Support for Lowering Cervical Cancer Screening Age To 25 for Women Living With HIV: Retrospective Cross-Sectional Programmatic Data From Botswana

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Abstract

Background:

Women living with human immunodeficiency virus (HIV) tend to develop cervical cancer at a younger age than HIV-negative women. The World Health Organization's (WHO) new guidelines for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention include a conditional recommendation for initiating screening at age 25 for women living with HIV (WLWH). This recommendation is based on low-certainty evidence, and WHO calls for additional data. We describe the association of age and HIV status with visual inspection with acetic acid (VIA) positivity and cervical intra-epithelial neoplasia grade two or higher (CIN2+) in Botswana.

Methods:

A retrospective cross-sectional study of 5,714 participants aged 25 through 49 years who underwent VIA screening. VIA-positive women received cryotherapy if indicated or were referred for colposcopy. Known cervical cancer risk factors, screening, and histological results were extracted from the program database. We compared the proportions and association of VIA positivity and CIN2+ by age and HIV status.

Results:

Median age was 35 years [IQR 31-39], and 18% of the women were aged 25-29. Ninety percent were WLWH; median CD4 count was 250 cells/μL [IQR 150-428], and 34.2% were on anti-retroviral treatment (ART). VIA-positivity was associated with younger age (OR 1.48, CI 1.28, 1.72 for 25-29 years versus age 30-49 years), and HIV-positivity (OR 1.85, CI 1.51, 2.28). CIN2+ was associated with HIV positivity (OR 6.12, CI 3.39, 11.10), and proportions of CIN2+ were similar for both age groups in WLWH (12.1% versus 10.8%).

Conclusions:

Younger WLWH in Botswana had a significant burden of CIN2+. This finding further supports lowering the screening age for WLWH from 30 to 25.

Background

Low- and middle-income countries (LMICs) carry the highest global burden of cervical cancer incidence and mortality.[1] Cervical cancer is the leading cause of cancer death in women in Southern Africa.[2, 3] While human papillomavirus (HPV) vaccination in young girls offers hope for a significant reduction in cervical cancer in future generations, effective cervical cancer screening services remain essential to reduce morbidity and mortality associated with cervical cancer in women across the globe.[4]

Women living with the human immunodeficiency virus (WLWH) have a higher risk of developing pre-invasive cervical disease and cervical cancer.[5–7] Although progression rates from pre-invasive cervical disease to cervical cancer are unknown due to standard intervention for high-grade cervical dysplasia, cervical cancer is diagnosed at younger ages in WLWH compared to HIV-negative women. [5, 8, 9] Guidelines for high-income countries (HICs) recommend cervical cancer screening initiation at an early age of 21.[10–12] Up till recently, guidelines for most LMICs recommended the initiation of cervical cancer screening at the age of 30 despite LMICs having the highest global prevalence of HIV in the reproductive-aged population.[13, 14]. The new WHO guidelines have a conditional recommendation based on low-certainty evidence for initiating screening at age 25 for WLWH, [15] and calls for more data. Further, many LMICs will not be able to change their guidelines straight away due to resource constraints.

Botswana has one of the highest HIV prevalences globally, at 25.1% in women aged 15–49.[16] Botswana's national guidelines prioritize screening in the 30 to 49 year-old age group with either cytology or visual inspection with acetic acid (VIA), regardless of HIV status. While practical, these guidelines may not adequately account for the high prevalence of HIV in Botswana and the higher risk of early cervical cancer progression. There is limited published data from Botswana on the prevalence of pre-invasive disease and the role of screening in younger women.

This study describes the association of age and HIV status with VIA positivity and high-grade cervical pre-cancer disease. We aimed to determine how initiating cervical cancer screening at age 25 years, instead of 30 years, in WLWH would improve the identification of high-grade pre-invasive cervical disease without unduly increasing overtreatment of low-grade cervical dysplasia. Data presented here could strengthen the evidence for the WHO recommendation on the target age group for cervical cancer screening in WLWH.

