

REVIEW ARTICLE

Screening and prevention of HPV-related anogenital cancers in women living with HIV in Europe: Results from a systematic review

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Abstract

Background: Women living with HIV (WLWH) are at increased risk of human papillomavirus (HPV)-related cancers. Throughout Europe, there is great heterogeneity among guidelines for screening programmes, access to HPV testing and HPV vaccination. The aim of this systematic review is to summarize available data on screening and prevention measures for HPV-related anogenital cancers in WLWH across the WHO European Region (WER).

Methods: The systematic review followed the PRISMA guidelines and was registered on Prospero. PubMed, Embase and Web of Science databases were searched to identify available studies, written in English and published between 2011 and 2022. A meta-analysis was conducted using random-effects models to calculate pooled prevalence of HPV. Subgroup analyses were conducted according to country and HPV testing.

Results: Thirty-four articles involving 10 336 WLWH met the inclusion criteria. Studies were heterogenous in their methodology and presentation of results: 73.5% of studies focused on cervical cancer prevention, and only 4.4% on anal cancer; 76.5% of studies conducted HPV testing as a routine part of screening. The prevalence of high-risk HPV was 30.5–33.9% depending on the detection method used. A total of 77% of WLWH had cervical cytology results reported. Six studies reported the positive association of CD4 cell count <200 cells/ μ L with HPV prevalence and cervical abnormalities. Anal HPV testing was conducted in <8% of participants. HPV vaccination was completed in 5.6% of women (106/1902) with known vaccination status. There was no information about the vaccination status of the majority of women in the analysed studies (8434/10336).

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Conclusion: Data about screening of HPV-related anogenital cancer in WLWH in Europe are heterogenous and lacking, especially in relation to anal cancer. HPV DNA testing is not routinely done as part of screening for HPV-related cancer; guidelines should include indications for when to use this test. Low CD4 count is a risk factor for HPV infection and cytological abnormalities. HPV vaccination data are poor and, when available, vaccination rates are very low among WLWH in Europe. This review concludes that significant improvements are required for data and also consistency on guidelines for HPV screening, prevention and vaccination in WLWH.

KEYWORDS

anal cancer, cervical cancer, HPV, prevention, screening, women living with HIV

INTRODUCTION

Cancers are one of the leading causes of death among people living with HIV. Women living with HIV (WLWH) have a five to eight times higher risk of developing invasive cervical cancer (ICC) than do women without HIV [1, 2]. High-risk human papillomaviruses (hrHPVs), including HPV 16, 18, 31, 33, 35, 45, 52 and 58 are responsible for more than 90% of all ICC cases [3]. HIV facilitates HPV infection through the disruption of epithelial tight junctions [4]. Moreover, low CD4 cell count is associated with a six- to 18-fold increased risk of HPV persistence [5, 6]. Other HPV-related cancers include vaginal, vulvar and anal cancers. WLWH have a higher risk of developing multifocal and multicentric lesions of the lower genital tract and have a higher rate of relapse of vulvar intraepithelial neoplasia (VIN) after treatment than do women without HIV [7]. HPV-related gynaecological cancers or precancerous lesions further increase the risk of developing anal cancer [8], the prevalence and risk of which are already increased in WLWH compared with women without HIV [9]. There is growing evidence that early detection and treatment of dysplastic lesions and anal high-grade anal intraepithelial neoplasia (AIN) significantly reduce progression to anal cancer [10, 11].

Despite the increased risk of HPV-related anogenital cancers among WLWH, data on screening methods in WLWH in Europe are scarce.

In 2020 the World Health Organization (WHO) approved the 90-70-90 global strategy to eliminate cervical cancer with targets that 90% of girls aged < 15 years should be vaccinated against HPV, 70% of women aged between 35 and 45 years will be screened with a high-performance HPV test and 90% of those with identified cervical disease will receive treatment. However, despite these universal recommendations, the heterogeneity of healthcare settings

throughout Europe leads to enormous variability and discrepancies in guidelines, screening programmes and access to HPV testing and vaccination [9, 12–15].

Therefore, the aim of this systematic review is to summarize available data on screening and prevention measures for HPV-related anogenital cancers in WLWH across the WHO European Region (WER).

MATERIALS AND METHODS

The study protocol for this systematic review was registered on the platform for the International Prospective Register of Systematic Review (PROSPERO database registration number CRD42022318901).

Pubmed, Embase and Web of Science databases were searched to identify studies, written in English, and published between 01 January 2011 and 31 April 2022, and investigating screening and prevention of HPV-related dysplasia and anogenital cancer (cervical, vulvar, anal) in adult WLWH in the WER. Eight searches combined synonyms for ‘cervical cancer’, ‘anal cancer’, ‘vulvar cancer’, ‘dysplasia’, ‘High-grade squamous intraepithelial lesions (HSIL)’, ‘cytology’, ‘HPV DNA testing’, ‘vaccination against HPV’ and ‘women living with HIV’. Studies performed outside of the WER, including pregnant women, regarding HPV pathophysiology, case reports, posters and systematic reviews, were excluded (Table 1).

Four reviewers (DK, EO, HA, MM) independently screened potentially eligible studies and a quality check was conducted by two reviewers (DK, HA). A secondary screening process was performed before the full text analysis. Duplicate studies were removed and eligibility for studies to be included was qualified by using the PICO question format (population, intervention, comparators, outcomes). The screening process was presented in a flow diagram according to PRISMA guidelines (Figure 1).

TABLE 1 Screening checklist.

1. Was the study published in 2011 or later?	Yes/unclear, go to Q2	No – exclude
2. Was the study carried out in any of the countries from the WHO region? Albania, Andorra, Armenia, Austria; Azerbaijan, Belarus, Belgium; Bosnia and Herzegovina, Bulgaria; Croatia, Cyprus; Czech Republic; Denmark; Estonia; Finland; France; Georgia, Germany; Greece; Hungary; Iceland; Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia; Lithuania; Luxembourg; Malta; Monaco, Montenegro, The Netherlands; North Macedonia, Norway; Poland; Portugal; Republic of Moldova, Romania; Russian Federation, San Marino, Serbia, Slovakia; Slovenia, Spain, Sweden, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, UK, Uzbekistan	Yes/unclear, go to Q3	No – exclude
3. Is this article about HPV-related dysplasia or cervical or anogenital cancer; and/or is it about screening or prophylaxis of these cancers?	Yes/unclear, go to Q4	No – exclude
4. Does the paper include data on adult women living with HIV (≥ 18 years old, cis- and transwomen)?	Yes/unclear, go to Q5	No – exclude
5. Is the paper a primary study or based on surveillance or mathematical modelling or a report (e.g. randomized or non-randomized controlled trials, prospective or retrospective cohorts, cross-sectional studies/prevalence studies, mathematical models, surveillance studies, qualitative studies, conference communications, feasibility/pilot studies)?	Yes/unclear, go to Q6	No – exclude
6. Does the paper include information about incidence of and/or screening method (cytology/HPV testing/anoscopy) of HPV-related anogenital dysplasia or cancer and/or vaccination against HPV?	Yes – include	No – exclude

A database was created including the following variables: authors, year of publication, study design, country, number of study participants, mean age, mean CD4 cell count, HIV viral load, antiretroviral treatment (ART) status, cervical and anal HPV DNA testing, method of HPV testing, HPV DNA test positivity, hrHPV DNA positivity, cervical and anal cytology results, vaccination status.

Statistical analysis

Statistical analysis was performed using the Comprehensive Meta-Analysis (CMA) version 2.0 (Biostat, Inc., Englewood, NJ, USA) software. The z -test was used to analyse the ratios. Using the random-effects model, we calculated the aggregate prevalence of HPV in WLWH, the corresponding p -value and 95% confidence interval (CI), the Cochran's Q -statistic and its p -value. The random-effects model was employed due to expected heterogeneity across the studies and for consideration of subject-specific effects. I^2 value was used to assess heterogeneity among studies. Level of significance was set at 5%. We evaluated publication bias using the Kendall's tau and Egger's regression method. If publication bias was present and significant, we performed the classic failsafe test to determine the number of missing studies required for the p -value of publication bias between the observed studies to approximate >0.05 . Categorical variables were summarized as frequencies and percentages and continuous variables as means and standard

deviation. Subgroup analyses were conducted according to country and hrHPV testing.

Some studies combined data on atypical squamous cells of undetermined significance (ASC-US) with low-grade squamous intraepithelial lesions (LSIL), or the atypical squamous cells could not rule out high-grade atypical squamous cells (ASC-H) together with high-grade squamous intraepithelial lesions (HSIL), negating the ability to do a separate analysis; thus prevalence rates of ASC-US or LSIL and ASC-H or HSIL were analysed together. Some studies included only women who underwent cervical excision or with cervical intraepithelial neoplasia (CIN) or cervical cancer. These studies were excluded from the analysis of pooled prevalence of cytology changes.

