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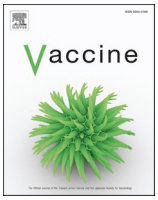
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High prevalence of human papillomavirus (HPV) in unvaccinated adolescent girls in South Africa, particularly those living with HIV

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ABSTRACT

Introduction: In 2014, South Africa implemented a national two-dose HPV vaccination programme using the bivalent vaccine for girls aged 9 years and older attending Grade 4 at public schools. We assessed HPV prevalence and risk factors among South African adolescent girls and young women (AGYW) aged 17–18 years who were ineligible for vaccination.

Methods: From June to December 2019, we surveyed AGYW aged 17–18 years attending primary care clinics in four South African provinces. Consenting participants completed a questionnaire, underwent HIV counselling and testing, and self-collected a vaginal swab for HPV testing. Samples were tested by Seegene AnyPlex™ II HPV28. We used summary statistics to describe the population characteristics and logistic regression to examine the association between risk factors and high-risk HPV detection.

Results: 910 participants were screened, 900 enrolled, 896 had valid HPV results, and 819 were unvaccinated and included in this study. Of these, 248 (30.3 %) were living with HIV and 597 (72.9 %) reported ever having vaginal sex. Overall, 463 (56.5 %) had at least one high-risk HPV detected, and 177 (21.6 %) had HPV16/18 detected. AGYW living with HIV had a higher prevalence of any high-risk HPV (65.3 % vs 52.7 %, $p < 0.001$) and HPV 16/18 (29.4 % vs 18.2 %, $p < 0.001$) compared to those without HIV. Multiple infections were also more common in participants living with HIV, with three or more high-risk HPV types detected in 32.3 % compared with 15.4 % of those without HIV ($p < 0.001$). In multivariate analyses, HIV status ($p < 0.001$) and higher number of lifetime sexual partners (p-trend<0.001) were associated with high-risk HPV detection.

Conclusions: High-risk HPV was very common in unvaccinated South Africa AGYW, especially among those living with HIV, highlighting the importance of HPV vaccination in settings with high HIV prevalence.

1. Introduction

Cervical cancer is the fourth most common malignancy in women worldwide, with 604,127 new cases and 341,831 deaths recorded in 2020 [1]. The vast majority occur in low and middle-income countries (LMICs) [1]. The situation is further compounded in Sub-Saharan Africa, where the impact of HIV contributes to a six-fold increase in cervical cancer burden [2]. Adult women living with HIV have higher rates of HPV persistence, faster progression to high-grade disease and are likely to be younger at cervical cancer diagnosis, suggesting more rapid progression to cancer [3]. HIV impacts the immune competence of the vaginal mucosa, rendering it more vulnerable to high-risk infections. This effect concurrently diminishes the efficiency of the body's ability to clear infections and accelerates the progression of pre-cancerous lesions. Cervical screening delivered through well-organised programmes has significantly reduced cervical cancer incidence and mortality in high-income countries [4,5]. However, replicating such programs in LMICS has proven challenging due to constraints such as inadequate healthcare

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systems, resource scarcity, affordability concerns and competing health priorities [6,7].

Prophylactic HPV vaccines have been available since 2006 and provide high levels of protection against infection with HPV types that cause most cases of cervical cancer worldwide [8]. These vaccines have been included in national immunisation programmes in 88 % of high-income countries, originally as a 3-dose schedule and are recommended for girls aged 9–14 year [8]. Surveillance and evaluation activities have provided definitive evidence for the population-level impacts of 3-dose programmes in reducing rates of infection and pre-cancerous disease [9]. Data confirming the protective benefits of these vaccines against cervical cancer are now also emerging from early adopting countries [9–14]. The picture, however, is very different for LMICs, particularly in Africa, where scale-up of HPV vaccination has been slow, mainly due to high vaccine and delivery costs [8,15].

To accelerate HPV vaccine uptake, in 2014, the World Health Organisation (WHO) recommended a 2-dose schedule based on non-inferiority studies of antibody titres following vaccination [15–17]. In the same year, South Africa implemented a national 2-dose HPV vaccination programme using the bivalent vaccine. The program targets girls attending public schools aged 9 years and older and in Grade 4. In 2022, the WHO updated its recommendation to include an option of a single dose but still advises that immunocompromised individuals, including those living with HIV, should receive a minimum of two doses and, where possible, three doses [18]. The current vaccination programme in South Africa is implemented in schools and does not include any HIV testing. HIV prevalence in young girls at the age of vaccination is estimated to be 2.9 % [19]. The country's extreme socio-economic diversity and high burden of HIV infection are important characteristics that have not been previously considered in population-level vaccine impact evaluations. Notably, up to two-thirds of cervical cancer cases in South Africa can be attributed to the influence of HIV [2].