Methods

Study design and patient selection

We conducted a retrospective cross-sectional study based on the Botswana Ministry of Health and Wellness (MOHW) National Cervical Cancer Prevention Programme “see-and-treat” pilot programmatic database.[17] The database included women screened with visual inspection after acetic acid (VIA) at Bontleng clinic and those referred to Princess Marina Hospital (PMH) for colposcopy in Gaborone, Botswana, from March 2009 through August 2015. Cervical cancer screening services were initially provided for WLWH as part of comprehensive HIV care and were later extended to HIV-negative women at these sites. Screening services were offered free of charge to all Botswana citizens.

Screening services were linked to a physician-led referral colposcopy and loop electrosurgical excision procedure (LEEP) clinic at PMH. Through various channels, women came to screening services, including provider referral, self-referral following sensitization by written materials, and health education talks. Women were excluded from screening if they had previously had a hysterectomy, pelvic radiation for lower genital tract cancer, or a cervical cancer diagnosis. Screening for women who were menstruating heavily, pregnant, or had a persistent vaginal discharge was re-scheduled for after resolution of the condition.

Cervical cancer screening procedures

All patients underwent a speculum examination of the cervix by a nurse who had participated in the Botswana MOHW VIA training program. Visual assessment was performed after applying 5% acetic acid to the cervix using a cotton swab, and findings were categorized as normal, abnormal with a recommendation for cryotherapy, or abnormal with a recommendation for LEEP. Those with abnormal lesions eligible for cryotherapy were offered same-day treatment and had no histopathology specimen collected. Women with abnormal lesions ineligible for cryotherapy based on appearance, size, or extension into the cervical os, were referred to the colposcopy/LEEP clinic and evaluated by a specialist gynecologist or trained medical officers. The colposcopic appearance of lesions determined diagnostic and treatment decisions. Low-grade appearing lesions were treated with cautery after taking a biopsy; high-grade appearing lesions or those extending into the cervical were treated by LEEP. Histopathology specimens were read by pathologists blinded to VIA findings.

HIV procedures

Women with unknown HIV status at the time of screening or with documented HIV negative status more than six months prior were referred to an HIV testing center and requested to share their results. Throughout the study period, the Botswana National HIV program initiated anti-retroviral treatment (ART) at a CD4 count of $\leq$ 350 cells/μL.

Data collection

All women undergoing VIA screening completed a questionnaire capturing a limited set of patient-level cervical cancer risk factors, including smoking, age of sexual debut, and parity. HIV status was recorded, and for WLWH, CD4 count at the time of HIV diagnosis and whether on ART at the time of screening was documented. VIA screening outcomes were recorded in the programmatic database. Histology results of women referred for colposcopy/LEEP were extracted from the National Health Laboratory (NHL) electronic medical record when available and entered into the programmatic database.

Outcomes

The primary outcome was the association of VIA positivity and age adjusting for cervical cancer risk factors. The secondary outcomes were the association of histopathologically confirmed high-grade pre-cancer and age adjusting for cervical cancer risk factors; HIV-status association with VIA positivity and high-grade pre-cancer; and the proportions of VIA positivity and high-grade pre-cancer by both age and HIV status.

Data analysis

The analyzed dataset included only women between the ages of 25 and 49. Patient records with missing data for VIA or histopathology that could not be corrected by cross-reference with primary records were excluded from the primary and secondary analysis, respectively. The sample size for the primary outcome was calculated using a 1-sided alpha of 0.05. To attain a 99% power, we assumed VIA positivity to be 30% in women aged 25 to 29 years and 20% in women aged 30 to 49 years based on previous findings.[17] The sample size required to detect a statistically significant difference in VIA-positivity between the two age groups was 2,076 women (374 women aged 25 to 29 years and 1,702 women aged 30 to 49 years).

The cervical cancer risk factors adjusted for included: HIV status, parity, smoking, and age of sexual debut. CD4 count and ART were included in the analysis of WLWH. Descriptive statistics for these variables are presented as median [interquartile range (IQR)] and proportions. Continuous variables were categorized into binary variables and compared using the chi-square test. Categorical variables included age groups of younger and older women (25 to 29 years; 30 to 49 years), age of sexual debut (≤18; >18 years), parity (≤2; >2), CD4 count (≤350 cells/μL; >350 cells/μL), and histopathology results (benign or CIN 1 [≤CIN1] for low-grade pre-cancer; CIN2+ for high-grade pre-cancer). Patterns of missing data were described for the study cohort using percentages.

