IARC HANDBOOKS

World Health Organization

CERVICAL CANCER SCREENING

VOLUME 18

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met remotely, 12–16 October 2020

LYON, FRANCE - 2022

IARC HANDBOOKS OF CANCER PREVENTION

5. SCREEN-AND-TREAT APPROACH AND WOMEN AT DIFFERENTIAL RISK

5.1 Screen-and-treat approach

The primary aim of cervical cancer screening is to identify women with cervical precancerous lesions that need to be treated to prevent invasion (Schiffman et al., 2016; Wentzensen et al., 2017). Although cervical screening involves the whole population of women over a wide age range, only very few women actually need treatment. Many cervical cancer screening programmes rely on a multistep process to achieve efficient cervical cancer prevention, including an initial screening test with or without triage testing, colposcopic evaluation with cervical biopsies, and treatment decisions based on histological evaluation of cervical biopsies, followed by removal or destruction of the transformation zone, including the precancerous tissue (Arbyn et al., 2010; Perkins et al., 2020). This approach enables treatment to be limited to women with a very high probability of an existing precancer, and avoids over-treatment of women without precancer. A few guidelines in multistep screening programmes recommend immediate treatment without histological confirmation in women with a very high probability of an existing precancer, as indicated by screening and triage tests (Perkins et al., 2020). Before treatment, all women with a positive screening test result should undergo visual evaluation to assess the lesion size and the type of the transformation zone and to rule out suspected invasive cancer (WHO, 2011, 2014, 2019).

5.1.1 Rationale for screen-and-treat strategies

Multistep cervical cancer screening programmes involving colposcopy and histology require considerable investment in infrastructure, training of a skilled workforce, and quality control efforts (Arbyn et al., 2010). These programmes have typically been developed over decades and are difficult to establish in resource-constrained settings. Furthermore, multistep cervical cancer screening strategies require multiple visits with patient–provider interactions, including visits for screening, surveillance, colposcopy, and treatment. At each step there is a risk of loss to follow-up, with the consequence that a prevalent precancer may progress to cancer if left untreated. Loss to follow-up is a particular concern in resource-constrained settings, where women may have to travel long distances to health facilities and cannot be easily contacted to communicate test results and invite them to return for follow-up visits and treatment if needed. Loss to

follow-up can be decreased when fewer visits to a clinic are required, and it is minimized when screening and treatment are performed during the same visit.

Screen-and-treat approaches are designed to require fewer resources compared with multistep programmes, and to decrease the need for repeat visits (Denny et al., 2017; Cherniak et al., 2019). Although different screen-and-treat strategies exist, the unifying feature is that treatment is performed without a colposcopy-directed biopsy and histological confirmation of precancer. Typically, in screen-and-treat programmes more women need to undergo treatment than in multistep screening programmes, in which the positive predictive value (PPV) increases at each step. A variation of the screen-and-treat approach is the screen-triage-and-treat strategy, known as the see-and-treat strategy when colposcopy triage is used, in which screen-positive women undergo a second test to increase the specificity and PPV for precancer, to decrease unnecessary treatment.

Ideally, screening and triage tests should be performed with a fast turnaround, to enable both screening and treatment to be carried out during a single visit. In some settings, delayed processing of screening tests may be the only option and may require women to return for treatment.

5.1.2 Screening and triage modalities in screen-and-treat programmes

The screening modalities used in screen-and-treat programmes are either visual tests, such as visual inspection with acetic acid (VIA) and automated visual evaluation, or molecular tests, such as human papillomavirus (HPV) testing with or without genotyping. See-and-treat strategies include colposcopic evaluation before treatment. Because cytology involves delayed processing and requires substantial infrastructure and training, it is not suitable for screen-and-treat programmes. Accuracy data and effectiveness studies of the underlying screening tests outside of screen-and-treat programmes are summarized elsewhere (see Section 4.2, Section 4.4, and Section 1.2.5).

(a)   Visual inspection with acetic acid (VIA)

VIA was the first screening approach used in screen-and-treat programmes. VIA is a very simple and low-cost screening approach, which is conducted by applying acetic acid to the cervix, followed by visual inspection and assessment of acetowhitening (see Section 4.2.1).

The advantages of VIA are its wide availability, the lack of infrastructure requirements, and the possibility of making immediate treatment decisions and performing treatment in the same session. However, despite its appeal as a simple test, VIA requires training and quality control; it is also a highly subjective and variable test that has low accuracy. Any screen-and-treat strategy requires visual evaluation of the cervix to determine eligibility for treatment by either ablation or incision; assessment of eligibility for treatment is part of the visual evaluation performed for VIA.

(b)   Automated visual evaluation

Recently, automated approaches have been developed to provide objective evaluation of cervical images (see Section 4.6.1).

Although automated visual evaluation has shown good performance in primary screening, it requires a health worker to take a high-quality image in the entire screening population. Alternatively, automated visual evaluation can be used as a triage test for women with positive HPV test results from self-collected samples; this dramatically decreases the number of women for whom automated visual evaluation is needed. This approach may enable the implementation of single-visit screen-and-treat strategies in the future, which would decrease the proportion of women who need treatment compared with VIA-and-treat or HPV test-and-treat strategies.

(c)   HPV testing

HPV testing is an objective test that has higher accuracy for the detection of precancer compared with VIA (see Section 4.4.3).

The turnaround time for HPV tests is important for the implementation of screen-and-treat approaches. When HPV testing is not performed immediately, women need to be contacted to communicate test results and screen-positive women need to return to the clinic for treatment. However, rapid HPV testing, or point-of-care testing, which can be performed in clinics where women undergo screening, is possible and enables the implementation of single-visit strategies similar to those of VIA programmes.

5.1.3 Treatment modalities in screen-and-treat programmes

Treatment of cervical cancer and of precancerous lesions as commonly performed in organized screening programmes is described in Section 1.2.5.

(a)   Ablative treatment

Ablative treatment approaches, such as cryotherapy and thermal ablation, are based on the destruction of the tissue at risk, without tissue excision. Ablative treatment is efficacious for ectocervical lesions, but endocervical lesions cannot be treated efficiently using this method. In addition, in postmenopausal women the transformation zone is located in the endocervical canal and cannot be reached with ablative treatment modalities.

The most widely evaluated screen-and-treat strategy is the combination of VIA with cryotherapy. This approach can be conducted in a single visit by a health worker who performs the screening, evaluates eligibility for treatment, and then performs cryotherapy. Cryotherapy uses gas (typically carbon dioxide or nitrous oxide) to cool down a metallic probe to −90 °C; this probe is applied to the surface of the cervix for topical tissue destruction. A reliable supply of gas can be a challenge in resource-constrained settings, and this has led to the failure of cryotherapy programmes in some settings (Maza et al., 2018). Cryotherapy was shown low recurrence rates with limited harms, but with low-quality evidence, which limits the assessments of efficacy and harms (Chamot et al., 2010; Santesso et al., 2016).

Recently, thermal ablation has been evaluated as an alternative to cryotherapy. Thermal ablation is based on the application of a heated probe to the surface of the cervix for topical tissue destruction. Thermal ablation does not require gas and can be performed with a hand-held battery-powered device; this decreases the infrastructure requirements compared with cryotherapy. Several studies have suggested that thermal ablation has a performance comparable to that of cryotherapy, and that it is safe and acceptable (Dolman et al., 2014; Randall et al., 2019; Sandoval et al., 2019; Pinder et al., 2020; Zhao et al., 2020). In 2019, WHO published evidence-based guidelines on the use of thermal ablation to treat cervical precancer (WHO, 2019).

(b)   Excisional treatment

In some settings, excisional treatment has been used as the primary treatment modality in screen-and-treat programmes (Chamot et al., 2010; Santesso et al., 2016; Greene et al., 2019). Excisional treatment using electrical loops or surgical knives requires more infrastructure in clinics and providers who are trained and experienced. Tissue specimens that are removed with excisional treatment can be used for histological evaluation to confirm the presence of cervical precancer and to rule out invasive cancer. Although establishing an infrastructure for excisional treatment on a large scale is challenging in resource-constrained settings, excisional treatment needs to be available for women who are not eligible for ablative treatment.

5.1.4 Evaluation of screen-and-treat strategies

Evaluation of the efficacy, benefits, and harms of screen-and-treat strategies requires different study designs compared with strategies that rely on colposcopy-directed biopsy with histological confirmation and excisional treatment. Large screening trials have evaluated the detection of cervical precancer and cancer at baseline and the detection of precancer in the second screening round as indicators of screening efficacy. These evaluations require histological end-points, which are not available in screen-and-treat strategies. When no histological information is available, the effects of screen-and-treat strategies can be evaluated only by using population-wide estimates of cancer incidence. However, in low-resource settings cancer registries are often either non-existent or unreliable, and substantial lead time is needed to observe a reduction in cancer incidence. Therefore, clinical trials evaluating screen-and-treat strategies usually include a histology component, with biopsy sampling at the time of ablative treatment and/or during follow-up after treatment.

Screen-and-treat strategies typically lead to the treatment of a larger proportion of the screened population compared with multistep screening strategies, treating many women without prevalent precancer. Therefore, assessment of treatment harms plays a greater role compared with strategies in which treatment is restricted to women with histological confirmation of precancer.

Ten studies reported on the effectiveness of screen-and-treat strategies to prevent precancerous lesions or cervical cancer (Table 5.1). The screening modality included VIA in seven studies and HPV DNA testing in two studies, and VIA and HPV DNA testing were compared in one randomized controlled trial (RCT). The treatment modalities used in women with a positive screening test result in these studies included cryotherapy in seven studies, a combination of cryotherapy and thermal ablation in two studies, and thermal ablation in one study.

In a large RCT in South Africa, 6555 women (5001 HIV-negative women, 784 women living with HIV [WLHIV], and 770 women of unknown status) were randomized into three groups: to receive cryotherapy if an HPV DNA test result was positive, to receive cryotherapy if a VIA test result was positive, or to undergo delayed evaluation (Denny et al., 2005). All women underwent colposcopy and biopsy of all acetowhite lesions after 6 months or 12 months to ascertain cervical intraepithelial neoplasia grade 2 or worse (CIN2+) end-points. In both the HPV DNA test screening arm and the VIA screening arm, 22% of women were referred for treatment with cryotherapy. In an analysis restricted to the HIV-negative women at the 6-month visit, CIN2+ was diagnosed in 0.85% (95% confidence interval [CI], 0.40–1.29%) of the women screened with HPV DNA testing, 2.11% (95% CI, 1.42–2.79%) of the women screened with VIA, and 2.75% (95% CI, 1.96–3.54%) of the women in the delayed evaluation group. Over 12 months, an HPV screen-and-treat protocol would have led to a 56% reduction in the prevalence of CIN2+, whereas a VIA screen-and-treat protocol would have led to a 27% reduction in the prevalence of CIN2+ compared with the delayed evaluation group (Denny et al., 2005). In both treatment groups, 36% of women reported pain or light-headedness during the procedure. Vaginal discharge was common after cryotherapy, and abdominal pain occurred in a few women, but serious adverse events were very rare. There was a significant reduction in the cumulative prevalence of CIN2+ in the HPV DNA testing arm compared with the delayed evaluation arm (1.4% vs 4.6%; relative risk [RR], 0.31; 95% CI, 0.20–0.50), but there was no significant reduction in the VIA arm compared with the delayed evaluation arm (3.5% vs 4.6%; RR, 0.76; 95% CI, 0.52–1.1). In WLHIV, similar reductions in the

Table 5.1 Studies on the effectiveness of screen-and-treat strategies for the prevention of HSIL+/CIN2+

Reference Design Country	Pathway/ comparison	Screened population size Age (years) HIV prevalence	Sample and test Screen positivity (%)	Number of visits Treatment	Follow-up time Follow-up population	Ascertainment of end-points	Summary findings
Denny et al. (2005) RCT South Africa	VIA + treatment vs HPV + treatment vs delayed evaluation	6555 35–65 12% (782 HIV-positive of 6542 results)	Cervical specimen on HC2 VIA positivity: 22 HPV positivity: 22	2 Cryotherapy	6 mo and 12 mo 5667	Colposcopy and biopsy	6 mo: CIN2+ prevalence (95% CI): HPV DNA group: 0.80% (0.4–1.2%) VIA group: 2.23% (1.57–2.89%) Control group: 3.55% (2.71–4.39%) 12 mo: CIN2+ prevalence (95% CI): HPV DNA group: 1.42% (0.88–1.97%) VIA group: 2.91% (2.12% – 3.69%) Control group: 5.41% (4.32–6.5%)
Sankaranarayanan et al. (2007) Prospective cohort India	VIA (+ colposcopy + biopsies) + treatment	1879 30–59 NR	NA NR	1 Cryotherapy	6 mo 1026 (treated with cryotherapy at enrolment)	Histology or colposcopy	CIN2+: 2.04% Invasive cancer: 0.2% Cure rates: 71.4% for women with CIN2 and 68.0% for women with CIN3

Table 5.1   (continued)

Reference Design Country	Pathway/ comparison	Screened population size Age (years) HIV prevalence	Sample and test Screen positivity (%)	Number of visits Treatment	Follow-up time Follow-up population	Ascertainment of end-points	Summary findings
Parham et al. (2010) Prospective cohort Zambia	VIA-DC	6572 33 (median age) 100%	NA VIA positivity: 54	1 where possible Cryotherapy	20% of women who underwent treatment returned for FU at 6–12 mo NA	Estimation of cervical cancer deaths prevented	58.5% of VIA-positive women were eligible for ablative treatment 1 cervical cancer death was prevented per 46 WLHIV screened using the screen-and-treat programme 34% of women who underwent cryotherapy had abnormal VIA test result at 6 mo (34% of them had CIN2+) 68% of women who underwent LEEP had abnormal VIA test result at 6 mo (40% of them had CIN2+)
Martin et al. (2014) Prospective cohort Guyana	VIA + treatment	21 597 25–49 8%	NA VIA positivity: 13 WLHIV: 16 HIV-negative women: 13	1 Cryotherapy	12 mo 1027 of 2046 VIA-positive at baseline (69% of WLHIV screened vs 48% HIV-negative/ unknown screened)	VIA	85% of women who were eligible received immediate cryotherapy 95% of women were VIA-negative at second screening Non-physician providers were more likely than physicians to continue offering services
Starks et al. (2014) Prospective cohort Mexico	HPV + treatment	2522 30–50 NR	Vaginal sample on HC2 HPV positivity: 20	NR Cryotherapy	6 mo and 2 yr for women treated with cryotherapy 226 at 6 mo 137 at 2 yr (of 291 women treated with cryotherapy)	6 mo: HPV + VIA + colposcopy + biopsy 2 yr: HPV + VIA + colposcopy + biopsy	VIA false-positive rate: 5% At 6-mo FU, 68% women were hrHPV-negative Of 32% ($n = 73$) hrHPV-positive: 5 CIN2+ At 2-yr FU, 85% of women were hrHPV-negative Of 15% ($n = 21$) hrHPV-positive: 0 CIN2+

Table 5.1 (continued)

Reference Design Country	Pathway/ comparison	Screened population size Age (years) HIV prevalence	Sample and test Screen positivity (%)	Number of visits Treatment	Follow-up time Follow-up population	Ascertainment of end-points	Summary findings
Thida et al. (2015) Community-based evaluation study Myanmar	VIA + treatment	1617 30–49 Known HIV-positive cases and those with other gynaecological problems were referred for further management	NA VIA positivity: 7.5	1 Cryotherapy	12 mo 103 of 119 (treated with cryotherapy at enrolment)	VIA	Treatment rate: 98.4% FU: 3 women with persistent lesions Cure rate: 97.1%
Chigbu et al. (2017) Prospective cohort Nigeria	VIA + treatment	653 30–50 NR	NA VIA positivity: 10.9	1 Cryotherapy	12 mo 649	VIA (by same provider) + biopsies (if VIA-positive)	HSIL at enrolment: 4.1% HSIL at 1 yr: 0.5% (reduction statistically significant; $P = 0.0001$) Cryotherapy cure rate: 87.9% (95% CI, 76.82–94.33%)
Tran et al. (2017) Prospective cohort Cameroon	"HPV16/18/45-positive" or "positive to other hrHPV + VIA/ VILI abnormal" + treatment	1012 30–49 NR	Vaginal sample on Xpert HPV test hrHPV prevalence: 18.6 HPV16/18/45 positivity: 6 Other hrHPV + VIA/VILI: 6	1 Thermal ablation	6 mo and 12 mo 130 at 6 mo 112 at 12 mo	Persistence of high-grade disease on cytology	At baseline, treatment of < CIN2 (overtreatment): 9.9% At 6 mo, 89% had no evidence of disease Cure rate[a]: 58.8% At 12 mo, 87% had no evidence of disease Cure rate[a]: 70.6% Treatment failure (higher risk of persistent disease) was associated with the presence of occult endocervical lesions at baseline diagnosis

Table 5.1 (continued)

Reference Design Country	Pathway/ comparison	Screened population size Age (years) HIV prevalence	Sample and test Screen positivity (%)	Number of visits Treatment	Follow-up time Follow-up population	Ascertainment of end-points	Summary findings
Cholli et al. (2018) Prospective cohort Cameroon	VIA/VILI-DC hrHPV testing (for research purposes)	913 ≥ 30 42%	Cervical specimen on *care*HPV test VIA/VILI-DC positivity: 4.8 WLHIV: 7.6 HIV-negative women: 2.8 hrHPV positivity: 24.4 WLHIV: 41 HIV-negative women: 12	1 Cryotherapy Thermal ablation	12 mo 136 of 245 (positive for VIA/VILI-DC and/or hrHPV)	VIA/VILI-DC + hrHPV testing (co-testing)	50% of VIA/VILI-DC-positive women were hrHPV-negative VIA/VILI-DC-positive women with HIV infection were 3 times as likely to be hrHPV-positive than HIV-negative women (65% vs 20%) FU: 49% of women who were HPV-positive at enrolment retested negative (44% cleared infection without treatment)
Pinder et al. (2020) RCT (pilot phase) Zambia	VIA + treatment (VIA-positive women randomized to thermal ablation or cryotherapy or LLETZ) (HPV testing for research purposes)	NR ≥ 25 52%	Cervical specimen on Xpert HPV test NR	1 Thermal ablation vs cryotherapy vs LLETZ	6 mo 750	VIA + HPV testing (participants who were VIA-negative but HPV-positive were advised to attend a repeat FU visit at 12 mo)	Treatment success (*P* = 0.31): Cryotherapy: 60% Thermal ablation: 64% LLETZ: 67% Few participants reported moderate to severe pain in any group immediately after the procedure None of the participants reported any complication requiring medical consultation or admission to hospital

CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; FU, follow-up; HC2, Hybrid Capture 2; HPV, human papillomavirus; hrHPV, high-risk HPV; HSIL, high-grade squamous intraepithelial lesion; LEEP; loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone; mo, month or months; NA, not applicable; NR, not reported; RCT, randomized controlled trial; VIA, visual inspection with acetic acid; VIA-DC, VIA enhanced by digital cervicography; VIA/VILI, visual inspection with acetic acid and Lugol's iodine; VILI-DC, visual inspection with Lugol's iodine enhanced by digital cervicography; WLHIV, women living with HIV; yr, year or years.

