associated factors of delayed ART initiation among PLHIV after WHO endorsed “Universal Test and Treat” strategy.

Methods

Study Design and Period

An institution-based cross-sectional study was conducted at ART Clinic, Nekemte Referral Hospital, Western Ethiopia between January 1, 2020 and March 31, 2020 for the time period of January 1, 2016 to December 31, 2019.

Study Setting

The hospital is located in Western Ethiopia, which is 321 km away from the capital, Addis Ababa. The hospital has more than 295 beds and gives services to a catchment population

of three million people. The hospital provides integrated ART services and currently about 3500 PLHIV were on treatment and of them nearly 1500 PLHIV were tested and initiated ART after “Test and Treat” strategy was implemented. HIV testing strategies in the ART center were voluntary counseling and testing (VCT) and provider-initiated testing and counseling (PITC). The HIV treatment cascade in the ART center was adopted from the WHO model that outlines the steps of care that PLHIV go through from initial diagnosis to achieving viral suppression. The cascade embraces linking and retaining of PLHIV in HIV care after confirmed HIV diagnosis. Rapid ART will be initiated in those retained in HIV care. Achieving viral suppression is the goal of ART.

Study Subjects and Variables

The source population was PLHIV on ART who had follow-up at ART Clinic, Nekemte Referral hospital. The study population was PLHIV who had follow-up at ART Clinic, Nekemte Referral hospital, aged 18 years and above, and initiated ART between January 1, 2016 and December 31, 2019. Individuals whose date of HIV diagnosis and ART initiation were not recorded were excluded from the study.

Study Variables

Dependent variable: Delayed initiation of ART.

Independent variables: 1) Socio-demographic characteristics include age, sex, religion, level of education, marital status, occupation, income level, and residence; 2) Clinical characteristics include base line CD4 count, WHO clinical stage, functional status, nutritional status, TB/HIV co-infection, and HIV testing approach; 3) Behavioral factors include alcohol use, use of traditional treatment, and knew ART user(s).

Sample Size and Sampling Procedure

The sample size was determined using a single population proportion formula with the assumption of 95% confidence level, 5% margin of error, and taking 50% magnitude of delayed ART initiation. The consecutive sampling method was used to recruit 417 study subjects among those who initiated ART between January 1, 2016 and December 31, 2019.

Data Collection Instrument and Procedures

Data were collected through an investigator administered pre-designed questionnaire. The questionnaire was prepared in English and translated into local languages, Amharic and

Afan Oromo, for data collection and then re-translated back to English with maintaining its consistency. The patients' charts were retrieved by using the patients' registration number from the database. Patients were interviewed to obtain socio-demographic data. Relevant medical history and laboratory parameters were obtained from patients' HIV intake and follow-up care form. One supervisor (BSc Nurse) and two data collectors (Clinical Nurses) participated in the data collection process. Quality of data was ensured through training and supervising of data collectors.

Data Analysis

Data were entered into a computer using EPI data version 4.4.1 statistical program. Data were cleaned and exported to STATA windows version 14.0 for analysis. Patient characteristics were reported as counts (percentages) for categorical variables, and mean with standard deviation for continuous variables. Both bi-variable and multi-variable logistic regression analyses were used to identify associated factors with delayed ART initiation. Those variables with a P -value <0.2 in the bi-variable analysis were exported to multi-variable analysis to control the possible effect of confounders. Adjusted odds ratio (AOR) with 95% confidence interval (CI) and P -value <0.05 were used to select significantly associated variables with delayed ART initiation.

Ethical Considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) of College of Medicine and Health Sciences, University of Gondar. A formal letter of permission was obtained from Nekemte Referral hospital administrative body. Study subjects were recruited only after informed written consent was obtained from them. All data obtained were treated confidentially.

Definition of Terms

Delayed ART initiation was defined as receiving ART at any time after 7 days of post-HIV diagnosis in those who have no opportunistic infections (OIs).^{5,7} For those diagnosed and found to have both HIV and OI(s) at the same time, delayed ART initiation was defined as ART initiation after 2 months following anti-TBC regimen started,^{5,10} ART initiation after 4 weeks following amphotericin B-based regimen or after 6 weeks following fluconazole based regimen started for Cryptococcal meningitis,^{5,11} or ART initiation after 2 weeks following *Pneumocystis jirovecii* pneumonia (PCP) treatment started.¹²

Functional status is defined by WHO, working as able to perform usual work inside or outside home; ambulatory as able to perform Activity of Daily Living (ADL) but not able to work; bedridden as not able to perform ADL.