HPV vaccination rates in South Africa vary over time. The school-based two-dose vaccination programme started in 2014, and 87 % of eligible grade four girl learners received the first dose of the vaccine and 68 % received both doses [20]. This steadily decreased over time, and in 2019, only 70 % and 43 % received first and second doses, respectively. [21]."

The Human Papillomavirus One and Two Dose Population Effectiveness (HOPE) study was initiated in 2019 and concluded in 2023. HOPE aimed to evaluate the impact of a one-dose schedule delivered as an adolescent catch-up program and the national two-dose program on community-level HPV prevalence in South African adolescent girls and young women (AGYW) aged 17–18 years, including those living with HIV [22]. We report here the HPV prevalence in unvaccinated AGYW who were too old to have received the HPV vaccine following the introduction of the school-based HPV vaccination programme in 2014.

2. Methods

2.1. Study population

Details of the study design and methodology have been published elsewhere [22]. Briefly, from June to November 2019, AGYW aged 17–18 years attending one of 18 public sector primary health care clinics for various primary health care services (including contraception, HIV testing and treatment, pre-exposure prophylaxis or acute minor illnesses) located in one of four South African provinces (Free State, Gauteng, Mpumalanga, and Northwest) were invited to participate in the survey. Reasons for site selection have been detailed else where [22]. Briefly, the four provinces were selected as together they provided a diverse geography that includes urban, peri-urban, and rural areas; and are representative of the diversity of South African population. The provinces varied in size, HIV prevalence and HPV vaccination coverage. [22].Written informed consent was obtained from all participants by trained research staff stationed at the clinic during recruitment. For those under 18, the requirement for parental consent was waived, given that the study involved minimal risk. Participants were included in the study if they were adolescent females aged 17–18 years at the time of sample collections, presenting at participating sentinel clinics for routine care and willing and able to provide written consent for all study procedures. The procedures to recruit survey participants were consistent across study clinics.

2.2. Study procedures

Consenting participants completed a computer-assisted self-interview (CASI) covering questions on socio-demographic characteristics HPV risk factors; and vaccination history. This method of data collection was selected to reduce social desirability bias. The CASI was conducted in English as most participants spoke English and were in school, which is conducted in English. They were also consented in English. Research assistants were available at all times to confirm meaning of any questions that participants may not have understood. Participants provided their HIV status based on recent test results. AGYW who were not known to be living with HIV and those who had not had an HIV test in the previous three months were offered HIV counselling and testing. AGYW who tested HIV positive received post-test counselling and were linked to care as per national guidelines. [23] For participants who self-reported having HIV infection, data on HIV diagnosis date, and most recent treatment regimen, viral load and CD4 count (where available) were abstracted from medical records, with participant consent. Participants self-collected a vaginal sample for HPV testing using a dry flocked swab (Copan Diagnostics, Inc., Brescia, Italy), following guidance from the research staff.

2.3. HPV detection and genotyping

All samples were stored at 4 °C or lower before being transported to a central laboratory for processing. Swabs were swirled in 1 mL of Digene transport medium (Qiagen, Hilden, German) to suspend cellular material. A 400 μL aliquot of the cell suspension underwent nucleic acid extraction that was conducted using an automated procedure of MagNA Pure Compact (Roche Molecular Systems, Inc., Branchburg, NJ, USA) and MagNA Pure Compact Nucleic Acid Isolation Kit (Roche Molecular Systems, Inc., Branchburg, NJ, USA). After nucleic acid extraction, all specimens were tested for HPV DNA and genotyped using Seegene Anyplex II HPV28 (Seegene, Seoul, South Korea), a multiplexed quantitative PCR melting-curve assay for the detection of up to 28 HPV genotypes.

2.4. HPV vaccination status

In the Free State, doses administered in the national programme or the single-dose catch-up campaign conducted by the HOPE study were validated against records captured in the Department of Health and study vaccination registers, respectively [22]. Approximate string matching was used to assign a match probability (i.e. 0 to 100 %) between identifying information (given name, surname and date of birth) provided by the study participants and those held in the registers. A probability of $\geq$90 % was considered a match. Participants with a match were excluded from the study. All provinces implemented two-dose vaccination schedules in 2014. Validation of vaccination status delivered in the national school programme was performed for participants recruited at sites in the Free State province as the province with the largest recruitment.

2.5. Statistical analysis

We calculated crude prevalence and 95 % confidence intervals (CIs) using the exact binomial method for the following groups of HPV types: i) any Group 1 and 2 A high-risk HPV type (16, 18, 31, 33, 35, 39, 45, 51,

