

Magnitude of HIV and syphilis seroprevalence among pregnant women in Gondar, Northwest Ethiopia: a cross-sectional study

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Background: Human immunodeficiency virus (HIV) and syphilis are major public health problems in sub-Saharan Africa, causing numerous adverse pregnancy outcomes. The aim of study was to assess the magnitude of HIV and syphilis seroprevalence among pregnant women at University of Gondar Teaching Hospital.

Method: The study was conducted between March and May, 2012. Sociodemographic data were collected through face-to-face interview. HIV1/2 was tested following current national HIV1/2 testing algorithm. Syphilis infection was also tested using the rapid plasma reagin test for screening and *Treponema pallidum* hemagglutination as a confirmatory test. Both bivariate and multivariate analysis were used to identify factors associated with HIV and syphilis seroprevalence from selected sociodemographic variables.

Results: Of 300 women, 31 (10.33%), eleven (3.7%), and three (1%) were seroreactive for HIV, syphilis, and HIV–syphilis coinfection, respectively. High seroprevalence of HIV was found in women ages 25–30 years (13.4%), and women whose husbands attended primary school (19.7%). Syphilis was high in women occupationally housewives (15.2%) and whose husbands were illiterate (11.5%). HIV was associated with husband illiteracy (AOR [adjusted odds ratio] of 4.13, 95% CI [confidence interval] [1.01, 16.95]) and primary educational level of husbands (AOR [95% CI] =3.83 [1.50, 9.90]), whereas syphilis was associated with illiteracy of husband (AOR [95% CI] =7.25 [1.74, 30.30]).

Conclusion: Seroprevalence of HIV and syphilis was high. Low husband educational status was a risk factor for HIV and syphilis. Therefore, substantial efforts have to be made to reinforce prevention strategies and to screen as early as possible to prevent mother-to-child and further horizontal transmission.

Keywords: HIV, magnitude, seroprevalence, syphilis

Introduction

Sexually transmitted infections (STIs) including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) are an emerging public health concern, especially in developing countries.^{1–3} Globally, an estimated 1.3 billion people are suffering from STIs.^{4,5} The magnitude of STIs is high in all regions, with highest rates in World Health Organization (WHO) regions of America and Africa.^{6,7} In Africa, a significant portion of pregnant women have been suffering from STIs, and it is the major cause of maternal and perinatal morbidity.^{8–10} HIV and syphilis infections are epidemiologically interrelated, and coinfection is common.

Despite the efforts made to eliminate syphilis, the disease still continues to be a cause of morbidity and mortality worldwide.^{9,11} For several decades, syphilis had

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been considered eradicated throughout the Western world. However, its incidence is now on the rise again, and it becomes one of a major health concern. This has been linked with the rapidly rising number of HIV/AIDS positive people and population migration.¹² Globally, an estimated 12 million people test positive for syphilis each year, of which over 2 million are pregnant women.^{13,14} In Ethiopia though, there are few institutional-based, cross-sectional studies published; still, there is a lack of comprehensive national epidemiological information about syphilis.^{10,15–17} Despite the initiative launched by the WHO to eliminate congenital syphilis with the aim to achieve at list 90% antenatal syphilis screening and adequate treatment for approximately 90% seropositive pregnant women, the achievement is low due to low antenatal care (ANC) coverage.¹³

Syphilis during pregnancy has been associated with numerous adverse pregnancy outcomes such as perinatal death and disability, stillbirth, prematurity, low birth weight, neonatal mortality, and congenital syphilis.^{18–20} Also, it facilitates mother-to-child transmission of HIV.^{21,22}

HIV is another major cause of death in women of reproductive age globally.²³ Sub-Saharan Africa is the region where 90% of the total number of pregnant women with HIV have been residing.²⁴ It is also estimated that one-quarter of deaths of pregnant and postpartum women in sub-Saharan Africa are attributable to HIV.^{4,25}

HIV during pregnancy is associated with various undesirable consequences for the mother, fetus, and neonates such as maternal death, abortion, stillbirth, and low birth weight.^{26–30} Though the use of antiretroviral therapy reduces the rate of mother-to-child transmission of HIV, vertical transmission of HIV and antiretroviral therapy-induced adverse pregnancy outcomes are becoming and emerging challenges.^{31–33}