Logistic regression models computed unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CI). Only exposure variables with a p-value of less than 0.1 for unadjusted ORs were included in the adjusted regression models.[18] A p-value of less than 0.05 was considered to be statistically significant. We used Stata 14.0 (StataCorp LLC, College Station, Texas).

Results

Overall patient characteristics

The database included 5,724 women aged 25 through 49 years screened with VIA between March 2009 and August 2015 (Fig. 1). Ten women had missing VIA data, leaving 5,714 women for the VIA analysis. As shown in Table 1, the median age was 35 years [IQR 31–39], and 1029 (18%) were between 25 and 29 years of age. Smoking was reported by 285 (5%) of the women. The median age of sexual debut was 18 years [IQR 17–20], and the median parity was two [IQR 1–3]. HIV status was known in 5,583 (98%), and 5,026 (90%) of those with a known status were WLWH. Eight hundred and forty nine (86%) of the women aged 25 to 29 years and 4,177 (91%) of the those aged 30 to 49 years were WLWH. Among the WLWH, the median CD4 count was 250 cells/μL [IQR 150–428], and 1628 (34.2%) were on ART. Missing data was ≤ 5% for all the variables except for CD4 count (11%, n = 551). The level of CD4 count missing data was similar for both age groups (10.5% for 25 to 29 year-olds versus 11.1% for 30 to 49 year-olds).

Table 1
Demographic and clinical characteristics of all study participants

Variable	All		Age 25–29 years	Age 30–49 years	P-Value for X^2 test
	n (%)	Median [IQR]	n [a] (%)	n [a] (%)	
Age	**5,714**	**35 [31, 39]**			
Smoking	**5,661**		**1,018 (18.0)**	**4,643 (82.0)**	0.008[b]
Yes	285 (50.0)		68 (6.7)	217 (4.7)	
No	5,376 (94.1)		950 (93.3)	4,426 (95.3)	
Missing	53 (1.0)				
Sexual debut	**5,689**	**18** [17, 21]	**1,024 (18.0)**	**4,665 (82.0)**	0.02[b]
≤ 18	3,150 (55.3)		533 (52.1)	2,617 (56.1)	
> 18	2,539 (44.4)		491 (47.9)	2,048 (43.9)	
Missing	25 (0.4)				
Parity	**5,612**	**2** [1, 3]	**1,001 (17.8)**	**4,611 (82.2)**	< 0.001[b]
≤ 2	3,223 (56.4)		815 (81.4)	2,408 (52.2)	
> 2	2,389 (41.8)		186 (18.6)	2,203 (47.8)	
Missing	102 (1.8)				
HIV Status	**5,583**		**989 (17.7)**	**4,594 (82.3)**	< 0.001[b]
Negative	557 (9.7)		140 (14.2)	417 (9.1)	
Positive	5,026 (88.0)		849 (85.8)	4,177 (90.9)	
Missing	131 (2.3)				
Initial CD4 at HIV Diagnosis [c]	**4,475**	**250 [150, 428]**	**760 (16.9)**	**3,715 (83.1)**	< 0.001[b]
≤ 350	2,308 (45.9)		304 (40.0)	2,004 (53.9)	
> 350	2,167 (43.1)		456 (60.0)	1,711 (46.1)	
Missing	551 (11.0)				
On ART at time of screening [c]	**4,766**		**802 (16.8)**	**3,964 (83.2)**	< 0.001[b]
Yes	1,628 (32.4)		346 (43.1)	1,282 (32.3)	
No	3,138 (62.4)		456 (56.9)	2,682 (67.7)	
Missing	260 (5.2)				
VIA Results	**5,714**		**1,029 (18.0)**	**4,685 (82.0)**	< 0.001[b]
Positive	1,959 (34.3)		428 (41.6)	1,531 (32.7)	
Negative	3,755 (65.7)		601 (58.4)	3,154 (67.3)	

Abbreviation: ART, anti-retroviral treatment; CIN, cervical intraepithelial neoplasia; IQR, inter-quartile range; VIA, visual inspection after acetic acid.

The number of women in levels of categorical variable may not add up to total "n" because missing category has been removed.

[b] for $p < 0.05$.