52, 56, 58, 59, 68) [24,25]; ii) HPV16 and/or 18; iii) high-risk HPV types other than 16 and 18; iv) high-risk types other than 16 or 18 that are targeted by the nine-valent vaccine (31, 33, 45, 52, 58); v) remaining high-risk HPV types not targeted by any HPV vaccine (35, 39, 51, 56, 59, 68); vi) all low-risk HPV types (6, 11, 26, 40, 42, 43, 44, 53, 54, 61, 66, 69, 70, 73, 82); vii) HPV6 and/or 11 and viii) any of the 28 HPV types detected by the assay, as well as for individual HPV types. We summarised baseline characteristics using frequencies and medians. We used Pearson's $\chi 2$ test to analyse the association between HPV detection and individual characteristics, including HIV status. Odds ratios (ORs) and 95 % CIs were estimated using logistic regression in univariate and adjusted analyses. Variables that were associated with the outcome at $p < 0.100$ were considered in the multivariable model. A priori age and province of residence were included in all multivariate analyses. Our primary regression analysis included only AGYW who reported ever having vaginal sex, given that subsequent questions on sexual behaviour were only collected from this population. In further sensitivity analyses including the entire study population, participants who reported not having vaginal sex were included as the reference category. Data analyses were performed using STATA version 16 (Stata Corporation).

2.6. Ethics statements

The study was reviewed and approved by research ethics committees of the University of the Witwatersrand (HREC #181005) and the University of New South Wales (#181–005).

3. Results

3.1. Participant disposition and characteristics

We screened 910 AGYW aged 17–18 years and enrolled 900 participants. Ten participants declined consent following an informed consent discussion. Of those enrolled ($n = 900$), four had invalid HPV results. A further 77 Free State participants matched vaccination registers and were excluded: 70 had received the HPV vaccine earlier in the year as part of the single-dose catch-up campaign, and 7 were vaccinated in 2014 (when aged 12 or 13) in the school-based programme.

A total of 819 participants were included in this analysis. The majority were aged 18 years ($n = 423$; 51.7 %) and from the Free State province ($n = 506$; 61.8 %), and 30.3 % ($n = 248$) were living with HIV (Table 1). Overall, 74.1 % ($n = 607$) of participants reported ever having had any sex, including 72.9 % ($n = 597$) who reported ever having had vaginal sex, 18.7 % ($n = 152$) oral sex, and 12.3 % ($n = 100$) anal sex. Among those who reported vaginal sex, the median age at first sex was 16 (interquartile range [IQR] 16—17), and the median number of lifetime sex partners was 2 (IQR 1—3). Most participants reported contraceptive use ($n = 640$; 78.1 %), even though some ($n = 33$) did not report sexual activity. Condoms were the most frequently reported contraceptive ($n = 360$; 44.0 %), followed by injectable progestins ($n = 204$; 24.9 %) and implants ($n = 44$; 5.4 %).

Thirty-one ($n = 31$) participants declined HIV testing and were categorised as having an unknown HIV status. This group was combined with HIV-negative participants for analysis because they shared similar characteristics (Supplementary Table 1). Compared to those without HIV, participants living with HIV were less likely to be currently in school or work (<0.001), less likely to be using any contraception ($p = 0.006$), less likely to report ever having had any sex (including vaginal, oral or anal sex) ($p = 0.006$) including vaginal sex ($p = 0.024$) (Table 1). Among those who were sexually active, a higher proportion of participants living with HIV reported an earlier age of sexual debut ($p < 0.001$) (Table 1).

3.2. HPV prevalence

Overall, 66.3 % of all participants had any HPV detected, with high-risk HPV detected in 56.5 % ($n = 463$) of AGYW. HPV16 or HPV18 was detected in 21.6 % ($n = 177$), and additional high-risk HPV types targeted by the nonavalent vaccine (HPV types 31,33,45,52 & 58) were detected in 33.1 % ($n = 271$) (Table 2). All groups of HPV types examined were significantly more prevalent in participants living with HIV than those without HIV (Table 2). In particular, the prevalence of any high-risk HPV was 65.3 % compared to 52.7 % ($p = 0.001$), HPV16/18 prevalence was 29.4 % compared to 18.2 % ($p < 0.001$), and the prevalence of the additional high-risk HPV types targeted by the nonavalent vaccine was 41.9 % compared to 29.3 % respectively ($p < 0.001$) (Table 2). Multiple HPV infections were also significantly more common in participants living with HIV, with three or more high-risk HPV types detected in 32.3 % compared to 15.4 % of participants without HIV ($p < 0.001$) (Table 2).

The most common high-risk HPV types detected were HPV16 (13.7 %), followed by HPV52 (13.6 %), HPV39 (12.2 %), HPV35 (12.0 %), and HPV56 (11.2 %). Among participants living with HIV, the most common frequent high-risk HPV types detected were HPV52 (19.8 %), followed by HPV18 (17.7 %), HPV58 (17.3 %), HPV16 (16.9 %), and HPV35 (16.1 %). Of the 13 high-HPV types, seven, including HPV18, HPV33,

Table 1
Characteristics of 819 adolescent girls and young women aged 17–18 years, by HIV status.