RESULTS

Of 2686 articles, 34 (involving 10 336 WLWH) met the inclusion criteria (Table 2).

Most articles (31/34, 91%) were from the western part of the WER, and mainly from Italy (10/34, 29%), while only one was from eastern Europe (Table 2). One-third of studies were retrospective (10/34, 29%) and one-third were prospective (10/34, 29%). Studies were mostly carried out in infectious diseases (ID) or HIV services (14/34, 39%) and combined (13/34, 38%) ID/HIV services, gynaecological services and sexual health clinics.

Studies were heterogenous by methodology, inclusion criteria and presentation of results [e.g. some included

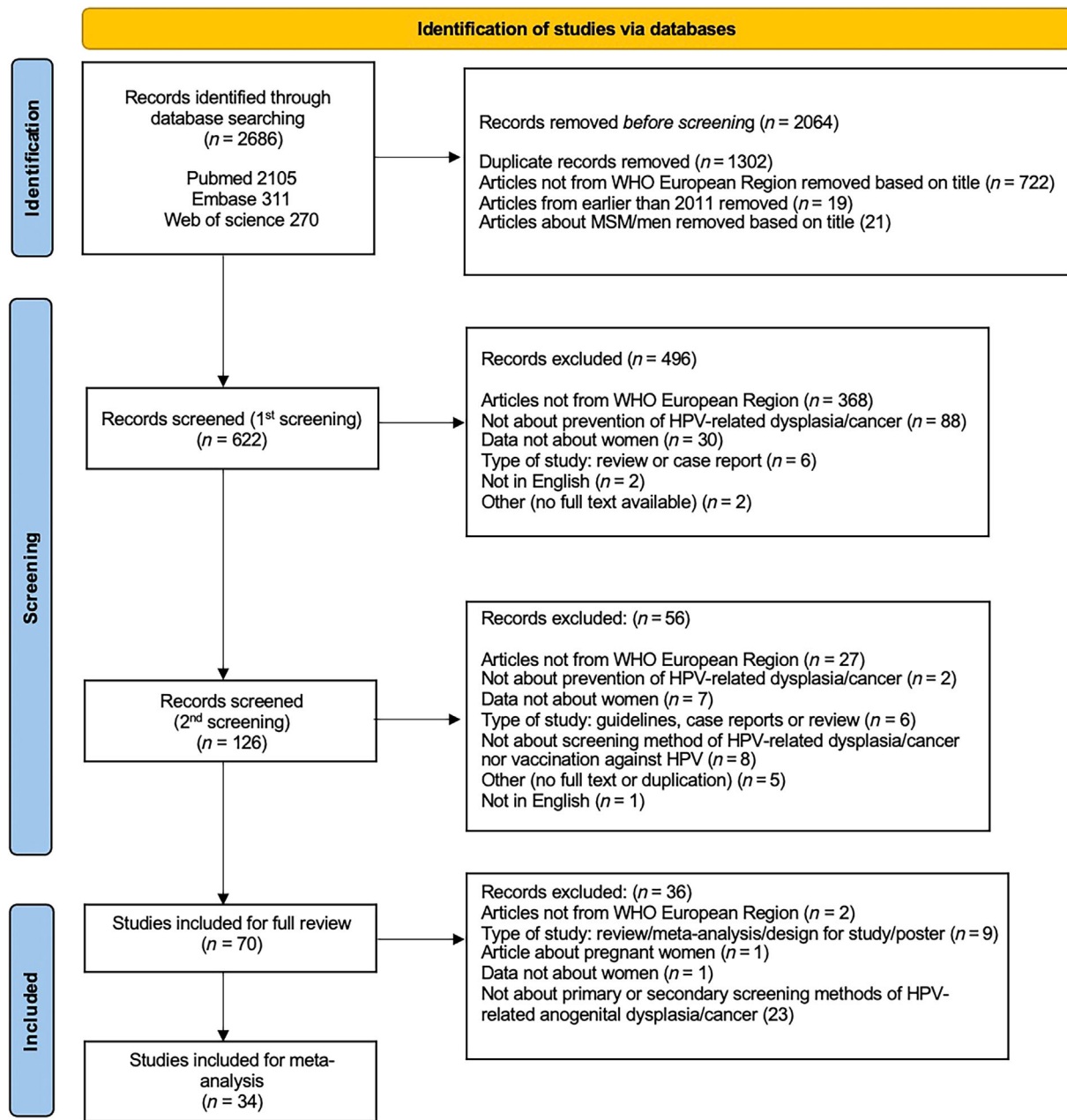


FIGURE 1 Summary of selection process of articles and outcomes at each stage according to PRISMA guidelines.

only women with a history of CIN; some categorized the finding of ASC-US together with the finding of LSIL; some carried out genotyping of both high- and low-risk HPV (IrrHPV) and some only hrHPV].

Among 23 studies presenting data on age, the mean age of 5615 participants was 37 years [95% confidence interval (CI): 34.678–39.513]. Data on CD4 cell count was available from 17 studies with a mean CD4 count of 517.1 cells/ μ L (95% CI: 469.51–564.68). Overall, 1129/10 336 (11%) women were not on ART and had a detectable HIV viral load (≥ 40 or ≥ 50 copies/mL depending on the detection limit of the study).

Cervical cancer prevention was the main focus in the majority of studies (25/34, 73%), followed by anal cancer (5/34, 15%). Three studies (3/34, 9%) focused on more than one type of cancer and only one study (3%) reported data on vulvar cancer (Table 3). In 13/25 (52%) studies on cervical cancer prevention, methods detecting both hr- and IrrHPV (e.g. linear assay) were used. In 7/25 (28%) studies, methods detecting only hrHPV (hybrid capture or PCR) were used, 4/25 studies did not report HPV testing, and one reported only mRNA testing. Two studies included only women with CIN or cervical cancer in the analysis [16, 17], and one

TABLE 2 Data on 34 studies included in the review.

Variables		Number of studies
Years of publication	2011–2012	6
	2013–2014	2
	2015–2016	11
	2017–2018	7
	2019–2020	3
	2021–2022	5
Region where study was conducted	West	29
	Centre	3
	East	1
	West and centre	1
Country where study was conducted	Belgium	2
	Denmark	3
	France	3
	Germany	1
	Ireland	1
	Israel	1
	Italy	9
	Poland	1
	Portugal	1
	Romania	2
	Spain	3
	Sweden	2
	Switzerland	1
	UK	1
	Ukraine	1
	France, UK, USA	1
France, Ireland, Italy, Poland, UK	1	
Study type	Prospective	10
	Retrospective	10
	Observational	14
Service in which the study was conducted	Infectious diseases/HIV service	14
	Gynaecological service	3
	Multiple services	13
	National cohort	3
	Pathology department	1
Anogenital region studied in this study	Cervical	25
	Anal	5
	Cervical and anal	3
	Vulval	1

(Continues)

TABLE 2 (Continued)

Variables		Number of studies
Method of screening for cervical cancer used in study	Cytology only	4
	HPV testing only	1
	Both cytology and HPV testing	23
Method of screening for anal cancer used in study	Cytology only	1
	Anoscopy only	1
	HPV testing only	3
	Cytology and anoscopy	0
	Cytology and HPV testing	2
Cytology and anoscopy and HPV testing		1
		8
Primary prophylaxis	HPV vaccination status of analysed women given	8

study included only women after cervical excision [18] (Table 3).

In total, 6294/10 336 (61%) women had cervical HPV DNA testing performed, of whom 2328 (37%) tested positive (Table 4).

The hrHPV prevalence was 33.9% in women who were tested for both hrHPV and lrHPV and 30.5% when only hrHPV DNA was tested. One study which analysed only women with history of CIN/ICC had hrHPV prevalence of 89.7%.

Eight prospective studies [19–26] performed sequential screening of cervical HPV DNA with a mean follow-up of 3 years (range 6–33 months) and reported hrHPV DNA was positive in 287/1657 (17.3%) of women who underwent follow-up (pooled prevalence was 17.5%, 11–26.9%, $I^2 = 93.3$) (Table 5).

Cervical cytology was reported in approximately 77% of all WLWH (7935/10 336). After exclusion of studies that analysed only women with CIN, cervical cancer or after cervical excision [16–18] abnormal cytology was found in 26.3% of women (6444). In women who had hrHPV DNA and had cervical cytology, the calculated pooled prevalence rates of cervical ASC-US, LSIL and HSIL were 3.5%, 9.5% and 4.2%, respectively. Cervical cancer was diagnosed in 14 women.