[c] for HIV positive patients only

Via-positivity

The overall VIA positivity of the study population was 34.3% (n = 1,959). The proportion was higher in the 25 to 29 year-olds (41.5%, n = 428) than the 30 to 49 year-olds (32.7%, n = 1,531). The WLWH had a higher VIA positivity rate (35.9%, n = 1,841) than HIV-negative women (24.1%, n = 141) (Table 2).

Table 2
Study participants' characteristics with bivariate and multivariable odds ratio for VIA positivity

Variable	All n (%)	VIA Positive n [a] (%)	VIA Negative n [a](%)	VIA Positivity BVA Odds Ratios (95% CI)	P-value	VIA Positivity MVA Odds Ratios (95% CI)	P-value for X^2 test
Age Group	**5,714**	**1,959 (34.3)**	**3,755 (65.7)**	1.47 (1.28, 1.69)	< 0.001[b]	1.48(1.28, 1.72)	< 0.001[b]
25–29 years	1,029 (18.0)	428 (41.6)	601 (58.4)	Ref			
30–49 years	4,685 (82.0)	1,531 (32.7)	3,154 (67.3)				
Smoker	**5,661**	**1,937 (34.2)**	**3,724 (65.8)**	Ref	0.053	1.14(0.89, 1.46)	0.31
No	5,376 (94.1)	1,825 (33.9)	3,551 (66.1)	1.27(1.00, 1.62)			
Yes	285 (5.0)	112 (39.3)	173 (60.7)				
Missing	53 (0.9)						
Age Sexual debut	**5,689**	**1,950 (34.3)**	**3,739 (65.7)**	0.99(0.88, 1.10)	0.79	N/A	N/A
≤ 18	3,150 (55.1)	1,075 (34.1)	2,075 (65.9)	Ref			
> 18	2,539 (44.4)	875 (34.5)	1,664 (65.5)				
missing	25 (0.5)						
Parity	**5,612**	**1,924 (34.3)**	**3,688 (65.7)**	Ref	0.009[b]	0.88 (0.79, 0.99)	0.04[b]
≤ 2	3,223 (56.40)	1,151 (35.7)	2,072 (64.3)	0.86 (0.77, 0.96)			
> 2	2,389 (41.81)	773 (32.4)	1,616 (67.6)				
Missing	102 (1.79)						
HIV Status	**5,583**	**1,941 (34.8)**	**3,642 (65.2)**	Ref	< 0.001[b]	1.85 (1.51, 2.28)	< 0.001[b]
Negative	557 (9.74)	134 (24.1)	423 (75.9)	1.77 (1.45, 2.17)			
Positive	5,026 (87.96)	1,807 (35.9)	3,219 (64.1)				
Missing	131 (2.30)						

Abbreviations: ART, anti-retroviral therapy; BVA, bivariate analysis; MVA, multivariate analysis; VIA, visual inspection after acetic acid.

[a] The number of women in levels of categorical variable may not add up to total "n" because missing category has been removed.

[b] for $p < 0.05$.

[c] for HIV positive patients only.

Variable	All n (%)	VIA Positive n [a] (%)	VIA Negative n [a](%)	VIA Positivity BVA Odds Ratios (95% CI)	P-value	VIA Positivity MVA Odds Ratios (95% CI)	P-value for X^2 test
CD4 Count at HIV Diagnosis [c]	**4,475**	**1,620 (36.2)**	**2,855 (63.8)**	0.90 (0.80, 1.02)	0.10	0.96 (0.83, 1.10)	0.52
≤ 350	2,308 (45.9)	809 (35.1)	1,499 (64.9)	Ref			
> 350	2,167 (43.1)	811 (37.4)	1,356 (62.6)				
Missing	551 (11.0)						
ART at time of screening [c]	**4,766**	**1,710 (35.9)**	**3,056 (64.1)**	0.89 (0.78, 1.00)	0.06	0.91 (0.78, 1.05)	0.19
No	3,138 (62.4)	1,096 (34.9)	2,047 (65.1)	Ref			
Yes	1,628 (32.4)	614 (37.7)	1,014 (62.3)				
Missing	260 (5.2)						

Abbreviations: ART, anti-retroviral therapy; BVA, bivariate analysis; MVA, multivariate analysis; VIA, visual inspection after acetic acid.

