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Factors associated with condom breakage among female sex workers in the Western Region of Ghana

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Abstract

Condoms have been extensively demonstrated as being effective in reducing Human Immunodeficiency Virus (HIV) infection rates among both men and women. With proper use and production, condom breakage is ideally minimal. However, breakage is reportedly a widespread problem among Female Sex Workers (FSWs), who are classified as a Key Population and warrant special transmission prevention efforts. Nationally, Ghana records an average rate of 5% of condom breakage. This study sought to identify the factors associated with condom breakage among FSWs in the western region of Ghana, a region with an extensive sex worker population and HIV incidence rate of 2.5%, higher than the national average. This study employed a cross-sectional survey among FSW populations in the Western region, Ghana. A sample of 416 participants were proportionately invited between brothel based and roamer communities to participate in the surveys. A total of 403 consented to participate indicating a response rate of 96.9%. Data were analysed for frequencies and prevalence of variables including condom breakage. At the bivariate level, associations with breakage were examined and statistically significant variables were analysed with simple and multiple logistic regression analysis. Of the 403 research participants who consented to participate, 17.4% had experienced breakage over the past week. Brothel-based FSWs were only half as likely to report condom breakage as non-brothel based FSWs (aOR = 0.526; 95% CI, 0.296 - 0.936). Notably, FSWs who consumed alcohol-containing drinks every day were only 65.2% as likely as those who consumed alcohol at least once a week or less than once a week or never to experience condom breakage (aOR = 0.348; 95% CI, 0.164 - 0.740). The study determined that the occurrence of condom breakage among FSWs in the western region was 17.4%. Factors significantly associated with condom breakage were being non-brothel based, frequency of alcohol consumption and parity. Condom use education programmes targeted at non-brothel based FSWs are necessary to reduce breakage and lower the risk of HIV transmission. (Afr J Reprod Health 2021; 25[4]: 34-42).

Keywords: HIV & AIDS, FSW, Condom breakage, Lubricants, Ghana

Résumé

Il a été largement démontré que les préservatifs sont efficaces pour réduire les taux d'infection par le virus de l'immunodéficience humaine (VIH) chez les hommes et les femmes. Avec une utilisation et une production appropriées, la casse du préservatif est idéalement minime. Cependant, la casse serait un problème répandu parmi les travailleuses du sexe (FSW), qui sont classées comme une population clé et justifient des efforts spéciaux de prévention de la transmission. Au niveau national, le Ghana enregistre un taux moyen de 5% de rupture de préservatifs. Cette étude visait à identifier les facteurs associés à la rupture du préservatif chez les FSW dans la région occidentale du Ghana, une région avec une importante population de travailleuses du sexe et un taux d'incidence du VIH de 2,5%, supérieur à la moyenne nationale. Cette étude a utilisé une enquête transversale parmi les populations de FSW dans la région de l'Ouest, au Ghana. Un échantillon de 416 participants ont été invités proportionnellement entre les communautés de bordels et les communautés itinérantes à participer aux enquêtes. Au total, 403 personnes ont consenti à participer, ce qui indique un taux de réponse de 96,9 %. Les données ont été analysées pour les fréquences et la prévalence des variables, y compris la rupture du préservatif. Au niveau bivarié, les associations avec la rupture ont été examinées et les variables statistiquement significatives ont été analysées avec une analyse de régression logistique simple et multiple. Sur les 403 participants à la recherche qui ont consenti à participer, 17,4 % ont subi une rupture au cours de la semaine précédente. Les FSW travaillant dans des maisons closes étaient deux fois moins susceptibles de signaler un bris de préservatif que les FSW non travaillant dans des maisons closes (aOR = 0,526; IC à 95 % : 0,296 - 0,936). Notamment, les FSW qui consommaient des boissons contenant de l'alcool tous les jours n'étaient que 65,2 % plus susceptibles que celles qui consommaient de l'alcool au moins une fois par semaine ou moins d'une fois par semaine ou

jamais de casser le préservatif (aOR = 0,348; IC à 95 % : 0,164 - 0,740). L'étude a déterminé que la fréquence des bris de préservatifs parmi les FSW dans la région de l'Ouest était de 17,4 %. Les facteurs significativement associés à la rupture du préservatif étaient l'absence de bordel, la fréquence de la consommation d'alcool et la parité. Des programmes d'éducation à l'utilisation du préservatif destinés aux FSW non basés dans des maisons closes sont nécessaires pour réduire la casse et le risque de transmission du VIH. (Afr J Reprod Health 2021; 25[4]: 34-42).