Variable	Participants without HIV ($n = 571$)	Participants living with HIV ($n = 248$)	*P*-value[1]
	n (Col %)	n (Col %)	
Age			
17 years	284 (49.7)	112 (45.2)	0.229
18 years	287 (50.3)	136 (54.8)	
Province of residence			
Free State	349 (61.1)	157 (63.3)	0.635
Gauteng	84 (14.7)	30 (12.1)	
Mpumalanga	59 (10.3)	30 (12.1)	
Northwest	79 (13.8)	31 (12.5)	
Currently in school[2]	496 (86.9)	188 (75.8)	**<0.001**
Head of household has an income			
Yes	244 (42.7)	92 (37.1)	0.146
No	216 (37.8)	94 (37.9)	
Don't know	97 (17.0)	55 (22.2)	
Missing	*14 (2.5)*	*7 (2.8)*	
In a relationship	260 (45.5)	112 (45.2)	0.922
Current contraceptive use	461 (80.7)	179 (72.2)	**0.006**
Condom use[3]	263 (46.1)	97 (39.1)	0.066
Current cigarette smoker[4]	54 (9.5)	32 (12.9)	0.136
Frequency of alcohol use[5]			
Never	315 (55.2)	140 (56.5)	0.923
Monthly or less	194 (34.0)	81 (32.7)	
2+ times per month	62 (10.9)	26 (10.5)	
Ever had sex[6]	439 (76.9)	168 (67.7)	**0.006**
Ever had vaginal sex (n = 597)	432 (75.7)	165 (66.5)	**0.024**
Age at first vaginal sex[7]			
14 years or younger	16 (3.7)	19 (11.5)	**<0.001**
15–16 years	190 (44.0)	84 (50.9)	
17–18 years	177 (41.0)	58 (35.2)	
Missing	*49 (11.3)*	*4 (2.4)*	
Number of lifetime sex partners[7]			
One	157 (36.3)	50 (30.3)	0.215
Two	138 (31.9)	51 (30.9)	
Three or more	137 (31.7)	64 (38.8)	

Col: column; 1: Pearson chi-squared test for difference between categories; 2: 3 no response (2 without HIV, 1 with HIV); 3: Condom use is condom is reported as a method of contraception. 4: 22 no response (15 without HIV, 7 without); 5: 1 no response (1 with HIV); 6: Includes vaginal, anal or oral sex.; 7: N = 597 These questions were only asked to those individuals who reported having vaginal sex.

Table 2
Crude HPV prevalence among 819 adolescent girls and young women aged 17–18 years, by HIV status.

HPV groups	Overall (N = 819)	Participants without HIV (n = 571)	Participants living with HIV (n = 248)	P-value[1]
	n; % (95 % CI)	n; % (95 % CI)	n; % (95 % CI)	
Any HPV	543; **66.3** (63.0—69.5)	364; **63.8** (59.7—67.7)	179; **72.2** (66.2—77.7)	**0.019**
Any high-risk HPV type	463; **56.5** (53.1—60.0)	301; **52.7** (48.5—56.9)	162; **65.3** (59.0—71.2)	**0.001**
HPV16/18	177; **21.6** (18.8—24.6)	104; **18.2** (15.1—21.6)	73; **29.4** (23.8—35.5)	**<0.001**
High-risk HPV not 16/18[2]	428; **52.3** (48.8—55.7)	276; **48.3** (44.2—52.5)	152; **61.3** (54.9—67.4)	**0.001**
HPV31/33/45/52/58[3]	271; **33.1** (29.9—36.4)	167; **29.3** (25.5—33.2)	104; **41.9** (35.7—48.3)	**<0.001**
HPV35/39/51/56/59/66[4]	335; **40.9** (37.5—44.4)	215; **37.7** (33.7—41.8)	120; **48.4** (42.0—54.8)	**0.004**
Any low-risk HPV type	409; **49.9** (46.5—53.4)	267; **46.8** (42.6—51.0)	142; **57.3** (50.8—63.5)	**0.006**
HPV6/11[5]	136; **16.6** (14.1—19.3)	75; **13.1** (10.5—16.2)	61; **24.6** (19.4—30.4)	**<0.001**
Any HPV				
Not detected	276; **33.7** (30.5—37.1)	207; **36.3** (32.3—40.4)	69; **27.8** (22.3—33.8)	**<0.001**
Single infection	138; **16.9** (14.4—19.6)	113; **19.8** (16.6—23.3)	25; **10.1** (6.6—14.5)	
Two HPV types	98; **12.0** (9.8—14.4)	65; **11.4** (8.9—14.28)	33; **13.3** (9.3—18.2)	
Three or more types	307; **37.5** (34.2—41.0)	186; **32.6** (28.7—36.6)	121; **48.8** (28.7—55.2)	
Median no. (IQR)	1; (0–4)	1;(0–3)	2; (0–6)	
Any high-risk HPV				
Not detected	356; **43.5** (40.0—46.9)	270; **47.3** (43.1—51.5)	86; **34.7** (28.8—41.0)	**<0.001**
Single infection	171; **20.9** (18.1—23.8)	129; **22.6** (19.2—26.3)	42; **16.9** (12.5—22.2)	
Two HPV types	124; **15.1** (12.8—17.8)	84; **14.7** (11.9—17.9)	40; **16.1** (11.8—21.3)	
Three or more types	168; **20.5** (17.8—23.4)	88; **15.4** (12.6—18.6)	80; **32.3** (26.5—38.5)	
	1 (0–2)	1 (0–2)	1 (0–3)	