[a] The number of women in levels of categorical variable may not add up to total "n" because missing category has been removed.

[b] for $p < 0.05$.

[c] for HIV positive patients only.

In multivariate analyses, VIA positivity was more likely in 25 to 29 year-olds than in 30 to 49 year-olds (OR 1.48, CI 1.28, 1.72), and in WLWH compared to HIV-negative women (OR 1.85, CI 1.51, 2.28). Among WLWH, VIA positivity was not affected by CD4 count (OR = 0.96, CI 0.83, 1.10) or by ART (OR = 0.91, CI 0.78, 1.05) (Table 2).

High-grade Pre-cancer

The majority of the VIA-positive lesions were ineligible for treatment with cryotherapy (68%, n = 1,330); this was similar for both the 25 to 29 year-olds and the 30 to 49 year-olds (67.1% versus 68.1%, respectively). Of the 1,330 women referred to colposcopy/LEEP, 878 (66%) attended and had recorded histopathology results (58.5% for 25 to 29 year-olds, and 68.1% for 30–49 year-olds). The overall population CIN2 + point prevalence was 10.1% (10.9% for 25 to 29 year-olds and 9.9% for 30 to 49 year-olds) (Fig. 1 &Table 3).

Table 3
VIA and histological outcomes by age group and HIV status

VIA outcomes						
	All participants		HIV positive [a]		HIV negative [b]	
	25–29 Age group	30–49 Age group	25–29 Age group	30–49 Age group	25–29 Age group	30–49 age group
Number Screened with VIA	N = 1029	N = 4685	n = 849	N = 4177	N = 140	N = 417
VIA Results	601(58.4%)	3154(67.3%)	472(55.6%)	2747(65.8%)	95(67.9%)	328(78.7%)
Negative	428(41.6%)	1531(32.7%)	377(44.4%)	1430(34.2%)	45(32.1%)	89(21.3%)
Positive						
Eligible for cryotherapy	141(32.9%)	488(31.9%)	121(32%)	477(33.4%)	18(40%)	34(38.2%)
Not eligible for cryotherapy	287(67.1%)	1043(68.1%)	256 (68%)	953(66.6%)	27(60%)	55(61.8%
Histology outcomes						
Not eligible for cryotherapy, arrived at Colposcopy with histology results	N = 168	N = 710	n = 149	n = 659	N = 16	N = 46
≤CIN 1	56(33.3%)	247(34.8%)	46((30.9%)	209(31.7%)	8(50%)	36(78.2%)
≥CIN2+	112(66.7%)	463(65.2%)	103(69.1%)	450(68.3%)	8(50%)	10(21.8%)
≥CIN2 + in screened population	112/1029 (10.9%)	463/4685 (9.9%)	103/849 (12.1%)	450/4177 (10.8%)	8/140 (5.7%)	10/417 (2.4%)

Abbreviation: CIN, cervical intraepithelial neoplasia; VIA, visual inspection after acetic acid.

Figures for [a] and [b] do not add up to 5,714 due to missing HIV status in 131 records.

In multivariate analyses, CIN2 + was associated with a positive HIV status (aOR 6.12, CI 3.39, 11.10), but not with age (OR 1.07, CI 0.75–1.52 for 25 to 29 year-olds compared to 30 to 49 year-olds). In WLWH, neither CD4 count nor ART was associated with CIN2+ (Table 4).

Table 4
All Study participants' characteristics with bivariate and multivariable odds ratio for CIN2+

Variable	All n (%)	≥CIN2+ n [a] (%)	≤CIN1 n [a] (%)	CIN2+ BVA Odds Ratios (95% CI)	P-value	CIN2+ MVA Odds Ratios (95% CI)	P-value for X^2 test
Age Group	**878**	**575 (65.5)**	**303 (34.5)**	1.07(0.75, 1.52)	0.72	N/A	N/A
25–29 years	168 (19.1)	112 (66.7)	56 (33.3)	Ref			
30–49 years	710 (80.9)	463 (65.2)	247 (34.8)				
Smoker	**867**	**566 (65.3)**	**301 (34.7)**	Ref	0.30	N/A	N/A
No	817 (93.1)	530 (64.9)	287 (35.1)	1.38(0.74, 2.62)			
Yes	50 (5.7)	36 (72.0)	14 (28.0)				
Missing	11 (1.2)						
Age Sexual debut	**873**	**572 (65.5)**	**301 (34.5)**	1.16(0.87, 1.54)	0.31	N/A	N/A
≤ 18	505 (57.5)	338 (66.9)	167 (33.1)	Ref			
> 18	368 (41.9)	234 (63.6)	134 (36.4)				
missing	5 (0.6)						
Parity	**861**	**566 (65.7)**	**295 (34.3)**	Ref	0.08	1.30(0.96, 1.75)	0.09
≤ 2	517 (58.9)	328 (63.4)	189 (36.6)	1.29(0.97, 1.73)			
> 2	344 (39.2)	238(69.2%)	106 (30.8)				
Missing	17 (2.0)						