Traditional healing refers to health practices, approaches, knowledge, and beliefs incorporating plant, animal, and mineral-based medicines, spiritual therapies, manual techniques, and exercises, applied singularly or in combination to treat, diagnose, and prevent illnesses or maintain well-being.¹³

Results

Socio-Demographic Characteristics of Study Participant

A total of 417 PLHIV were included in the study. The mean age of study subjects was 33.49 (SD \pm 9.81) years. The majority of participants were females (55%), married (57%), and Christian by religion (54%). Most respondents attended formal education (77%) and were urban dwellers (82%) (Table- 1).

Clinical Characteristics of Study Participants

Most study subjects had working functional status (83%). Two-thirds of participants (64%) had early stage HIV infection (clinical stage I and II). The mean CD4 count was 321 (SD \pm 221) cells/mm³, and less than half (44%) had CD4 count >446 cells/mm³. Two-thirds (62%) had normal nutritional status (body mass index (BMI)=18.5--24.9 kg/m²) and were screened for HIV by PITC (58%). Ten percent of respondents were co-infected with TBC (Table-2).

Behavior-Related Characteristics

The majority (60%) of study subjects visited traditional healer(s) before they enrolled into HIV care. Less than half (42%) of participants knew other ART user(s). Two-thirds (59%) used alcohol as substance before knowing their HIV status.

Health Facility-Related Characteristics

Most study subjects (82%) came from the catchment area of the ART center. The majority (58%) of PLHIV were enrolled into HIV care via PITC.

Table 1 Socio-Demographic Characteristics of PLHIV Attending ART Services at Nekemte Referral Hospital, Western Ethiopia, January 1–March 31, 2020 (n=417)

Types of Variables	Freq. (%)	Delayed ART Initiation		X ² -value/df	P-value
	Total (%)	Yes (%)	No (%)		
Age					
18–25	112 (26.9)	35 (31.3)	77 (68.7)	X ² =6.7 df=3	0.08
26 – 33	112 (26.9)	44 (39.3)	68 (60.7)		
34–41	112 (26.9)	29 (25.9)	83 (74.1)		
≥42	81 (19.3)	33 (40.7)	48 (59.3)		
Gender					
Female	228 (54.7)	77 (33.8)	15 (66.2)	X ² =0.0004 df=1	0.98
Male	189 (45.3)	64 (33.9)	125 (66.1)		
Marital status					
Married	236 (56.6)	71 (30.1)	165 (69.9)	X ² =6.8 df=3	0.08
Single	80 (19.2)	26 (32.5)	54 (67.5)		
Divorced	78 (18.7)	32 (41.0)	46 (59.0)		
Widowed	23 (5.5)	12 (52.2)	11 (47.8)		
Level of Education					
Cannot read and write	97 (23.3)	47 (48.5)	50 (51.5)	X ² =13.2 df=3	<0.01
Primary school (1–8)	141 (33.8)	45 (31.9)	96 (68.1)		
Secondary school (9–12)	70 (16.8)	21 (30.0)	49 (70.0)		
College & above	109 (26.1)	28 (25.7)	81 (74.3)		
Occupational status					
Unemployed	12 (2.9)	5 (41.7)	7 (58.3)	X ² =6.6 df=7	0.48
Student	28 (6.7)	7 (25.0)	21 (75.0)		
Gov't employed	76 (18.2)	25 (32.9)	51 (67.1)		
Daily labor	39 (9.3)	16 (41.0)	23 (59.0)		
Farmer	47 (11.3)	10 (21.3)	37 (78.7)		
Merchant	45 (10.8)	17 (37.8)	28 (62.2)		
Housewife	135 (32.4)	50 (37.0)	85 (63.0)		
Others*	35 (8.4)	11 (31.4)	24 (68.6)		
Religion					
Protestant	225 (54.0)	68 (30.2)	157 (69.8)	X ² =5.2 df=3	0.16
Orthodox	149 (35.7)	54 (36.2)	95 (63.8)		
Muslim	38 (9.2)	18 (47.4)	20 (52.6)		
Other**	5 (1.1)	1 (20.0)	4 (80.0)		
Residence					
Urban	343 (82.3)	111 (32.4)	232 (67.6)	X ² =1.8 df=1	0.18
Rural	74 (17.7)	30 (40.5)	44 (59.5)		

Notes: *Car servant, house servant. **Catholic, Wakefata.