1: Pearson chi-squared test for difference between categories; 2: Includes HPV types 31,33,35,39,45,51,52,56,58,59 & 68 3: Denotes HPV types additionally prevented by the nonavalent vaccine (High-risk HPV types /31/33/45/52/58) 4: Denotes HPV types currently not covered by any vaccine type 5: Denotes HPV types additionally prevented by the quadrivalent vaccine.

HPV35, HPV52, HPV56, HPV58 and HPV68, were significantly more frequently detected in those living with HIV than in participants without HIV. Low-risk HPV types HPV6 and HPV11 were also more prevalent, with 15.7 % having HPV6 and 13.3 % having HPV11, compared to 10.0 % and 4.2 %, respectively (Fig. 1).

3.3. Factors associated with high-risk HPV prevalence

In analyses limited to 597 participants who reported being sexually active, those living with HIV ($p < 0.001$) and who reported more lifetime sexual partners (p-trend<0.001) had a higher likelihood of having any high-risk HPV. Compared to participants in the Free State, participants in all other provinces had a lower likelihood of high-risk HPV detection, although this was only statistically significant for residents of Gauteng ($p = 0.016$). Participants who reported a head of household with an income/employment ($p = 0.047$) had a lower likelihood of having high-risk HPV. In multivariate analyses, only HIV status (<0.001) and having more lifetime sexual partners (p-trend<0.001) remained independently associated with any high-risk HPV detection (Table 3). The results of a sensitivity analysis, which included all 819 participants enrolled, was consistent with that of the primary analysis (Supplementary Table 2).

Among participants living with HIV, 51.6 % ($n = 128$) were diagnosed with HIV at the age of 15 years or older (Table 4). Most ($n = 232$; 93.6 %) were already on antiretroviral therapy (ART) at the time of the recruitment, and 44.8 % ($n = 111$) had been on treatment for two or more years. Recent data on CD4+ count and HIV RNA were incomplete. However, of those with a documented CD4 + count (174 of 248; 70.7 %), 64.8 % ($n = 112$) had been recorded in the past 2 years, with a median CD4+ count of 475 cells/mm3 (IQR 322—682). Of those with a documented HIV RNA result (136 of 248, 56.1 %), 89.9 % ($n = 122$) were recorded in the past 2 years, and 50.4 % ($n = 68$) had <50 HIV RNA copies/ml consistent with viral suppression. Using a composite outcome (including participants who were virally suppressed with signs of immune reconstitution with a CD4 > 350 cells/mm3), 15.7 % were on ART and had evidence of viral suppression and immune reconstitution in the past two years.

Among participants living with HIV, detection of any high-risk HPV was associated with older age at HIV diagnosis, with a significant association observed for those diagnosed between the ages of 15–18 years ($p < 0.001$). Shorter time on ART appeared to also be associated with a higher likelihood of high-risk HPV detection ($p = 0.027$). After adjusting for age, province of residence and lifetime number of sexual partners, only older age at HIV diagnosis (15–18 years) ($p = 0.011$) and being on ART for less than 2 years (p = 0.027) remained significantly associated with any high-risk HPV detection (Table 4).

4. Discussion

In this cross-sectional survey of 819 South African AGYW aged 17–18 years who were age-ineligible for the national vaccination programme, presenting for routine services in primary health care clinics, over half (56.5 %) were positive for high-risk HPV. Nearly a quarter (21.6 %) were positive for HPV 16 or HPV18, which are responsible for 70 % of cervical cancers globally and are preventable by all commercially available HPV vaccines. We observed significantly higher HPV prevalence among participants living with HIV for all HPV groups examined and for seven of the 13 individual high-risk HPV types. Of note, HPV16 was the most prevalent HPV type overall, likely reflecting its pathogenicity and highest likelihood of persistence independent of HIV status. We also observed that participants living with HIV had a higher prevalence of infection with high-risk HPV types even after adjusting for sexual behaviour, suggesting an independent effect. This paper adds to the relatively small body of knowledge on HPV incidence in young women who would benefit from vaccination, given the high burden of HIV in our setting and the fact that HIV is a strong risk factor for the development of cervical cancer.