Prevention and control of STIs and improving access to STI services are critical components of the global strategies to achieve the Millennium Development Goals (MDGs) in the areas of maternal and child health (MDGs 4 and 5) and combating HIV (MDG 6).⁷ As part of these strategies, antenatal screening of HIV and syphilis plays a vital role in reducing vertical and horizontal transmission and related adverse pregnancy outcomes. However, ANC coverage and utilization is low in Ethiopia (54%), and there is also remarkably wide inequities of ANC utilization between urban and rural areas, across economic and educational stratas.^{34,35} Hence, the aim of this study was to assess the magnitude of HIV and syphilis seroprevalence among ANC attendees in the University of Gondar Teaching Hospital.

Methods

A cross-sectional study was conducted from March to May, 2012, to determine seroprevalence of HIV, syphilis, and HIV–syphilis coinfection among pregnant women. During the study period, pregnant women who were attending ANC service in the University of Gondar Teaching Hospital were invited to participate in the study.

A single population proportion formula,

$$[n = (Z\alpha/2)^2 p(1-p)/d^2] \quad (1)$$

was used to estimate the sample size. Though there are few previous studies done in this particular setting regarding seroprevalence of HIV and syphilis, the sample calculated in these studies was considered small for generating statistical inference.^{15,16} Due to this reason, 50% seroprevalence was used for sample size calculation with the intention of getting maximum sample size. Records of daily flow of pregnant women for ANC utilization indicate that, on average, 30 pregnant women visit the hospital for ANC utilization each day. During the study period, approximately 1,350 pregnant women were estimated to visit ANC clinic. Since the population during the study period was below 10,000, the sample size correction formula was applied. Then, a total of 300 pregnant women were included in the study. The study participants were chosen at regular intervals from their sequence of ANC visit using systematic random sampling techniques. The sampling interval for this research was $1,350/300=4.5$. It was approximated to four by assuming nonrespondents from the total 1,350 estimated pregnant women. The first sample order to be included in the study was selected by lottery from the order of four pregnant women. The third order was selected as a first sample. Thereafter, at every fourth interval pregnant women were included in the study until the total sample was achieved.

A face-to-face interview using a structured, pretested questionnaire was employed to obtain data about socio-demographic, obstetric, and medical conditions. After the interview, a blood sample was drawn for HIV and syphilis testing. HIV infection was investigated following the national HIV1/2 testing algorithm currently in use (KHB Shanghai Kehua Bio-engineering Co, LTD, Shanghai, People's Republic of China) as screening test, Stat-PAK (Chembio Diagnostic Systems, Inc., New York, NY, USA) as a confirmatory test for positive samples, and Uni-Gold™ (Trinity Biotech Plc, Bray, Ireland) as a tie-breaker test

when samples gave discordant results in the first two tests. These HIV testing methods were immunochromatographic assays. Performance evaluation studies demonstrated that the sensitivity and specificity of Stat-PAK ranged from 97.6% to 100% and 99.8% to 100%, respectively.³⁶⁻³⁸ KHB has a sensitivity ranging from 94% to 100% and specificity ranging from 99.1% to 100%.^{36,37,39} Similarly, the performance evaluation studies conducted in Africa also claimed that the sensitivity and specificity of Uni-Gold ranged from 98.5% to 100% and 99% to 100%, respectively.^{37,38,40,41} Syphilis seroreactivity was tested using the rapid plasma reagin (RPR) test (Human GmbH-Wiesbaden, Germany) as per the manufacturer's instructions and recommendations. All RPR positive sera/plasma were subjected to the *Treponema pallidum* hemagglutination (TPHA) test (Guangzhou Wondfo Biotech Co, Ltd, Guangzhou, People's Republic of China) as a confirmatory test. Pregnant women who tested positive for both RPR and TPHA were diagnosed as having syphilis infection.

All information collected was coded and entered to EPI Info version 3.5.3 and then transferred to SPSS version 20 statistical package for analysis. Study participants were characterized according to the variables using descriptive and summary statistics and were presented in tables. Seroprevalence of the respective infections was defined as the percentage of positive cases for each serology, and the standard error and 95% confidence interval (95% CI) were calculated for each prevalence value. The association between HIV and syphilis with selected sociodemographic variables was tested with the logistic regression model. The magnitude of associations was assessed using odds ratios with respective 95% CI. Explanatory variables having a *P*-value less than 0.2 in univariate binary logistic regression were included in multivariate analysis to control confounders. Variables having a *P*-value less than 0.05 in multivariate binary logistic regression model were considered to be statistically significant.