Mots-clés: HIV & AIDS, FSW, Rupture de préservatif, Lubrifiants, Ghana

Introduction

Condoms have been extensively demonstrated to be effective in reducing HIV transmission and infection among both men and women¹⁻⁴. Condom failures have been reported globally and errors associated with the use of condoms have been demonstrated over a wide spectrum of populations⁶⁻⁸. Condom breakage refers to the breakage or lapse in material integrity of a condom at any time of opening the package, putting on, during intercourse, or withdrawal⁹. It is mathematically presented as the number of condoms that reportedly open or split any time from opening the package to removing the condom from the penis, divided by the total number of condoms opened¹⁰. Condom breakage has been widely reported as a common problem among female sex workers (FSWs) and is especially pronounced among those who use drugs which often results in incorrect use¹¹. Globally, the highest rates of condom breakage are recorded in Africa and Asia and also in some sub-populations in the Americas¹²⁻ ¹⁴. In an Ethiopian study among the general population of condoms users in North Gondar Province, the condom breakage rate recorded was 26.6%⁹. Among an African American population of young men in the United States of America, 21.2% reported condom breakage¹⁴. In a study conducted among FSWs in Cape Town, condom breakage was reported by 90% of participants, a remarkably high prevalence¹⁰. In Asian studies, 34% prevalence of condom breakage was recorded among a Chinesebased sample¹¹. Early multi-country studies on condom breakage reported a prevalence of 13.3% in Ghana¹⁵.

Notwithstanding current advances in condom manufacturing technology and extensive interventions aimed at promoting correct condom use, evidence of condom breakage remains a perennial challenge worldwide. Condom breakage may be attributable to a multitude of reasons, as reported by studies to that effect. Among a sample of African-American men, Crosby and colleagues discovered that men who used an oil-based lubricant were over three times as likely to report breakage¹⁴.

Incorrect application of the condom has also been reported frequently as an indicator for breakage^{7,16-18}. By extension, experience with condom use is also significantly correlated with breakage; studies have indicated that breakage reduces with increasing experience⁹. An early Ethiopian study by Mokenon & Mokenon reported higher experience with condom use being negatively correlated with breakage, which was supported by the Nevada Brothel study^{9,19}. In a more recent study in Uganda, inexperience with condom use correlated with a more than double increased odds of breakage¹². People who employed excessive force and sharp objects in opening condom packets also reported higher rates of condom breakage²⁰.

In terms of behavioural factors, substance and drug use remains one of the most strongly reported correlates of breakage. Among a population of men who have sex with men (MSM), breakage was twice as likely to be reported among people who get high²¹. Among an FSW population in China, drug use increased the odds of breakage by over four times (OR 4.01)¹¹. In India, a study on FSWs reported a 63% increased odds of breakage among regular alcohol consumers¹².

Another behavioural correlate of breakage is partner violence. This may be primarily attributable to its restriction of condom negotiation. Given that between 14.6% to 64% of FSWs are exposed to physical and sexual violence worldwide, this is a matter of concern^{22,23}. Chen and colleagues recorded an OR of 2.30 for breakage in encounters of high violence¹¹. Similar studies in Rwanda and Uganda have found that HIV-positive women were more likely to report sexual violence than HIV-negative women, which is of concern in HIV transmission intervention efforts^{24,25}.

Condom breakage has significant implications for the health of female sex workers and by extension, the entire population. Breakage increases exposure to infection with HIV and other STIs as well as unwanted pregnancies^{26,27}. Standardized production coupled with perfect use of condoms has been proven to be highly effective against the transmission of STIs^{28,29}. Consequently,

some studies have explored correlations between condom breakage and the high prevalence of STIs, with varying findings. In a study that involved 264 recently diagnosed young African-American men with STDs, more than one-fifth (21.2%) reported condom breakage within the preceding three months¹⁴. In a diagnostic study in the Benin Republic, a higher prevalence of HIV was reported among women who had experienced condom breakage³⁰. In the absence of an explicit establishment of a causal relationship, there is still a dearth of evidence on the strong correlation between condom breakage and the high prevalence of STIs HIV among FSWs and and the general population^{11,31-33}

This study sought to identify the factors associated with condom breakage among FSWs in the Western Region of Ghana. This region has large proportions of FSWs as well as migrant workers who work in the booming oil and gas sector. Additionally, the region perennially continues to report HIV prevalence that is higher than the national average and is a source of concern for HIV prevention efforts in the country.