[a] In women with CIN2+ disease at enrolment who underwent thermal ablation (*n* = 17).

cumulative prevalence of CIN2+ over 36 months were observed in the HPV DNA testing arm compared with the delayed evaluation arm (3.1% vs 15.5%; RR, 0.20; 95% CI, 0.06–0.69), and to a lesser extent in the VIA arm (7.6%; RR, 0.51; 95% CI, 0.29–0.89) (Kuhn et al., 2010) (see also Section 5.2.1).

The observational studies on VIA screen-and-treat approaches reported a wide range of test positivity, ranging from 5% to 22%, and in HPV screen-and-treat studies the test positivity ranged from 19% to 24% (Table 5.1). Several studies included WLHIV, with variable proportions ranging from 8% to 100%. Test positivity was higher for both VIA and HPV testing in WLHIV compared with HIV-negative women. The assessment of treatment success was heterogeneous; some studies used biopsy-confirmed end-points at different time points, in part triggered by positive VIA test results in follow-up, whereas other studies accepted a negative VIA result on follow-up examination as an indicator of treatment success. [This limited the comparability of treatment success across studies.]

In a study of VIA and cryotherapy in 653 women in Nigeria (Chigbu et al., 2017), the cure rate was reported to be 88% at a follow-up of 1 year. However, follow-up biopsy and histological confirmation was obtained only from women with a persistent positive VIA test result or a new positive VIA test result at 1 year. [This possibly inflates the estimate.] In a study of a screen-and-treat strategy in 1012 women in Cameroon (Tran et al., 2017), women with positive test results for HPV16, HPV18, HPV45, or other carcinogenic types and abnormal VIA results were treated using thermal ablation. A cure rate of 71% at 12 months was reported. [Follow-up diagnosis was based on cytology, not histologically verified CIN.]

Several studies did not report the initial test positivity, and others did not have enough case numbers to assess treatment success.

5.2 Screening of women at differential risk

5.2.1 Screening of women living with HIV

Based on the most recent report, in 2019 an estimated 36.2 million people aged 15 years or older were living with HIV, 53% of whom were women (UNAIDS, 2020). Fig. 5.1 shows the prevalence of HIV infection in the global population by country (Roser & Ritchie, 2019). There are significant differences between world regions: sub-Saharan Africa has the highest number of WLHIV (15.1 million), and 64% (12.3 million) of all WLHIV live in countries in eastern and southern Africa (UNAIDS, 2020); this is also the region with the highest age-standardized incidence rates of invasive cervical cancer (ICC) (Bray et al., 2018). In 2018, 569 478 incident cases of ICC were reported worldwide, and an estimated 33 000 of those cases (5.8%; 95% CI, 4.3–7.6%) were in WLHIV (Stelzle et al., 2021). The fraction of cervical cancer cases attributable to HIV varies dramatically according to region and is highest in eastern and southern Africa, where more than 29.7% of cases of cervical cancer can be attributed to HIV (Stelzle et al., 2021).

After significant advances in the treatment of HIV infection with antiretroviral therapy (ART) and the worldwide use of treatment-as-prevention measures, a reduction in HIV-associated mortality was observed in the past decade, resulting in an increase in HIV prevalence as people with HIV survived longer on ART. Longer survival times in WLHIV may be associated with an increase in the incidence of cervical cancer, because WLHIV remain susceptible to the acquisition and persistence of carcinogenic HPV infections and the incidence and progression of cervical lesions. Compared with HIV-negative women, WLHIV have an increased risk of acquisition and persistence of carcinogenic HPV infections (Looker et al., 2018).

(a) Natural history of HPV infection in WLHIV

(i) Association between HIV and HPV

Compared with HIV-negative women, WLHIV are more likely to acquire carcinogenic HPV infections (adjusted RR, 2.18; 95% CI, 1.58–3.01), are less likely to clear carcinogenic HPV infections (adjusted RR, 0.71; 95% CI, 0.58–0.91), and are more likely to be infected with multiple carcinogenic HPV types (Looker et al., 2018) (see Section 1.2.2). HPV can also act as a cofactor of HIV acquisition (Looker et al., 2018), and WLHIV have high rates of co-infection with HPV because the risk profiles for acquisition of HIV and HPV are similar. Furthermore, both HIV and HPV infections elicit and thrive on viral and host factors that impair the immune system.

(ii) Association between HIV and progression of HSIL to ICC

WLHIV have a 2–5-fold higher incidence of high-grade squamous intraepithelial lesion (HSIL) and a 4-fold higher incidence of ICC compared with HIV-negative women (De Vuyst et al., 2008; Denslow et al., 2014; Liu et al., 2018). Case reports on the rapid progression of HSIL to ICC in WLHIV (Rellihan et al., 1990; Saccucci et al., 1996; Holcomb et al., 1998) were published before the wide availability of ART. Starting in 1993, the United States Centers for Disease Control and Prevention (CDC, 1992) and the European Commission (Ancelle-Park et al., 1993) classified ICC as an AIDS-defining illness. WLHIV have an increased risk of developing ICC 7–15 years earlier than HIV-negative women (Gichangi et al., 2003; van Aardt et al., 2015; Rudd et al., 2017; Awolude & Oyerinde, 2018; Trejo et al., 2020), and WLHIV more frequently present with poorly differentiated tumours and more advanced disease with poorer prognosis (Moodley, et al., 2001; Dryden-Peterson et al., 2016) (see Section 1.2.2).

(iii) Association between ART and the natural history of HPV, SIL, and ICC in WLHIV

In 2015, WHO issued new guidelines on when to start ART, which recommended that all people living with HIV should start ART as soon as HIV infection is confirmed, irrespective of the CD4+ T-cell count (WHO, 2015).

A systematic review and meta-analysis that assessed the interactions between ART, carcinogenic HPV infections, and cervical lesions in WLHIV found that WLHIV taking ART had a lower prevalence of carcinogenic HPV infections compared with those not taking ART (adjusted odds ratio [OR], 0.83; 95% CI, 0.70–0.99) (Kelly et al., 2018). WLHIV taking ART had a lower incidence of HSIL or worse (HSIL+) (adjusted OR, 0.59, 95% CI, 0.40–0.87), a lower risk of SIL progression (adjusted hazard ratio [HR], 0.64; 95% CI, 0.54–0.75), a higher likelihood of SIL regression (adjusted HR, 1.54; 95% CI, 1.30–1.82), and a lower incidence of ICC (crude HR, 0.40; 95% CI, 0.18–0.87) compared with those not taking ART (Kelly et al., 2018). The greatest reductions were observed in women taking ART for a prolonged duration with sustained HIV viral suppression and in women initiating ART at a high CD4+ cell count. [A limitation acknowledged in the review is that most studies used a binary category of ART users and ART-naive women and few evaluated the effect of ART duration or ART use with prolonged HIV viral suppression. This limits the comparability in women initiating ART with decreasing CD4+ cell count compared with those with higher CD4+ cell count who do not yet need treatment. Women who initiated ART before the universal ART guidelines were issued were more likely to have advanced HIV disease, lower nadir CD4+ cell counts, and higher HIV viral loads than those who had not yet started ART.]

Access to effective cervical cancer screening, timely treatment of precancerous lesions, and timely access to ART all have an impact on ICC
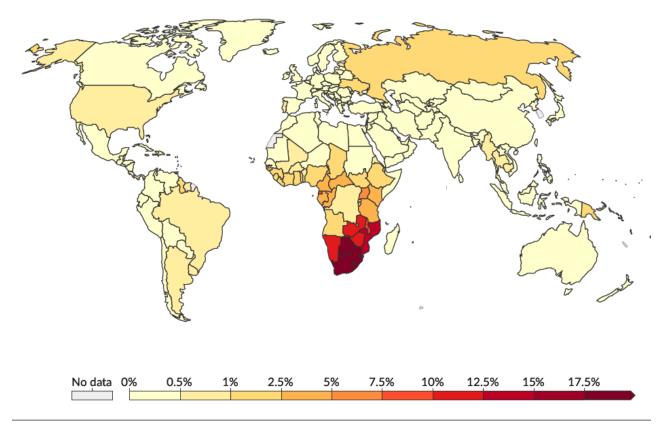
Fig. 5.1 Proportion of the global population aged 15–49 years living with HIV, 2019

From Roser & Ritchie (2019).

incidence in WLHIV. In a study in WLHIV who initiated ART in 1996–2014 across four continents, ICC incidence rates were high in WLHIV in all regions but were observed to be 11-fold higher in South Africa (adjusted HR, 10.66; 95% CI, 6.73–16.88) and 2-fold higher in Latin America (adjusted HR, 2.43; 95% CI, 1.27–4.68) compared with the ratios observed in WLHIV in Europe or North America (Rohner et al., 2020). WLHIV who initiate ART at a higher CD4+ cell count and are adherent to treatment have more complete immune restoration, better virological control, a lower risk of HPV acquisition, and a higher likelihood of regression of cervical lesions (Palefsky, 2017). In a 21-year multisite prospective cohort study in the USA that enrolled 1807 WLHIV and 488 HIV-negative women in a

prevention programme (20 561 person-years of observation), the estimated incidence of ICC did not differ significantly by HIV status (HIV-negative: 0 per 100 000 person-years vs HIV-positive: 19.5 per 100 000 person-years; $P = 0.53$) (Massad et al., 2017). [The findings from these studies might be different in WLHIV in low- and middle-income countries (LMICs), who may not have early access to effective ART and frequent cervical cancer screening.]

(b)   *Cervical cancer screening options for WLHIV*

There is growing evidence from countries with a high burden of HIV infection that cervical cancer screening is associated with a reduction in the incidence of ICC. A study in 10 640 WLHIV

in South Africa in 2004–2011 reported that ICC incidence decreased in WLHIV initiating ART from 2009 onwards, when the cytology-based cervical cancer screening programme and access to treatment of cervical lesions were expanded (260 vs 615 per 100 000 person-years for post-2009 vs pre-2005; adjusted HR, 0.42; 95% CI, 0.20–0.87) (Rohner et al., 2017).

Considering the differences in the natural history of HPV infection in WLHIV compared with women in the general population, WHO has developed cervical cancer screening guidelines adapted for WLHIV (WHO, 2021). In developing these guidelines, WHO considered the cost, availability, and performance of the screening tests and ready access to treatment facilities allowing rapid scale-up in LMICs. In an effort to increase the coverage of cervical cancer screening for WLHIV, several countries have adopted an approach that integrates HIV health care with cervical cancer screening services. Integration of cervical cancer screening services within HIV treatment services ensures that women at high risk of developing cervical cancer precursor lesions are screened; it also leads to continuity in primary prevention, favouring the early detection and management of HPV-associated cervical lesions, with minimal loss to follow-up (Sigfrid et al., 2017). The long-term effectiveness of such integration programmes on cervical cancer and HIV care is still unknown.

Initiatives to support cervical cancer screening in HIV care have been shown to increase screening participation in WLHIV. In a cross-sectional survey of WLHIV attending HIV clinics in Côte d'Ivoire, 1444 of 1991 women (72.5%) had been offered cervical cancer screening, mainly in the HIV clinic (88.9%). Factors associated with participation in cervical cancer screening included being informed about cervical cancer at the HIV clinic (adjusted OR, 1.5; 95% CI, 1.1–2.0), identifying HIV infection as a risk factor for cervical cancer (adjusted OR, 1.4; 95% CI, 1.1–1.8), being offered cervical cancer screening in the HIV clinic (adjusted OR, 10.1; 95% CI, 7.6–13.5), and university education level (adjusted OR, 2.1; 95% CI, 1.4–3.1) (Tchounga et al., 2019). [For this approach to achieve the desired effect of cervical cancer prevention in WLHIV, adequate treatment facilities offering ablative (cryotherapy, thermal ablation) and excisional (large loop electrosurgical excision procedure [LEEP]) treatment methods need to be readily available within screening facilities, and referral structures need to be established.]

(i)   Cytology

The performance of cytology in cervical cancer screening in WLHIV has been shown to be similar to that in women in the general population. Conventional cervical cytology using the Papanicolaou method has variable sensitivity and specificity for both CIN2+ and CIN3+ in WLHIV. The sensitivity of cytology at a threshold of atypical squamous cells of undetermined significance or worse (ASC-US+) for detection of CIN2+ ranges from 52.5% to 100.0%, and the specificity from 13.2% to 94.5% (Maiman et al., 1998; Branca et al., 2001; Cohn et al., 2001; Anderson et al., 2006; Kitchener et al., 2007; Sahasrabuddhe et al., 2012; Mabeya et al., 2012; Chung et al., 2013; Firnhaber et al., 2013; Joshi et al., 2013; Bateman et al., 2014; Ndizeye et al., 2019). A large variability has also been observed for low-grade squamous intraepithelial lesion or worse (LSIL+): the sensitivity ranges from 52.0% to 97.4% and the specificity from 35.1% to 96.0%; and for HSIL+: the sensitivity ranges from 20.0% to 78.4% and the specificity from 58.3% to 99.2%. In countries with well-established cytology-based screening programmes, cytology has good accuracy for detection of CIN2+. High sensitivity and specificity for CIN2+ using HSIL+ cytology were reported in 1193 WLHIV in South Africa (sensitivity, 75.8%; 95% CI, 70.8–80.8%; specificity, 83.4%; 95% CI, 80.9–85.9%) (Firnhaber et al., 2013) and in 498 WLHIV in Kenya (sensitivity,

71.8%; 95% CI, 62.8–79.4%; specificity, 97.1%; 95% CI, 94.7–98.4%) (Chung et al., 2013).

The long-term impact of a cytology-based screening programme in WLHIV was evaluated in the Women's Interagency HIV Study (WIHS) in the USA, in which WLHIV were followed up for a median of 11 years with 6-monthly cytology and early referral for treatment of HSIL+. Four cases of ICC were observed in 1807 WLHIV during 20 561 person-years of observation, corresponding to an incidence rate of 19.5 cases per 100 000 person-years. No ICC cases were observed in HIV-negative women identified from regional cancer registries ($P = 0.53$) (Massad et al., 2017).

Few studies have evaluated the association between HIV-related factors and the diagnostic accuracy of cervical cytology. A study in 498 WLHIV in Kenya reported no association between CD4+ T-cell count or ART status and the diagnostic accuracy of cytology for CIN2+, irrespective of the cytology threshold used (Chung et al., 2013). In studies that provided a direct comparison of test strategies in WLHIV, HSIL+ cytology had a similar sensitivity for CIN2+ but a higher specificity compared with HPV DNA testing, whereas HSIL+ cytology had a lower sensitivity but a higher specificity (Kitchener et al., 2007; Chung et al., 2013; Firnhaber et al., 2013; Ndizeye et al., 2019).

(ii)   Visual inspection methods

The performance of VIA or visual inspection with Lugol's iodine (VILI) in screening WLHIV has been in evaluated in several studies. Ten studies (eight in sub-Saharan Africa and two in India) evaluated VIA for the detection of histologically verified CIN2+ in WLHIV; the sensitivity of VIA ranged from 48.4% to 86.6% and the specificity ranged from 47.3% to 96.7% (Kuhn et al., 2010; Mabeya et al., 2012; Sahasrabuddhe et al., 2012; Chung et al., 2013; Firnhaber et al., 2013; Joshi et al., 2013; Huchko et al., 2014; Bansil et al., 2015; Chibwesha et al.,

2016; Ndizeye et al., 2019). The sensitivity of VIA for the detection of CIN3+ was similarly heterogeneous (range, 53.8–100.0%). The sensitivity was lower in studies with a high proportion (> 70%) of women with histological verification of CIN2+ or CIN3+ (Mabeya et al., 2012; Chung et al., 2013; Firnhaber et al., 2013; Bansil et al., 2015; Chibwesha et al., 2016). The sensitivity was highest in studies that had frequent training and supervision of VIA providers and for which quality assurance and quality control procedures, including review of digital cervicography, were undertaken (Firnhaber et al., 2013; Joshi et al., 2013; Bateman et al., 2014; Huchko et al., 2014; Chibwesha et al., 2016). In a study in 498 WLHIV attending routine HIV care in Kenya, the sensitivity of VIA was lower in WLHIV aged 40 years or older (47.3%) than in those younger than 40 years (78.2%) (Chung et al., 2013). In four studies, the sensitivity of VIA was lower in WLHIV with a CD4+ T-cell count > 350 cells/µL (range, 54.9–87.9%) than in those with a CD4+ T-cell count ≤ 350 cells/µL (range, 69.5–94.1%) but with correspondingly higher specificity (Sahasrabuddhe et al., 2012; Chung et al., 2013; Firnhaber et al., 2013; Huchko et al., 2014). The higher sensitivity of VIA in WLHIV with a lower CD4+ T-cell count could be attributed to the larger, well-demarcated, and more easily identifiable acetowhite lesions observed in those women (Sahasrabuddhe et al., 2012).

Two studies evaluated the diagnostic accuracy of VIA for CIN2+ according to HIV status, with contrasting findings. In 1756 HIV-negative women and 386 WLHIV in a population-based cervical cancer screening study in Uganda, the sensitivity and specificity of VIA for CIN2+ were lower in WLHIV than in HIV-negative women (sensitivity, 77.1% vs 93.8%; specificity, 47.3% vs 60.5%) (Bansil et al., 2015). In a randomized clinical trial of two screen-and-treat strategies in 6555 women in South Africa, 956 of whom were HIV-positive, the sensitivity of VIA for the cumulative detection of CIN2+ over 36 months

was higher in WLHIV than in HIV-negative women (63.9% vs 47.8%), but the specificity was marginally lower (73.6% vs 80.3%) (Kuhn et al., 2010).

In a two-arm randomized study comparing VIA and VILI in detecting cytology-diagnosed SIL in Nigeria, VILI was found to be less sensitive and less specific in WLHIV, especially those with severe immunosuppression (Ezechi et al., 2016). In an RCT in 654 WLHIV randomized to undergo either VIA or VILI in Kenya, the performances of VIA and VILI were found to be similar; the sensitivity was 84.0% for VIA and 84.2% for VILI, and the specificity was 78.6% for VIA and 76.4% for VILI (Huchko et al., 2015). The use of VILI as a sequential test in WLHIV with a positive VIA test result did not increase the detection rate or the PPV for histologically verified CIN2+.

(iii) HPV testing

Several studies have evaluated HPV DNA testing in WLHIV, mostly in sub-Saharan Africa (Table 5.2); they have reported consistently high sensitivity but variable specificity of HPV DNA tests for histologically verified CIN2+. Sensitivity estimates for CIN2+ were 88.8–94.6% (Hybrid Capture 2 [HC2]) (Womack et al., 2000; Cohn et al., 2001; Kitchener et al., 2007; Kuhn et al., 2010; Firnhaber et al., 2013; Joshi et al., 2013; Ngou et al., 2013), 88.0–93.6% (GeneXpert) (Chibwesha et al., 2016; Mbulawa et al., 2016; Kuhn et al., 2020); 92.2–100.0% (careHPV) (Bansil et al., 2015; Segondy et al., 2016), and 78.0–83.6% (GP5+/6+ polymerase chain reaction [PCR] enzyme immunoassay [EIA]) (Chung et al., 2013; Kremer et al., 2019), and the specificity was 41.3–77.4% (HC2), 48.3–60.0% (GeneXpert), 54.7–62.4% (careHPV), and 55.7–72.2% (GP5+/6+ PCR EIA).