Six studies evaluated the association of CD4 cell count <200 cells/ μ L with HPV prevalence [19, 20, 27–30] and six the association of CD4 count <200 cells/ μ L with cervical abnormalities [16, 29, 31–34]. Two studies showed

TABLE 3 Summary of 34 papers included in the review.

Author [Reference]	Title	Study type	Year of publication	Country	Sample size	Mean or median age (Range or IQR), [years]	Mean or median CD4 cell count (current) (if available – median or mean nadir CD4 cell count also given) [cells/ μ l]; Interquartile range (IQR) or range supplied if available
Leibenson et al. [5]	The prevalence of human papillomavirus and cervical cytology abnormalities in women infected with human immunodeficiency virus in southern Israel	Observational, prevalence study	2011	Israel	84	Median 36 (range: 17–71)	Mean 461.1; (CD4 “at diagnosis”: 315.35)
Garbuglia et al. [16]	Frequency and multiplicity of human papillomavirus infection in HIV-1 positive women in Italy	Retrospective, observational	2012	Italy	553	Median 40.3	Median 501 (IQR: 332–681)
Bailey et al. [17]	Cervical screening within HIV care: findings from an HIV-positive cohort in Ukraine	Observational	2012	Ukraine	1120	Median 27.3 (IQR: 24.2–30.6)	Median 468
Rocco et al. [18]	HPV infection and intraepithelial lesions: comparison between HIV positive and negative women	Retrospective and prevalence	2012	Italy	93	Mean 38.4 \pm 8.6	Mean 513 (range: 28–1700)
Stuardo et al. [19]	Human papillomavirus infection in HIV-1 infected women in Catalonia (Spain): implications for prevention of cervical cancer	Observational, prevalence study	2012	Spain	479	Median 42	Median 480 (IQR: 331–702)
Heard et al. [20]	Characteristics of HPV infection over time in European women who are HIV-1 positive	Prospective	2012	Ireland, UK, Italy, France, Poland	518	Median 35	No mean or median given for full cohort; CD4+ cell count available for 480 WLWH: 141 (29.4%) had a CD4+ cell count 200–400; 80 (16.7%) had a CD4+ cell count <200 cells/ μ l
Maddedu et al. [21]	HPV infection in HIV-positive females: the need for cervical cancer screening including HPV-DNA detection despite successful HAART	Observational	2014	Italy	57	Median 40 (IQR: 35–44)	Mean 547 \pm 227
Loy et al. [22]	Human papillomavirus DNA and mRNA prevalence and association with cervical cytological abnormalities in the Irish HIV population	Observational	2014	Ireland	321	Median 34.6 (range: 17–71)	44 (13.8%) WLWH had a CD4 cell count <200; no mean or median given for full cohort
Heard et al. [23]	High Prevalence of Anal Human Papillomavirus-Associated Cancer Precursors in a Contemporary Cohort of Asymptomatic HIV-Infected Women	Observational	2015	France, UK, USA	171	Median 47.3 (IQR: 41.3–51.2)	Median 655 (IQR 476–844); Median nadir 222 (IQR: 110–320)
Ursu et al. [24]	The Need for Cervical Cancer Control in HIV-Positive and HIV-Negative Women from Romania by Primary Prevention and by Early Detection Using Clinically Validated HPV/DNA Tests	Observational and prevalence	2015	Romania	40	Mean 22.9 (range: 17–30)	Median 369 (range: 14–774)
Ene et al. [25]	Cervical HPV infection in Romanian women infected with HIV during early childhood	Prospective	2015	Romania	65	Mean 23.1 \pm 1.1	Median 513 (IQR: 365–905); Median nadir 165 (IQR: 63–260)
Clifford et al. [26]	Immunodeficiency and the risk of cervical intraepithelial neoplasia 2/3 and cervical cancer: A nested case-control study in the Swiss HIV cohort study	Retrospective	2015	Switzerland	548	Women with ICC: mean age 34.3 years; Women with CIN2/3: mean age 29.7 years	No mean or median given for full cohort

TABLE 3 (Continued)

Heard et al. [27]	Prevalence of and Risk Factors for Anal Oncogenic Human Papillomavirus Infection Among HIV-Infected Women in France in the Combination Antiretroviral Therapy Era	2016	France	352	Median 45.3 (IQR: 39.5–50.3)	Median 612 (IQR: 450–802); Median nadir 196 (IQR: 100–312)
Konopnicki et al. [28]	High-risk human papillomavirus genotypes distribution in a cohort of HIV-positive women living in Europe: epidemiological implication for vaccination against human papillomavirus	2016	Belgium	508	Median 42 (IQR: 35–48)	Median 555
Abramowitz et al. [29]	Determinants of macroscopic anal cancer and precancerous lesions in 1206 HIV-infected screened patients	2016	France	258	Median 39 (IQR: 33–45)	Median 405 (IQR: 261–605); Median nadir: 194 (IQR: 83–327)
Carlander et al. [30]	Impact of immunosuppression and region of birth on risk of cervical intraepithelial neoplasia among migrants living with HIV in Sweden	2016	Sweden	893	Median 31 (IQR: 26–37)	Median nadir 178
Thorsteinsson et al. [31]	Prevalence and distribution of cervical high-risk human papillomavirus and cytological abnormalities in women living with HIV in Denmark - the SHADE	2016	Denmark	334	Median 42.5 (IQR: 36.8–48.3)	No mean or median given for full cohort; 12 (3.9%) WLWH had a CD4 cell count <200/ μ l
Sansone et al. [32]	Screening for cervical carcinoma in HIV-infected women: Analysis of main risk factors for cervical cytologic abnormalities	2016	Italy	540	Mean 33.4 \pm 7.4	No mean or median given for full cohort; 115 (21.3%) WLWH had a CD4 cell count <200/ μ l
Kowalska et al. [33]	Barriers to cervical cancer screening exist despite integrating HIV and gynaecological services for HIV-positive women in Poland	2018	Poland	240	Median 30.1 (IQR: 26.2–35.1)	Median 366 (IQR: 179–545); Median nadir: 260 (142–416)
Orlando et al. [34]	Cervical Human Papillomavirus genotypes in HIV-infected women: a cross-sectional analysis of the VALHIDATE study	2017	Italy	805	Range 26–64; no mean/median given	No mean or median given for full cohort
Thorsteinsson et al. [35]	Prevalence of cervical, oral, and anal human papillomavirus infection in women living with HIV in Denmark - The SHADE cohort study	2018	Denmark	214	Median 42.9 (IQR 36.3–48.4)	No mean or median given for full cohort; 9 (4.6%) WLWH had CD4 cell count <200/ μ l at inclusion
Nasseridine et al. [36]	Interest of cytology combined with Xpert ^(®) HPV and Anyplex ^(®) II HPV28 Detection human papillomavirus (HPV) typing: differential profiles of anal and cervical HPV lesions in HIV-infected patients on antiretroviral therapy	2018	France	190	Median 46 (range: 23–79)	Median 630 (IQR: 486–812)
Videla et al. [37]	Incidence of cervical high-grade squamous intraepithelial lesions in HIV-1-infected women with no history of cervical pathology: up to 17 years of follow-up	2018	Spain	67	Mean 36 (SD 6.5)	Median 304; Median nadir 294 (SD 180)
Fusco et al. [38]	HPV infection and pre-neoplastic cervical lesions among 321 HIV+ women in Florence, Italy, 2006-2016: prevalence and associated factors	2018	Italy	321	Mean 41 (range: 18–76), Median 42	Median 576; Median nadir 216

(Continues)

TABLE 3 (Continued)