Methods

Study design

The study was designed as a cross-sectional survey among female sex workers. Data were gathered through structured interviewer-administered questionnaires between June and July 2016 in the Western region of Ghana.

Study sites

The study was undertaken in the Western Region of Ghana. Respondents were recruited from four major localities: Takoradi, (Ghana's third largest city), Sekondi, Essiama, and Elubo (a border town with Cote D'Ivoire). These areas have large FSW communities as they are in close proximity to vibrant nightlife areas as well as areas where migrant patrons from the oil and gas sector usually congregate.

Sampling procedure

Different sampling procedures were used for brothel-based and non-brothel-based sex

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workers. However, for both, a multi-stage sampling procedure was utilized for selecting respondents. The respondents were selected through the following process:

Sampling procedure for brothel-based FSWs

- i. Brothels were identified from a list obtained from an earlier FSW size estimation project; all brothels were confirmed to be in operation.
- ii. The estimated number of FSWs was obtained for each brothel.
- Respondents were allocated according to the relative population size of FSWs present in each brothel (probability proportional to size (PPS)).

Sampling procedure for non-brothel-based FSWs

- i. Non-brothel sites from a list compiled in an earlier size estimation project were identified.
- ii. Through local knowledge, the sites were stratified into three based on perceived prices FSWs charge: low-cost, medium, and high-class spots.
- iii. Respondents were allocated according to the relative population size of FSWs for each site (probability proportional to size (PPS).

The sample size of 416 was determined using the Cochran formula for cross-sectional studies. This was calculated from a proportion of condom breakage from a previous study (13.3%), an error margin of 3.5%, and a confidence level of $95\%^{15}$. Non-response was estimated at 15%.

Data collection instruments

Data were collected with the aid of standardized, pre-coded questionnaires. The instrument covered, among others, the following broad areas:

- Socio-economic and personal characteristics including age, tribe, level of formal education, occupation and religion, region of operation/location and understanding of the legal environment surrounding sex work.
- Nature of sex work such as clients seen per day, fees charged, the incidence of unwanted pregnancy/history of abortion, type of intercourse practiced.

- Sexual behaviour and relationship types (commercial and non-commercial sex; types of clients; progressive and changing nature of relationship commitments and associated risks
- Knowledge, attitudes, opinions & exposure to HIV transmission, prevention, and care
- Knowledge and use of condoms and lubricants with different types of clients.
- Knowledge about STIs and STI treatmentseeking behaviour
- Personal risk perception

All concepts of the Information Motivation Behavioural Skills (IMBS) model were covered in the questionnaire.

Data collection

Street savvy and locally knowledgeable interviewers were recruited and trained for the purpose of data collection. To encourage high response rates, brothel-based interviews were conducted during offpeak business periods from mid-morning to early afternoon. Non-brothel-based interviews were conducted at street corners at the selected sites at night. Interviewers worked in pairs at night for security reasons but interviews were always conducted one-on-one out of earshot of others.

Data management and analysis

Data were double entered in CSPro software (U.S, Census Bureau & ICF Macro) and subsequently exported to IBM SPSS Statistics for Windows version 20.0 for cleaning and analysis. New categorized and dichotomized variables were generated from continuous variables including age, marital status, educational status, parity, length of sex work, alcohol consumption, time taken to obtain condom, pieces of condom on hand, number of clients per day, and condom use attitudes. Working full or part-time in sex work was dichotomized as was the type of lubricant used, perception of HIV risk, level of HIV knowledge, and stigma index. Attitude to condom use was measured by computing all scores to each statement in the affirmative and subsequently categorizing into poor, fair, and good condom use attitude. Bivariate analysis was conducted to examine the association between condom breakage and selected characteristics.

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Pearson chi-square statistics were used to determine statistically significant explanatory variables. Statistical significance was set at p-value < 0.05. Simple and multiple logistic regression modelling produced unadjusted and adjusted associations between each of the key outcome variables and selected independent variables. In the simple regression model selected characteristics were assessed independently with the outcome variable. Odds ratios with accompanying 95% CI were used to assess the strength of the relationships.