A meta-regression of 20 studies on the relationship between the prevalence of carcinogenic HPV infection and the specificity of HPV DNA testing (HC2) for the presence of CIN2+ reported that for a 10% increase in the prevalence of carcinogenic HPV infection, the specificity of HC2 decreased by 8.4% (95% CI, 8.02–8.81%), and that the variation in the prevalence of carcinogenic HPV types explained 98% of the variability in the specificity of HC2 (Giorgi-Rossi et al., 2012). In WLHIV, the high prevalence of HPV infection and co-infection with multiple carcinogenic HPV types, many of which may be transient infections, results in low specificity of HPV DNA tests for CIN2+.

The prevalence of carcinogenic HPV types has been shown to be lower in women who are controlling HIV, i.e. those with prolonged ART use, sustained HIV viral suppression, and stable high CD4+ cell counts (Kelly et al., 2018). Therefore, HPV DNA tests have higher specificity to distinguish CIN2+ in women with a higher CD4+ cell count and/or prolonged ART use. In three studies that evaluated the diagnostic accuracy of HPV DNA tests (two using HC2 and one using GP5+/6+ PCR EIA) by CD4+ cell count, the specificity ranged from 31.6% to 45.7% in WLHIV with a CD4+ cell count ≤ 350 cells/µL and from 59.7% to 63.5% in WLHIV with a CD4+ cell count > 350 cells/µL, with some loss in sensitivity (Chung et al., 2013; Firnhaber et al., 2013; Segondy et al., 2016).

Because of the high prevalence of infection with multiple carcinogenic HPV types and the broad range of carcinogenic HPV types in WLHIV (Clifford et al., 2006), which may be a combination of incident and persistent infections, an approach using restricted genotyping may increase specificity for CIN2+. A cross-sectional study in 535 WLHIV in South Africa reported specificity to distinguish CIN2+ of 59.9% (95% CI, 54.1–65.7%) when using the GeneXpert five-channel approach (positive for any of 14 high-risk HPV [hrHPV] types: HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and/or 68) and specificity of 67.5% (95% CI, 62.0–73.1%) when using a restricted GeneXpert three-channel approach (positive for any of 8 hrHPV types: HPV types

Table 5.2 Sensitivity and specificity of HPV DNA testing for the detection of histologically verified CIN2+ in women living with HIV

Reference	Country	No. of WLHIV	Test evaluated	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Womack et al. (2000)	Zimbabwe	249	Hybrid Capture 2	90.7 (77.9–97.4)	41.3 (34.5–48.3)
Cohn et al. (2001)	USA	109	Hybrid Capture 2	90 (60–100)	48 (38–59)
Kitchener et al. (2007)	England, France, Ireland, Italy, Poland, Scotland, South Africa	1534	Hybrid Capture 2	91.3 (82.9–99.1)	47.7 (44.2–51.4)
Kuhn et al. (2010)	South Africa	956	Hybrid Capture 2	94.4 (81.3–99.3)	64.4 (58.0–70.3)
Chung et al. (2013)	Kenya	500	GP5+/6+	83.6 (75.6–89.4)	55.7 (50.4–60.9)
Firnhaber et al. (2013)	South Africa	1202	Hybrid Capture 2	91.9 (88.5–95.3)	51.4 (48.0–54.8)
Joshi et al. (2013)	India	1128	Hybrid Capture 2	94.6 (84.9–98.9)	77.4 (74.8–79.9)
Bansil et al. (2015)	Uganda	272	*care*HPV	94.3 (80.8–99.3)	62.4 (55.9–68.6)
Ngou et al. (2015)	Burkina Faso, South Africa	1224	Hybrid Capture 2	88.8 (82.9–93.2)	55.2 (52.1–58.4)
Chibwesha et al. (2016)	Zambia	200	GeneXpert	88 (71–97)	60 (52–68)
Mbulawa et al. (2016)	South Africa	1161	GeneXpert	88.3 (83.6–93.0)	48.4 (44.9–51.9)
Segondy et al. (2016)	Burkina Faso	444	*care*HPV	100.0 (66.4–100.0)	54.7 (49.9–59.5)
Segondy et al. (2016)	South Africa	499	*care*HPV	92.2 (81.1–97.8)	60.9 (56.3–65.5)
Kremer et al. (2019)	South Africa	285	GP5+/6+	78.0 (69.5–86.5)	72.2 (65.9–78.5)
Ndizeye et al. (2019)	Burundi	680	Riatol quantitative PCR	100.0 (100.0–100.0)	63.6 (59.9–67.3)
Kuhn et al. (2020)	South Africa	535	GeneXpert	93.6 (90.0–97.3)	59.9 (54.1–65.7)

CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus; PCR, polymerase chain reaction; WLHIV, women living with HIV.
Compiled with data from Viviano et al. (2017).

16, 18, 31, 33, 35, 45, 52, and/or 58), with minimal loss in sensitivity (93.6% and 90.7%, respectively) (Kuhn et al., 2020). The corresponding screen positivity for the five-channel approach and the three-channel approach was 48.8% and 41.5%, respectively, and the PPV was 31.7% and 35.0%, respectively. In the same study, a user-applied modification to increase the threshold to define screen-positive results using the three-channel approach further increased specificity to 77.0%, with some loss in sensitivity (85.0%). The corresponding estimates for screen positivity and PPV were 33.5% and 43.1%, respectively. [Such user-applied modifications for genotype restriction and screen-positivity threshold enable implementers to balance the capacity to refer hrHPV-positive women for colposcopy or treatment. In settings where colposcopy resources are limited or over-treatment is less tolerated, a high PPV is preferable, and in settings where women may be screened less frequently and/or few alternative treatment options are available, higher sensitivity may be preferred at a cost of a lower PPV.]

Few prospective studies have evaluated the effectiveness of HPV DNA screening in WLHIV. In an RCT of two screen-and-treat strategies in 956 WLHIV enrolled in South Africa in 2002–2002, before widespread availability of

ART, women were randomized to screen-and-treat with either HPV DNA testing or VIA or to a control group (evaluation or treatment was delayed for 6 months) and followed up for 36 months. In the screen-and-treat group with HPV DNA testing, there was an 80% reduction in CIN2+ over 36 months (RR, 0.20; 95% CI, 0.06–0.69), but in the screen-and-treat group with VIA, the reduction was 49% (RR, 0.51; 95% CI, 0.29–0.89) [possibly resulting from the low sensitivity of VIA at enrolment to detect CIN2+ over 36 months (63.9%; 95% CI, 46.2–79.2%) compared with that of HPV DNA testing (94.4%; 95% CI, 81.3–99.3%) and its lower negative predictive value (NPV) (VIA, 90.9%; 95% CI, 85.8–96.0%; HPV DNA, 97.2%; 95% CI, 87.0–99.4%)] (Kuhn et al., 2010).

As the technology of HPV testing becomes cheaper and less cumbersome to use, with the development of near-to-patient testing technologies, HPV testing is becoming easier to implement in LMICs where the burden of HIV infection remains very high. The available near-to-patient testing technologies for the detection of HPV require limited infrastructure, and with some tests the results can be available within 1 hour, potentially enabling same-day screen-and-treat approaches (Chibwesha et al., 2016). HPV testing can be effective in addressing many of the barriers to screening faced in low-resource settings. In a study in Uganda that compared the performance of HPV testing and VIA, the sensitivity of HPV testing in detecting HSIL+ was higher in WLHIV than in HIV-negative women (Bansil et al., 2015). In the HPV in Africa Research Partnership (HARP) study, conducted in Burkina Faso and South Africa, in 1052 WLHIV, the sensitivity of *care*HPV in detecting HSIL+ was 93.3% (95% CI, 83.8–98.2%) and the specificity was 57.9% (95% CI, 54.5–61.2%), and the specificity was observed to increase with the CD4+ cell count (Segondy et al., 2016).

In an effort to increase the coverage of cervical cancer screening in WLHIV, testing for HPV in self-collected cervicovaginal samples has been evaluated and found to be accurate and acceptable; the agreement between self-collected and clinician-collected samples ranged from 92% to 94% (kappa range, 0.71–0.88) (Petignat et al., 2005; Safaeian et al., 2007; Adamson et al., 2015; Obiri-Yeboah et al., 2017; Elliott et al., 2019; Thay et al., 2019), and agreement did not differ by HIV status (Safaeian et al., 2007; Obiri-Yeboah et al., 2017). A study in WLHIV and HIV-negative women in Zimbabwe also found that self-sampling was well accepted in both groups (Dube Mandishora et al., 2017).

(c) Triage options for WLHIV after a positive hrHPV test result

Given the high prevalence of carcinogenic HPV types and the low specificity of HPV DNA tests to distinguish CIN2+ in WLHIV, studies have evaluated various triage options in WLHIV after a positive hrHPV test result. A study in 300 WLHIV in Botswana evaluated different triage methods in hrHPV-positive (using GeneXpert) WLHIV, 33.0% of whom had histologically verified CIN2+. The study reported a sensitivity for CIN2+ of 83% with colposcopy, 59% with VIA, and 62% with cytology at a threshold of ASC-US+, a specificity of 49% with colposcopy, 49% with VIA, and 77% with cytology at a threshold of ASC-US+, and a PPV of 47% with colposcopy, 39% with VIA, and 60% with cytology at a threshold of ASC-US+ (Luckett et al., 2019). A study in 251 hrHPV-positive (using GP5+/6+ PCR EIA) WLHIV in Kenya, 37.5% of whom had CIN2+, reported a sensitivity of 70%, a specificity of 63%, and a PPV of 54% for CIN2+ with VIA, and a sensitivity of 95%, a specificity of 46%, and a PPV of 51% for CIN2+ with cytology at a threshold of ASC-US+. The use of HSIL+ cytology decreased sensitivity (75%) but with an increase in specificity (97%) and PPV (93%) (Chung et al., 2013). A study in 256 hrHPV-positive (using Riatol PCR) WLHIV in Burundi, 7.4% of whom had CIN2+, reported a sensitivity of 84.2%, a specificity of

94.5%, and a PPV of 55.2% for CIN2+ with VIA ([Ndizeye et al., 2019](#)).

When screening for cervical cancer with HPV testing in WLHIV, adequate consideration should be given to sequential testing ([WHO, 2021](#)).

(d) Age to start screening for cervical cancer in WLHIV

There is no good-quality evidence on when cervical cancer screening should be started in WLHIV. On the basis of studies on the epidemiology and natural history of HPV infection in WLHIV, the updated WHO guidelines recommend that cervical cancer screening should be started in sexually active women and girls as soon as HIV infection is confirmed ([WHO, 2021](#)).

(e) Frequency of screening for cervical cancer in WLHIV

In WLHIV, the prevalence of HPV infection remains high across different age groups, unlike the progressive decrease with age observed in HIV-negative women ([Mbulawa et al., 2015](#)). WLHIV have a higher risk of incident and persistent infections with multiple carcinogenic HPV types, with the potential to develop ICC at a younger age compared with HIV-negative women ([Moscicki et al., 2004](#); [Phanuphak et al., 2020](#)). On the basis of studies on the natural history of HPV infection in WLHIV, most guidelines have recommended screening intervals as short as 12 months, taking prior screening test results into consideration ([WHO, 2021](#)).

5.2.2 Screening of older women

After menopause, the marked reduction in estrogen levels results in atrophy of the female genital tract, which is associated with cervical stenosis and thinning of the epithelium; this results in potential difficulty in cervical cancer screening and interpretation of results. In post-menopausal women, speculum examination and the collection of cervical cancer screening specimens can sometimes cause significant discomfort and contact bleeding. Also, the cervix becomes more difficult to expose and the transformation zone gets smaller, moves into the endocervical canal, and becomes less accessible for correct specimen sampling, which may lead to cytological reports of unsatisfactory sample. These physiological changes result in challenges in screening older women, who often also experience changes with age that may make screening more prone to discomfort, may lower the accuracy of the result, and may result in potential harm from overtreatment. Therefore, it is imperative to determine the balance of benefits and harms of cervical cancer screening in older women and to define the age at which women with average or above-average risk should stop screening. In older women who still need to undergo cervical cancer screening, there is also the need to determine the best screening modality and the frequency of screening appropriate for this age group.

(a) Current recommendations

In well-screened populations, most guidelines recommend stopping screening at age 65 years in women with prior adequate negative screening history ([Table 5.3](#)). However, empirical evidence is scant on when to stop screening in inadequately screened or previously unscreened women, in women aged 65 years or older with previous treatment for HSIL+, and in women with continuing risk factors for the development of cervical cancer, such as immunosuppression (e.g. WLHIV). Although the evidence is limited, recently published guidelines for cervical cancer screening from the American Cancer Society (ACS) ([Fontham et al., 2020](#)) and for management of abnormal cervical cancer screening tests from the American Society for Colposcopy and Cervical Pathology (ASCCP) ([Perkins et al., 2020](#)) have addressed the issue of when to stop screening in these subpopulations of women.

(b) Cessation of screening

In general, a woman's previous screening history, continuing risk factors for the development of cervical cancer, and her wishes should be considered to determine the age at which to stop screening.

(i) Cessation of screening based on age and prior adequate screening history

The 2020 ACS and ASCCP guidelines in the USA recommend against cervical cancer screening in women older than 65 years who have prior adequate negative screening history and no history of CIN2 or a more severe diagnosis within the past 25 years (Fontham et al., 2020; Perkins et al., 2020). Adequate negative screening was defined as three negative results from cytology alone, two negative co-test results, or two negative primary HPV test results within the past 10 years, with the most recent test having occurred within the recommended interval of the test used (Fontham et al., 2020). For women with a history of treated lesions with high-grade histology or cytology who reach age 65 years and have completed the 25-year surveillance period (or when this period is completed after age 65 years), continuing surveillance at 3-year intervals is acceptable, provided the women are in reasonably good health (Perkins et al., 2020). In many other high-income countries, in women with prior adequate negative screening history, cessation of cervical cancer screening occurs at ages varying between 60 years and 69 years, although some countries, such as Japan and the Republic of Korea, screen women after age 70 years (Dowling et al., 2010; Castañón et al., 2014).

Because empirical data are lacking, these recommendations are based on the interpretation of the natural history of HPV infection, surveillance trends, expert opinion, and modelling. Although incident HPV infections in women aged 65 years or older are observed to be rare and are thought to have insufficient time to progress to ICC in the woman's lifetime, emerging data from co-testing and primary HPV screening call for caution in this interpretation (Gravitt et al., 2018).

(ii) Cessation of screening in women aged 65 years or older who have had no screening or an irregular screening history

In most LMICs, it is not unusual to find women aged 65 years or older who have never undergone screening for cervical cancer. In these women, the risk of cervical cancer is relatively high (Díaz del Arco et al., 2019). Even in high-income countries with well-established cervical cancer screening programmes, the proportion of women who attend screening decreases with increasing age (Pankakoski et al., 2020). Women with an inadequate screening history will probably benefit from continued screening beyond age 65 years, but limited clear empirical data are available to guide on when the screening should eventually stop. The current ACS guidelines specify that women with an inadequate screening history in the 10-year period before age 65 years should continue screening until a 10-year history of adequate negative screening is achieved, and for women with a prior diagnosis of CIN2+, the ASCCP and ACS guidelines recommend that screening should continue until a 25-year history of adequate negative screening is achieved, even if screening is extended beyond age 65 years (Fontham et al., 2020; Perkins et al., 2020). The guidelines of both organizations state that women can stop screening once these milestones are achieved.

(iii) Cessation of screening in women aged 65 years or older with previous treatment for HSIL+ and those with continuing risk factors such as immunosuppression

Women treated for histologically confirmed HSIL+ have a higher risk of recurrence and development of ICC (Soutter et al., 2006). The ACS and ASCCP guidelines recommend that cervical

Table 5.3 National guidelines on when to stop screening for cervical cancer

Country	Screening test (frequency of screening)	Age to stop screening (years)	Authority (reference)
Australia	Cytology (every 5 yr) Primary HPV (every 5 yr)	74 74	Australian National Cervical Screening Program, 2017 (AIHW, 2019)
Brazil	Primary HPV (every 5 yr)	64	Brazil, 2016 (Zeferino et al., 2018)
China	Cytology (every 2 yr) HPV (every 5 yr)	65 65	China, 2017 (Aoki et al., 2020)
India	Cytology (every 5 yr) HPV (every 5 yr) VIA (every 5 yr)	65 65 50[a]	Federation of Obstetrics and Gynaecologic Societies of India (FOGSI), 2019 (Bhatla et al., 2020)
Indonesia	VIA (every 3–5 yr) Cytology (every 3–5 yr)	50 50	Indonesia, 2017 (Aoki et al., 2020)
Japan	Cytology (every 2 yr) HPV (every 2 yr)	75 75	Japan (Aoki et al., 2020)
Netherlands	Primary HPV (every 5 yr)	60	Netherlands, 2020 (RIVM, 2020)
South Africa	Cytology (every 10 yr)	50	Cervical Cancer Prevention and Control Policy, 2017 (National Department of Health South Africa, 2020)
Sweden	Cytology (every 3 yr) Cytology (every 5 yr) Primary HPV (every 5 yr)	49 60 60	Swedish national cervical screening programme, 2015 (NordScreen, 2017)
Thailand	VIA (every 5 yr) Cytology (every 5 yr) HPV primary screening (every 5 yr)	60 60 60	Thailand, 2020 (Aoki et al., 2020)
United Kingdom	Cytology (every 3 yr) HPV (every 5 yr)	65	United Kingdom National Screening Committee, 2016 (Public Health England, 2020)
USA	Cytology (every 3 yr) Primary HPV (every 5 yr) HPV with cytology co-testing (every 5 yr)	65[b]	American Cancer Society, 2020 (Fontham et al., 2020) United States Preventive Services Task Force Recommendations, 2018 (Curry et al., 2018)

CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus; VIA, visual inspection with acetic acid; yr, year or years.

[a] Preferable.

[b] Adequate screening: a woman aged > 65 yr with no history of CIN2+ within the past 25 yr.

cancer screening should continue for 25 years from the time of treatment, even if screening is extended beyond age 65 years (Fontham et al., 2020; Perkins et al., 2020). Women with immunosuppression need to continue with cervical cancer screening for life (Perkins et al., 2020).

(c) *Benefits of stopping screening at age 65 years*

Although the benefit of the last negative cytology result decreases over time, the absolute risk of developing cervical cancer still remains very low in adequately screened older women.

In a case–control study in the United Kingdom, women with an adequate negative screening history at age 65 years had the lowest risk of cervical cancer compared with those not screened at age 50–64 years (20-year risk: 8 cancers per 10 000 women vs 49 cancers per 10 000 women) (Castañón et al., 2014; Malagón et al., 2018; Landy et al., 2020). The risk of a false-positive screening test result also increases significantly in women older than 50 years (Armaroli et al., 2008). Therefore, extending screening beyond age 65 years in adequately screened women is associated with potential harms of treating women

with false-positive results. [Unfortunately, the data on potential harms come mostly from modelling and not from empirical evidence.] Some authors have suggested that it may be necessary to re-evaluate model assumptions, because the published literature suggests that factors such as the high occurrence of hysterectomies, HPV latency and possible reactivation of infection, possible changes in sexual habits, and the age-specific differences in the sensitivity and specificity of screening strategies in older women may influence potential harms of screening in older women (Grainge et al., 2005; Rositch et al., 2012, 2014; Ermel & Fife, 2016).