Orlando et al. [39]	Incident genital HPV infections and potential impact of HPV vaccines in adult women living with HIV/AIDS	Prospective	2018	Italy	805	Median 43 (IQR: 37–47)	Median 569.5 (IQR: 409–770.8); Median nadir: 200 (IQR: 100–300)
Todorova et al. [40]	Evaluation of anal carcinoma screening in male and female HIV patients at an interdisciplinary HIV therapy centre	Prospective	2019	Germany	17	Mean 50 (SD \pm 13.24)	No data for women specifically
Thorsteinsson et al. [41]	Persistence of cervical high-risk human papillomavirus in women living with HIV in Denmark – the SHADE	Prospective	2019	Denmark	71	Median 42.5 (IQR: 33.8–49.5)	No mean or median given for full cohort; 16 WLWH had a CD4 cell count <350 μ l
Gilles et al. [42]	Cervical, anal and oral human papillomavirus (HPV) infection in young women: A case control study between women with perinatally HIV infection and women with non-perinatally HIV infection	Observational	2019	Belgium	44	Median 28 (IQR: 24–30)	Median 500 (380–850); Median nadir: 301 (170–504)
Agarossi et al. [43]	High-risk HPV positivity is a long-term risk factor for recurrence after cervical excision procedure in women living with HIV	Retrospective	2021	Italy	271	mean 35.5 \pm 7.9	Median 365 (IQR: 240–500)
Brito et al. [44]	Detection of HIV mRNA in routine liquid-based cytology specimens of HIV-infected women	Observational and prevalence	2021	Portugal	80	No mean/median given for whole cohort, Range: 23–78	No mean or median given for full cohort
Squillace et al. [45]	HPV 16 and 18 contribute to development of anal dysplasia in HIV infection irrespective of gender and sexual orientation	Retrospective	2021	Italy	61	Median 45.55 (IQR: 37.05–49.79)	Median 650 (IQR: 499.25–812.25); Median nadir 313.50 (IQR: 179.25–598.5)
Carlander et al. [46]	Nonvaccine human papillomavirus genotype common in women with HIV failing cervical precancer treatment	Retrospective	2021	Sweden	116	Mean 35 (SD 7.5)	Median 370 (IQR: 225–493); Median nadir 140 (IQR: 50–246)
Cicconi et al. [47]	Re-valuation of annual cytology using HPV self-sampling to upgrade prevention (REACH UP): A feasibility study in women living with HIV in the UK	Observational	2022	UK	67	Median 47 (range: 24–60)	Median 683 (IQR: 527–910); Median nadir: 247 (IQR: 117–410)
Bradbury et al. [7]	Vulvar intraepithelial neoplasia: clinical presentation, management and outcomes in women infected with HIV	Prospective	2016	Spain	33	Median 37 (range 23–47)	Median 209 (range: 50–1008)
Author [Reference]	Number of WLWH not on ART dependent on availability of data)	Screening method	Results in this study	Prevalence in general population in the country where the study was performed (as given in the analysed article)	Recommendations	Limitations	

TABLE 3 (Continued)

Leibenson et al. [5]	13	60	Cervical cytology and cervical HPV DNA testing	34/84 (40.5%) of participants had a HR HPV genotype. Of those with HR HPV genotype 12 women (35.3%) had an abnormal cervical cytology. HSIL was in 1/84 (1.2%) participants, cervical cancer was in 1/84 women (1.2%), CIN 1-2 was in 1/84 (1.2%), CIN 3 was in 5/84 (6%). A high number of women who underwent colposcopy had changes requiring treatment.	HSIL in 0.69% and LSIL in 0.29%. Incidence of cervical cancer 1/100 000.	Low CD4 cell count predictor of HPV-associated cervical disease (not statistically significant). No correlation between duration of HIV infection, HAART, HIV RNA and prevalence of HPV	HPV testing and cytology are recommended tests for screening for cervical cancer in women living with HIV Colposcopy should be considered a routine workup in women with HIV.	Small sample size. No information about previous cervical cytology results of participants. Genotyping was performed in 87.8% of participants who were HPV-positive. No information about type of abnormal cytology (ASCUS, LSIL or HSIL) in women with HR HPV
Garbuglia et al. [16]	92	86.1%	Cervical cytology and cervical HPV DNA testing	142/553 (25.7%) had a HR HPV genotype. Most common types were HPV 16, 53, 31 and 66. Dyskariosis was in 122/500, 24.4% women (ASC-US 4.4%, LSIL 15.6%, HSIL 4.4%), HR HPV more frequent in those with dyskariosis than in those with normal samples (72.9% vs. 36.8%). HPV more often in women <35 years (vs. 235 years) Multiple HPV infections associated with dyskariosis. Women with HIV might be more susceptible to infection with other HR HPV types than the general population.	In general population HPV 16, 31 and 18 are most common.	HPV was more frequent in those with low CD4 cell count (<200). Not associated with ongoing HAART and known AIDS status. Multiple HPV infections associated with low CD4 cell count. Low CD4 cell count associated with increased risk of dyskariosis.	Women with HIV, with low CD4 cell count and with multiple HPV infections might be at higher risk of cervical abnormalities and need improved clinical management. Inclusion of HPV 53, 31, 66 in vaccines is needed.	Retrospective study. No information about previous cervical cytology results of participants. Detection of HPV DNA based on MY09/MY11 primers result in false negative. Genotyping was performed in 87.8% of participants who were HPV-positive. No follow-up of HPV DNA which might changed over time. No information about type of abnormal cytology (ASCUS, LSIL or HSIL) was in women with HR HPV
Bailey et al. [17]	905	No data	Cervical cytology	337/1120 (30%) received a cervical cancer screening. 68/325 (21%) had cervical abnormalities (17% LSIL and 4% HSIL).	Mortality rate for cervical cancer is two-fold higher in Eastern than in Western Europe (7.1 vs. 3.4/100 000).	Abnormal cytology findings associated with low CD4 cell count (CD4 <200 cells/mm ³)	An organized screening programme, as part of the HIV care could increase the uptake of cervical cancer screening and reach those who are economically and socially marginalized.	No HPV DNA testing. High percentage of women with BV could affect the results of abnormal cytologies.
Roccio et al. [18]	0	No data	Cervical cytology and cervical HPV DNA testing	Prevalence of HPV 56 was higher in WLWH than in those without HIV. Rates of 6, 11, 16 and 18 were similar in both groups. Median number of HPV genotypes was higher in WL WH.	N/A	No stratification based on CD4 cell count was conducted. All patients were on HAART.	Quantification and genotyping of HPV among women living with HIV are needed. Long colposcopic follow-up of low-grade cervical lesions are needed.	Retrospective nature of study. No stratification based on CD4 cell count.

(Continues)

TABLE 3 (Continued)

Stuardo et al. [19]	30	No data	Cervical cytology and HPV DNA testing	The prevalence of hr-HPV infection was 33.2%. 11% of participants never had a Pap smear. 60% of women had one Pap smear within the last 2 years. 16% had a Pap smear more than 3 years ago. HSIL was present in 3.8%. Most prevalent HPV types were 16, 53 and 52.	In general Spanish population HR-HPV prevalence is >10%. HSIL in general Spanish population is 10/100 000	LSL and HSIL were associated with low CD4 cell count (CD4 <200 cells/mm ³) and high HIV RNA (>10 000 copies/ml)	Better preventive efforts needed: vaccination against HPV, better accessibility to screening programs, training of health professionals, better health education for women with HIV.	Prevalence of HR-HPV determined by sensitivity level of HC2. No data about the prevalence of HR HPV in women with abnormal cytologies. Sample included only women who had a prolonged history of HIV infection (median 119 months)
Heard et al. [20]	283	No data	Cervical cytology and cervical HPV DNA testing	The prevalence of baseline HR-HPV was 49.5%. 77.2% of women with ASCUS/LSIL had HR-HPV and 90.8% of those with HSIL had a HR-HPV. Persistence of any high-risk type was 55.8%. HSIL in 7.9%. No cervical cancer observed in this cohort.	N/A	hr-HPV prevalence increased with decreasing CD4 cell count and with not receiving ART. HPV 53 and 58 most common in women with CD4 cell count <200 cells/mm ³ . Prevalence of HPV 58, 66 and 82 increasing with decreasing CD4 cell count. Prevalence of multiple HPV types increased with lower CD4 cell count.	The risk of progression of HPV-related lesions remains low and thus women with well-controlled HIV infection should have a 3-yearly cervical screening	No data on behavioural risk factors for cervical cancer (e.g., Lifetime number of partners, pregnancies, OC, smoking). No information about previous cervical cytology results of participants. No information about HIV RNA.
Madeddu et al. [21]	5	45 (78.9%)	Cervical cytology and cervical HPV DNA testing	Prevalence of HPV was 33.3%	In the general Italian population 7-16%	CD4 cell count and HIV VL did not affect the prevalence of HPV.	Immune recovery and suppression of VL are not sufficient to reduce the prevalence of HPV. Screening for cervical cancer is recommended for all WLWH.	Small sample size. No data on behavioural risk factors for cervical cancer
Loy et al. [22]	No data	163 (51.4%)	Cervical cytology and cervical HPV DNA testing, cervical HPV mRNA testing	HPV DNA was in 51.1% women. Abnormal cervical cytology was in 28.7% women (LSIL in 13.1% and HSIL in 4.3%). mRNA screening was more specific for low-grade LSIL and HSIL (84.53% vs. 57.36%), but less sensitive (51.59% vs. 91.07%). No significant difference in HPV DNA nor mRNA HPV prevalence between women <30 and ≥30 years	In general population of Ireland: 19.8% of women had HPV DNA, 11.1% had abnormal cervical cytology	Prevalence of HPV DNA and mRNA was higher in women with lower CD4 (<200). Women with undetectable VL had less frequently HPV DNA.	Further studies evaluating HPV mRNA are needed. HPV mRNA could be used to triage women with ASCUS and decide whether they are at risk of progressing to HSIL.	-