Participation was voluntary, with written consent provided by each pregnant woman after the purpose and importance of the study was explained to each participants. The study was approved by the Institutional Review Board of the University of Gondar. Results were communicated with clinicians working in the ANC unit for appropriate management. Pregnant women who were reactive for syphilis were treated with standard treatment, and they were also advised not to have sexual contact unless their sexual partner gets tested of syphilis and treated. Pregnant women who

were seropositive for HIV were linked to the prevention of mother-to-child transmission clinic for specific follow-up and proper management.

Results

A total of 300 pregnant women who were attending ANC service between March and May, 2012, were screened for HIV and syphilis. The seroprevalence of HIV, syphilis, and HIV-syphilis coinfection were 10.33% (95% CI: 6.7, 14), 3.7% (95% CI: 1.7, 6.0), and 1% (95% CI: 0.1, 2.2), respectively.

Table 1 Sociodemographic characteristics of study participants

Variable	Frequency	Percentage
Age		
≤20 years	37	12.3
21–25 years	109	36.3
26–30 years	109	36.3
30–35 years	22	7.3
>35 years	23	7.7
Residence		
Rural	60	20
Urban	240	80
Marital status		
Single	13	4.3
Married	282	94
Other*	5	1.7
Maternal educational status		
Illiterate	69	23
Primary school	53	17.7
Secondary school	105	35
Tertiary	73	24.3
Husband educational status		
Do not have husband	18	6
Illiterate	52	17.3
Primary school	61	20.3
Secondary school	91	30.4
Tertiary	78	26
Occupation		
Housewife	193	64.3
Government employee	26	8.7
Private sector employee	62	20.7
Other**	19	6.3
Family monthly income		
<1,000 ETB	71	23.7
1,000–1,500 ETB	101	33.7
1,501–2,800 ETB	55	18.3
>2,800 ETB	73	24.3
Family size		
≤2	122	40.7
3–4	123	41
≥5	55	18.3

Notes: *Includes divorced and widowed; **includes students, farmers, merchants, and day laborers.

Abbreviation: ETB, Ethiopian birr.

Sociodemographic characteristic of study participants

The age (\pm standard deviation) of the study population averaged 27.4 (\pm 5.6). The majority 282 (94%), 240 (80.0%), 193 (64.3%), and 172 (57.4%) were married, urban residents, housewives by occupation, having a family monthly income less than 1,501 ETB (1 US dollar is nearly equivalent to 20 ETB), respectively. Moreover, 169 (56.4%) of the study participants had attended secondary and tertiary education, and 55 (18.3%) of them were living in a family consisting of five or more family members (Table 1).

Characteristics of participants associated with HIV and syphilis seropositivity

Of the total 31 HIV seropositive pregnant women, 13 (42%) were secundigravidae, whereas, of the total of eleven syphilis seroreactive pregnant women, five (45%) of them were 3–4 gravida. Five (16.13%) of HIV and one (9%) syphilis seropositive pregnant women had a history of spontaneous abortion. Concerning the medical conditions, of the total HIV seropositive pregnant women, 24 (77.42%) of them were infected with one or more intestinal parasite. Furthermore, of the total syphilis seropositive, seven (63.64%) were infected with intestinal parasite (Table 2).

The magnitude of HIV seroprevalence was high in women age 25–30 years; 13.4% of them were seropositive. Surprisingly, all HIV seropositive pregnant women were married. A high proportion of the pregnant women who were urban residents (11.2%), had a family size of three to four members (15.4%),

had a family monthly income less than 1,000 ETB (11.3%), and had attended secondary school (16.2%) were HIV seropositive. HIV infection was significantly more prevalent in those women whose husbands had attended primary school (crude odds ratio [COR] [95% CI]=2.71 [1.18, 6.25]) and had a family size of three to four members (COR [95% CI]=1.85 [1.02, 3.90]). HIV infection was not associated with maternal educational status, occupation, age, residence, and history of abortion (Table 3).