Abbreviations: ART, anti-retroviral therapy; BVA, bivariate analysis; MVA, multivariate analysis; VIA, visual inspection after acetic acid.

[a] The number of women in levels of categorical variable may not add up to total "n" because missing category has been removed.

[b] for $p < 0.05$.

[c] for HIV positive patients only.

Variable	All n (%)	≥CIN2+ n [a] (%)	≤CIN1 n [a] (%)	CIN2+ BVA Odds Ratios (95% CI)	P-value	CIN2+ MVA Odds Ratios (95% CI)	P-value for X^2 test
HIV Status	**870**	**571 (65.6)**	**299 (34.4)**	Ref	< 0.001[b]	6.12(3.39, 11.10)	< 0.001[b]
Negative	62 (7.1)	18 (29.0)	44 (71.0)	5.30(2.96, 9.49)			
Positive	808 (92.0)	553 (68.4)	255 (31.6)				
Missing	8 (0.9)						
CD4 Count at HIV Diagnosis [c]	**701**	**494 (70.5)**	**207 (29.5)**	0.93(0.67, 1.28)	0.65	N/A	N/A
≤ 350	336 (41.6)	234 (69.6)	102 (30.4)	Ref			
> 350	365 (45.2)	260 (71.2	105 (28.8)				
Missing	107 (12.2)						

Abbreviations: ART, anti-retroviral therapy; BVA, bivariate analysis; MVA, multivariate analysis; VIA, visual inspection after acetic acid.

[a] The number of women in levels of categorical variable may not add up to total “n” because missing category has been removed.

[b] for $p < 0.05$.

[c] for HIV positive patients only.

Variable	All n (%)	≥CIN2+ n [a] (%)	≤CIN1 n [a] (%)	CIN2+ BVA Odds Ratios (95% CI)	P-value	CIN2+ MVA Odds Ratios (95% CI)	P-value for X^2 test
ART at time of screening [c] No Yes Missing	**773** 455 (56.3) 318 (39.4) 35 (4.3)	**527 (68.2)** 315 (69.2) 212 (66.7)	**246 (31.8)** 140 (30.8) 106 (33.3)	1.13(0.83, 1.53) Ref	0.45	N/A	N/A

Abbreviations: ART, anti-retroviral therapy; BVA, bivariate analysis; MVA, multivariate analysis; VIA, visual inspection after acetic acid.

[a] The number of women in levels of categorical variable may not add up to total "n" because missing category has been removed.

[b] for $p < 0.05$.

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Via-positivity And High-grade Pre-cancer By Age And Hiv-status

In WLWH, the 25 to 29 year-olds were more likely to be VIA positive than the 30 to 49 year-olds (44.41%, n = 377 versus 34.2%, n = 1430, respectively). We observed a similar pattern for HIV-negative women (32.1%, n = 45 for 25 to 29 year-olds, compared to 21.3%, n = 89 for 49 year-olds). The overall proportion of CIN2 + in WLWH was 11% (12.1% for the 25 to 29 year-olds and 10.8% for the 30 to 49 year-olds). The overall proportion of CIN2 + in HIV-negative women was 3.2% (5.7% for 25 to 29 year-olds and 2.4% for 30 to 49 year-olds) (Table 3).

Discussion

WLWH aged 25 through 29 years attending routine cervical cancer screening in our national program had the same odds of having high-grade cervical pre-cancer as women aged 30 to 49 years. Prior research has indicated a link between younger age and cervical cancer among WLWH.[5, 8, 9] Our findings confirm the presence of a significant level of cervical cancer precursors requiring intervention in women as young as 25 years, particularly in WLWH, thus supporting the new WHO recommendation to lower the age of initiation of cervical cancer screening from 30 to 25 years in WLWH.