Results

Background and socio-demographic characteristics

The sociodemographic characteristics of respondents are presented in Table 1. A majority of respondents were brothel-based (60.9%) and had at least secondary school level education (64.3%). Over half (51.9%) had ever been married although 55.5% reported currently not living with any spouse or sexual partner. A majority (62%) worked full-time in sex work. Only 19.4% of the FSWs have never had a child, with 20.6% reporting having three or more children.

Sexual history and related behaviours

The sexual histories and related behaviours of respondents are presented in Table 2. It shows that a majority of respondents had their sexual debut between 16 and 20 years (63.5%). About a third reported having non-paying clients - The client rate was about three or four per day with a median charge of GHC 20.00. Almost half of interviewees confirm consuming alcohol before or during sexual acts over once a week (48.8%). Again, over a third had used recreational drugs and substances recreationally in the 12 months preceding the survey.

Condom use

Details about FSWs condom use behaviours are presented in Table 3. The ability to obtain a condom in under 15 minutes was almost universally reported (97.5%). Within the week preceding the survey, 17.4% of respondents reported encountering breakage which rose to 40.0% for a month preceding

Table 1: Sociodemographic characteristics of female sex

 workers (FSW) in Western Region, Ghana

Characteristics	Frequency n (%)	
Age of respondent (years)		
15 – 19	35 (8.8)	
20 - 24	115 (28.8)	
25 - 29	123 (30.8)	
30 and above	126 (31.6)	
Total	399(100.0)	
Educational status	577(100.0)	
Primary	122(33.8)	
Secondary	122(55.8) 232(64.3)	
Tertiary	7(1.0)	
Total	361(100.0)	
Poligion	501(100.0)	
No Poligion	20(5.0)	
Christianity	20(3.0) 318(78.0)	
Lalam	510(70.9)	
Islalli Tur didi ang l	03(13.0)	
	2(0.5)	
Ethnic group	011(50.4)	
Akan	211(52.4)	
Ga-Adangbe	55(13.6)	
Ewe	32(7.9)	
Mole-Dagbon	51(12.7)	
Guan	11(2.7)	
Non-Ghanaian	43(10.7)	
Classification		
Brothel based	238(60.9)	
Non brothel (street, night club) based	153(39.1)	
Total	391(100.0)	
Ever been married		
Yes	209(51.9)	
No	194(48.1)	
Marital status		
Currently married, living with spouse /	45(21.5)	
other partner	43(21.3)	
Not living with any spouse or sexual	11((55 5))	
partner	110(55.5)	
Separated, Divorced, Widow	48 (23.0)	
Total	209(100.0)	
Full/Part Time		
Combine with other trade	153(38.0)	
Work full time as a FSW	250(62.0)	
Parity		
None	78(19.4)	
1	140(34.7)	
2	102(25.3)	
3 and above	83 (20.6)	
Number of dependent children		
None	57(14.8)	
1	82(21.4)	
2	83(21.6)	
>3	162(42.2)	
Total	384(100.0)	

the survey. Over two-thirds reported using condom lubricants with condoms and out of these, waterbased lubricants were almost universally used (95.6%). Almost all FSWs had at least a fair knowledge of condom use although only 68.0% had heard or seen messages/film/radio or TV programme about HIV, AIDS, or condoms within the 12 months prior to the study.

HIV knowledge, perception, and risk behaviours

The HIV knowledge, perceptions, and behaviours of participants are presented in Table 4. Only 15.6% of respondents had comprehensive knowledge about HIV. HIV testing within the twelve months prior to the study was highly reported (93.6%) among respondents although fewer (87.4%) were willing to test at the time of interview. Over a third of respondents perceived themselves as having no risk at all for contracting HIV (35.4%).

Predictors of condom breakage

Condom breakage was regressed against selected potential predictors selected from previous studies on condom breakage (Table 5). At the simple logistic level, FSWs over the age of 30 years and brothel-based FSWs showed a statistically significant elevated odds of condom breakage. FSWs with non-paying partners were also 30% more likely to experience condom breakage (OR = 1.313; 95% CI = 0.745 - 2.314). A protective predictor against breakage was the ability to negotiate condom use with non-paying clients (OR = 0.527; 95% CI = 0.197 - 1.411). After adjusting for a number of covariates, working in a brothel, alcohol consumption and parity were the three statistically significant predictors of condom breakage at the multivariate level. The odds of experiencing condom breakage reduced among brothel-based FSWs. It was found, however, that alcohol consumption and higher parity were associated with less condom breakage.