TABLE 3 (Continued)

Heard et al. [23]	5	151 (89.3%)	Cervical cytology and HPV DNA testing; High Resolution anoscopy and anal cytology and anal HPV DNA testing	Prevalence of anal HR-HPV: 57.9% Prevalence of abnormal anal cytology: 29.3% Prevalence of HG-AIN+: 12.9%.	N/A	Current CD4 cell count and nadir CD4 cell count <350 cells were not significant risk factors for HG- AIN+.	Women living with HIV with a history of HPV-associated cervical squamous intraepithelial lesions and with anal HPV-16 infection are at increased risk for HG-AIN+ and should be offered anal screening (anal cytology and HPV 16 genotyping).	Only 2 women included in this study had CD4 cell count <200 cells/ μ l
Ursu et al. [24]	0	No data	Cervical cytology and cervical HPV DNA testing	45% of WLWH had HPV DNA. 32.5% of WLWH had multiple HPV types 1/40 LSIL 1/40 ASC-US HPV more frequent in women younger than <25 years	35.2% of women without HIV had HPV DNA. 20% of women without HIV had multiple HPV types.	HPV prevalence increased with lower CD4 cell count (<200 cells/ μ l) and with higher VL (>20 000 copies/ml)	Screening for cervical cancer with cytology in countries where HPV prevalence is low is recommended. HPV DNA tests should be used in countries where it is affordable.	Small sample size. Younger age of patients with HIV in comparison to patients without HIV could have affected the difference in prevalence of HPV.
Ene et al. [25]	0	51	Cervical cytology and cervical HPV DNA testing	21/65 (32%) of WLWH had HR-HPV. 25% women had abnormal Pap smears. Those with multiple HPV subtypes had more often abnormal smears. Annual incidence of HR-HPV 0.52. 30% of all HPV due to preventable subtypes.	6/25 (24%) of women without HIV had HR-HPV Cervical cancer mortality in Romanian women: 10.5/1000	No difference between number of HPV subtypes between women with HIV and without. Most prevalent subtype of HPV in women with HIV was HPV-52 and HPV-67. More abnormal smears in group of women with HIV in comparison to those without HIV. Those with HPV had a lower median CD4 cell count than those without HPV. Those who acquired a new HPV subtype had a lower CD4 cell count (nadir and current).	Vaccination against HPV of all young WLWH is needed.	Small sample size. Women without HIV younger and less likely to be on social support
Clifford et al. [26]	No data	183	Cervical cytology and cervical HPV DNA testing	Screening for cervical cancer suboptimal. No previous screening in 20%–30% of all (both in the CIN2/3 and ICC group and in the control group).	N/A	CIN2/3 associated with low CD4 cell count and negatively associated with low CD4/CD8 ratio. The OR for > 2-years ART use was associated with a significant reduction in CIN2/3 risk	HPV vaccination and regular cervical cancer screening are crucial elements of cervical cancer prevention.	ICC case numbers low therefore limited statistical power. Pap smear history was based on self-report, being added in 2001 only, without any information on cytological diagnoses

(Continues)

TABLE 3 (Continued)

Heard et al. [27]	10	259	Anal cytology and anal and cervical HPV DNA testing	HR-HPV present in: 47.6% anal and 26.4% of cervical region of women respectively. Presence of cervical HR-HPV DNA was a risk factor of the anal HR-HPV infection. HPV-16 was the most prevalent genotype at both anatomic sites (2.6x higher in the anus than in the cervix).	Anal HR-HPV in 22% of general population.	CD4 cell count <350 cells/ μ l associated with anal HR-HPV DNA presence. Nadir CD4 cell count <200 was NOT associated with anal HR-HPV DNA	Anal cytology and anal HPV-16 detection are recommended methods for screening of anal cancer in women living with HIV	Lack of data on women's sexual behaviours.
Konopnicki et al. [28]	76	370	Cervical cytology and cervical HPV DNA testing	23% of WLWH had HR-HPV DNA. 38% of those had abnormal cytology (10% had HSIL). Age of > 35 years was associated with lower HPV 16 prevalence. HPV-52 was the most frequent HR-HPV vaccines against HPV 16 and 18 prevent only a fraction of HR HPV infection.	In European general population the most frequent HR-HPV type was HPV 16 (23%).	History of AIDS stage C was associated with HPV other than 16 and 18 (OHR). Vaccination with the nonavalent vaccine against HPV in this specific cohort could offer protection to 80% of women.	Nanovalent vaccine should be offered to women living with HIV. The HRHPV genotypes distribution found in this cohort of women living in Europe with a successfully treated HIV infection for several years is similar to the one found in Central Africa even in women of Caucasian origin. In this population of HIV-positive women, the bivalent or the quadrivalent vaccines including HRHPV 16 and 18 could offer protection in only 30% of the subjects; in contrast this protection could be extended up to 80% with the ninevalent vaccine covering for HRHPV 16/18/31/33/45/52/58.	HPV 18 may be underestimated due different lab methods used. Interpreting genotypes distribution from different studies should be done with cautions due to differences in study population.

TABLE 3 (Continued)

Abramowitz et al. [29]	71	149	Anal cytology	311 of 1206 had histologically proven lesions related to HPV. 123 (10%) low-grade dysplasia, 70 (6%) high-grade dysplasia and 7 (0.6%) anal cancers were diagnosed.	N/A	CD4 cell count <200/ μ l is related to any HPV lesions.	Anoscopy is an alternative method for anal screening in the HIV positive population. This screening has to be compared with other tools in populations at high risk of anal cancer.	Only 21% of the participants were women
Carlander et al. [30]	21	No data	Cervical cytology and cervical HPV DNA testing	The cumulative incidence for CIN3 was 13.1% WLWH born in the East region, dominated by Thai women, had a two times higher risk of CIN3 compared with WLWH born in Sweden (HR 2.47;95% CI 1.2–5.0).	N/A	Among WLWH there was a difference in risk of CIN2 and CIN3 depending on the region of birth, remaining after adjusting for immunosuppression. Late HIV diagnosis, leading to immunosuppression, might be one of the most important risk factors for persistent HPV-infection and thereby HPV-related cervical intraepithelial neoplasia among women with HIV	Early HIV diagnosis and attendance to cervical cancer screening, with focus on migrants, is of crucial importance to minimize the incidence of cervical intraepithelial neoplasia.	Low attendance to screening. Asylum-seeking population was excluded from this study.
Thorsteinsson et al. [31]	17	250	Cervical cytology and cervical HPV DNA testing	26.4% of 334 WLWH had hrHPV. 10.4% of them had cytological abnormalities.	16.6% hrHPV positive in women in general. Cytological abnormalities were prevalent in 5.2% ($p = 0.0003$) in general women population.	Short duration of HAART, AIDS prior to inclusion and CD4 <350 cells/ μ L WLWH had a higher risk of having hrHPV in the cervix, had a higher frequency of multiple infections, a different genotype distribution and more cytological abnormalities than women without HIV. Cervical HPV and ASCUS+ were predicted by short duration of HAART.	Nil	There are no previous or subsequent sampling results. A higher number of inadequate HPV samples were collected in the study.