Within our study sample, 30 % of AGYW were living with HIV, with the majority being on ART but not all virally suppressed. It has been well established that compared to women without HIV, women living with HIV have higher HPV prevalence, infection with multiple high-risk HPV types, increased high-risk HPV persistence and progression to pre-neoplastic lesions and cancer [26–32]. This is believed to be due to compromised mucosal immune competence, which can increase susceptibility to HPV infection [3]. The findings from our study of higher prevalence of HPV among participants living with HIV, are consistent with published data in adult women and suggest that differences are already present within a few years of initiating sexual activity. High rates of HPV in such a young cohort where, although the majority are expected to clear HPV infection, is particularly concerning in a population living with HIV who are less likely to clear the infection [32].

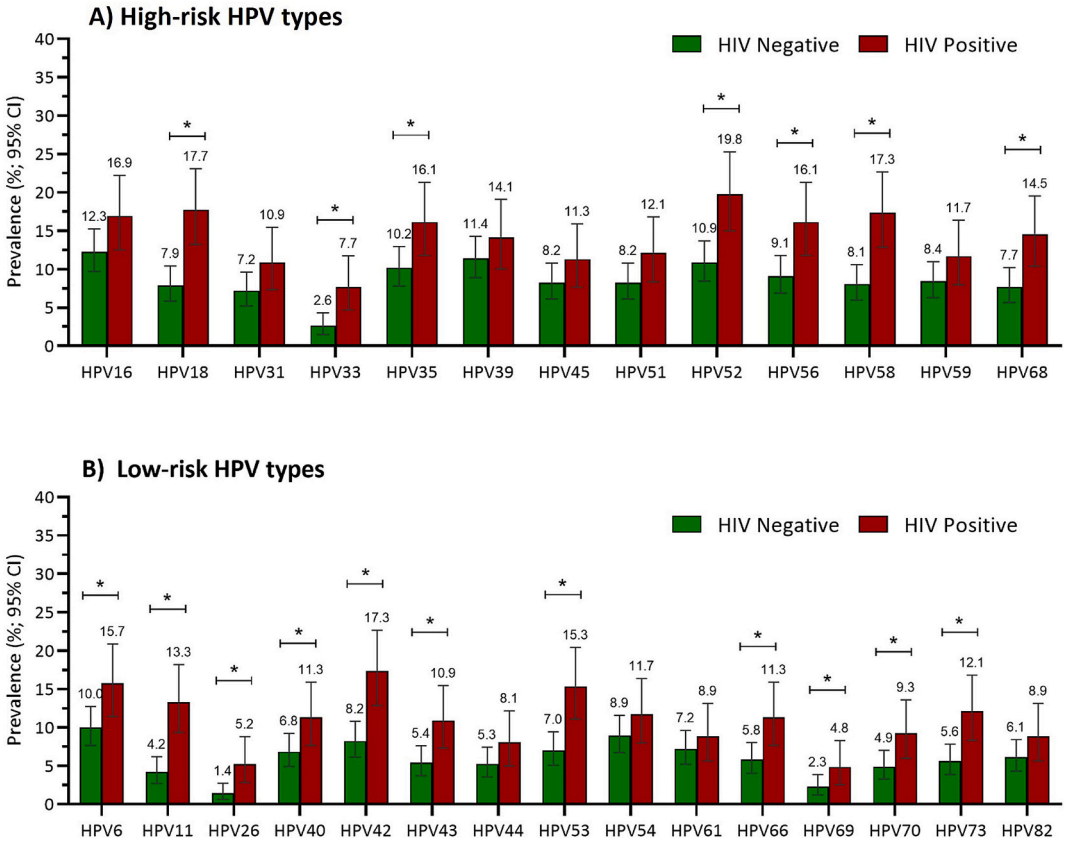


Fig. 1. Individual HPV type prevalence among 819 adolescent girls and young women aged 17–18 years, by HIV status.
Footnote: *Denotes where prevalence was significantly higher among participants living with HIV compared with those without HIV.

Modelling suggests that an estimated 50 % of women will acquire their "causal" HPV infection that develops into cervical cancer before the age of 21, with HPV16 causal infections acquired at an even earlier age [33]. This highlights the importance of primary prevention in the form of prophylactic vaccination programmes, but also the important role ART and ongoing cervical screening play in HPV management in populations living with HIV.

The higher burden of HPV in AGYW living with HIV may be partly due to behavioural factors, as both infections are sexually acquired. Our data showed that HPV detection was associated with being on ART for less than two years and being more recently diagnosed with HIV, which may indicate a similar timing of acquisition of both HIV and HPV infections. There may, however, also be biological contributing factors as the risk remained even after adjusting for available information on sexual history. Published data suggest that HIV infection itself can increase the risk of HPV acquisition [27]. Data from a South African cervical cancer prevention trial found that HPV prevalence more than doubled during the first year of HIV infection and was similar to HPV prevalence among women with a long-standing HIV infection [34]. The authors suggest that this may be due to HIV-associated immune dysfunction of the cervical mucosa, which may occur at an early stage of HIV infection. Acute HIV infection in the first 3–6 months post-acquisition can result in the depletion of the genital tract immunity immediately, which could result in an increased susceptibility to high-risk HPV infection. [34–36].