Regarding the magnitude of syphilis seropositivity, high seroprevalence was found in pregnant women who were occupationally housewives (15.2%), whose husbands were illiterate (11.5%), whose age was older than 30 years (11.1%), and who were living in a family having five and more members (9.1%). Syphilis infection was significantly more prevalent in pregnant women older than 30 years (COR [95% CI]=6.49 [1.21, 33.3]) and in those women whose husbands were illiterate (COR [95% CI]=7.20 [1.72, 30.30]). Syphilis seropositivity was not associated with maternal educational status, occupation, residence, family size, family monthly income, or history of abortion (Table 4).

Multivariate models for factors associated with HIV and syphilis seropositivity

To control the possible confounders and assess independently associated factors for HIV and syphilis infection, multivariate logistic regression analysis was done. Seroprevalence of HIV remained significantly associated with illiteracy of husband (AOR [adjusted odds ratio] [95% CI]=4.13

Table 2 Some obstetric, anthropometric, and medical conditions of pregnant women in relation to seropositivity for HIV and syphilis

Variable	HIV seroreactivity		Syphilis seroreactivity	
	Reactive n (%)	Nonreactive n (%)	Reactive n (%)	Nonreactive n (%)
Gravidity				
Primigravidae	11 (35.48)	118 (43.87)	3 (27.27)	126 (43.60)
Secundigravidae	13 (41.94)	64 (23.79)	1 (9.09)	76 (26.30)
3–4 gravida	7 (22.58)	57 (21.19)	5 (45.45)	59 (20.42)
\geq 5 gravida	0 (0)	30 (11.15)	2 (18.18)	28 (9.69)
History of abortion				
Yes	5 (16.13)	36 (13.38)	1 (9.09)	40 (13.84)
No	26 (83.87)	233 (86.62)	10 (90.91)	249 (86.16)
Gestational age				
1st trimester	1 (3.23)	7 (2.60)	0 (0)	8 (2.77)
2nd trimester	13 (41.94)	85 (31.60)	2 (18.18)	96 (33.23)
3rd trimester	17 (54.83)	177 (65.80)	9 (81.82)	185 (64.00)
Body mass Index				
Underweight	8 (25.81)	27 (10.04)	0 (0)	35 (12.11)
Normal	15 (48.39)	170 (63.20)	9 (81.82)	176 (60.90)
Overweight	7 (22.58)	63 (23.43)	2 (18.18)	68 (23.53)
Obese	1 (3.23)	9 (3.35)	0 (0)	10 (3.46)

Abbreviation: HIV, human immunodeficiency virus.

Table 3 Seroprevalence of HIV and bivariate and multivariate analysis according to selected sociodemographic characteristics and medical conditions of study participants

Variable	HIV seroreactivity		COR (95% CI)	P-value	AOR (95% CI)
	Reactive n (%)	Nonreactive n (%)			
Age					
<25 years	7 (6.6)	99 (93.4)	0.72 (0.2, 2.61)	0.21	
25–30 years	20 (13.4)	129 (86.6)	1.59 (0.51, 4.93)		
>30 years	4 (8.9)	41 (91.1)	1		
Residence					
Urban	27 (11.2)	213 (88.8)	1.78 (0.6, 5.3)	0.303	
Rural	4 (6.7)	56 (93.3)	1		
Marital status					
Married	31 (11)	251 (89)			
Other*	0 (0)	18 (100)			
Maternal educational status					
Below secondary school	8 (6.6)	114 (93.4)	0.78 (0.26, 2.35)	0.055	0.33 (0.08, 1.33)
Secondary school	17 (16.2)	88 (83.8)	2.16 (0.81, 5.78)		1.54 (0.54, 4.38)
Tertiary school	6 (8.2)	67 (91.8)	1		1
Husband educational status					
Illiterate	5 (9.6)	47 (90.4)	1.18 (0.40, 3.44)	0.125	4.13 (1.01, 16.95) [†]
Primary school	12 (19.7)	49 (80.3)	2.71 (1.18, 6.25)		3.83 (1.50, 9.90) ^{††}
Secondary and above	14 (8.3)	155 (91.7)	1		1
Occupation					
Housewife	20 (10.4)	173 (89.6)	1.32 (0.47, 3.68)	0.807	
Government employee	5 (8.1)	57 (91.9)	1		
Private sector employee	3 (11.5)	23 (88.5)	1.5 (0.33, 6.76)		
Other**	3 (15.8)	16 (84.2)	2.14 (0.46, 9.9)		
Family monthly income					
< 1,000 ETB	8 (11.3)	63 (88.7)	1.03 (0.41, 2.6)	0.845	
1,000–1,500 ETB	9 (8.9)	92 (91.1)	0.8 (0.33, 1.92)		
> 1,500ETB	14 (10.9)	114 (89.1)	1		
Family size					
≤2	11 (9.00)	111 (91.00)	1	0.043	1
3–4	19 (15.4)	104 (84.6)	1.85 (1.02, 3.90)		1.97 (0.85, 4.57)
≥5	1 (1.8)	54 (98.2)	0.19 (0.02, 1.49)		0.23 (0.03, 1.85)
History of abortion					
Yes	5 (12.2)	36 (87.8)	1.25 (0.45, 3.45)	0.674	
No	26 (10)	233 (90)	1		