A concern about lowering the cervical cancer screening age is that clinically insignificant lesions from transient HPV infections would be intervened upon unnecessarily, resulting in overtreatment of young women.[19, 20] Although women in this cohort aged 25 through 29 years had higher rates of VIA positivity than women aged 30 to 49 years, similar proportions were referred for the excisional procedure. The histopathology results indicate that the proportions of CIN2 + detected and appropriately treated were similar for the two age groups in WLWH. The proportion of CIN2 + was more than three times lower in HIV-negative women than in WLWH, and younger women were twice more likely to have CIN2+. If overtreatment did occur, it would primarily have occurred in the group of women treated with cryotherapy, a treatment that ultimately has minimal side effects.[21]

We had expected to find a correlation between patient age and high-grade dysplasia because older women would have had a longer time to progress from HPV infection to cervical pre-cancer without opportunities for intervention.[22] However, our data do not support this hypothesis. Instead, younger women overall and in WLWH had a similar proportion of CIN2 + to older women. Data is limited on HPV progression to cervical pre-cancer and cancer in women aged 20 to 29 years. Adolescent WLWH are more likely to have HPV co-infections and coexisting abnormalities, albeit low-grade, relative to their HIV-negative counterparts.[23] The shorter timeline from HPV infection to the development of pre-cancer in adolescent WLWH is in line with our finding of high rates of high-grade pre-cancer in the 25 to 29 year-olds because of the likey accelerated timeframe of progression of pre-cancer from low- to high-grade.

Our analysis has limitations because it utilized a programmatic database that collected limited patient-level demographic and risk factor data. CD4 count had 11% missing data; however, this was similar for both age groups, and we doubt that it would have had a significant effect on the outcomes. The rate of cryotherapy ineligibility was high, but high rates have been observed in other high HIV burden areas.[24] This high rate could be related to lack of prior screening and high rates of cervicitis.[25] Documentation of colposcopy/LEEP referral

appointment attendance was not recorded, and thus histopathology results may not represent the entire cohort of women who had a colposcopic evaluation. However, the population point prevalence of the screened cohort was similar for the two age groups when computed using the available histology results proportions. Key HIV-related variables, including viral load and timing of HIV treatment, were not collected, and therefore, the full extent of the immune status of WLWH could not be assessed. Finally, the determination of the proportion of women with high-grade dysplasia was further limited by the lack of histopathology data in women who underwent cryotherapy and the sensitivity of VIA. The accuracy of VIA positivity is affected by the prevalence of cervicitis related to sexually transmitted infections, and high rates of cervicitis have been reported in WLWH in Botswana.[25]

Conclusions

Despite the limitations of this study, we present new evidence of the significant burden of CIN2 + in younger WLWH in Botswana. Until the population-level effects of HPV vaccination and universal ART to improve overall immune competence in WLWH are realized,[26] the reduction in cervical cancer in LMICs will depend on effective, comprehensive screening programs for WLWH. This additional evidence further supports the current WHO conditional recommendation for initiating screening at age 25.

Abbreviations

ART: Anti-retroviral treatment; CI: Confidence interval; CIN: Cervical intraepithelial neoplasia; HIC: High-income country; HIV: Human immunodeficiency virus; HPV: Human papillomavirus; HRDC: Health research and development committee; LEEP: Loop electro-surgical excision procedure; LMIC: Low-middle income county; IQR: Interquartile range; MOHW: Ministry of health and wellness; NHL: National health laboratory OR: Odds ratio; PMH: Princess Marina hospital; VIA: Visual inspection after acetic acid; WHO: World Health Organization; WLHV: Women living with HIV

Declarations

Ethics approval and consent to participate

The Health Research and Development Committee (HRDC) of the Botswana Ministry of Health and Wellness (MOHW) approved this analysis (HPDME-13/181). Patient consent was waived as this was a secondary analysis of routinely collected programmatic data. All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during the current study are available from the corresponding author on reasonable request.