(d) Benefits of screening in women aged 65 years or older

Cytological abnormalities and ICC are not rare occurrences in women aged 65 years or older (Çakmak & Köseoğlu, 2014; Díaz del Arco et al., 2019). In a nationwide audit of the cervical cancer screening programme in Sweden, 390 (31.7%) of 1230 cases of cervical cancer reported to the Swedish Cancer Registry in 1999–2001 occurred in women aged 66 years or older, most of whom (91.8%; 358 of 390) had not undergone screening in the preceding screening interval (Andrae et al., 2008). In women who are diagnosed with ICC after age 65 years, the disease is usually advanced and the prognosis is poor (Darlin et al., 2014).

Limited data are also available from small non-randomized studies, which have shown a benefit of screening older women in reducing the risk of ICC. A case–control study in the USA showed that even in older women, the protective benefit of a negative cytology test result does not last a lifetime but is lost 5–7 years after the last screening test (Kamineni et al., 2013). A case–control study in the United Kingdom examined the risk of developing ICC in women aged 65–83 years who had adequate negative screening (i.e. whose last three test results were negative) between ages 50 years and 64 years and

those who were not screened between those ages. The risk of developing ICC after age 65 years was 4.0 per 100 000 women in the group who had adequate negative screening compared with 24.5 per 100 000 women in the unscreened group, corresponding to an 84% reduction in risk (Castañón et al., 2014). The risk of developing ICC in women whose screening was stopped at age 55 years was observed to be almost double that in women whose screening was stopped at age 65 years (379 vs 208 ICC cases per 100 000 women at age 55–84 years).

A mortality audit of the cervical cancer screening programme in Finland assessed the impact of screening at age 65 years on mortality reduction. The relative risk of death from cervical cancer for women invited for cervical cancer screening at age 65 years compared with those not invited was 0.52 (95% CI, 0.29–0.94). The relative risk of death for women not attending screening versus those not invited was 1.28 (CI, 0.65–2.50), and the relative risk of death for women attending screening versus those not invited was 0.28 (CI, 0.13–0.59) (Pankakoski et al., 2019).

In another mortality audit study in Finland, screening between ages 55 years and 69 years was observed to be as effective as screening between ages 40 years and 54 years. Odds ratios of the association between cervical cancer death and screening participation were calculated, to approximate the risk of death from ICC with diagnosis in the interval between screening invitations, and corrected for self-selection. The odds ratios were 0.33 (95% CI, 0.20–0.56) for women screened at age 40–54 years and 0.29 (95% CI, 0.16–0.54) for women screened at age 55–69 years (Lönnberg et al., 2013). The values suggest a trend towards a higher reduction in risk in women screened at age 65–69 years compared with women screened at age 40–54 years.

Other case–control studies and audits of national cervical cancer screening programmes have also shown some degree of protective benefit of screening older women (Sasieni et al., 2003,

2009). Using colposcopy referral (i.e. the clinical burden of screening) as a proxy for harm, modelling was used to estimate the possible harm of extending screening to age 75 years with screening intervals of 5 years. Extending screening beyond age 65 years was found to be associated with very small gains in life expectancy, at the expense of a large number of colposcopies (Kulasingam et al., 2013) [increasing the risks of potential harm].

Using data from the cervical cancer screening programme in Canada in a Markov model, it was shown that women without HPV vaccination but with cytology screening every 3 years between ages 25 years and 69 years would have a lifetime risk of cervical cancer of 1 in 532, and that increasing the age at which women stopped cytology screening from 55 years to 75 years led to incremental decreases in cancer risk later in life. In a woman aged 70 years with unknown screening history, the average lifetime risk of ICC was 1 in 588 (< 1%; 95% percentile interval, 1 in 451 to 1 in 873). The lifetime risk at age 70 years was decreased 2.0-fold (to 1 in 1206) with negative cytology alone, 12.9-fold (to 1 in 6525) with a negative HPV test result alone, and 18.1-fold (to 1 in 9550) with a negative co-test result for cytology and HPV testing (Malagón et al., 2018).

5.2.3 Screening of women with a personal history of precancerous lesions

Women with abnormal screening or diagnostic test results, with lesions that are either histologically confirmed or visually judged to be HSIL/CIN2+ or adenocarcinoma in situ (AIS), usually undergo treatment for the precancerous lesions to prevent progression to ICC. Although most women who have undergone treatment for precancerous cervical lesions do not experience a recurrence of disease, women who have undergone treatment for known or suspected combined CIN2+/AIS or HSIL/AIS are at higher risk of CIN3+, and thus should undergo post-treatment management and surveillance for

test of cure (TOC) before returning to routine screening (Table 5.4). This section focuses on screening after treatment for biopsy-confirmed HSIL/CIN2+ or AIS.

During the past two decades, particularly because of the shift towards HPV-based cervical cancer screening, guidelines and national programmes have continued to evolve to manage abnormalities identified at screening that benefit from short-term surveillance rather than referral for colposcopy, or from surveillance after colposcopy rather than proceeding directly to treatment. These surveillance algorithms before or after colposcopy are intended to avoid overtreatment, especially in women of reproductive age. However, for women who are treated for known or suspected precancerous lesions, national and international guidelines specify post-treatment follow-up protocols for TOC before recommending the return to routine screening. Over time, and with longer post-treatment follow-up studies (Soutter et al., 1997), there has been greater recognition of continuing risk and, more recently, the degree to which test results before and after treatment are predictive of risk (Katki et al., 2013). In higher-resource settings, recommendations have evolved with a greater understanding of the role of persistent infection with carcinogenic HPV types and the critical role of HPV testing in defining risk and follow-up algorithms. Given the complexity of an overwhelming number of potential combinations of testing and triage, some guidelines are replacing results-based protocols with simpler, risk-based protocols based on prior screening test results, current test results, and a woman's age, following the principle of equal management for equal risk; these extend to post-treatment surveillance and return-to-screening protocols (WHO, 2014; Cheung et al., 2020; Demarco et al., 2020; Egemen et al., 2020; Perkins et al., 2020; Schiffman et al., 2020).

Table 5.4 Screening after treatment for precancerous lesions, by pre-treatment diagnosis and country or authority

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
Squamous intraepithelial lesions				
Australia Cancer Council Australia ([Cancer Council Australia Cervical Cancer Screening Guidelines Working Party, 2020](#))	HSIL/CIN2/3	HPV-based test with LBC at 12 mo. Annual testing after the first follow-up test until 2 negative co-tests	Return to routine screening every 5 yr	Any positive carcinogenic HPV (HPV16/18) test result should lead to referral for colposcopy, regardless of the cytology result Consult recommendations for positive non-HPV16/18 test findings, glandular abnormality, or abnormal LBC findings with negative HPV test findings
Brazil Brazilian Association for the Lower Genital Tract Pathology and Colposcopy (ABPTGIC) ([Zeferino et al., 2018](#))	CIN2/3	HPV DNA test between 6 mo and 12 mo after treatment (A)	If cleared of oncogenic types, return to cytology screening every 3 yr (A)	None
Canada Multi-organization guideline ([Bentley et al., 2012](#))	CIN2+	Colposcopy and cytology every 6 mo for 1–2 yr	If follow-up tests are normal, return to annual cytology	None
France National Cancer Institute: Post-treatment surveillance of precancerous lesions of the uterine cervix ([INCa, 2019](#))	HSIL	Regardless of margin status, hrHPV test at 6 mo (B). If negative, repeat HPV test after 3 yr, then again after 3 yr (B), then prolonged surveillance (B) (test and testing interval not specified) without age limit (C); if positive, colposcopy with examination of vulva and vagina and biopsy if deemed necessary (B). If colposcopy satisfactory and no lesion identified, HPV test at 12 mo (B)	If hrHPV-negative at 6 mo after treatment, followed by 2 negative HPV tests every 3 yr, continue prolonged surveillance (B), without age limit (C)	Data from the literature did not enable the precise modalities or periodicity of this surveillance to be determined
New Zealand ([Ministry of Health New Zealand, 2020](#))	HSIL/CIN2/3	Co-testing (cytology and hrHPV test) at 6 mo; repeat after 12 mo for TOC	Cytology every 3 yr	Where there are clinical concerns, perform colposcopy with co-testing at 6 mo after treatment. If HPV test is positive at 6 mo or 18 mo after treatment, return to colposcopy. If colposcopy is negative, continue annual co-testing until 2 consecutive negative co-tests 1 yr apart

Table 5.4   (continued)

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
South Africa (National Department of Health South Africa, 2020)	CIN2/3	Cytology (conventional or LBC) after 12 mo. After the follow-up visit at 12 mo, women should have another screening test 3 yr after treatment (NG)	When cytology has returned to normal, the recommended screening interval should be followed, i.e. every 3 yr for women at high risk (e.g. HIV-positive women, recipients of organ transplant, and women with immunosuppressive disease or undergoing immunosuppressant treatment) and every 10 yr for women at low risk (NG)	None
Spain Spanish Association of Cervical Pathology and Colposcopy (AEPCC, 2015)	HSIL/CIN2/3	If negative margins, co-test at 6 mo; if negative, co-test at 24 mo; if negative, co-test at 3 yr	HPV test every 5 yr for up to 20 yr regardless of age	None
United Kingdom (Public Health England, 2016)	Previous treatment for CIN	Cytology at 6 mo, with triage based on cytology findings	Cytology every 3 yr	At 6 mo, women with negative, borderline, or low-grade findings should undergo reflex hrHPV testing; women with negative test results should be returned to community-based routine recall for cytology in 3 yr

Table 5.4 (continued)

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
USA ASCCP ([Perkins et al., 2020](#))	HSIL/CIN2+	At 6 mo, regardless of margin status: HPV-based testing (preferred) (BII); after the initial test, HPV-based testing annually for 3 yr (preferred) (AII) Follow-up with colposcopy and ECC (acceptable)	Upon completion of short-term protocol, HPV-based testing every 3 yr for 25 yr, even if surveillance extends beyond age 65 yr (BII) If 25-yr surveillance has been completed, continued screening every 3 yr is acceptable as long as the patient is in good health (BIII). Patients with limited life expectancy can discontinue screening	If HPV-based tests are positive, colposcopy and biopsies should be performed (AII)
		At 6 mo, regardless of margin status, cytology alone. Followed by cytology every 6 mo for 3 yr (NG)	Upon completion of short-term protocol, cytology every year for 25 yr, even if surveillance extends beyond age 65 yr Implied: Transition to HPV testing at the earliest opportunity (NG)	Cytology alone is acceptable only if HPV-based testing is not feasible Cytology should only be used for patients younger than age 25 yr, with transition to HPV-based testing after age 25 yr
World Health Organization ([WHO, 2014](#))	HSIL/CIN2+	At 12 mo, primary HPV test, cytology, or VIA (NG) If CIN3 confirmed on histopathology at the time of treatment, rescreening is recommended annually for 3 yr. If these rescreens are negative, return to routine screening	If normal results at 12 mo, return to routine screening If annual rescreening for CIN3 detected at the time of treatment is negative, return to routine screening at programme intervals	If the follow-up test is positive, indicating persistence or recurrence of cervical precancer, retreatment is needed, following protocols based on biopsy results and second treatment considerations
Adenocarcinoma				
Brazil Brazilian Association for the Lower Genital Tract Pathology and Colposcopy (ABPTGIC) ([Zeferino et al., 2018](#))	AIS	HPV DNA test between 6 mo and 12 mo after treatment (A)	If cleared of oncogenic types, return to cytology screening every 3 yr (A)	None

Table 5.4 (continued)

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
Canada Multi-organization guideline (Bentley et al., 2012)	AIS	For women who wish to preserve fertility, colposcopy, ECC, and cytology every 6–12 mo for at least 5 yr If childbearing is complete, hysterectomy should be considered	Consider hrHPV testing Annual cytology testing	If negative margins cannot be achieved, hysterectomy should be considered
France National Cancer Institute: Post-treatment surveillance of precancerous lesions of the uterine cervix (INCa, 2019)	AIS	For women who wish to preserve fertility, if margins are disease-free, hrHPV test at 6 mo (C). If negative, annual follow-up; if positive, colposcopy with examination of vulva and vagina and biopsy if deemed necessary, ± ECC (C). If colposcopy satisfactory and no lesion identified, HPV test at 12 mo (C) If childbearing is complete, hysterectomy is recommended. Surveillance is similar to that of HSIL (C)	If HPV test at 6 mo is negative, do not return to routine screening; annual follow-up is recommended (C)	Data from the literature did not enable the modalities of this surveillance to be determined precisely; it will be based on existing tests (cytology, HPV test, colposcopy, and ECC). After childbearing is complete, hysterectomy should be discussed with the woman
New Zealand (Ministry of Health New Zealand, 2020)	AIS	Management will depend on age, fertility expectations, and clear excision margins. Follow-up colposcopy and cytology (including endocervical brush sample) at 6 mo after treatment. Repeat cytology at 12 mo	Annual cytology	The guideline cites a lack of randomized studies of people with AIS, but notes for people with fertility expectations who have clear margins, 2 consecutive negative annual HPV tests have a PPV for no identifiable disease of 100%
Spain Spanish Association of Cervical Pathology and Colposcopy (AEPCC, 2015)	AIS	If childbearing is complete, hysterectomy is recommended For women who wish to preserve fertility, if margins are disease-free, follow-up with colposcopy, endocervical sampling, and cytology every 6 mo for 24 mo, with HPV test at 24 mo	HPV test every 3 yr	None

Table 5.4   (continued)

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
USA ASCCP (Perkins et al., 2020) SGO (Teoh et al., 2020)	AIS, with fertility-sparing treatment	HPV-based testing with endocervical sampling every 6 mo for 3 yr	After 3 yr, annual HPV-based testing with or without endocervical sampling for a least 2 yr, or until hysterectomy is performed (NG) or Continue HPV-based screening every 3 yr until hysterectomy, or for at least 25 yr	After year 5, women who have consistent negative test results may extend the surveillance interval to 3 yr, and continued surveillance is acceptable after childbearing. Hysterectomy is preferred after childbearing if the patient has had positive HPV or cytology results during surveillance (NG)
ASCCP (Perkins et al., 2020) SGO (Teoh et al., 2020)	AIS, with hysterectomy	Vaginal HPV-based testing annually for 3 yr	Vaginal HPV-based testing every 3 yr for at least 25 yr	Follow ASCCP for 25 yr. Vaginal colposcopy is recommended for women with high-grade cytology results, persistent low-grade cytology results, or 2 or more positive HPV test results
World Health Organization (WHO, 2014)	AIS	At 12 mo, primary HPV test, cytology, or VIA (NG) If AIS confirmed on histopathology at the time of treatment, rescreening is recommended annually for 3 yr. If these rescreens are negative, return to routine screening	If normal results at 12 mo, return to routine screening If annual rescreening for AIS detected at the time of treatment is negative, return to routine screening at programme intervals	If the follow-up test is positive, indicating persistence or recurrence of cervical precancer, retreatment is needed, following protocols based on biopsy results and second treatment considerations
	Previous treatment for CIN	HPV-based testing at 6 mo If negative, repeat after 12 mo (18 mo after treatment)	If follow-up tests are normal, return to cytology every 3 yr	None

AIS, adenocarcinoma in situ; ASCCP, American Society for Colposcopy and Cervical Pathology; CIN, cervical intraepithelial neoplasia; CIN2+, CIN grade 2 or worse; ECC, endocervical curettage; HPV, human papillomavirus; hrHPV, high-risk HPV; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; mo, month or months; NG, not graded; PPV, positive predictive value; SGO, Society of Gynecologic Oncology; TOC, test of cure; VIA, visual inspection with acetic acid; yr, year or years.

[a] Each grade according to the specific grading of the respective authority.

A sample of current recommendations for follow-up of women treated for precancerous lesions is shown in Table 5.4, organized by the pre-treatment diagnosis, the date of issue, and the issuing authority, to highlight the variation in protocols and, to some extent, the evolution in recommendations over time with the accumulation of evidence on post-treatment risk and other considerations. The recommendations are heterogeneous for HSIL/CIN2+ or AIS; this probably reflects varying health resources, the available testing technology, the available evidence within the guideline development cycle, and whether follow-up protocols are based on an indication of risk associated with pre-treatment indications and absence of clear margins after treatment, or calculated estimates of absolute risk based on prior screening test and biopsy results, current surveillance test results, and individual factors such as age, pregnancy, and immunosuppression (WHO, 2014; von Karsa et al., 2015; Perkins et al., 2020). Recommendations that take into account fertility preservation, pregnancy, diagnosis of AIS, and high-risk immunosuppressed conditions (HIV infection, autoimmune conditions, persistent HPV infection, use of immunosuppressant therapy, etc.) show greater similarity (Chin-Hong, 2016; Davis et al., 2016; Carriero et al., 2018; Kim et al., 2018; Moscicki et al., 2019). In some instances, follow-up protocols for TOC are the same for HSIL/CIN2+ or AIS. [All recommendations shown in Table 5.4 are current, but updates may be in progress and/or prevalent protocols in a country may have evolved ahead of a guideline update in response to new evidence.]

(a)   Personal history of HSIL/CIN2+

(i)   Increase in risk

An increased risk of HSIL/CIN2+ and ICC has been observed in long-term follow-up studies of women treated for precancerous lesions. A study in the United Kingdom, commissioned by the National Health Service Cervical Cancer Screening Programme, sought to determine the duration of an elevated rate of ICC and vaginal cancer after treatment for CIN (Soutter et al., 2006). Analysis of 26 cohorts in 25 studies in Asia, Europe, and North America, in which follow-up ranged from 5 years to 25 years, showed an increased risk (~2.8 times the background risk) of post-treatment ICC for up to 20 years. The incidence rate of reported post-treatment CIN ranged from 76 to 6036 per 100 000 women-years (median, 1413 per 100 000 women-years) and was greatest in the first year after treatment; this was probably due to a combination of residual and recurrent disease. In contrast to the persistent elevated incidence of ICC, rates of post-treatment CIN fell steadily during the 10 years after treatment (Soutter et al., 2006).

Similar risks were observed in a retrospective cohort study in Finland, in which 7564 women were treated in 1974–2001 for CIN1–3 or CIN grade not otherwise specified. The average follow-up was 11.9 years (range, 0.5–28 years), and the standardized incidence ratio (SIR) for invasive disease was 2.8 (95% CI, 1.7–4.2) (Kalliala et al., 2005). In Sweden, 132 493 women were followed up after treatment for CIN3 in 1958–2002. Women with previous CIN3 had an increased risk of ICC compared with the general female population (SIR, 2.3; 95% CI, 2.2–2.5) (Strander et al., 2007). Both studies observed persistent elevated risk over more than 20 years. In the study in Finland, risk was highest in the second decade after treatment (Kalliala et al., 2005), whereas in the study in Sweden, risk decreased over time but remained elevated 25 years after treatment (Strander et al., 2007). In a study in Canada, the risk of CIN3+ within 1–5 years after treatment was evaluated in 14 668 women who had undergone treatment for CIN3 in 2006–2010, and a 5-year recurrence rate of CIN3 of 6.1% was observed, with increased risk independently associated with abnormal post-treatment cytology and age older than 45 years (Swift et al., 2020).