Delayed Antiretroviral Therapy Initiation

Among a total of 417 study subjects who commenced ART, 34% of participants initiated ART delayed, beyond 7 days of confirmed HIV diagnosis. Among delayed

initiators, 80% of them initiated 8 days to 8 weeks, the remaining 20% started after 8 weeks. Nearly half (46%) of TBC co-infected cases started ART delayed (after 2 months).

Table 2 Clinical Characteristics of PLHIV Attending ART Services at Nekemte Referral Hospital, Western Ethiopia, January 1–March 31, 2020 (n=417)

Types of Variables	Freq. (%)	Delayed ART Initiation		X ² value/df	P-value
	Total (%)	Yes (%)	No (%)		
Baseline CD4 count					
≤150/mm ³	78 (18.7)	16 (20.5)	62 (79.5)	X ² =13.6 df=2	<0.01
151–350/mm ³	159 (38.1)	48 (30.2)	111 (69.8)		
>350/mm ³	180 (43.2)	77 (42.8)	103 (57.2)		
WHO clinical stage					
WHO stage I	155 (37.1)	66 (42.6)	89 (57.4)	X ² =11.6 df=3	<0.01
WHO stage II	110 (26.4)	37 (33.6)	73 (66.4)		
WHO stage III	123 (29.5)	33 (26.8)	90 (73.2)		
WHO stage IV	29 (7.0)	5 (17.2)	24 (82.8)		
Functional status					
Working	346 (83.0)	126 (36.4)	220 (63.6)	X ² =6.3 df=2	0.04
Bed ridden	37 (8.9)	7 (18.9)	30 (81.1)		
Ambulatory	34 (8.1)	8 (23.5)	26 (76.5)		
TBC Co-infection					
Yes	41 (9.8)	19 (46.3)	22 (53.7)	X ² =3.2 df=1	0.07
No	376 (90.2)	122 (32.4)	254 (67.6)		
Nutritional status (BMI)					
Normal (18.5–24.9 kg/m ²)	259 (62.1)	99 (38.2)	160 (61.8)	X ² =6.4 df=2	0.04
Mild underweight (17.0–18.5 kg/m ²)	94 (22.5)	27 (28.7)	67 (71.3)		
Moderate/severe underweight (<17.0 kg/m ²)	64 (15.4)	15 (23.4)	49 (76.6)		
HIV testing approach					
PITC	240 (57.6)	91 (37.9)	149 (62.1)	X ² =4.3 df=1	0.04
VCT	177 (42.4)	50 (28.2)	127 (71.8)		

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; PLHIV, people living with HIV/AIDS; df, degree of freedom; PITC, provider-initiated testing and counseling; TBC, tuberculosis; VCT, voluntary counseling and testing; X², chi-square value.

Factors Associated with Delayed Antiretroviral Therapy Initiation

Binary logistic regression was done to determine the association between each independent variable with delayed antiretroviral therapy initiation. On multivariable binary logistic regression analysis, subjects with normal nutritional status (BMI=18.5–24.9 kg/m²) (AOR=3.12, 95% CI=1.29–7.57; *P*=0.012), CD4 count ≥351 cells/mm³ (AOR=2.89, 95% CI=1.27–6.58; *P*=0.011), TBC co-infection (AOR=2.76, 95% CI=1.13–6.70; *P*=0.025), use of traditional treatment (AOR=4.03, 95% CI=2.03–8.00; *P*<0.001), and did not know other ART user(s) (AOR=2.86, 95% CI=1.52–5.37; *P*=0.001) were signifi-

cantly associated with delayed ART initiation. Delayed antiretroviral therapy initiation was 59% (AOR=0.41, 95% CI=0.18–0.91; *P*=0.03) lower among those who came from out of the catchment area of ART center (Table 3).