Of note, 23 % of participants acquired their HIV infection before the age of 9 years; it is likely that most of those HIV infections were perinatally acquired. Notably, 45 % of these participants had high-risk HPV detected (see Table 4). These data highlight that a small proportion of individuals vaccinated by the national HPV vaccination programme will be living with HIV. The WHO still recommends two or three doses of vaccine for people living with HIV [3]. Nevertheless, the long-term effectiveness of HPV vaccines administered in any schedule among populations living with HIV is not known. Available evidence suggests that even with ART, this group have lower HPV antibody levels following vaccination as compared to HIV-negative individuals, with evidence of a decline in antibodies over time [37,38].

The study has limitations. First, validation of vaccination status delivered in the national school programme was performed for participants recruited at sites in the Free State province only. Among this group, 7 of 585 (1.2 %) participants were confirmed to be vaccinated in the schools-based programme. If the proportion who had been vaccinated in other provinces under the schools-based program were the same as in Free State, we would have potentially misclassified 4 of the 315 girls from these provinces as unvaccinated. From a statistical point of view, it would make little difference to extrapolate this to the other provinces as the numbers of vaccinations reported in the other provinces were negligible. Second, of the 819 AGYW who were included in the primary analysis, 597 reported ever having vaginal sex. Of those girls who reported never having had vaginal sex, we detected high-risk HPV in 25.9 % of their swabs (Supplementary Table 2), suggesting that this question was poorly answered or the presence of information bias, whether it be due to a lack of understanding of the question or want to withhold the information, even in the context of a CASI. To assess the impact this may have had on the analysis, we ran a sensitivity analysis, and the results remained consistent when we included those who reported no vaginal sex. Third, the sample size for participants living with HIV was relatively small, with limited power to examine other risk factors related to HIV status. Lastly, we reported on the prevalence among AGYW engaged in care and cannot generalise findings to the whole population of this age group, even in the selected provinces and districts. Despite this, these estimates remain congruent with global prevalences in this age group and provide important baseline estimates with which to compare future similar cohorts that were age-eligible for

Table 3
Risk factors associated with the detection of any high-risk HPV among 597 adolescent girls and young women aged 17–18 years who reported ever having vaginal sex.

Variable	N	n Detected (Row %)	OR (95 % CI)	Adjusted OR[1] (95 % CI)	P-value
HIV status					
Participants without HIV	432	268 (62.0)	*1.00 (ref)*	*1.00 (ref)*	
Participants living with HIV	165	137 (83.0)	2.99 (1.91–4.70)	3.09 (1.90–5.02)	**<0.001**
Age					
17 years	249	164 (65.9)	*1.00 (ref)*		
18 years	348	241 (69.3)	1.17 (0.83–1.65)	1.01 (0.69–1.48)	0.954
Province					
Free State	365	261(71.5)	*1.00 (ref)*	*1.00 (ref)*	
Gauteng	83	48(57.8)	0.55 (0.33–0.89)	0.78 (0.45–1.34)	0.366
Mpumalanga	70	48 (68.6)	0.87 (0.50–1.51)	0.89 (0.48–1.62)	0.693
Northwest	79	48(60.8)	0.62 (0.37–1.02)	0.69 (0.39–1.21)	0.198
Currently in school					
No	111	78(70.3)	*1.00 (ref)*		
Yes	484	326(67.4)	0.87 (0.56–1.37)		
Relationship status					
Not in a relationship	263	176 (66.9)	*1.00 (ref)*		
In a relationship	334	229 (68.6)	1.08 (0.76–1.52)		
Head of household employed					
No	234	166 (70.9)	*1.00 (ref)*	*1.00 (ref)*	
Yes	250	156 (62.4)	0.68 (0.46–1.00)	0.75 (0.50–1.14)	0.175
Current cigarette use					
No	505	338 (66.9)	*1.00 (ref)*		
Yes	77	56 (72.7)	1.32 (0.77–2.25)		
Alcohol use					
Never	290	194 (66.9)	*1.00 (ref)*		
Monthly or less	229	161 (70.3)	1.17 (0.81–1.70)		
2+ times per month	77	49 (63.6)	0.87 (0.51–1.46)		
Age at first sex					
<15 years	35	24 (68.6)	*1.00 (ref)*		
15–16 years	274	194 (70.8)	1.11 (0.52–2.38)		
17–18 years	235	151 (64.3)	0.82 (0.38–1.77)		
Number of lifetime sex partners					
One	207	110 (53.1)	*1.00 (ref)*	*1.00 (ref)*	
Two	189	136 (72.0)	2.26 (1.49–3.44)	2.21 (1.41–3.46)	**0.001[2]**
Three or more	201	159 (79.1)	3.34 (2.16–5.16)	3.05 (1.89–4.93)	
Reported current condom use					
No	278	196 (70.5)	*1.00 (ref)*		
Yes	319	209 (65.5)	0.79 (0.56–1.12)		

1: Adjusted for age, province and lifetime number of sexual partners; 2: *P* value presented are score test of trend.

vaccination, providing estimates of the relative reductions in vaccine type-specific prevalence as a measure of the vaccination programme impact at a population-level [22].