Notes: *Includes single, divorced, and widowed; **includes students, farmers, merchants, and day laborers; Bold numerical values indicate significance in bivariate analysis; Significance [†]($P<0.05$) and ^{††}($P<0.01$) in multivariate analysis.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; ETB, Ethiopian birr; HIV, human immunodeficiency virus.

[1.01, 16.95]) and primary educational level of husband (AOR [95% CI]=3.83 [1.50, 9.90]) (Table 3). Likewise, women who had illiterate husbands (AOR [95% CI]=7.25 [1.74, 30.30]) were more likely to be seropositive for syphilis (Table 4).

Discussion

In the current study, the overall seroprevalence of HIV among pregnant women was 31 (10.33%). This prevalence was consistent with previous studies conducted at the same study area, Gondar teaching hospital (9.6%)¹⁵ and Gondar health centers (11.9%).¹⁶ Contrary to this, it was higher than studies conducted in Bahir Dar, Ethiopia (6.6%),⁴² a rural area of Tanzania (2%),⁴³ rural Northern Tanzania (2%),⁴⁴ Democratic Republic of the Congo (1.9%),⁴⁵ and Southern

Ethiopia (1.8%).¹⁰ The difference might be attributed to the variation in sexual behavior risk and other contributing risk factors for HIV transmission between these population. High HIV seroprevalence was found in those age 25–30 years (13.4%). This was in line with a previous report from Gondar, Ethiopia, where 13% of pregnant women age 25–29 years old were seropositive for HIV.¹⁵ Women in this age group are highly vulnerable to HIV infection because this age group comprises a sexually active segment of the population.

The seroprevalence of syphilis in the current study was 3.7%, which was comparable to studies conducted in Madagascar (3%),⁹ Bangladesh (3%),⁴⁶ and Addis Ababa, Ethiopia (2.9%)⁴⁷ In contrast, it was higher than the studies done in Gondar health centers, Ethiopia (2.3%),¹⁶ Tanzania (1.6%),⁴³

Table 4 Seroprevalence of syphilis and bivariate and multivariate analysis according to selected sociodemographic characteristics and medical conditions of study participants