Discussion

Condom breakage is a widely reported phenomenon worldwide, especially among FSWs¹². This population was chosen due to their reported increased risk of sexually transmitted infections and their classification as HIV key population¹³. In the week prior to the study, 17.4% had experienced

Table 2: Sexual history and related behaviour of female

 sex workers (FSWs) in Western Region, Ghana

Condom breakage among sex workers

Table 3: Condom use behaviours of female sex workers(FSWs) in Western Region, Ghana

	D (A())		
Characteristics	Frequency n (%)		
Age at first sex	00(247)		
≤1 3	98(24.7)		
16 - 20	252(63.5)		
<u>221</u>	47/(11.8)		
Total	397(100.0)		
Type of Partner	100(00.5)		
Has non-paying partner	123(30.5)		
Has no non-paying partner	280(69.5)		
Age of entry into sex work (years)	150/20 7)		
<20	150(39.7)		
20- 39	181(47.9)		
<u>2</u> 39 T-t-1	4/(12.4)		
	378(100.0)		
Duration in sex work (months)	147(29.4)		
1 - 12	14/(38.4)		
15 - 24 25 - 26	61(15.9)		
23 - 30 >27	44(11.3) 121(24.2)		
$\leq 3/$	131(34.2)		
lotal	383(100.0)		
Number of paying clients on the last			
work day	21(7.7)		
None	31(7.7)		
1 - 2	116(28.8)		
3-4	151(37.5)		
≥5	105(26.1)		
Charge per round of sex			
≤15	95(23.6)		
20 - 29	166(41.2)		
≥ 30	142(35.2)		
Alcohol consumption during sex work			
Everyday	66(17.2)		
At least once a week	121(31.6)		
Never or Less than once a week	196(51.2)		
Total	383(100.0)		
Recreational drug use during sex work			
Yes	156(38.7)		
No	247(61.3)		
Encountered forcible unprotected sex			
Yes	41(10.4)		
No	355(89.6)		
Total	396(100.0)		

breakage whilst 40.0% had experienced breakage in the month prior. These rates are considerably higher than the figures reported in previous research^{12,30,35}. The rate was also marginally less than the upper limits reported in a systematic review of literature conducted for 15 peer-reviewed articles between 1995 and 2011 which reported breakage rates between 0.8% and 40.7%⁸. The higher incidence of condom breakage found among this population may be partly explained by their reported likelihood to engage in high-risk sexual behaviours¹⁰.

Characteristics	Frequency n (%)			
Considers condoms affordable	.			
Yes	352(87.3)			
No	51(12.7)			
Time taken to obtain a condom (minutes)				
< 15	386(97.5)			
> 15mins	10(2.5)			
Total	396(100.0)			
Condom breakage over past week				
Yes	64(17.4)			
No	304(82.6)			
Total	368(100.0)			
Condom breakage over past month				
Yes	161(40.0)			
No	242(60.0)			
Lubricant use with condoms				
Yes	320(79.4)			
No	83(20.6)			
Type of lubricant used				
Oil-based	14(4.4)			
Water-based	306(95.6)			
Total	320(100.0)			
Frequency of lubricant use				
Every time	177(55.5)			
Not always	s 142(44.5)			
Total	319(100.0)			

Table 4: HIV knowledge, perceptions and behaviours of female sex workers (FSWs) in Western Region, Ghana

Characteristics	Frequency n (%)				
Most recent HIV test (Years)					
<1	329(86.4)				
1-2	40(10.5)				
2-4	6(1.6)				
>4	6(1.6)				
Total	381(100.0)				
Willingness to test again					
Yes	320(87.4)				
No	46(12.6)				
Total	366(100.0)				
Self-perceived risk of getting HIV					
At risk	259(64.6)				
No risk	142(35.4)				
Total	401(100.0)				
Heard/ seen any messages/film/radio/TV					
program about HIV, AIDS, or condoms					
within prior 12 months					
Yes	274(68.0)				
No	129(32.0)				
Comprehensive knowledge on HIV					
Comprehensive Knowledge of HIV	63(15.6)				
No knowledge	340(84.4)				