In an effort to update estimates of the risks of developing and dying from cervical cancer after treatment of precancerous lesions, Kalliala et al. (2020) conducted a pooled analysis of 27 studies of cervical cancer incidence after treatment of predominantly CIN3 (some studies included CIN1/2), with a mean or median follow-up of 5–27.5 years. [The analysis included some studies that were included in the pooled analysis by Soutter et al. (2006) as well as studies published since 2006, including several large national and regional population-based studies.] The investigators limited inclusion to studies with nationwide or regionwide cancer registries as a source of follow-up data, and presented data with at least 5 years of follow-up (Kalliala et al., 2020). A pooled absolute incidence rate of cervical cancer after treatment of CIN of 39 per 100 000 women-years was reported, with follow-up of more than 20 years after treatment (range, 31–38 per 100 000 women-years based on duration of follow-up). This is compared with the estimate from Soutter et al. (2006) of 56 per 100 000 women-years up to 20 years after treatment.

Incomplete excision of CIN also is associated with an increased risk of CIN of any grade or ICC. In a meta-analysis of 66 studies including 35 109 women who underwent treatment for CIN using excisional methods, 8091 (23%) of whom had at least one excisional margin with residual disease (incomplete excision), post-treatment high-grade disease (HSIL or CIN2/3) occurred in 18% of women who had incomplete excision compared with 3% of women who had complete excision (RR, 6.09; 95% CI, 3.87–9.60) (Ghaem-Maghami et al., 2007). A systematic review and meta-analysis was undertaken of 97 studies including 44 446 women treated for cervical precancer that evaluated the association between incomplete excision of precursor lesions and treatment failure, defined as the occurrence of residual or recurrent CIN2+. An increased risk of treatment failure was observed in women with positive resection margins compared with those with negative resection margins (17.1% vs 3.7%; RR, 4.8; 95% CI, 3.2–7.2) (Arbyn et al., 2017). However, additional analysis revealed that margin status was a lesser predictor of risk of residual or recurrent CIN2+ compared with hrHPV test results. The risk of post-treatment CIN2+ was 3.7% when margins were clear, whereas the risk of post-treatment CIN2+ associated with a concurrent negative hrHPV test result was 0.8% (Arbyn et al., 2017).

Five-year risks of CIN3+ after treatment for CIN2 or CIN3 (conservatively based on treatment for CIN3) were estimated on the basis of current HPV and cytology test results in women aged 25–65 years who underwent cervical cancer screening in the USA, to support the 2019 ASCCP Risk-Based Management Consensus Guidelines (Egemen et al., 2020). Women with a negative HPV test result after treatment had a 5-year risk of CIN3+ of 2.0%. A negative HPV test result combined with cytology negative for intraepithelial lesion or malignancy (NILM) was associated with a 5-year risk of CIN3+ of 1.7%, and a negative HPV test result combined with cytology negative for ASC-US/LSIL was associated with a 5-year risk of CIN3+ of 3.8%. In contrast, women with a negative HPV test result combined with high-grade cytology (atypical squamous cells, cannot exclude HSIL [ASC-H]/ atypical glandular cells [AGC]/HSIL+) had a 5-year risk of CIN3+ of 18% (Egemen et al., 2020). In a second study, also to support the ASCCP Risk-Based Management Consensus Guidelines, a systematic review was conducted of 23 studies in Asia, Europe, and North America published in 2012–2019 and including a broader spectrum of tests or diagnostic assays for post-colposcopy and post-treatment surveillance (Clarke et al., 2020). Follow-up periods, with interim examinations, ranged from 6 months to 121 months, although most were 24–36 months. In all studies combined, women who were HPV-negative after treatment had a risk of CIN2+ of 0.69% (95% CI, 0.3–1.5%), and women who were HPV-positive

after treatment had a risk of CIN2+ of 18.3% (95% CI, 12.1–26.6%). The risk of CIN2+ after treatment was higher in women with concurrent positive (ASC-US+) cytology (36.6%; 95% CI, 28.4–45.7%) than in women with concurrent negative cytology (1.7%; 95% CI, 1.0–3.1%) (Clarke et al., 2020).

(ii)   Follow-up recommendations for return to screening

Recommendations for follow-up of women treated for HSIL/CIN2+ have evolved over time (Table 5.4). Most guidelines are based on currently available evidence, i.e. the follow-up interval (6 or 12 months) is determined by the pre-treatment diagnosis of SIL/CIN and the margin status after treatment. Although most recommendations shown in Table 5.4 specify initial *testing* protocols (cytology alone, co-testing, or primary HPV testing), surveillance intervals may be fixed (i.e. 6 months or 12 months after treatment) or they may be lengthened after successive normal test results while still accumulating a history of normal findings to support TOC. Surveillance periods range from a single test at 6 months after treatment to consecutive testing events over 3 years or more to establish TOC, after which women may be recommended to return to routine screening intervals. However, some recommendations also provide flexibility to allow for longer periods of surveillance on the basis of clinical concerns (Ministry of Health New Zealand, 2020). The WHO recommendations stress the importance of post-treatment surveillance for 3 years after a diagnosis of CIN3 but provide options for choice of test (HPV test, cytology, or VIA) to accommodate local capacity (WHO, 2014). Follow-up testing using HPV-based testing predominates after 2018, with variable criteria to determine TOC. For example, Cancer Council Australia recommends co-testing using liquid-based cytology (LBC) and HPV testing at 12 months and annually thereafter until there have been two consecutive negative co-test results before returning women to routine screening every 5 years (Cancer Council Australia Cervical Cancer Screening Guidelines Working Party, 2020). In contrast, in New Zealand, co-testing (cytology and HPV testing) is recommended at 6 months and again at 12 months to determine TOC, after which women may return to cytology-only testing every 3 years (Ministry of Health New Zealand, 2020).

In the USA, the ASCCP consensus guidelines are based on current screening test results and previous screening test and biopsy results (Perkins, et al., 2020). Risk-based post-treatment surveillance protocols recommend short-term HPV-based testing (6 months after treatment), followed by annual HPV-based tests for 3 years before returning women to a schedule approximating routine screening (HPV testing every 3 years [preferred] or annual cytology) (Perkins et al., 2020). When there are two or three negative follow-up HPV-based tests after treatment of CIN2/3, the 5-year risk of CIN3 is less than 1.0%, and it is considerably less with three negative test results than with two negative test results. When there are two consecutive negative follow-up co-test results after treatment, the 5-year risk of CIN3+ is 0.68%. One more negative co-test result decreases this risk to 0.35% (Egemen et al., 2020). Routine screening for women at average risk would be HPV-based testing every 5 years, but because the 5-year risk of CIN3 after three negative HPV-based test results is above the risk threshold (0.15%) set by ASCCP for 5-year HPV-based screening, and because this risk remains elevated for up to 25 years, screening every 3 years is recommended for a minimum of 25 years. As is the case with the ASCCP guidelines, some countries, such as South Africa, extend risk-stratified screening intervals into a long-term follow-up period (National Department of Health South Africa, 2020).

(b) Personal history of AIS

AIS is less common than HSIL/CIN2+, and there are fewer studies measuring post-treatment risk. Furthermore, in women with a diagnosis of AIS, post-treatment risk is influenced by the course of treatment; hysterectomy is preferred if women do not wish to maintain fertility, and excisional treatment is used if fertility-sparing treatment is chosen.

(i) Increase in risk

In 119 women treated conservatively using cold-knife conization, LEEP, laser conization, and needle excision and followed up for a mean of 40.9 months, the observed cumulative rate of AIS, CIN, or ICC (adenocarcinoma or squamous cell carcinoma) was 12.6%, whereas no residual disease was observed during the follow-up period in women treated with hysterectomy because of margin involvement in the conization specimen (Costa et al., 2012). Risk of AIS after treatment was included in the above-mentioned study by Swift et al. (2020), of 15 177 women who had undergone treatment for CIN3 or AIS (with LEEP, laser, or conization) in 2006–2010, 509 of whom were treated for AIS, and a 5-year recurrence rate of AIS of 9.0% was observed. A higher recurrence rate was observed in younger women (9.8% in women younger than 45 years compared with 4.9% in women 45 years or older), but this difference was not significant ($P = 0.13$) (Swift et al., 2020).

(ii) Follow-up recommendations for return to screening

For women with a diagnosis of AIS, the recommended post-treatment surveillance protocols depend on whether simple or radical hysterectomy is performed (the preferred treatment) or fertility-sparing treatment is chosen (in patients of reproductive age who wish to preserve the ability to have future pregnancies). Hysterectomy is preferred because AIS is often found in the endocervical canal, which complicates excision; it is often multifocal, which complicates the interpretation of negative margins on the excisional specimen, and biopsy results that indicate AIS warrant an excisional procedure to rule out the presence of invasive adenocarcinoma (Teoh et al., 2020). However, the mean age of diagnosis of AIS is 35–37 years, and women in this age group may wish to have fertility-sparing treatment, which postpones the preferred treatment indefinitely; when childbearing has been completed or is no longer a possibility, hysterectomy is advised.

For women who wish to preserve fertility, post-treatment surveillance after a prior diagnosis of AIS is more intensive than that for HSIL/CIN2+ (Table 5.4). In 2012, the Canadian multi-organization guideline recommended colposcopy, endocervical curettage, and cytology every 6–12 months for at least 5 years, with consideration of hrHPV testing during this period for reassurance [interval not specified]; afterwards, the patient should receive annual cytology testing (Bentley et al., 2012). The Spanish Association of Cervical Pathology and Colposcopy also recommended short-interval testing with colposcopy, cytology, and endocervical sampling for 2 years, and an HPV test at 2 years for TOC, with subsequent HPV testing every 3 years thereafter for women who wish to preserve fertility, if margins are free of disease (AEPCC, 2015).

Although women of reproductive age who wish to preserve fertility may be followed up with intensive surveillance if the excisional specimen (or a re-excisional specimen in cases where negative margins cannot be achieved) has negative margins, fertility-sparing management generally is not recommended (Bentley et al., 2012; Perkins et al., 2020; Teoh et al., 2020). Post-treatment surveillance is most important when the risk of recurrence is high. Localized treatment of AIS has not been shown to decrease the subsequent incidence of invasive adenocarcinoma in women at highest risk of recurrence (Swift et al., 2020).

For women who have undergone fertility-sparing treatment, both the Society of Gynecologic Oncology and ASCCP recommended short-term follow-up with HPV-based testing and endocervical sampling every 6 months for 3 years. If the results are consistently negative, annual HPV-based testing with or without endocervical sampling should be undertaken for 2 years, or until hysterectomy is performed; if test results remain negative, HPV testing should be undertaken every 3 years for at least 25 years, or until hysterectomy is performed (Teoh et al., 2020). For women who have elected to undergo hysterectomy, the initial short-term follow-up consists of annual vaginal HPV-based testing for 3 years, followed by vaginal HPV-based testing every 3 years for at least 25 years, even if testing extends beyond age 65 years (Perkins et al., 2020; Teoh et al., 2020).

5.2.4 Screening of HPV vaccinated populations

(a) The basis for complementary strategies of primary and secondary prevention

HPV vaccination began in earnest in late 2006, 1 year after the publication of the first *IARC Handbook* on cervical cancer screening (IARC, 2005). HPV vaccination was adopted gradually by high-income countries and subsequently by middle- and low-income countries. HPV vaccination is the only evidence-based primary prevention strategy for cervical cancer. At least one of the three approved HPV vaccine formulations (bivalent, quadrivalent, and nonavalent) are currently available in most high-income settings, although the availability is currently limited in LMIC settings (Bruni et al., 2016).

The first results of RCTs on vaccine efficacy were published in 2004 for the bivalent vaccine against HPV types 16 and 18 (Harper et al., 2004) and in 2005 for the quadrivalent vaccine against HPV types 6, 11, 16, and 18 (Villa et al., 2005). Because these vaccines target the two most carcinogenic HPV types that are etiologically linked to cervical cancer (i.e. HPV16 and HPV18), they have the potential to prevent up to 70% of all cervical cancers. The newer nonavalent vaccine (Joura et al., 2015), which targets HPV types 31, 33, 45, 52, and 58 in addition to 6, 11, 16, and 18, has the potential to prevent 90% of all cervical cancers. The screening of future cohorts of vaccinated women has become a complementary policy to accelerate the reduction of cervical cancer incidence to levels below the WHO target of 4 new cases per 100 000 women per year, which is the established threshold to achieve the elimination of cervical cancer as a public health problem (Simms et al., 2019).

(b) Performance of cervical cancer screening in HPV vaccinated populations

Although the two above-mentioned approaches for cervical cancer prevention are clearly complementary, their effects are not simply additive. The interplay between HPV vaccination and cervical cancer screening is complex, because they apply to different periods in a woman's lifetime and because of the different factors that are involved in the health-care system (Fig. 5.2). In spite of these limitations, they can both be viewed as preventive steps in the same continuum in the natural history of cervical cancer.

Fig. 5.2 also illustrates how one strategy (HPV vaccination) influences the performance of the other (cervical cancer screening). For any disease, screening can have clinical value when the condition that needs to be detected is sufficiently common. In the absence of HPV vaccination, the prevalence of CIN is sufficiently high for screening to perform with reasonable accuracy, to enable screening programmes to achieve their intended effect of reducing the incidence of and mortality from cervical cancer with acceptably low risks, such as those stemming from overdiagnosis and harms from overtreatment.
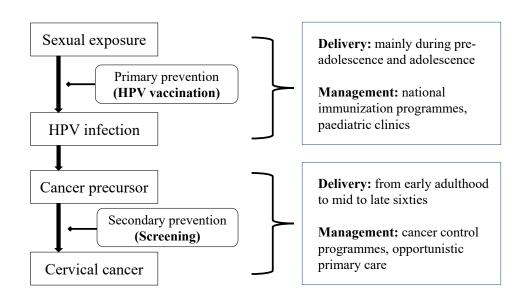
Fig. 5.2 Interplay between primary and secondary prevention strategies for cervical cancer

Created by the Working Group.

The simplified trajectory depicted in Fig. 5.2 from the onset of sexual exposure during a woman's late adolescence until the development of cervical cancer, with the highest incidence at ages 40–45 years, implies a long window of opportunity for disease prevention. As successive birth cohorts of vaccinated women reach the age of screening, about 15 years after they were vaccinated, the prevalence of cervical precancerous lesions that can be detected by screening and treated is expected to decrease substantially.

The PPV of cervical cancer screening for detection of CIN2+ is positively correlated with the prevalence of cervical lesions, assuming that test sensitivity and specificity remain unchanged. Therefore, the lower the prevalence of disease, the lower the PPV, and thus there may be a higher proportion of false-positive test results, which may lead to unnecessary diagnostic procedures, such as colposcopies and biopsies, and possible overtreatment. This potential outcome was recognized before HPV vaccination programmes had started, and thus before mass immunization

of girls led to a decrease in the prevalence of cervical precancerous lesions in the first birth cohorts to benefit from HPV vaccines (Franco et al., 2006). The decrease in the PPV of cervical cancer screening after vaccination has been reported in a few populations, mostly those in Australia and in the United Kingdom, which were early adopters of organized, high-coverage HPV vaccination programmes (Palmer et al., 2016; Munro et al., 2017; Sultana et al., 2019).

(c)   Impact of HPV vaccination on screening policies

There has been a steady decrease in the prevalence of vaccine-targeted HPV types and of cervical lesions associated with these types in numerous populations after vaccination (Brotherton et al., 2011; Powell et al., 2012; Baldur-Felskov et al., 2014; Pollock et al., 2014; Carozzi et al., 2016; Cruickshank et al., 2017; Kavanagh et al., 2017; Niccolai et al., 2017; Guo et al., 2018; McGregor et al., 2018; Thamsborg et al., 2018). Infections with HPV16 and HPV18

have become rare in these settings after vaccination (Lynge et al., 2020). Evidence has recently been published that population-based HPV vaccination has decreased the incidence of ICC in Sweden (Lei et al., 2020).

This raises the question of whether high-frequency screening – every 3 years using cytology or every 5 years using HPV testing (irrespective of triage algorithms) – should be sustained. An ancillary question is whether screening should start as early as at age 21 years or 25 years, which is the prevailing policy in many high-resource settings. In many countries that implemented HPV vaccination soon after initial regulatory approval (Australia, Canada, the United Kingdom, and the USA), the first birth cohorts of vaccinated women have now reached age 25 years and are thus being invited to attend screening. In these populations, should screening be started at age 30 years and performed less frequently?

Women who are older than the ages targeted by vaccination programmes fall under the prevailing guidelines for screening frequency. Even in populations targeted by vaccination programmes, participation may be suboptimal because of parental refusal or other reasons that cause people to opt out of vaccination programmes. Therefore, the question of adapting screening algorithms for the entire female population also requires consideration.

Modelling studies have shown that the combination of vaccination and screening is cost-effective and is good value for money, with screening starting later in life – for example at age 30 years for the bivalent or quadrivalent vaccines and at age 35 years for the nonavalent vaccine – and with longer screening intervals (Kim et al., 2017; Pedersen et al., 2018). A related point is that the risk of histologically ascertained precancer after the detection of low-grade abnormalities on cytology has been shown to be much lower in vaccinated women than in unvaccinated women (Castle et al., 2019). [This affects the validity of current guidelines for managing cervical abnormalities detected by cytology.]

[The expected decrease in the PPV of current screening strategies for detection of CIN2+ after population-based HPV vaccination, and its consequences in terms of potential increased harms from overdiagnosis as well as issues of costs from overscreening or over-referral for colposcopy, apply to all cervical cancer screening tests. However, after vaccination, molecular assays that target nucleic acid sequences of carcinogenic HPV types in cervical samples are a more suitable option than cytology.]

(d) Screening policies for vaccinated women

Only a few countries have considered modifying screening policies in the HPV vaccination era or tailoring guidelines independently for vaccinated and unvaccinated women (Franco et al., 2006; Kim et al., 2017; Pedersen et al., 2018).

In 2012, a consortium led by professional societies and health agencies in the USA reached the conclusion that age-specific screening recommendations should be the same for vaccinated and unvaccinated women (Saslow et al., 2012). At that time, the available vaccines protected only against HPV16 and HPV18, and thus it was expected that about 30% of all cervical cancers would continue to occur. The decision was also made based on the low coverage of HPV vaccination in the USA, which was much lower than the coverage in countries with national vaccination programmes. In addition, the lack of reliable vaccination records implied that physicians could not assume that women who reported having been vaccinated were indeed protected.

The United States Preventive Services Task Force (USPSTF) issued similar recommendations in 2012 for cervical cancer screening irrespective of HPV vaccination status (Moyer et al., 2012). The USPSTF revisited its guidelines in 2018, and the conclusion from a review of the evidence was that the new recommended policies were to be implemented independently of HPV vaccination

status, because the evidence was still insufficient to support a later age to start screening or less frequent screening for vaccinated women (US Preventive Services Task Force, 2018).

The same professional society and health agency stakeholders in the USA that produced the above-mentioned 2012 guidelines (Saslow et al., 2012) reconvened for an update in 2019 (Perkins et al., 2020). Although the focus of the new guidelines was on risk-based management and not on screening algorithms, the recommendation was to omit HPV vaccination status to guide management. This decision was influenced by the low coverage of HPV vaccination in young women, as well as the lack of vaccination registries that would enable clinicians to link primary care records with vaccination histories. Similarly, the 2020 ACS guideline for cervical cancer screening issued recommendations that were independent of vaccination status (Fontham et al., 2020).

A comparable in-depth assessment of the evidence was completed by the Canadian Task Force on Preventive Health Care in 2013. The evidence about the impact that population-based HPV vaccination has on the prevalence of cervical lesions or the incidence of cervical cancer was judged to be insufficient to justify a separate cervical cancer screening policy for vaccinated women (Canadian Task Force on Preventive Health Care, 2013).