Variable	Syphilis seroreactivity		COR (95% CI)	P-value	AOR (95% CI)
	Reactive n (%)	Nonreactive n (%)			
Age					
<25 years	2 (1.9)	104 (98.1)	1	0.032	1
25–30 years	4 (2.7)	145 (97.3)	1.43 (0.26, 8.0)		1.28 (0.23, 7.25)
>30 years	5 (11.1)	40 (88.9)	6.49 (1.21, 33.3)		3.62 (0.62, 22.22)
Residence					
Urban	7 (2.9)	233 (97.1)	1	0.179	1
Rural	4 (6.7)	56 (93.3)	5.59 (0.67, 8.4)		1.02 (0.21, 5.00)
Maternal educational status					
Below secondary school	7 (5.7)	115 (94.3)	2.65 (0.76, 9.26)	0.127	0.75 (0.13, 4.48)
Secondary and above	4 (2.2)	174 (97.8)	1		1
Husband educational status					
Illiterate	5 (11.5)	46 (88.5)	7.2 (1.72, 30.30)	0.007	7.25 (1.74, 30.30)**
Primary school	2 (3.3)	59 (96.7)	1.88 (0.31, 11.5)		1.88 (0.31, 11.50)
Secondary and above	3 (1.8)	166 (98.2)	1		1
Occupation					
Housewife	10 (15.2)	183 (84.8)	5.78 (0.73, 45.45)	0.091	7.19 (0.88, 50.00)
Other*	1 (0.9)	106 (99.1)	1		1
Family monthly income					
<1,000 ETB	4 (5.6)	67 (95.4)	3.76 (0.67, 21.28)	0.132	1.75 (0.11, 11.76)
1,000–1,500 ETB	5 (5.00)	96 (95.00)	3.28 (0.62, 17.24)		2.54 (0.43, 14.90)
>1,500 ETB	2 (1.6)	126 (98.4)	1		1
Family size					
≤2	3 (2.5)	119 (97.5)	1	0.087	1
3–4	3 (2.4)	120 (97.6)	0.99 (0.20, 5.00)		0.57 (0.09, 3.40)
≥5	5 (9.10)	50 (90.90)	3.97 (0.91, 17.24)		1.11 (0.16, 7.69)
History of abortion					
Yes	1 (2.4)	40 (97.6)	0.62 (0.08, 5.00)	0.656	
No	10 (3.9)	259 (96.1)	1		

Notes: *Other occupations include: private sector employees, governmental employees, students, farmers, merchants, and day laborers. Bold numerical values indicate significance in bivariate analysis; **significance ($P < 0.01$) in multivariate analysis.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; ETB, Ethiopian birr.

and Gondar teaching hospital, Ethiopia (1%).¹⁵ However, it was lower than previous studies conducted in Northwest Ethiopia (13.7%),¹⁷ Southwestern Nigeria (10%),⁴⁸ and Northeast Brazil (7.7%).⁴⁹ The variation might be the result of differences in culture, socioeconomic status, prevention and control measures, risk factors, level of awareness, and methods used for diagnosis.

In this study, low educational level of husbands (including illiteracy and primary school) was the risk factor for high seroprevalence of HIV. Similarly, having an illiterate husband increased the risk of being seropositive for syphilis. In our study, pregnant women whose husbands had no formal education were at seven times greater risk of being seropositive for syphilis compared to pregnant women having husband with secondary school and above educational attainment. This finding was consistent with a study conducted in Bangladesh.⁴⁶ Husbands with low educational levels may not have adequate knowledge about transmission mechanisms

of HIV and syphilis, so they may be exposed to the diseases unintentionally. This has been further compounded by low levels of maternal education, low socioeconomic status, low access to health care facilities, gender inequality, and high rate of risky extramarital sexual practices of husbands.^{50,51} This indicates that improvement of education level in the population should have a positive impact in reducing the disease.

Limitations of the study

One of the limitations of this study is that it is a tertiary hospital-based, cross-sectional design, which might not represent the general population of pregnant women. Another limitation is the use of only serological tests for the diagnosis of HIV and syphilis, which may lead to false positivity and negativity and, ultimately, underestimate or overestimate of the results of our study. Furthermore, since sexual related issues were socially sensitive, risk factors other than selected

sociodemographic characteristic were not assessed in the present study.

Conclusion

This study revealed that HIV and syphilis were prevalent among pregnant women, indicating that they are significant public health problems. This indicates the need to enhance antenatal screening to reduce and ultimately prevent vertical and horizontal transmission of HIV and syphilis. Likewise, appropriate strategies should be devised for prevention and control of HIV, syphilis, and other sexually transmitted diseases in women of reproductive age and general population. Low educational level of husbands was found to be a factor that significantly increases the risk of being infected with HIV and syphilis among pregnant women. Therefore, improvement of education level in the general population may play an important role in the prevention of HIV and syphilis. Moreover, societal factors that contribute to HIV and syphilis transmission need to be further studied in the general population, which will be helpful to prevent future HIV and syphilis transmission in the general population.

Author contributions

MM participated in designing the study, performing the data collection and statistical analysis, and was a lead author of the paper. AK and ZA participated in the study design and helped in drafting the paper. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. All authors read and approved of the final paper.

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Disclosure

The authors report no conflicts of interest in this work.

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