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TABLE 3 (Continued)

Sansone et al. [32]	279	109	Cervical cytology	117 of 540 had cytological abnormalities, classified as follows: 17.9% ASCUS; 43.6% LSIL; 35.0% HSIL; and 3.4% cervical cancer.	N/A	Women with CD4 cell count of <200/ μ l had a higher risk of developing cervical cytological abnormalities compared to those with a CD4 level >500/ μ l. Similarly women with CD4 cell count of 200–499/ μ l had a higher risk of developing cervical cytological abnormalities compared to those with a CD4 level >500/ μ l	An adequate screening and follow up must be modelled on HIV clinical status, CD4+ cell count, drug regimen and adherence. The screening should be interdisciplinary (cooperation between doctors)	Retrospective, single centred. Rates of intra or inter variability of Pap smears and colposcopies were not determined. Examinations considering the oncogenic subtypes of HPV were not carried out nor was a consideration of the association between cervical cancer in WLWH and socioeconomic status.
Kowalska et al. [33]	52	No data	Cervical cytology and cervical HPV DNA testing	In total 126 women, 85.5% of had at least one cytology, 65 (51.6%) of them more than once. Seventy-five women (51.7%) were tested for HPV infection.	N/A	The number of cervical cytology tests performed per patient was higher in women on antiretroviral therapy, yet with no statistical difference.	Screening approaches for women with HIV in Poland, especially for those not yet on ART or those newly registered in HIV clinics, need special attention. Integrating gynaecological services into HIV care is suggested as a way of improving coverage for cervical cancer screening; however, barriers to gynecological consultations exist even in the presence of such integration.	Lack of central registration of women living with HIV across the country. No genotyping and HPV DNA testing.
Orlando et al. [34]	No data	No data	Cervical cytology and cervical HPV DNA testing	Women living with HIV had a 3.8, times higher risk for ASCUS 3.6 times higher for LSIL, and 2.7 times higher for HSIL than women without HIV respectively.	HPV-DNA prevalence was 28.4% in WLWH and 11.81% (95%CI 10.14–13.49) among women without HIV ($p < 0.0001$).	No differences were observed in the proportion of infections sustained by at least one of the HPV types included in 2v-, 4v-, or 9v-HPV vaccines between HIV and SPW with normal cytology: The cumulative prevalence of the two main oncogenic types (HPV-16/18), broken down by cytological outcome, is lower in LSIL and HSIL among the HIV than in the SPW and the general Italian population.	A primary prophylaxis with a 9v-HPV vaccine could have prevented infections in over 50% of the women included in this study, whether with HIV or not. The assessment of the impact of HPV vaccines in the study population shows how immunization with a 9vHPV-vaccine could prevent a significantly higher proportion of viral infections, both in people with HIV and in the control population, than 2v- and 4v-HPV vaccines.	Limited number of cases with abnormal cytology.

TABLE 3 (Continued)

Thorsteinsson et al. [35]	10	154	Cervical HPV DNA testing, Anal HPV DNA testing	High-risk HPV prevalence among a total of 214 of 334 WLWH who had sufficient DNA for analysis are cervical (28%), oral (3.7%), and anal (39.3%). Among present cervical, oral, and anal hrHPV genotypes, 6.7%, 12.5% and 17.9% were targeted by the 2-or 4-valent HPV vaccines, whereas 50.0%, 50.0% and 42.9% of hrHPV genotypes were covered by the 9-valent HPV vaccine.	N/A	hrHPV in WLWH is related to immunosuppression CD4 cell count <350/ μ l, prior AIDS and short duration of combined antiretroviral treatment.	The 9-valent HPV vaccination in childhood/adolescence, could prevent hrHPV infections at all anatomical sites. Thus three doses regimen of the 9-valent HPV vaccine in WLWH is recommended to be applied through the age of 26.	Rather high number of inadequate samples to assess for the study.
Nassereddine et al. [36]	0	190	Cervical cytology and cervical HPV DNA testing	Compared with the cervical samples, the anal samples exhibited more numerous cytological lesions, which were histologically proven; a higher hrHPV infection prevalence; a higher hrHPV coinfections and a predominance of HPV16 and HPV18/45 types. There was an absolute agreement of 90.3% between the two HPV typing assays.	N/A	N/A	Co-testing consisting of cytology and HPV typing is a useful screening tool in the population with HIV on cART. It allows detection of prevalence differences between anal and cervical HPV-related lesions. Anal examination should be regularly performed especially in MSM with HIV but also in WLWH with genital hrHPV lesions.	HPV16 is the only HPV type that can be individually detected by Xpert; all other HPV types are detected in groups, so it is not possible to identify HPV coinfections in the same group.
Videla et al. [37]	18	49	Cervical cytology and cervical HPV DNA testing	Cumulative incidence of HSIL was 18% (12/67; 95%CI: 11–29%).	The estimated prevalence of HSIL in WLWH women was 3.2% (data from PISCIS cohort, Catalonia)	All women with HSIL had poor adherence to cART and/or a poor engagement with the cervical screening program. Nadir CD4 cell count was not a predictive factor associated with cervical lesions.	The incidence of cervical HSIL in WLWH with poor antiretroviral therapy adherence or poor immunological status reinforces the need to identify those with HIV at risk of developing cervical cancer.	Observational retrospective design. The population analyzed is from a single geographical site. Small sample size.

(Continues)

TABLE 3 (Continued)

Fusco et al. [38]	16	284	Cervical cytology and cervical HPV DNA testing	Being Caucasian, smoking 1–20 cigarettes/day, having 2 partners in the last year, and being an injective-drug-user are associated with cervical lesions.	HPV prevalence in general population in Italy of 15%–23%, and a prevalence of multiple infections among HPV+ women of 17%.	Increasing year of HIV infection is a protective factor, but this is probably the effect of the increasing age of the population. No other HIV-related or clinical factors are linked to the risk of HPV acquisition in this population.	The use of bi-valent, 4-valent and 9-valent HPV vaccines would potentially prevent lesions in 19%, 33%, and 48%. Among WLWH efficaciously in care for HIV, demographic and behavioral factors mainly contribute to acquisition of HPV and to development of cervical lesions.	Lack of information about HPV vaccine coverage in the population of the study. Monocentric study.
Orlando et al. [39]	No data	437	Cervical cytology and cervical HPV DNA testing	High HPV incidence rates and high percentages of multiple HR-HPV infections were observed in a cohort of women with HIV receiving effective antiretroviral treatment.	Global adjusted HPV prevalence of 11.7% (95%CI 11.6–11.7) and an adjusted prevalence of 9.1% (95%CI 9.0–9.2) in women aged 35–44 years in Italy.	Even women receiving effective antiretroviral therapy with high CD4 cell count and a well-controlled HIV viremia are at increased risk of infection, thus suggesting that the risk of infection may be due to factors other than immunosuppression.	Primary prevention strategies based on the new 9v-HPV vaccine may help to prevent incident infections and disease progression in this cohort of women.	There is no information about risk factors in dysplasia and HPV groups. The effectiveness of the 9-valent vaccine is only hypothetical.
Todorova et al. [40]	No data	No data for women specifically	High resolution anoscopy, Anal cytology	Smoking and two common STIs, condylomata acuminata and syphilis, are risk factors associated with advanced anal intraepithelial neoplasia (AIN) stages in PLWH.	N/A	Our study did not show significant association between abnormal screening results and CDC classification, nor CD4 cell count, nor HIV viral load, respectively.	Interdisciplinary lifestyle prevention strategies are required to reduce the risk factors for AIN in PLWH in an outpatient setting.	Results of women and men are mixed. Unfortunately, the study did not include enough female PLWH to investigate risk factors specific to this group.
Thorsteinssson et al. [41]	4	51	Cervical cytology and cervical HPV DNA testing	High rate of persistent hrHPV infections with predominantly non-16/18 hrHPV genotypes.	N/A	CD4 count <350 cells/ μ l predicted hrHPV persistence, while prior AIDS predicted @HLSL.	Focus on previously and currently immunocompromised WLWH with respect to screening for HPV-related cancers.	Lack of a control group. Some patients did not participate in all planned visits. Small sample size

TABLE 3 (Continued)

Gilles et al. [42]	0	28	Cervical cytology and cervical HPV DNA testing	In women using cART and with adequate immunity, there was no difference in prevalence of cervical dysplasia, HPV oral, anal or cervical infection in relation to the route of HIV acquisition	N/A	Risk factors for pathological cervical cytology were a viral load higher than 20 copies/ml ($p < 0.05$), CD4 levels lower than 350/ μ l ($p < 0.01$), a CD4/CD8 ratio lower than 0.5 ($p < 0.01$), CD4 levels lower than 350/ μ l ($p < 0.05$) were found to be a risk factor for a cervical HPV infection.	The high prevalence of HPV infection other than 16 and 18 supports the use of 9-valent vaccination.	Small number of patients. It was not possible to match patients for other confounding factors such as cervical cytology results, smoking status or hormonal contraception.
Agrossi et al. [43]	73	No data	Cervical cytology and cervical HPV DNA testing	21.4% women had a high-grade recurrence. Age >41 years and HR-HPV positivity were significantly associated with the risk of disease recurrence after cervical excision.	N/A	CD4 cell count at the time of cervical treatment or at the time of the last control was not associated with a higher risk of recurrence after cervical excision	Vaccinating women living with HIV who underwent treatment (cervical excision) of high-grade cervical disease against HPV might be beneficial.	Retrospective study, absence of HPV genotyping, HR-HPV not performed in all included women because available only from 2002
Brito et al. [44]	No data	63	Cervical cytology and cervical HPV mRNA testing	Detection of HIV RNA in cervical liquid based cytology is a risk factor for high-grade squamous intraepithelial lesion or malignancy. HSIL in WLWH is more often associates with HPV types other than 16 or 18	N/A	HSIL was more prevalent in HIV VL in liquid-based cytology	Assessment of HIV mRNA VL in cervical liquid-based cytology might be useful for cytological assessment in WLWH with undetectable VL in PB	Small number of patients included
Squillace et al. [45]	7	47	Anal HPV DNA testing, High resolution anoscopy, Anal cytology	Regardless of sexual orientation, HPV 16 and 18 are associated with the development of cytological abnormalities	The prevalence rates of HPV infection in men who have sex with women (MSW) and in women (W) were about 56% and 75%, respectively [2, 3]. (not country specific)	N/A	HPV 16/18 genotyping could be useful in targeting PLWH at risk of cytological abnormalities independent of gender and sexual behaviour.	Retrospective study design