Discussion

This is the first study in Ethiopia to report the promising result of the “Test and Treat” strategy for newly HIV infected patients. Two-thirds of study subjects initiated ART early, within 7 days, and nearly half (45%) initiated ART on the same day of confirmed HIV diagnosis. Recent analysis of routine data in Zimbabwe and South Africa revealed 72% and 67%

Table 3 Bivariable and Multivariable Analysis for Delayed Antiretroviral Therapy Initiation (DARTI) Among PLHIV on ART at Nekemte Referral Hospital, West Ethiopia, January 1–March 31, 2020 (n=417)

Variables	Category	DARTI		Bivariable Analysis		Multivariable Analysis		
		Yes	No	COR	95% CI	AOR	95% CI	P-value
Marital status	Married	71	165	1.00	–	1.00	–	–
	Single	26	54	1.12	0.65–1.93	1.17	0.55–2.45	0.675
	Divorced	32	46	1.62	0.95–2.75	1.18	0.58–2.39	0.633
	Widowed	12	11	2.54	1.07–6.02	2.26	0.73–7.04	0.156
Educational Level	Cannot read and write	47	50	2.71	1.51–4.88	1.54	0.72–3.30	0.258
	Primary school	45	96	1.35	0.77–2.36	1.22	0.60–2.50	0.574
	Secondary school	21	49	1.23	0.63–2.41	0.67	0.28–1.60	0.374
	College & above	28	81	1.00	–	1.00	–	–
Residence	Rural	30	44	1.42	0.85–2.38	1.87	0.91–3.84	0.086
	Urban	111	232	1.00	–	1.00	–	–
CD4 count	≤150	16	62	1.00	–	1.00	–	–
	151–350	48	111	1.67	0.87–3.19	1.46	0.64–3.29	0.359
	>351	77	103	2.89	1.55–5.40	2.89	1.27–6.58	0.011
WHO clinical stage	Stage I	66	89	3.55	1.29–9.81	2.98	0.73–12.06	0.124
	Stage II	37	73	2.43	0.85–6.89	2.86	0.70–11.72	0.142
	Stage III	33	90	1.76	0.62–4.99	2.12	0.51–8.68	0.296
	Stage IV	5	24	1.00	–	1.00	–	–
Functional status	Working	126	220	2.45	1.04–5.75	2.92	0.90–9.39	0.721
	Ambulatory	8	26	1.31	0.42–4.13	2.84	0.65–12.29	0.162
	Bed ridden	7	30	1.00	–	1.00	–	–
TB Co-infection	Yes	19	22	1.79	0.93–3.44	2.76	1.13–6.70	0.025
	No	122	254	1.00	–	1.00	–	–
Nutritional status	Normal	99	160	2.02	1.07–3.79	3.12	1.29–7.57	0.012
	Mild underweight	27	67	1.31	0.63–2.73	2.62	0.95–7.21	0.061
	Moderate/severe underweight	15	49	1.00	–	1.00	–	–
Alcohol use before ART	Yes	94	153	1.60	1.05–2.45	1.04	0.59–1.86	0.870
	No	47	123	1.00	–	1.00	–	–
Visit traditional healer	Yes	105	145	2.63	1.68–4.11	4.03	2.03–8.00	0.000
	No	36	131	1.00	–	1.00	–	–
Knew ART user(s)	Yes	45	129	1.00	–	1.00	–	–
	No	96	147	1.87	1.22–2.86	2.86	1.52–5.37	0.001
HIV testing approach	PITC	91	149	1.55	1.02–2.35	1.72	0.96–3.08	0.068
	VCT	50	127	1.00	–	1.00	–	–
Site of ART center	Within catchment	125	215	1.00	–	1.00	–	–
	Without catchment	16	61	0.45	0.24–0.81	0.41	0.18–0.91	0.031

Abbreviations: ART, antiretroviral therapy; DARTI, delayed antiretroviral therapy initiation; PLHIV, people living with HIV/AIDS.

of HIV positive patients, respectively, initiated ART within 7 days, and two-thirds (65% and 64%) initiated ART on the same day of enrollment into HIV care.^{16,17} This figure indicated better linkage to ART care to implement the “treat-all” strategy. Rapid ART initiation

to all HIV positive individuals regardless of CD4 count level or WHO clinical stage improves a continuum (or cascade) of HIV care and reduces HIV-related morbidity and mortality, and curtails the spread of HIV infection.^{5,–7–9,14,15}