Competing interests

No competing interests declared by the authors

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Author contributions

Study conception and design: DRM, RL, SG; Acquisition of data: BM, DRM; Analysis and interpretation of data: DRM, RL, SG, GJH, AM, CM, LG ; Drafting of manuscript: DRM, RL, SG; Critical revision: GJH, CM, LBM, AM. All authors approved the manuscript before submission.

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Figures

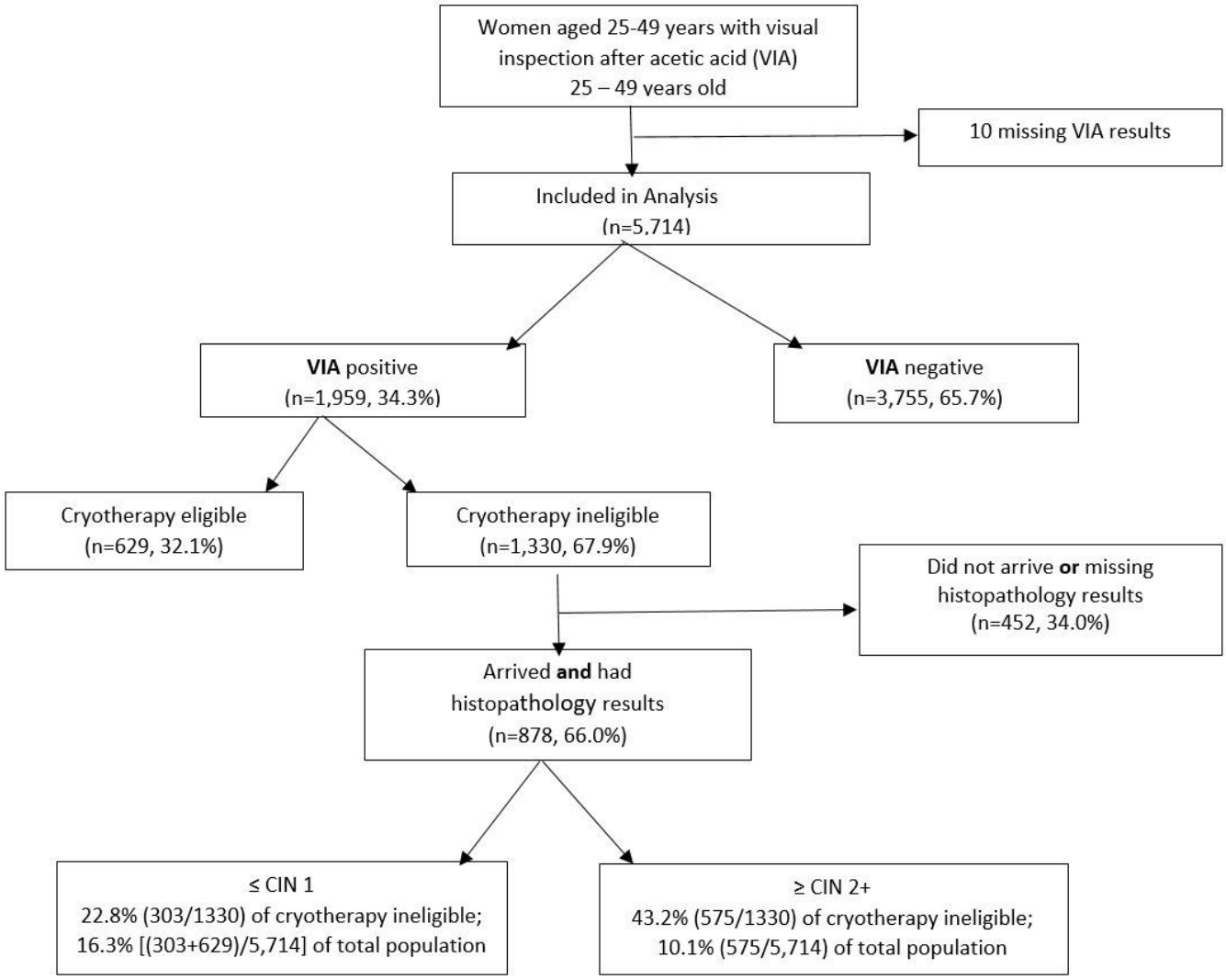

Figure 1

Study flow chart