(Continues)

TABLE 3 (Continued)

Carlander et al. [46]	No data	62	Cervical cytology and cervical HPV DNA testing	HIV per se increases the risk to fail treatment. HPV16 and HPV35 are the genotypes mostly related to treatment failure in WLWH.	N/A	Vaccination with non-valent vaccine recommended	Close follow-up is essential in WLWH treated for CIN2+, regardless of HPV type pretreatment. Our results indicate that when considering adjuvant treatment in WLWH undergoing treatment for CIN2+, vaccines containing many HPVVs are preferable.	Recording bias, the risk of treatment failure was not assessed, HPV testing post-treatment not performed, residual disease not assessed.
Cicconi et al. [47]	No data	58	Cervical cytology and cervical HPV DNA testing. Self-sampling	The prevalence of HR-HPV in the UK is very low	N/A	Median CD4 T-cell count 683 cells/ μ l (527–910) 95.4% had viral load \leq 50 copies/ml	Self-testing strategies are well accepted.	Study not powered to assess self-testing acceptability, lack of information about 10 women
Bradbury et al. [7]	No data	23	Cervical cytology and cervical HPV DNA testing	HIV increases the risk of developing vulvar intraepithelial neoplasia, accelerated the disease progression, which is more likely to be present at a younger age and in multifocal sites. Survival and recurrence rate are lower in WLWH.	N/A	Women with HIV are at increased risk of developing VIN and frequently present at a younger age with multifocal and multicentric disease. They have shorter recurrence free survival and progression free survival compared with HIV-negative women.	Close surveillance of the lower genital tract is essential in HIV-positive women including thorough examination of the vulva, vagina and cervix. Any suspicious lesions should be promptly biopsied and treated. Close follow-up after treatment is mandatory to exclude early recurrence or progression.	Limited number of patients for the rare occurrence of VIN.

TABLE 4 Data on screening methods of cervical and anal cancer in studies included in the review.

Method of screening		Number of WLWH
Cervical HPV DNA testing	Carried out	6294/10336 (61%)
	Positive test, not genotype-specific	2328/6294 (37%)
	Known hrHPV	1600/6294 (25.4%)
Cervical cytology	Carried out	7935/10336 (77%)
	Abnormal cytology	1909/7935 (24%)
	ASC-US and LSIL	1210/1909 (63.4%)
	ASC-US and known HPV DNA (+) test	168/1909 (8.8%)
	LSIL and known HPV DNA (+) test	389/1909 (20.4%)
	ASC-H and HSIL	621/1909 (32.5%)
	HSIL and known HPV DNA (+) test	158/1909 (8.2%)
	Cervical cancer	14/1909 (0.7%)
Anal HPV DNA testing	Carried out	800/10336 (7.7%)
	Positive HPV test	445/800 (56.6%)
	Known hrHPV	350/800 (43.7%)
Anal cytology	Carried out	228/10336 (1.2%)
	ASC-US or LSIL	41/228 (18%)
	ASC-H or HSIL	16/228 (7%)

Abbreviations: ASC-H, high-grade atypical squamous cells; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesions; hrHPV, high-risk HPV; LSIL, low-grade squamous intraepithelial lesions; WLWH, women living with HIV.

TABLE 5 Data on results of prospective studies about cervical cancer.

Number of prospective studies	8
Number of prospective studies which showed data on HPV persistence in cervix	3
Countries where the study was conducted	Multicentre (Ireland, UK, Italy, France, Poland) – 1; Italy – 1; Denmark – 1
Length of follow-up (years) (mean)	3
How often was the screening performed (months) [range]	6–33
hrHPV persistence in follow-up	287/1657, pooled prevalence 17.5% (11–26.9%, $I^2 = 93.3$)

Abbreviation: hrHPV, high-risk HPV.

increased risk of HPV or HPV persistence in women with CD4 count <350 cells/ μ L [26, 35]. One study reported that women with a high viral load >20 000 copies/mL were more often carriers of HPV [28], and another showed a correlation between viral load >10 000 copies/mL and cervical cytological abnormalities [30].

Less than 8% of women underwent testing for anal HPV DNA and 2% of women had anal cytology (800/10 336 and 228/10 336, respectively). The calculated pooled prevalence of anal hrHPV was 47.3% (39–55.6). Approximately 19.2% of those who had anal cytology had ASC-US or LSIL and 5.2% had ASC-H or HSIL. HPV DNA testing in women with anal abnormalities was rarely conducted and we were unable to calculate the prevalence of hrHPV in this group.

Only one study (1/34, 3%) presented data on vulvar cancer. This prospective study of VIN showed that WLWH were younger at diagnosis than women without HIV (median age of 37 vs. 44 years), more frequently had multifocal and multicentric disease than women without HIV and had a lower survival than women without HIV. However, there was no significant difference in the hrHPV distribution between the two groups [7].

Only eight studies commented on the number of women who were vaccinated against HPV; only one of these looked at anal cancer, and another at both anal and cervical cancer. There was no information about the vaccination status in the majority of women in the analysed studies (81.6%, 8434/10 336). In total, 5.6% of women (106/1902) whose vaccination status was known were vaccinated. A study conducted in Romania showed that 30% of newly identified HPV infections among WLWH aged ≥ 20 years were vaccine-preventable HPV [20].

In another study 60% of HPV infections detected in the HSIL group could have been prevented by vaccination [25].

DISCUSSION

This systematic review explored available data on screening and prevention of HPV-related anogenital cancers in WLWH across the WER.

Most of the studies included in this review focused on screening for cervical cancer, and even though it is an important topic, screening for other HPV-related cancers is not documented. HPV-related anogenital cancers are clearly a multidisciplinary disease area incorporating HIV, infectious diseases, gynaecology and sexual health services. The heterogeneity of studies illustrated the enormous variety in screening strategies and guidelines for anogenital cancers in WLWH across Europe.

HPV testing as part of screening for cervical cancer among WLWH

Most of the studies included in this review (24/34) described HPV testing as part of screening for cervical cancer. The majority of studies used HPV DNA testing based on PCR.

Prevalence estimates of hrHPV for WLWH differed across the various countries of WER; however, overall, prevalence of cervical hrHPV was reported at over 30%, more than double the hrHPV prevalence of their HIV-negative peers [36].

Studies focusing on general populations of women have demonstrated that testing for HPV DNA provides fewer false-negative results than cervical cytology [37]. Yet there are still large variabilities in guidelines of screening for cervical cancer among WLWH. The WHO guidelines for screening and treatment of cervical precancerous lesions for cervical cancer prevention recommends using HPV DNA detection as the primary screening test and suggests starting screening of WLWH every 3–5 years from the age of 25 years [12]. The European AIDS Clinical Society (EACS) recommends doing a PAP smear or a liquid-based cytology for WLWH from the age of 21 years every 1–3 years with varying indications for HPV DNA testing. The European Society of Gynaecological Oncology (ESGO) and European Federation of Colposcopy (EFC) in 2020 stated that uncertainty remains over the recommended age of first screen as well as the optimal screening frequency for all those at risk of cervical cancer. Given that cervical cancer can develop within 5–10 years after hrHPV acquisition in WLWH without ART [38] and many girls have their sexual debut before the age of 16 [39], a younger age at first screen may be more appropriate in many areas of Europe. Alternatively, screening at a certain number of years after sexual debut rather than a biological age could be used; however, this may be more difficult to implement.

Only one study [40] mentioned self-sampling for cervical HPV DNA, yet this method has been approved by the WHO and the ESGO as it has comparable sensitivity to physician-collected samples and has shown improvement in reaching those who do not routinely attend cervical cancer screening [12, 13, 38]. Data on HPV self-sampling among WLWH mainly come from outside Europe [41], and therefore Cicconi et al.'s finding that WLWH in England found self-sampling acceptable is of value and could support expanding the use of this method in the WER, particularly for women who decline standard screening [40].