To date, only Italy has proposed specific screening policies for vaccinated women since 2017 (Giorgi Rossi et al., 2017). The multi-stakeholder position statement recommended to start screening at age 30 years in vaccinated women, with an HPV test, whereas for unvaccinated women the age to start screening remained at 25 years, with cytology until age 29 years and HPV testing with cytology triage for women aged 30–64 years. The recommendation was based on thresholds of attained risk of CIN3+ for successive birth cohorts of vaccinated women. As risk is maintained at acceptably low levels or decreases

further, the screening interval increases by 1 year for the next birth cohort. At a minimum, the stakeholders defined as essential the adoption of an organized screening programme with high coverage and efficient call–recall, to minimize risks.

As an initial step to modify screening policies in the HPV vaccination era, the Canadian Partnership Against Cancer issued a statement in 2019 recommending that provinces and territories in Canada should stop screening women younger than age 25 years (Popadiuk et al., 2019). The recommendation was based on the high coverage of HPV vaccination in Canada attained since 2007; hence, most young women reaching that age have been protected against the most carcinogenic HPV types (HPV16 and HPV18).

(e) Integration of vaccination and screening

Implementation of HPV testing in screening for cervical cancer enables the accumulation of the evidence needed to inform screening practices. Consistent with the framework shown in Fig. 5.2, it would be helpful for health systems within countries to harmonize their policies on HPV vaccination and screening, with a view to sharing information and resources (Franco et al., 2008). Establishing HPV testing registries with data from women who attend cervical cancer screening and linking the screening data with vaccination registries and cancer registries would provide an efficient surveillance mechanism that would enable the evaluation of the impact of vaccination in reducing the prevalence of carcinogenic HPV types and the incidence of cervical precancerous lesions and cancer (Brotherton et al., 2019). High-level integration of vaccination data and screening data has been shown to work in the state of New Mexico in the USA (Benard et al., 2017).

The integration of planning and systems resources for HPV vaccination and cervical cancer screening has many advantages, in addition to the obvious economy of scale that comes from
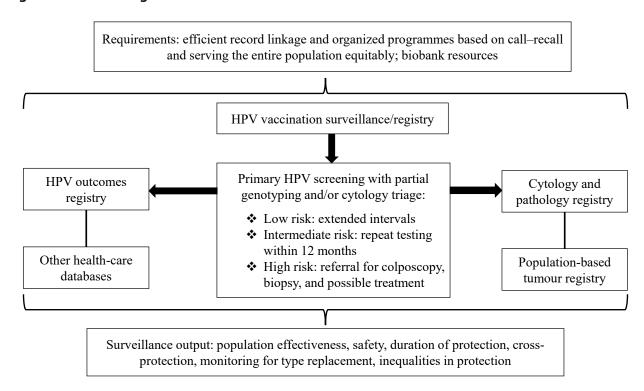
Fig. 5.3 Schematic rationale for an ideal integration of vaccination and screening programmes in high-resource settings

```
┌─────────────────────────────────────────────────────────────────────┐
│  Requirements: efficient record linkage and organized programmes      │
│  based on call–recall and serving the entire population equitably;     │
│  biobank resources                                                     │
└─────────────────────────────────────────────────────────────────────┘

                    ┌─────────────────────────────────┐
                    │ HPV vaccination surveillance/    │
                    │ registry                         │
                    └─────────────────────────────────┘

┌──────────────┐    ┌─────────────────────────────────┐    ┌──────────────┐
│ HPV outcomes │ ◄─ │ Primary HPV screening with      │ ─► │ Cytology and │
│ registry     │    │ partial genotyping and/or        │    │ pathology    │
│              │    │ cytology triage:                 │    │ registry     │
└──────────────┘    │                                  │    └──────────────┘
                    │ ❖ Low risk: extended intervals   │
┌──────────────┐    │ ❖ Intermediate risk: repeat      │    ┌──────────────┐
│ Other health-│    │   testing within 12 months       │    │ Population-  │
│ care         │    │ ❖ High risk: referral for        │    │ based tumour │
│ databases    │    │   colposcopy, biopsy, and        │    │ registry     │
└──────────────┘    │   possible treatment             │    └──────────────┘
                    └─────────────────────────────────┘

┌─────────────────────────────────────────────────────────────────────┐
│ Surveillance output: population effectiveness, safety, duration of    │
│ protection, cross-protection, monitoring for type replacement,         │
│ inequalities in protection                                             │
└─────────────────────────────────────────────────────────────────────┘
```

The central component is a generic cervical cancer screening algorithm to inform a surveillance system after vaccination. Not all record linkage components are essential. Efficient epidemiological surveillance can be implemented with a subset of these components.
Created by the Working Group.

centralized procurement of supplies and shared information systems. As shown in Fig. 5.3, for a high-resource setting with centralized cancer control processes, the primary components of this integration are a vaccination registry that provides anonymized identifiers to the screening process, which is a generic screening programme based on a clinically validated HPV test and complemented by a triage algorithm, together with management decisions based on local best practices. Anonymized data generated by the screening programme are linked with administrative health-care databases for cytopathology, colposcopy, treatment outcomes, cancer incidence, and follow-up information. Such integration of processes and data has many dividends for surveillance. As outputs, it is possible to

determine in real time the population-level effectiveness of vaccination, the duration of vaccine protection, and any potential inequalities in the coverage of both vaccination and screening, as well as in their outcomes. An important goal for surveillance is to monitor for possible differences in the coverage of or participation in screening in relation to previous receipt of vaccination. Is there a perception by women who were vaccinated that their risk of cervical cancer is low and therefore they may skip screening visits? A better understanding could be achieved with an integrated system as depicted in Fig. 5.3. Other causes for differences in the coverage or participation, including disparities in access to health care, conscientious objection to vaccination, and refusal to be screened by a male provider, can

be monitored with the linkage system shown in Fig. 5.3.

The addition of a biobank to this integrated system would enable storage of cervical samples for partial HPV genotyping (if this was not already done via the core screening process) or full HPV genotyping. A biobank would also enable more elaborate molecular testing for DNA methylation and other prognostic biomarkers. The availability of genotyping data would enable population-level monitoring of cross-type protection, of herd immunity, and of potential type replacement. The above-mentioned integrated system would also enable the monitoring of the benefits of HPV vaccination in protecting against other HPV-associated cancer types in women. An independent linkage between HPV vaccination registries and cancer registries would also enable assessment of the impact of vaccination on HPV-associated cancer types in men.

Not all of the components shown in Fig. 5.3 are essential for the implementation of an efficient surveillance system with integration of screening and vaccination. Even high-resource regions may not have population-based cancer registries or cytology and pathology registries and may not have established biobanks. Different jurisdictions may decide to implement only the core linkages of vaccination records and screening records, to enable the outcomes of both prevention activities to be monitored.

References

Adamson PC, Huchko MJ, Moss AM, Kinkel HF, Medina-Marino A (2015). Acceptability and accuracy of cervical cancer screening using a self-collected tampon for HPV messenger-RNA testing among HIV-infected women in South Africa. *PLoS One*. 10(9):e0137299. doi:10.1371/journal.pone.0137299 PMID:26332236

AEPCC (2015). Prevention of cervical cancer 2014. Asociación Española de Patología Cervical y Colposcopia. Available from: https://www.aepcc.org/wp-content/uploads/2018/05/AEPCC_revista02_EN_PREVENTION-CC-2014_26032018.pdf.

AIHW (2019). Cervical screening in Australia 2019. Cancer series no. 123. Canberra, Australia: Australian Institute of Health and Welfare. Available from: https://www.aihw.gov.au/reports/cancer-screening/cervical-screening-in-australia-2019/contents/table-of-contents.

Ancelle-Park R, Klein JP, Stroobant A, Smith E, Haikala O, Koch MA, et al. (1993). Expanded European AIDS case definition. *Lancet*. 341(8842):441. doi:10.1016/0140-6736(93)93040-8 PMID:8094208

Anderson JR, Paramsothy P, Heilig C, Jamieson DJ, Shah K, Duerr A; HIV Epidemiology Research (HER) Study Group (2006). Accuracy of Papanicolaou test among HIV-infected women. *Clin Infect Dis*. 42(4):562–8. doi:10.1086/499357 PMID:16421802

Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W, et al. (2008). Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst*. 100(9):622–9. doi:10.1093/jnci/djn099 PMID:18445828

Aoki ES, Yin R, Li K, Bhatla N, Singhal S, Ocviyanti D, et al. (2020). National screening programs for cervical cancer in Asian countries. *J Gynecol Oncol*. 31(3):e55. doi:10.3802/jgo.2020.31.e55 PMID:32266804

Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. (2010). European guidelines for quality assurance in cervical cancer screening. Second edition – summary document. *Ann Oncol*. 21(3):448–58. doi:10.1093/annonc/mdp471 PMID:20176693

Arbyn M, Redman CWE, Verdoodt F, Kyrgiou M, Tzafetas M, Ghaem-Maghami S, et al. (2017). Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. *Lancet Oncol*. 18(12):1665–79. doi:10.1016/S1470-2045(17)30700-3 PMID:29126708

Armaroli P, Gallo F, Bellomi A, Ciatto S, Consonni D, Davi D, et al. (2008). Do women ≥ 50 years of age need as much screening as women < 50 years after they have had negative screening results? *Br J Cancer*. 99(2):239–44. doi:10.1038/sj.bjc.6604455 PMID:18594534

Awolude OA, Oyerinde SO (2018). Invasive cervical cancer in Ibadan: socio-sexual characteristics, clinical stage at presentation, histopathology distributions and HIV status. *Afr J Infect Dis*. 13(1):32–8. PMID:30596194

Baldur-Felskov B, Dehlendorff C, Junge J, Munk C, Kjaer SK (2014). Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program. *Cancer Causes Control*. 25(7):915–22. doi:10.1007/s10552-014-0392-4 PMID:24797870

Bansil P, Lim J, Byamugisha J, Kumakech E, Nakisige C, Jeronimo JA (2015). Performance of cervical cancer screening techniques in HIV-infected women in Uganda. *J Low Genit Tract Dis*. 19(3):215–9. doi:10.1097/LGT.0000000000000090 PMID:25551591

Bateman AC, Parham GP, Sahasrabuddhe VV, Mwanahamuntu MH, Kapambwe S, Katundu K, et al. (2014). Clinical performance of digital cervicography and cytology for cervical cancer screening in HIV-infected women in Lusaka, Zambia. *J Acquir Immune Defic Syndr*. 67(2):212–5. doi:10.1097/QAI.0000000000000270 PMID:24977474

Benard VB, Castle PE, Jenison SA, Hunt WC, Kim JJ, Cuzick J, et al.; New Mexico HPV Pap Registry Steering Committee (2017). Population-based incidence rates of cervical intraepithelial neoplasia in the human papillomavirus vaccine era. *JAMA Oncol*. 3(6):833–7. doi:10.1001/jamaoncol.2016.3609 PMID:27685805

Bentley J; Executive Council of the Society of Canadian Colposcopists; Special Contributors (2012). Colposcopic management of abnormal cervical cytology and histology. *J Obstet Gynaecol Can*. 34(12):1188–202. doi:10.1016/S1701-2163(16)35468-8 PMID:23231803

Bhatla N, Singhal S, Saraiya U, Srivastava S, Bhalerao S, Shamsunder S, et al.; FOGSI Expert Group (2020). Screening and management of preinvasive lesions of the cervix: good clinical practice recommendations from the Federation of Obstetrics and Gynaecologic Societies of India (FOGSI). *J Obstet Gynaecol Res*. 46(2):201–14. doi:10.1111/jog.14168 PMID:31814222

Branca M, Rossi E, Alderisio M, Migliore G, Morosini PL, Vecchione A, et al. (2001). Performance of cytology and colposcopy in diagnosis of cervical intraepithelial neoplasia (CIN) in HIV-positive and HIV-negative women. *Cytopathology*. 12(2):84–93. doi:10.1046/j.1365-2303.2001.00299.x PMID:11284952

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 68(6):394–424. doi:10.3322/caac.21492 PMID:30207593

Brotherton JML, Fridman M, May CL, Chappell G, Saville AM, Gertig DM (2011). Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *Lancet*. 377(9783):2085–92. doi:10.1016/S0140-6736(11)60551-5 PMID:21684381

Brotherton JML, Hawkes D, Sultana F, Malloy MJ, Machalek DA, Smith MA, et al. (2019). Age-specific HPV prevalence among 116,052 women in Australia's renewed cervical screening program: a new tool for monitoring vaccine impact. *Vaccine*. 37(3):412–6. doi:10.1016/j.vaccine.2018.11.075 PMID:30551987

Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. (2016). Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. [Erratum in: Lancet Glob Health. 2017 5(7):e662] *Lancet Glob Health*. 4(7):e453–63. doi:10.1016/S2214-109X(16)30099-7 PMID:27340003

Çakmak B, Köseoğlu DR (2014). Comparison of cervical cytological screening results between postmenopausal and elderly women. *Turk Patoloji Derg*. 30(1):38–42. doi:10.5146/tjpath.2014.01163 PMID:24448705

Canadian Task Force on Preventive Health Care (2013). Recommendations on screening for cervical cancer. *CMAJ*. 185(1):35–45. doi:10.1503/cmaj.121505 PMID:23297138

Cancer Council Australia Cervical Cancer Screening Guidelines Working Party (2020). National Cervical Screening Program: guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding. Available from: https://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening.

Carozzi FM, Ocello C, Burroni E, Faust H, Zappa M, Paci E, et al. (2016). Effectiveness of HPV vaccination in women reaching screening age in Italy. *J Clin Virol*. 84:74–81. doi:10.1016/j.jcv.2016.09.011 PMID:27728850

Carriero C, Fascilla FD, Cramarossa P, Lepera A, Bettocchi S, Vimercati A (2018). Colpocytological abnormalities in HIV infected and uninfected pregnant women: prevalence, persistence and progression. *J Obstet Gynaecol*. 38(4):526–31. doi:10.1080/01443615.2017.1373082 PMID:29390909

Castañón A, Landy R, Cuzick J, Sasieni P (2014). Cervical screening at age 50–64 years and the risk of cervical cancer at age 65 years and older: population-based case control study. *PLoS Med*. 11(1):e1001585. doi:10.1371/journal.pmed.1001585 PMID:24453946

Castle PE, Xie X, Xue X, Poitras NE, Lorey TS, Kinney WK, et al. (2019). Impact of human papillomavirus vaccination on the clinical meaning of cervical screening results. *Prev Med*. 118:44–50. doi:10.1016/j.ypmed.2018.10.001 PMID:30316878

CDC (1992). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. 41(RR-17):1–19. PMID:1361652

Chamot E, Kristensen S, Stringer JSA, Mwanahamuntu MH (2010). Are treatments for cervical precancerous lesions in less-developed countries safe enough to promote scaling-up of cervical screening programs? A systematic review. *BMC Womens Health*. 10(1):11. doi:10.1186/1472-6874-10-11 PMID:20359354

Cherniak W, Tyler N, Arora K, Lapidos-Salaiz I, Sczudlo E, Lin A, et al. (2019). From potential to practice: how accelerating access to HPV tests and screen and treat programmes can help eliminate cervical cancer. *Fam Med Community Health*. 7(4):e000182. doi:10.1136/fmch-2019-000182 PMID:32148728

Cheung LC, Egemen D, Chen X, Katki HA, Demarco M, Wiser AL, et al. (2020). 2019 ASCCP risk-based management consensus guidelines: methods for risk estimation, recommended management, and validation.

J Low Genit Tract Dis. 24(2):90–101. doi:10.1097/LGT.0000000000000528 PMID:32243306

Chibwesha CJ, Frett B, Katundu K, Bateman AC, Shibemba A, Kapambwe S, et al. (2016). Clinical performance validation of 4 point-of-care cervical cancer screening tests in HIV-infected women in Zambia. *J Low Genit Tract Dis*. 20(3):218–23. doi:10.1097/LGT.0000000000000206 PMID:27030883

Chigbu CO, Onyebuchi AK, Nnakenyi EF, Egbuji CC (2017). Impact of visual inspection with acetic acid plus cryotherapy "see and treat" approach on the reduction of the population burden of cervical preinvasive lesions in southeast Nigeria. *Niger J Clin Pract*. 20(2):239–43. doi:10.4103/1119-3077.187315 PMID:28091444

Chin-Hong PV (2016). Human papillomavirus in kidney transplant recipients. *Semin Nephrol*. 36(5):397–404. doi:10.1016/j.semnephrol.2016.05.016 PMID:27772624

Cholli P, Bradford L, Manga S, Nulah K, Kiyang E, Manjuh F, et al. (2018). Screening for cervical cancer among HIV-positive and HIV-negative women in Cameroon using simultaneous co-testing with *care*HPV DNA testing and visual inspection enhanced by digital cervicography: findings of initial screening and one-year follow-up. *Gynecol Oncol*. 148(1):118–25. doi:10.1016/j.ygyno.2017.11.002 PMID:29153541

Chung MH, McKenzie KP, De Vuyst H, Richardson BA, Rana F, Pamnani R, et al. (2013). Comparing Papanicolau smear, visual inspection with acetic acid and human papillomavirus cervical cancer screening methods among HIV-positive women by immune status and antiretroviral therapy. *AIDS*. 27(18):2909–19. doi:10.1097/01.aids.0000432472.92120.1b PMID:23842133

Clarke MA, Unger ER, Zuna R, Nelson E, Darragh TM, Cremer M, et al. (2020). A systematic review of tests for postcolposcopy and posttreatment surveillance. *J Low Genit Tract Dis*. 24(2):148–56. doi:10.1097/LGT.0000000000000526 PMID:32243310

Clifford GM, Gonçalves MAG, Franceschi S; HPV and HIV Study Group (2006). Human papillomavirus types among women infected with HIV: a meta-analysis. *AIDS*. 20(18):2337–44. doi:10.1097/01.aids.0000253361.63578.14 PMID:17117020

Cohn JA, Gagnon S, Spence MR, Harrison DD, Kluzak TR, Langenberg P, et al.; Cervical Disease Study Group of the American Foundation for AIDS Research Community Based Clinical Trials Network (2001). The role of human papillomavirus deoxyribonucleic acid assay and repeated cervical cytologic examination in the detection of cervical intraepithelial neoplasia among human immunodeficiency virus-infected women. *Am J Obstet Gynecol*. 184(3):322–30. doi:10.1067/mob.2001.109938 PMID:11228481

Costa S, Venturoli S, Negri G, Sideri M, Preti M, Pesaresi M, et al. (2012). Factors predicting the outcome of conservatively treated adenocarcinoma in situ of the uterine cervix: an analysis of 166 cases. *Gynecol Oncol*. 124(3):490–5. doi:10.1016/j.ygyno.2011.11.039 PMID:22188786

Cruickshank ME, Pan J, Cotton SC, Kavanagh K, Robertson C, Cuschieri K, et al. (2017). Reduction in colposcopy workload and associated clinical activity following human papillomavirus (HPV) catch-up vaccination programme in Scotland: an ecological study. *BJOG*. 124(9):1386–93. doi:10.1111/1471-0528.14562 PMID:28102928

Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al.; US Preventive Services Task Force (2018). Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 320(7):674–86. doi:10.1001/jama.2018.10897 PMID:30140884

Darlin L, Borgfeldt C, Widén E, Kannisto P (2014). Elderly women above screening age diagnosed with cervical cancer have a worse prognosis. *Anticancer Res*. 34(9):5147–51. PMID:25202106