At present, delayed ART initiation is defined as those who started ART after 7 days of enrollment into HIV care. Odds for delayed ART initiation were 3-fold higher in subjects with a CD4 count >351 cells/mm³ (AOR=2.89, 95% CI=1.27–6.58) as compared to those with a CD4 count <155 cells/mm³. Similar findings were reported from follow-up studies in other Sub-Saharan African countries.^{18–20} Patients with a higher CD4 count might feel “too healthy” to require ART. As well, odds for delayed ART initiation were 3-fold higher in subjects with normal nutrition status (BMI=18.5–24.9 kg/m²) (AOR=3.12, 95% CI=1.29–7.57) as compared to underweight individuals. Patients with normal nutritional status could have preserved immunity and might not be clinically ill, and deferred to take ART early.

In this study, nearly half (46%) of TBC co-infected HIV patients started ART delayed (after 2 months). Subjects who had tuberculosis co-infection were 3-fold more likely to delayed ART initiation as compared to their counterparts (AOR=2.76, 95% CI=1.13–6.70). This finding was in agreement with studies from Ethiopia and other developing countries. Various ART guidelines explained uncovering diagnosis of TBC delayed ART initiation by 2–8 weeks to avoid IRIS and minimize drug toxicities.^{5,7,10,21–23}

Odds for delayed ART initiation were 4-fold higher in those who used traditional treatment (AOR=4.03, 95% CI=2.03–8.00), consistent with a report from Tigray, Ethiopia. Alternative treatment users might have poor healthcare-seeking behavior, and delayed to initiate ART.²⁴ Those who did not know ART users were 3-fold more delayed for ART initiation as compared to those who knew ART users (AOR=2.86, 95% CI=1.52–5.37). Similarly, studies in South Africa and India showed patients having an HIV positive relative or friend were more likely to start ART early. Possible explanation includes having a relative or friend already on ART could help to be familiar with HIV care. As well, subjects who knew PLHIV who disclosed their HIV status to relatives or friends got better social support to ease stigma and discrimination.^{25,26} Surprisingly, subjects out of the catchment area were 59% less likely to have delayed ART initiation (AOR=0.41, 95% CI=0.18–0.91). In contrast, studies in Sub-Saharan Africa reported the distance from HIV care site to be associated with low engagement on HIV care.^{26–28} This clinical scenario could be explained by subjects who were distant from the HIV care site might have understood benefit of ART

care, but might have low confidence to initiate ART in their locality.

Limitation of the Study

Data were cross-sectional, not longitudinal, preventing assessment of whether identified associated factors caused or resulted from delayed ART initiation. Selection bias might reduce the generalizability of the study.

Conclusions

One-third (34%) of study subjects initiated ART delayed, beyond 7 days of confirmed HIV diagnosis. Identified characteristics of patients with delayed ART initiation (DARTI) included normal nutritional status, higher CD4 count, TBC co-infection, use of traditional treatment, did not know other ART user(s) and site of ART center.

Recommendations

Early HIV testing mechanisms and timely linkage to HIV care by advocating “Test-and-Treat” should be strengthened. Intensive counseling should be reinforced to subjects who had predictive health-related characteristics towards delayed ART initiation.

Abbreviations

ART, antiretroviral therapy; ADL, activity of daily living; AOR, adjusted odds ratio; BMI, body mass index; BSc, Bachelor of Science; COR, crude odds ratio; CI, confidence interval; DARTI, delayed ART initiation; EARTI, early ART initiation; HIV, Human Immunodeficiency Virus; IRIS immune reconstitution inflammatory syndrome; OIs, opportunistic infections; PCP, *Pneumocystis jirovecii* pneumonia; PLHIV, people living with HIV/AIDS; PITC, provider initiated testing and counseling; SD, standard deviation; TBC, tuberculosis; UTT, universal test and treat; VCT, voluntary counseling and testing; WHO, World Health Organization.

Data Sharing Statement

All data generated and analyzed are included in this research article.

Ethics Approval and Consent to Participate

Ethical approval was obtained from Institutional Review Board of College of Medicine and Health Sciences, University of Gondar. Formal letter of permission was

obtained from Nekemte Referral hospital administrative body. Study subjects were recruited only after informed written consent was obtained. The research was conducted in accordance with the “Declaration of Helsinki”.

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Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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