Women with low CD4 count and detectable HIV viral load have a higher risk of HPV infection and cytological abnormalities

Many studies included in this review showed that low CD4 count (defined as <200 cells/ μ L) is a predisposing factor for cervical HPV infection [19, 20, 27–30] and cervical abnormalities [16, 29, 31–34]. These results are consistent with studies showing that WLWH are at increased risk of cervical cancer, especially with significant immunosuppression [42, 43]. In addition, having a high or detectable HIV viral load is correlated with cervical HPV prevalence and cytological abnormalities [28, 30, 33]. By contrast, sustained HIV virological suppression (<50 copies/mL) for at least 40 months and median CD4 count >500 cells/ μ L for 18 months were associated with decreased risk of persistent hrHPV infection [44].

Shorter duration of ART and having a previous AIDS-defining illness were both associated with HPV infection [35], while good ART adherence decreased the risk of cervical abnormalities [16]. These results are in line with other studies showing that ART was associated with a decreased risk of both HSIL and CIN incidence [45].

Clear guidelines and screening for anal cancer in WLWH are needed

Of eight studies focusing on screening of anal cancer, only a small number of women had anal HPV testing ($<8\%$), while the calculated pooled prevalence of anal hrHPV was relatively high at 47.3%. This suggests that data are still inadequate. Moreover, even if digital rectal examination (DARE) every 1–3 years is the most frequently mentioned method of screening for anal cancer, the role of anal cytology and/or anal HPV DNA testing remains unclear [8].

The Anal Cancer HSIL Outcomes Research (ANCHOR) study results showed that the risk of progression to anal cancer is significantly lower when HSIL is treated, as compared with active monitoring [11]. Therefore, the New York State Department of Health AIDS Institute Committee recommended performing yearly anal cytology in people with HIV aged ≥ 35 years, men who have sex with men (MSM), cisgender women, transgender women and transgender men [15].

In our review, the prevalence of anal ASC-US or LSIL was 19.2% and the prevalence of ASC-H or HSIL was 5.2%.

The value of routine anal cytology remains controversial as it requires specific training and experience in reading slides, with variable sensitivity (55–93%) and specificity (32–81%) for detection of HSIL [46, 47]. Also,

high-resolution anoscopy (HRA) is expensive, not routinely available and poorly tolerated by patients. To date, the European Society for Medical Oncology (ESMO) does not recommend either of these methods for primary screening but recommends DARE [48]. The ESMO guidelines underline the importance of screening for synchronous cervical, vulvar and vaginal intraepithelial neoplasia in women who have AIN.

Lastly, none of the studies included in this review described the acceptability rate of screening for anal cancer, which is a crucial point in the diagnostic work-up. A study not included in this analysis, conducted in Quebec, showed that digital anorectal examination, anal cytology and high-resolution anoscopy were considered very acceptable methods of screening for anal cancer among WLWH [49]. Nonetheless, many WLWH are still not aware of the advantages of screening for anal cancer or of being at increased risk of having it [46, 47]. Thus, health-care providers should educate patients about the current knowledge, and barriers to attending screening should be addressed.

Barriers to screening of HPV-related anogenital cancers need to be addressed

Lack of access to gynaecological services [50], migrant status [29] and drug use [24] were the main barriers to cervical cancer screening we identified in our analysis.

Other barriers previously described include lack of knowledge about cervical cancer and screening, stigma, fear of the procedure or getting a positive diagnosis, absence of symptoms, financial concerns [51, 52], language barriers [53, 54], as well as lack of availability and affordability of HPV tests, trained workforce, proper health infrastructure [55] and long waiting lists [51]. Lack of sufficient prevention programmes, services and sexual education in many eastern European countries are additional contributing factors to the increase of sexually transmitted infections in this region and the highest incidence of cervical cancer in Europe [56, 57]. Improved funding and integration of screening with other services, such as HIV, are needed to achieve WHO goals [58].

Vaccination against HPV for WLWH is needed

Vaccination against HPV is an important method in prevention of cervical cancer and protection from anogenital warts [48].

Few (8/34) studies included in this review presented data on vaccination against HPV among WLWH, and the

vaccination rate was less than 6%, much lower than the WHO target of 90% [12]. It should be noted that the WHO target refers predominately to adolescent girls, whereas only studies involving adults (≥ 18 years of age) were included in this review.

Vaccination against HPV for WLWH was recommended by several studies due to the higher risk of HPV persistence and a greater risk of multiple HPV infections in this population [16, 33]. There are data showing that the non-16/18 hrHPV genotypes are more prevalent in WLWH and multiple HPV infections are associated with dysplasia and HSIL [31, 33, 59]. As WLWH have a wide distribution of hrHPV subtypes, the nonavalent vaccine could potentially bring more benefit than the dual or quadrivalent vaccine, as it would protect against more carcinogenic subtypes than the other vaccines [21, 22, 25, 30, 31, 35]. The EACS recommends nonavalent vaccination of PLWH until the age of 45 years [14].

There are not many studies on vaccination against HPV in older women. The VIVIANE study, though not involving WLWH, showed that the dual vaccine (HPV 16/18) continues to protect against infections, cytological abnormalities and lesions associated with HPV 16/18 and CIN1+ irrespective of HPV type over 7 years of follow-up in women older than 25 years [60]. In view of the fact that, with changing sexual partners, people have an increased risk of acquisition of new HPV, the Centers for Disease Control and Prevention recommended that all men and women aged 27–45 years who are not adequately vaccinated might be at risk for new HPV infection and might benefit from vaccination [61].

In addition, HPV vaccination may decrease recurrences of high-grade intraepithelial lesions in women after surgical treatment of dysplasia [62, 63].

To date, there are no clinical trials showing the protective value of vaccination of people living with HIV older than 27 years in terms of prevention of anal HSIL [64].

Our study has some limitations. The review did not include national guidelines regarding screening for anogenital cancers and thus some screening practices and standards might have been missed. Also, the studies included in this review were only in English.

The paucity of published literature from central and eastern Europe made it difficult to compare screening and vaccination practices between various regions of Europe. The heterogeneity of presentation of the results in studies included in this review meant that a small number of studies with similar methodology were included in the meta-analysis calculations.

CONCLUSIONS

Cervical cancer screening significantly decreases the incidence of the condition worldwide, but barriers to such screening still exist among WLWH. To improve the uptake of screening programmes, clear guidelines about HPV-related anogenital cancer screening are required.

Educational campaigns about HPV and cervical cancer screening methods are needed for both patients and healthcare providers. An integration of the gynaecological services into the HIV clinics is crucial. Shifting from cytology to HPV DNA testing as screening methods for cervical cancer could also improve attendance of screening programmes. Self-sampling for HPV might increase the uptake of cervical cancer screening to an even greater degree. Earlier HIV diagnosis, retention in care and effective HIV treatment may decrease the risk of HPV persistence. Women with CD4 count <200 cells/ μ L require more frequent cervical cancer screening. Women with a positive hrHPV test should be referred to the gynaecologist for colposcopy. Women with cervical abnormalities or cancer have an increased risk of anal cancer and need to be screened accordingly. Also, a visual inspection of the vulva must not be omitted.

Screening, early detection and treatment of AIN can prevent anal cancer. A DARE is a tolerated method of screening for anal cancer, and therefore integrating it into routine HIV consultation could help to detect anal cancer at an early and 'more easily curable' stage. In addition, clinicians should educate patients about anal cancer symptoms, which include bleeding, itching, palpable masses and pain. More education about vaccination against HPV among healthcare providers and WLWH is also needed.

Lastly, universally free vaccination of all WLWH screened for and affected by HPV-related cancers should be a public health priority.

AUTHOR CONTRIBUTIONS

DK and YG conceived the study. DK, MM, EO and HA performed the paper screening and the literature review. HNK performed statistical analysis. KAP and YG supervised the project. All the authors drafted the first version of the manuscript and read and approved the final version.

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CONFLICT OF INTEREST STATEMENT

DK has received honoraria for educational meetings from ViiV Healthcare and Gilead. MM has received speakers' honoraria and fees for advisory board from ViiV Healthcare, Gilead and MSD. EO, HM and HNK have no conflicts of interest. HA has received honoraria for advisory boards from Pfizer. KAP's institution has received travel grants from ViiV Healthcare, MSD and Gilead. YG has received conference sponsorship and honoraria for advisory boards and for the preparation and presentation of educational materials from ViiV and Gilead.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

ETHICS STATEMENT

Development of this manuscript did not involve direct research on human subjects and therefore approval by an institutional review board was not required. The study protocol was registered on PROSPERO (registration no. CRD42022318901).

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