Davis M, Perkins R, Cain J, Feldman S (2016). Cervical cancer screening and the immunosuppressed patient: the issues in screening high-risk populations. *Curr Obstet Gynecol Rep*. 5(4):307–17. doi:10.1007/s13669-016-0180-0

De Vuyst H, Lillo F, Broutet N, Smith JS (2008). HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *Eur J Cancer Prev*. 17(6):545–54. doi:10.1097/CEJ.0b013e3282f75ea1 PMID:18941376

Demarco M, Egemen D, Raine-Bennett TR, Cheung LC, Befano B, Poitras NE, et al. (2020). A study of partial human papillomavirus genotyping in support of the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis*. 24(2):144–7. doi:10.1097/LGT.0000000000000530 PMID:32243309

Denny L, de Sanjose S, Mutebi M, Anderson BO, Kim J, Jeronimo J, et al. (2017). Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. *Lancet*. 389(10071):861–70. doi:10.1016/S0140-6736(16)31795-0 PMID:27814963

Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright TC Jr (2005). Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA*. 294(17):2173–81. doi:10.1001/jama.294.17.2173 PMID:16264158

Denslow SA, Rositch AF, Firnhaber C, Ting J, Smith JS (2014). Incidence and progression of cervical lesions in women with HIV: a systematic global review. *Int J STD AIDS*. 25(3):163–77. doi:10.1177/0956462413491735 PMID:24216030

Díaz del Arco C, Jiménez Ayala B, García D, Sanabria C, Fernández Aceñero MJ (2019). Distribution of cervical lesions in young and older women. *Diagn Cytopathol*. 47(7):659–64. doi:10.1002/dc.24163 PMID:31184808

Dolman L, Sauvaget C, Muwonge R, Sankaranarayanan R (2014). Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review. *BJOG*. 121(8):929–42. doi:10.1111/1471-0528.12655 PMID:24597779

Dowling EC, Klabunde C, Patnick J, Ballard-Barbash R; International Cancer Screening Network (ICSN) (2010). Breast and cervical cancer screening programme implementation in 16 countries. *J Med Screen*. 17(3):139–46. doi:10.1258/jms.2010.010033 PMID:20956724

Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, Efstathiou JA, Grover S, Chiyapo S, et al. (2016). HIV infection and survival among women with cervical cancer. *J Clin Oncol*. 34(31):3749–57. doi:10.1200/JCO.2016.67.9613 PMID:27573661

Dube Mandishora RS, Christiansen IK, Chin'ombe N, Duri K, Ngara B, Rounge TB, et al. (2017). Genotypic diversity of anogenital human papillomavirus in women attending cervical cancer screening in Harare, Zimbabwe. *J Med Virol*. 89(9):1671–7. doi:10.1002/jmv.24825 PMID:28390142

Egemen D, Cheung LC, Chen X, Demarco M, Perkins RB, Kinney W, et al. (2020). Risk estimates supporting the 2019 ASCCP risk-based management consensus guidelines. *J Low Genit Tract Dis*. 24(2):132–43. doi:10.1097/LGT.0000000000000529 PMID:32243308

Elliott T, Kohler RE, Monare B, Moshashane N, Ramontshonyana K, Muthoga C, et al. (2019). Performance of vaginal self-sampling for human papillomavirus testing among women living with HIV in Botswana. *Int J STD AIDS*. 30(12):1169–76. doi:10.1177/0956462419868618 PMID:31558129

Ermel AC, Fife KH (2016). Human papillomavirus DNA detection in older women – implications for cancer screening and prevention. *J Infect Dis*. 214(5):657–8. doi:10.1093/infdis/jiw075 PMID:27009603

Ezechi OC, Odberg Petterson K, Gbajabiamila TA, Idigbe IE, Gab-Okafor CV, Okolo CA, et al. (2016). Evaluation of direct visual inspection of the cervix in detecting cytology diagnosed squamous intraepithelial lesion in women of known HIV status. a randomized trial (CANHIV study). *Afr J Reprod Health*. 20(4):77–88. doi:10.29063/ajrh2016/v20i4.8 PMID:29566322

Firnhaber C, Mayisela N, Mao L, Williams S, Swarts A, Faesen M, et al. (2013). Validation of cervical cancer screening methods in HIV positive women from Johannesburg South Africa. *PLoS One*. 8(1):e53494. doi:10.1371/journal.pone.0053494 PMID:23326441

Fontham ETH, Wolf AMD, Church TR, Etzioni R, Flowers CR, Herzig A, et al. (2020). Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 70(5):321–46. doi:10.3322/caac.21628 PMID:32729638

Franco EL, Cuzick J, Hildesheim A, de Sanjosé S (2006). Chapter 20: issues in planning cervical cancer screening in the era of HPV vaccination. *Vaccine*. 24(Suppl 3):S171–7. doi:10.1016/j.vaccine.2006.05.061 PMID:16844268

Franco EL, Tsu V, Herrero R, Lazcano-Ponce E, Hildesheim A, Muñoz N, et al. (2008). Integration of human papillomavirus vaccination and cervical cancer screening in Latin America and the Caribbean. *Vaccine*. 26(Suppl 11):L88–95. doi:10.1016/j.vaccine.2008.05.026 PMID:18945406

Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP (2007). Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol*. 8(11):985–93. doi:10.1016/S1470-2045(07)70283-8 PMID:17928267

Gichangi PB, Bwayo J, Estambale B, De Vuyst H, Ojwang S, Rogo K, et al. (2003). Impact of HIV infection on invasive cervical cancer in Kenyan women. *AIDS*. 17(13):1963–8. doi:10.1097/00002030-200309050-00015 PMID:12960829

Giorgi Rossi P, Carozzi F, Federici A, Ronco G, Zappa M, Franceschi S, et al.; Italian Screening in HPV vaccinated girls Consensus Conference group (2017). Cervical cancer screening in women vaccinated against human papillomavirus infection: recommendations from a consensus conference. *Prev Med*. 98:21–30. doi:10.1016/j.ypmed.2016.11.020 PMID:27894910

Giorgi-Rossi P, Franceschi S, Ronco G (2012). HPV prevalence and accuracy of HPV testing to detect high-grade cervical intraepithelial neoplasia. *Int J Cancer*. 130(6):1387–94. doi:10.1002/ijc.26147 PMID:21520039

Grainge MJ, Seth R, Guo L, Neal KR, Coupland C, Vryenhoef P, et al. (2005). Cervical human papillomavirus screening among older women. *Emerg Infect Dis*. 11(11):1680–5. doi:10.3201/eid1111.050575 PMID:16318718

Gravitt PE, Landy R, Schiffman M (2018). How confident can we be in the current guidelines for exiting cervical screening? *Prev Med*. 114:188–92. doi:10.1016/j.ypmed.2018.07.005 PMID:29981791

Greene SA, De Vuyst H, John-Stewart GC, Richardson BA, McGrath CJ, Marson KG, et al. (2019). Effect of cryotherapy vs loop electrosurgical excision procedure on cervical disease recurrence among women with HIV and high-grade cervical lesions in Kenya: a randomized clinical trial. *JAMA*. 322(16):1570–9. doi:10.1001/jama.2019.14969 PMID:31638680

Guo F, Cofie LE, Berenson AB (2018). Cervical cancer incidence in young US females after human papillomavirus vaccine introduction. *Am J Prev Med*. 55(2):197–204. doi:10.1016/j.amepre.2018.03.013 PMID:29859731

Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al.; GlaxoSmithKline HPV Vaccine Study Group (2004). Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human

papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*. 364(9447):1757–65. doi:10.1016/S0140-6736(04)17398-4 PMID:15541448

Holcomb K, Maiman M, Dimaio T, Gates J (1998). Rapid progression to invasive cervix cancer in a woman infected with the human immunodeficiency virus. *Obstet Gynecol*. 91(5 Pt 2):848–50. doi:10.1016/S0029-7844(97)00607-8 PMID:9572187

Huchko MJ, Sneden J, Leslie HH, Abdulrahim N, Maloba M, Bukusi E, et al. (2014). A comparison of two visual inspection methods for cervical cancer screening among HIV-infected women in Kenya. *Bull World Health Organ*. 92(3):195–203. doi:10.2471/BLT.13.122051 PMID:24700979

Huchko MJ, Sneden J, Zakaras JM, Smith-McCune K, Sawaya G, Maloba M, et al. (2015). A randomized trial comparing the diagnostic accuracy of visual inspection with acetic acid to visual inspection with Lugol's iodine for cervical cancer screening in HIV-infected women. *PLoS One*. 10(4):e0118568. doi:10.1371/journal.pone.0118568 PMID:25849627

IARC (2005). Cervix cancer screening. *IARC Handb Cancer Prev*. 10:1–302. Available from: https://publications.iarc.fr/380.

INCa (2019). Surveillance post-thérapeutique des lésions précancéreuses du col de l'utérus/thésaurus. Boulogne-Billancourt, France: French National Cancer Institute (INCa). [in French] Available from: https://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Thesaurus-Surveillance-post-therapeutique-des-lesions-precancereuses-du-col-de-l-uterus.

Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U (2013). Screening of cervical neoplasia in HIV-infected women in India. *AIDS*. 27(4):607–15. doi:10.1097/QAD.0b013e32835b1041 PMID:23079814

Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al.; Broad Spectrum HPV Vaccine Study (2015). A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 372(8):711–23. doi:10.1056/NEJMoa1405044 PMID:25693011

Kalliala I, Anttila A, Pukkala E, Nieminen P (2005). Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. *BMJ*. 331(7526):1183–5. doi:10.1136/bmj.38663.459039.7C PMID:16293840

Kalliala I, Athanasiou A, Veroniki AA, Salanti G, Efthimiou O, Raftis N, et al. (2020). Incidence and mortality from cervical cancer and other malignancies after treatment of cervical intraepithelial neoplasia: a systematic review and meta-analysis of the literature. *Ann Oncol*. 31(2):213–27. doi:10.1016/j.annonc.2019.11.004 PMID:31959338

Kamineni A, Weinmann S, Shy KK, Glass AG, Weiss NS (2013). Efficacy of screening in preventing cervical cancer among older women. *Cancer Causes Control*. 24(9):1653–60. doi:10.1007/s10552-013-0239-4 PMID:23744043

Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T, et al. (2013). Five-year risk of recurrence after treatment of CIN 2, CIN 3, or AIS: performance of HPV and Pap cotesting in posttreatment management. *J Low Genit Tract Dis*. 17(5 Suppl 1):S78–84. doi:10.1097/LGT.0b013e31828543c5 PMID:23519309

Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, et al. (2017). Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. *Lancet Infect Dis*. 17(12):1293–302. doi:10.1016/S1473-3099(17)30468-1 PMID:28965955

Kelly H, Weiss HA, Benavente Y, de Sanjose S, Mayaud P, Qiao Y, et al.; ART and HPV Review Group (2018). Association of antiretroviral therapy with high-risk human papillomavirus, cervical intraepithelial neoplasia, and invasive cervical cancer in women living with HIV: a systematic review and meta-analysis. *Lancet HIV*. 5(1):e45–58. doi:10.1016/S2352-3018(17)30149-2 PMID:29107561

Kim SC, Feldman S, Moscicki AB (2018). Risk of human papillomavirus infection in women with rheumatic disease: cervical cancer screening and prevention. *Rheumatology (Oxford)*. 57(Suppl 5):v26–33. doi:10.1093/rheumatology/kex523 PMID:30137592

Kim JJ, Burger EA, Sy S, Campos NG (2017). Optimal cervical cancer screening in women vaccinated against human papillomavirus. *J Natl Cancer Inst*. 109(2):djw216. doi:10.1093/jnci/djw216 PMID:27754955

Kitchener H, Nelson L, Adams J, Mesher D, Sasieni P, Cubie H, et al. (2007). Colposcopy is not necessary to assess the risk to the cervix in HIV-positive women: an international cohort study of cervical pathology in HIV-1 positive women. *Int J Cancer*. 121(11):2484–91. doi:10.1002/ijc.22947 PMID:17683070

Kremer WW, van Zummeren M, Breytenbach E, Richter KL, Steenbergen RDM, Meijer CJLM, et al. (2019). The use of molecular markers for cervical screening of women living with HIV in South Africa. *AIDS*. 33(13):2035–42. doi:10.1097/QAD.0000000000002325 PMID:31385866

Kuhn L, Saidu R, Boa R, Tergas A, Moodley J, Persing D, et al. (2020). Clinical evaluation of modifications to a human papillomavirus assay to optimise its utility for cervical cancer screening in low-resource settings: a diagnostic accuracy study. *Lancet Glob Health*. 8(2):e296–304. doi:10.1016/S2214-109X(19)30527-3 PMID:31981559

Kuhn L, Wang C, Tsai WY, Wright TC, Denny L (2010). Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women. *AIDS*. 24(16):2553–61. doi:10.1097/QAD.0b013e32833e163e PMID:20706107

Kulasingam SL, Havrilesky LJ, Ghebre R, Myers ER (2013). Screening for cervical cancer: a modeling study for the US Preventive Services Task Force. *J Low Genit Tract Dis*. 17(2):193–202. doi:10.1097/LGT.0b013e3182616241 PMID:23519288

Landy R, Schiffman M, Sasieni PD, Cheung LC, Katki HA, Rydzak G, et al. (2020). Absolute risks of cervical precancer among women who fulfill exiting guidelines based on HPV and cytology cotesting. *Int J Cancer*. 146(3):617–26. doi:10.1002/ijc.32268 PMID:30861114

Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. (2020). HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med*. 383(14):1340–8. doi:10.1056/NEJMoa1917338 PMID:32997908

Liu G, Sharma M, Tan N, Barnabas RV (2018). HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. *AIDS*. 32(6):795–808. doi:10.1097/QAD.0000000000001765 PMID:29369827

Lönnberg S, Nieminen P, Luostarinen T, Anttila A (2013). Mortality audit of the Finnish cervical cancer screening program. *Int J Cancer*. 132(9):2134–40. doi:10.1002/ijc.27844 PMID:22987437

Looker KJ, Rönn MM, Brock PM, Brisson M, Drolet M, Mayaud P, et al. (2018). Evidence of synergistic relationships between HIV and human papillomavirus (HPV): systematic reviews and meta-analyses of longitudinal studies of HPV acquisition and clearance by HIV status, and of HIV acquisition by HPV status. *J Int AIDS Soc*. 21(6):e25110. doi:10.1002/jia2.25110 PMID:29873885

Luckett R, Mogowa N, Li HJ, Erlinger A, Hacker MR, Esselen K, et al. (2019). Performance of two-stage cervical cancer screening with primary high-risk human papillomavirus testing in women living with human immunodeficiency virus. *Obstet Gynecol*. 134(4):840–9. doi:10.1097/AOG.0000000000003496 PMID:31503167

Lynge E, Thamsborg L, Larsen LG, Christensen J, Johansen T, Hariri J, et al. (2020). Prevalence of high-risk human papillomavirus after HPV-vaccination in Denmark. *Int J Cancer*. 147(12):3446–52. doi:10.1002/ijc.33157 PMID:32542644

Mabeya H, Khozaim K, Liu T, Orango O, Chumba D, Pisharodi L, et al. (2012). Comparison of conventional cervical cytology versus visual inspection with acetic acid among human immunodeficiency virus-infected women in western Kenya. *J Low Genit Tract Dis*. 16(2):92–7. doi:10.1097/LGT.0b013e3182320f0c PMID:22126834

Maiman M, Fruchter RG, Sedlis A, Feldman J, Chen P, Burk RD, et al. (1998). Prevalence, risk factors, and accuracy of cytologic screening for cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Gynecol Oncol*. 68(3):233–9. doi:10.1006/gyno.1998.4938 PMID:9570972

Malagón T, Kulasingam S, Mayrand MH, Ogilvie G, Smith L, Bouchard C, et al. (2018). Age at last screening and remaining lifetime risk of cervical cancer in older, unvaccinated women: a modelling study. *Lancet Oncol*. 19(12):1569–78. doi:10.1016/S1470-2045(18)30536-9 PMID:30392810

Martin CE, Tergas AI, Wysong M, Reinsel M, Estep D, Varallo J (2014). Evaluation of a single-visit approach to cervical cancer screening and treatment in Guyana: feasibility, effectiveness and lessons learned. *J Obstet Gynaecol Res*. 40(6):1707–16. doi:10.1111/jog.12366 PMID:24888938

Massad LS, Hessol NA, Darragh TM, Minkoff H, Colie C, Wright RL, et al. (2017). Cervical cancer incidence after up to 20 years of observation among women with HIV. *Int J Cancer*. 141(8):1561–5. doi:10.1002/ijc.30866 PMID:28670714

Maza M, Figueroa R, Laskow B, Juárez A, Alfaro K, Alonzo TA, et al. (2018). Effects of maintenance on quality of performance of cryotherapy devices for treatment of precancerous cervical lesions. *J Low Genit Tract Dis*. 22(1):47–51. doi:10.1097/LGT.0000000000000359 PMID:29271857

Mbulawa ZZA, Coetzee D, Williamson AL (2015). Human papillomavirus prevalence in South African women and men according to age and human immunodeficiency virus status. *BMC Infect Dis*. 15(1):459–459. doi:10.1186/s12879-015-1181-8 PMID:26502723

Mbulawa ZZA, Wilkin TJ, Goeieman B, Swarts A, Williams S, Levin S, et al. (2016). Xpert human papillomavirus test is a promising cervical cancer screening test for HIV-seropositive women. *Papillomavirus Res*. 2:56–60. doi:10.1016/j.pvr.2016.02.004 PMID:29074186

McGregor S, Saulo D, Brotherton JML, Liu B, Phillips S, Skinner SR, et al. (2018). Decline in prevalence of human papillomavirus infection following vaccination among Australian Indigenous women, a population at higher risk of cervical cancer: the VIP-I study. *Vaccine*. 36(29):4311–6. doi:10.1016/j.vaccine.2018.05.104 PMID:29880245

Ministry of Health New Zealand (2020). Clinical practice guidelines for cervical screening in New Zealand 2020. Wellington, New Zealand: Ministry of Health. Available from: https://www.nsu.govt.nz/system/files/resources/final_ncsp-guidelines-for-cervical-screening-new-zealand-5_june_2020.pdf.

Moodley M, Moodley J, Kleinschmidt I (2001). Invasive cervical cancer and human immunodeficiency virus (HIV) infection: a South African perspective. *Int*

J Gynecol Cancer. 11(3):194–7. doi:10.1046/j.1525-1438.2001.01022.x PMID:11437924

Moscicki AB, Ellenberg JH, Farhat S, Xu J (2004). Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. *J Infect Dis.* 190(1):37–45. doi:10.1086/421467 PMID:15195241

Moscicki AB, Flowers L, Huchko MJ, Long ME, MacLaughlin KL, Murphy J, et al. (2019). Guidelines for cervical cancer screening in immunosuppressed women without HIV infection. *J Low Genit Tract Dis.* 23(2):87–101. doi:10.1097/LGT.0000000000000468 PMID:30907775

Moyer VA; U.S. Preventive Services Task Force (2012). Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 156(12):880–91. doi:10.7326/0003-4819-156-12-201206190-00424 PMID:22711081

Munro A, Gillespie C, Cotton S, Busby-Earle C, Kavanagh K, Cuschieri K, et al. (2017). The impact of human papillomavirus type on colposcopy performance in women offered HPV immunisation in a catch-up vaccine programme: a two-centre observational study. *BJOG.* 124(9):1394–401. doi:10.1111/1471-0528.14563 PMID:28102931

National Department of Health South Africa (2020). Cervical cancer prevention and control policy, South Africa, 2019. Pretoria, South Africa: National Department of Health. Available from: https://cansa.org.za/files/2021/03/cervical_cancer_prevention_and_control_policy.pdf.