Despite these limitations, our study had several strengths. There are only a few small studies to have investigated HPV prevalence in young women living in LMIC. To our knowledge, this is the largest study among AGYW aged 17–18 years disaggregated by HIV status. Our study was conducted in South Africa, where HIV is endemic, and it is also the most geographically dispersed study with data from four provinces. Our data is congruent with the findings from these other studies [28,39,40].

In summary, these data have shown a high prevalence of high-risk HPV, including vaccine-preventable types, in a young population living with HIV and engaged in care. As South Africa continues to roll out the bivalent vaccine to 9-year-old girls through schools, results from our study provide important baseline data regarding the potential impact the vaccination programmes may have on infection prevalence and, ultimately, HPV-associated disease. These results also provide an indication of the potential that switching to the quadrivalent or non-valent may have in terms of preventing additional infection and disease as HPV 6/11 prevalence as well as in nonvalent vaccine-specific types were relatively high and, in addition, have a disproportionate effect on people living with HIV.

Disclosures

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Author contributions

The study was conceived by JK, DM, SD-M, and HR. All authors contributed to study design. SD-M led study implementation with support from AC, HR and DT. ZM developed the initial HPV testing protocols. RM and KP led the statistics plan. DT, DM and SD-M drafted the initial manuscript which was critically revised by all the authors.

Conflicts of interest and sources of funding

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CRediT authorship contribution statement

Danielle I. Travill: Writing – original draft, Visualization, Supervision, Project administration, Investigation, Formal analysis. **Dorothy A. Machalek:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Helen Rees:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Zizipho Mbulawa:** Writing – review & editing, Validation, Methodology, Investigation. **Admire Chikandiwa:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Richard Munthali:** Writing – review & editing, Formal analysis, Data curation. **Kathy Petoumenos:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **John M. Kaldor:** Writing – review & editing, Methodology, Funding acquisition,

Table 4
Risk factors associated with the detection of any high-risk HPV among 248 adolescent girls and young women aged 17–18 years living with HIV.

Variable	N	n Detected (Row %)	OR (95 % CI)	Adjusted OR[1] (95 % CI)	P-value
Age at HIV diagnosis					
<9 years of age	58 (23.4)	26 (44.8)	*1.00 (ref)*	*1.00 (ref)*	
9—14 years old	42 (16.9)	22 (52.4)	1.35 (0.61—3.00)	1.47 (0.58—3.76)	0.418
15—18 years old	128 (51.6)	103 (80.5)	5.07 (2.58—9.98)	2.81 (1.26—6.24)	**0.011**
Missing	20 (8.1)	11 (55.0)			
On ART					
No	16 (6.5)	10 (62.5)	*1.00 (ref)*		
Yes	232 (93.6)	152 (65.5)	1.14 (0.40—3.25)	1.33 (0.37—4.76)	0.662
Time on ART					
≥2 years	111 (44.8)	56 (50.5)	*1.00 (ref)*	*1.00 (ref)*	
< 2 years	119 (48.0)	95 (79.8)	3.89 (2.17—6.96)	2.19 (1.09—4.41)	**0.027**
Not on ART	16 (6.5)	10 (62.5)	1.64 (0.56—4.81)	1.15 (0.31—4.20)	0.837
Missing	2 (0.8)	1 (50.0)			
Last CD4 count					
≤200 cells/mm^3	18 (7.3)	9(50.0)	*1.00 (ref)*	*1.00 (ref)*	
>200 cells/mm^3	156 (62.9)	102 (65.4)	1.89 (0.71—5.04)	1.90 (0.57—6.30)	0.294
Missing	74 (29.8)	51 (68.9)			
Last viral load					
≤50 log10 copies/mL	68 (27.4)	40 (58.8)	*1.00 (ref)*		
>50 log10 copies/mL	68 (27.4)	35 (51.5)	0.74 (0.38—1.46)	0.60 (0.27—1.37)	0.228
Missing	112 (45.2)	87 (77.7)			
Composite variable					
Immune competent	39 (15.7)	21 (53.9)	*1.00 (ref)*		
Immunocompromised	37 (14.9)	19 (51.3)	0.90 (0.37—2.26)	0.72 (0.25—2.15)	0.566
Missing	*172 (69.4)*	*122 (70.9)*	*2.09 (1.03—4.26)*	*1.36 (0.59—3.15)*	0.466

1: Adjusted for age, province and lifetime number of sexual partners; 2: P value presented are score test of trend.

Conceptualization. **Sinead Delany-Moretlwe:** Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dorothy Machalek reports a relationship with MSD Merck Sharp & Dohme AG that includes: speaking and lecture fees and travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126442.

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