This is especially significant as condom breakage is established as a significant contributor to the

Condom breakage among sex workers

	Unadjusted		Adjusted	
Classification				
Brothel based	1.888*	1.091 - 3.267	0.526*	0.296 - 0.936
Non-brothel (street, night club) based	Ref			
Alcohol consumption during sex				
work				
Everyday	0.421*	0.205 - 0.863	0.348*	0.164 - 0.740
At least once a week	0.554	0.294 - 1.045	0.606	0.315 - 1.169
Never or less than once a week	Ref			
Parity				
None	Ref			
1	0.388*	0.151 - 0.999	0.300*	0.106 - 0.851
2	0.335*	0.126 -0.889	0.277*	0.094 - 0.818
<u>≥3</u>	0.370*	0.135 - 1.014	0.283*	0.094 - 0.855

Table 5: Predictors of condom breakage among female sex workers (FSWs) in Western Region, Ghana

transmission of HIV as well as unwanted pregnancies²⁹. This study found at the bivariate level that brothel-based FSWs were 90% more likely to experience breakage compared with non-brothelbased sex workers. This is similar to findings from Bradley and colleagues which reported that female sex workers who were brothel-based were more vulnerable and more likely to experience condom breakage than street-based sex workers¹². However, at the multivariate level and adjusting for covariates, the odds of breakage were halved among brothel-based FSWs compared to their non-brothelbased counterparts (aOR = 0.526; 95% CI, 0.296 -0.936). This may be partly reflective of the fact that sexual encounters in brothels usually are less rushed because the sex workers are domiciled compared with their non-brothel colleagues. Brothel-based sex workers may therefore have more time to carefully don and remove a condom. Our sample generally reported frequent alcohol consumption with almost a third (31.6%) of participants consuming alcohol at least once a week and 17.2% consuming alcohol daily on the job.

Although some studies have reported that alcohol consumption among FSWs was associated with higher levels of condom breakage^{11,12}, participants in this sample demonstrated a decreased odds of condom breakage with alcohol consumption (aOR = 0.348; 95% CI, 0.164 - 0.740). This finding is similar to the findings of a 2016 Australian study³⁶ which reported increased confidence in using condoms among alcohol-consuming youth. In another study³⁷, alcohol consumption was demonstrated to strengthen condom use self-efficacy

among a group of young women and increased the ability to negotiate condom use. This may be supportive of the idea that FSWs use alcohol as a coping mechanism to build confidence in negotiating proper condom use with their clients as demonstrated in a Ugandan study among FSWs who frequently consumed alcohol and were found to have higher condom use efficacy and negotiation³⁸.

In our study, we found that FSWs with high parity were less likely to experience condom breakage. A possible explanation for this is the increased caution that mothers who may not want more pregnancies or children may apply when using condoms. This is reflective of findings among young adult African American women that showed that women who did not want any children were almost nine times more likely to be careful with condom use to avoid failures³⁹.

Ethical approval

All sex workers signed informed consent forms. Ethical approval for the study was also obtained from the Ethics Committee for Humanities, University of Ghana (ECH 025/14-15).

Conclusion

This study establishes a high occurrence of condom breakage among female sex workers in the Western region of Ghana. High parity and alcohol consumption were found to be significant predictors of low condom breakage. Brothel-based sex work was found to be associated with higher levels of condom breakage. Condom breakages and failures

are established as a major contributor to unwanted pregnancies and HIV transmission and thus targeting future interventions toward sex workers is of significant value. Whilst there is extensive literature on attitudes towards condom use and the frequency of use, very little has focused on condom breakage among FSWs in Ghana. This study contributes to a growing body of evidence that emphasizes the association between characteristics of sex workers and incorrect use as well as resultant errors and breakages of condoms. This study furthermore highlights the need to better understand whether the availability and consistent use of condoms is predictive of proper condom use. Ultimately, the study has implications for HIV prevention and sexual health promotion in intervention development and implementation.

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Contributions of authors

The study was conceived and designed by AA. Data was collected and analysed by HH, BKA, and SA. The manuscript was developed by AA, HH, BKA, MA, PN, SA, and AM. All authors extensively reviewed and incorporated their intellectual inputs into this manuscript. All the authors read and approved the final draft of this manuscript

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