Ndizeye Z, Menon S, Van Geertruyden JP, Sauvaget C, Jacquemyn Y, Bogers JP, et al. (2019). Performance of OncoE6™ Cervical Test in detecting cervical precancer lesions in HIV-positive women attending an HIV clinic in Bujumbura, Burundi: a cross-sectional study. *BMJ Open.* 9(9):e029088. doi:10.1136/bmjopen-2019-029088 PMID:31494606

Ngou J, Gilham C, Omar T, Goumbri-Lompo O, Doutre S, Michelow P, et al. (2015). Comparison of analytical and clinical performances of the Digene HC2 HPV DNA assay and the INNO-LiPA HPV genotyping assay for detecting high-risk HPV infection and cervical neoplasia among HIV-positive African women. *J Acquir Immune Defic Syndr.* 68(2):162–8. doi:10.1097/QAI.0000000000000428 PMID:25394189

Ngou J, Magooa MP, Gilham C, Djigma F, Didelot MN, Kelly H, et al.; HARP Study Group (2013). Comparison of *care*HPV and Hybrid Capture 2 assays for detection of high-risk human papillomavirus DNA in cervical samples from HIV-1-infected African women. *J Clin Microbiol.* 51(12):4240–2. doi:10.1128/JCM.02144-13 PMID:24108613

Niccolai LM, Meek JI, Brackney M, Hadler JL, Sosa LE, Weinberger DM (2017). Declines in human papillomavirus (HPV)-associated high-grade cervical lesions after introduction of HPV vaccines in Connecticut, United States, 2008–2015. *Clin Infect Dis.* 65(6):884–9. doi:10.1093/cid/cix455 PMID:28520854

NordScreen (2017). Cancer screening fact sheet: Sweden – cervix – 2017. Stockholm, Sweden: Department of Laboratory Medicine, Karolinska Institutet. Available from: https://nordscreen.org/wp-content/uploads/2017/05/Cervix-Fact-Sheet-Sweden-2017.pdf.

Obiri-Yeboah D, Adu-Sarkodie Y, Djigma F, Hayfron-Benjamin A, Abdul L, Simpore J, et al. (2017). Self-collected vaginal sampling for the detection of genital human papillomavirus (HPV) using *care*HPV among Ghanaian women. *BMC Womens Health.* 17(1):86. doi:10.1186/s12905-017-0448-1 PMID:28950841

Palefsky JM (2017). Human papillomavirus-associated anal and cervical cancers in HIV-infected individuals: incidence and prevention in the antiretroviral therapy era. *Curr Opin HIV AIDS.* 12(1):26–30. doi:10.1097/COH.0000000000000336 PMID:27828801

Palmer TJ, McFadden M, Pollock KGJ, Kavanagh K, Cuschieri K, Cruickshank M, et al. (2016). HPV immunisation and cervical screening – confirmation of changed performance of cytology as a screening test in immunised women: a retrospective population-based cohort study. *Br J Cancer.* 114(5):582–9. doi:10.1038/bjc.2015.474 PMID:26931370

Pankakoski M, Anttila A, Sarkeala T, Heinävaara S (2019). Effectiveness of cervical cancer screening at age 65 – a register-based cohort study. *PLoS One.* 14(3):e0214486. doi:10.1371/journal.pone.0214486 PMID:30913262

Pankakoski M, Heinävaara S, Anttila A, Sarkeala T (2020). Differences in cervical test coverage by age, socioeconomic status, ethnic origin and municipality type – a nationwide register-based study. *Prev Med.* 139:106219. doi:10.1016/j.ypmed.2020.106219 PMID:32693176

Parham GP, Mwanahamuntu MH, Sahasrabuddhe VV, Westfall AO, King KE, Chibwesha C, et al. (2010). Implementation of cervical cancer prevention services for HIV-infected women in Zambia: measuring program effectiveness. *HIV Ther.* 4(6):713–22. doi:10.2217/hiv.10.52 PMID:25419240

Pedersen K, Burger EA, Nygård M, Kristiansen IS, Kim JJ (2018). Adapting cervical cancer screening for women vaccinated against human papillomavirus infections: the value of stratifying guidelines. *Eur J Cancer.* 91:68–75. doi:10.1016/j.ejca.2017.12.018 PMID:29335156

Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al.; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee (2020). 2019 ASCCP Risk-Based Management Consensus Guidelines for abnormal cervical cancer screening tests and cancer precursors. [Erratum in: J Low Genit Tract Dis. 2021 25(4):330–1] *J Low Genit Tract Dis.* 24(2):102–31. doi:10.1097/LGT.0000000000000525 PMID:32243307

Petignat P, Hankins C, Walmsley S, Money D, Provencher D, Pourreaux K, et al.; Canadian Women's HIV Study Group (2005). Self-sampling is associated with increased detection of human papillomavirus DNA in the genital tract of HIV-seropositive women. *Clin Infect Dis*. 41(4):527–34. doi:10.1086/432059 PMID:16028163

Phanuphak N, Teeraananchai S, Hansudewechakul R, Gatechompol S, Chokephaibulkit K, Dang HLD, et al. (2020). Incidence and persistence of high-risk anogenital human papillomavirus infection among female youth with and without perinatally acquired HIV infection: a 3-year observational cohort study. *Clin Infect Dis*. 71(8):e270–80. doi:10.1093/cid/ciz1143 PMID:31768522

Pinder LF, Parham GP, Basu P, Muwonge R, Lucas E, Nyambe N, et al. (2020). Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial. *Lancet Oncol*. 21(1):175–84. doi:10.1016/S1470-2045(19)30635-7 PMID:31734069

Pollock KGJ, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, et al. (2014). Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. *Br J Cancer*. 111(9):1824–30. doi:10.1038/bjc.2014.479 PMID:25180766

Popadiuk C, Decker K, Gauvreau C (2019). Starting cervical cancer screening at 25 years of age: the time has come. *CMAJ*. 191(1):E1–2. doi:10.1503/cmaj.181312 PMID:30617226

Powell SE, Hariri S, Steinau M, Bauer HM, Bennett NM, Bloch KC, et al. (2012). Impact of human papillomavirus (HPV) vaccination on HPV 16/18-related prevalence in precancerous cervical lesions. *Vaccine*. 31(1):109–13. doi:10.1016/j.vaccine.2012.10.092 PMID:23137842

Public Health England (2016). NHS Cervical Screening Programme: colposcopy and programme management. 3rd ed. London, UK: Public Health England. Available from: https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management.

Public Health England (2020). NHS cervical screening (CSP) programme. London, UK: Public Health England. Available from: https://www.gov.uk/health-and-social-care/population-screening-programmes-cervical.

Randall TC, Sauvaget C, Muwonge R, Trimble EL, Jeronimo J (2019). Worthy of further consideration: an updated meta-analysis to address the feasibility, acceptability, safety and efficacy of thermal ablation in the treatment of cervical cancer precursor lesions. *Prev Med*. 118:81–91. doi:10.1016/j.ypmed.2018.10.006 PMID:30342109

Rellihan MA, Dooley DP, Burke TW, Berkland ME, Longfield RN (1990). Rapidly progressing cervical cancer in a patient with human immunodeficiency virus infection. *Gynecol Oncol*. 36(3):435–8. doi:10.1016/0090-8258(90)90159-I PMID:2318457

RIVM (2020). Cervical cancer screening programme. Bilthoven, Netherlands: National Institute for Public Health and the Environment (RIVM). Available from: https://www.rivm.nl/en/cervical-cancer-screening-programme.

Rohner E, Bütikofer L, Schmidlin K, Sengayi M, Maskew M, Giddy J, et al. (2020). Cervical cancer risk in women living with HIV across four continents: a multicohort study. *Int J Cancer*. 146(3):601–9. doi:10.1002/ijc.32260 PMID:31215037

Rohner E, Sengayi M, Goeieman B, Michelow P, Firnhaber C, Maskew M, et al. (2017). Cervical cancer risk and impact of Pap-based screening in HIV-positive women on antiretroviral therapy in Johannesburg, South Africa. *Int J Cancer*. 141(3):488–96. doi:10.1002/ijc.30749 PMID:28440019

Roser M, Ritchie H (2019). HIV/AIDS. Published online at OurWorldInData.org. Available from: https://ourworldindata.org/hiv-aids.

Rositch AF, Burke AE, Viscidi RP, Silver MI, Chang K, Gravitt PE (2012). Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women. *Cancer Res*. 72(23):6183–90. doi:10.1158/0008-5472.CAN-12-2635 PMID:23019223

Rositch AF, Silver MI, Gravitt PE (2014). Cervical cancer screening in older women: new evidence and knowledge gaps. *PLoS Med*. 11(1):e1001586. doi:10.1371/journal.pmed.1001586 PMID:24453947

Rudd P, Gorman D, Meja S, Mtonga P, Jere Y, Chidothe I, et al. (2017). Cervical cancer in southern Malawi: a prospective analysis of presentation, management, and outcomes. *Malawi Med J*. 29(2):124–9. doi:10.4314/mmj.v29i2.9 PMID:28955419

Saccucci P, Mastrone M, Are P, Pisani G, Provenza C (1996). Rapidly progressive squamous cell carcinoma of the cervix in a patient with acquired immunodeficiency syndrome: case report. *Eur J Gynaecol Oncol*. 17(4):306–8. PMID:8856313

Safaeian M, Kiddugavu M, Gravitt PE, Ssekasanvu J, Murokora D, Sklar M, et al. (2007). Comparability of self-collected vaginal swabs and physician-collected cervical swabs for detection of human papillomavirus infections in Rakai, Uganda. *Sex Transm Dis*. 34(7):429–36. doi:10.1097/01.olq.0000243623.67673.22 PMID:17075437

Sahasrabuddhe VV, Bhosale RA, Kavatkar AN, Nagwanshi CA, Joshi SN, Jenkins CA, et al. (2012). Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among

HIV-infected women in India. *Int J Cancer*. 130(1):234–40. doi:10.1002/ijc.25971 PMID:21387289

Sandoval M, Slavkovsky R, Bansil P, Jeronimo J, Lim J, Figueroa J, et al. (2019). Acceptability and safety of thermal ablation for the treatment of precancerous cervical lesions in Honduras. *Trop Med Int Health*. 24(12):1391–9. doi:10.1111/tmi.13315 PMID:31622526

Sankaranarayanan R, Rajkumar R, Esmy PO, Fayette JM, Shanthakumary S, Frappart L, et al. (2007). Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. *Br J Cancer*. 96:738–43. doi:10.1038/sj.bjc.6603633 PMID:17311015

Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, et al. (2016). Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. *Int J Gynaecol Obstet*. 132(3):266–71. doi:10.1016/j.ijgo.2015.07.026 PMID:26643302

Sasieni P, Adams J, Cuzick J (2003). Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer*. 89(1):88–93. doi:10.1038/sj.bjc.6600974 PMID:12838306

Sasieni P, Castanon A, Cuzick J (2009). Effectiveness of cervical screening with age: population-based case-control study of prospectively recorded data. *BMJ*. 339:b2968. doi:10.1136/bmj.b2968 PMID:19638651

Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al.; ACS-ASCCP-ASCP Cervical Cancer Guideline Committee (2012). American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin*. 62(3):147–72. doi:10.3322/caac.21139 PMID:22422631

Schiffman M, Doorbar J, Wentzensen N, de Sanjosé S, Fakhry C, Monk BJ, et al. (2016). Carcinogenic human papillomavirus infection. *Nat Rev Dis Primers*. 2(1):16086. doi:10.1038/nrdp.2016.86 PMID:27905473

Schiffman M, Wentzensen N, Perkins RB, Guido RS (2020). An introduction to the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis*. 24(2):87–9. doi:10.1097/LGT.0000000000000531 PMID:32243305

Segondy M, Kelly H, Magooa MP, Djigma F, Ngou J, Gilham C, et al.; HARP Study Group (2016). Performance of *care*HPV for detecting high-grade cervical intraepithelial neoplasia among women living with HIV-1 in Burkina Faso and South Africa: HARP study. *Br J Cancer*. 115(4):425–30. doi:10.1038/bjc.2016.207 PMID:27434037

Sigfrid L, Murphy G, Haldane V, Chuah FLH, Ong SE, Cervero-Liceras F, et al. (2017). Integrating cervical cancer with HIV healthcare services: a systematic review. *PLoS One*. 12(7):e0181156. doi:10.1371/journal.pone.0181156 PMID:28732037

Simms KT, Steinberg J, Caruana M, Smith MA, Lew JB, Soerjomataram I, et al. (2019). Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020–99: a modelling study. *Lancet Oncol*. 20(3):394–407. doi:10.1016/S1470-2045(18)30836-2 PMID:30795950

Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. (1997). Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet*. 349(9057):978–80. doi:10.1016/S0140-6736(96)08295-5 PMID:9100623

Soutter WP, Sasieni P, Panoskaltsis T (2006). Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *Int J Cancer*. 118(8):2048–55. doi:10.1002/ijc.21604 PMID:16284947

Starks D, Arriba LN, Enerson CL, Brainard J, Nagore N, Chiesa-Vottero A, et al. (2014). Mexican Cervical Cancer Screening Study II: 6-month and 2-year follow-up of HR-HPV women treated with cryotherapy in a low-resource setting. *J Low Genit Tract Dis*. 18(4):333–7. doi:10.1097/LGT.0000000000000029 PMID:24977628

Stelzle D, Tanaka LF, Lee KK, Ibrahim Khalil A, Baussano I, Shah ASV, et al. (2021). Estimates of the global burden of cervical cancer associated with HIV. *Lancet Glob Health*. 9(2):e161–9. doi:10.1016/S2214-109X(20)30459-9 PMID:33212031

Strander B, Andersson-Ellström A, Milsom I, Sparén P (2007). Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population-based cohort study. [Erratum in: BMJ. 2008 377:a1186] *BMJ*. 335(7629):1077. doi:10.1136/bmj.39363.471806.BE PMID:17959735

Sultana F, Winch K, Saville M, Brotherton JML (2019). Is the positive predictive value of high-grade cytology in predicting high-grade cervical disease falling due to HPV vaccination? *Int J Cancer*. 144(12):2964–71. doi:10.1002/ijc.32050 PMID:30536935

Swift BE, Wang L, Jembere N, Kupets R (2020). Risk of recurrence after treatment for cervical intraepithelial neoplasia 3 and adenocarcinoma in situ of the cervix: recurrence of CIN 3 and AIS of cervix. *J Low Genit Tract Dis*. 24(3):252–8. doi:10.1097/LGT.0000000000000542 PMID:32384365

Tchounga B, Boni SP, Koffi JJ, Horo AG, Tanon A, Messou E, et al. (2019). Cervical cancer screening uptake and correlates among HIV-infected women: a cross-sectional survey in Côte d'Ivoire, West Africa. *BMJ Open*. 9(8):e029882. doi:10.1136/bmjopen-2019-029882 PMID:31473620

Teoh D, Musa F, Salani R, Huh W, Jimenez E (2020). Diagnosis and management of adenocarcinoma in situ: a Society of Gynecologic Oncology evidence-based review and recommendations. *Obstet Gynecol*.

135(4):869–78. doi:10.1097/AOG.0000000000003761 PMID:32168211

Thamsborg LH, Napolitano G, Larsen LG, Lynge E (2018). Impact of HPV vaccination on outcome of cervical cytology screening in Denmark – a register-based cohort study. *Int J Cancer*. 143(7):1662–70. doi:10.1002/ijc.31568 PMID:29707775

Thay S, Goldstein A, Goldstein LS, Govind V, Lim K, Seang C (2019). Prospective cohort study examining cervical cancer screening methods in HIV-positive and HIV-negative Cambodian women: a comparison of human papilloma virus testing, visualization with acetic acid and digital colposcopy. *BMJ Open*. 9(2):e026887.doi:10.1136/bmjopen-2018-026887PMID:30804036

Thida M, Thin KM, Thein ZM, Sein YY, Nyunt T, Sanda (2015). Effectiveness, safety and acceptability of the method of visual inspection with acetic acid (VIA) and cryotherapy based single-visit approach to cervical cancer prevention (CCP) in Kungyangon Township, Yangon Region, Myanmar. *Myanmar Medical Journal*. 57(3):48–56.

Tran PL, Kenfack B, Tincho Foguem E, Viviano M, Temogne L, Tebeu PM, et al. (2017). Efficacy of thermoablation in treating cervical precancerous lesions in a low-resource setting. *Int J Womens Health*. 9:879–86. doi:10.2147/IJWH.S142911 PMID:29238232

Trejo MJ, Lishimpi K, Kalima M, Mwaba CK, Banda L, Chuba A, et al. (2020). Effects of HIV status on non-metastatic cervical cancer progression among patients in Lusaka, Zambia. *Int J Gynecol Cancer*. 30(5):613–8. doi:10.1136/ijgc-2019-000987 PMID:32200353

UNAIDS (2020). Global HIV and AIDS statistics – 2019 fact sheet. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS. Available from: https://aidsinfo.unaids.org/.

US Preventive Services Task Force (2018). Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 320(7):674–86. doi:10.1001/jama.2018.10897 PMID:30140884

van Aardt MC, Dreyer G, Pienaar HF, Karlsen F, Hovland S, Richter KL, et al. (2015). Unique human papillomavirus-type distribution in South African women with invasive cervical cancer and the effect of human immunodeficiency virus infection. *Int J Gynecol Cancer*. 25(5):919–25. doi:10.1097/IGC.0000000000000422 PMID:25950128

Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. (2005). Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*. 6(5):271–8. doi:10.1016/S1470-2045(05)70101-7 PMID:15863374

Viviano M, DeBeaudrap P, Tebeu PM, Fouogue JT, Vassilakos P, Petignat P (2017). A review of screening strategies for cervical cancer in human immunodeficiency virus-positive women in sub-Saharan Africa. *Int J Womens Health*. 9:69–79. doi:10.2147/IJWH.S103868 PMID:28203108

von Karsa L, Arbyn M, De Vuyst H, Dillner J, Dillner L, Franceschi S, et al. (2015). European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. *Papillomavirus Res*. 1:22–31. doi:10.1016/j.pvr.2015.06.006

Wentzensen N, Arbyn M, Berkhof J, Bower M, Canfell K, Einstein M, et al. (2017). Eurogin 2016 Roadmap: how HPV knowledge is changing screening practice. *Int J Cancer*. 140(10):2192–200. doi:10.1002/ijc.30579 PMID:28006858

WHO (2011). WHO guidelines: use of cryotherapy for cervical intraepithelial neoplasia. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/44776.

WHO (2014). Comprehensive cervical cancer control: a guide to essential practice. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/144785.

WHO (2015). Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/186275.

WHO (2019). WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/329299.

WHO (2021). WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/342365.

Womack SD, Chirenje ZM, Gaffikin L, Blumenthal PD, McGrath JA, Chipato T, et al. (2000). HPV-based cervical cancer screening in a population at high risk for HIV infection. *Int J Cancer*. 85(2):206–10. doi:10.1002/(SICI)1097-0215(20000115)85:2<206::AID-IJC10>3.0.CO;2-Q PMID:10629079

Zeferino LC, Bastos JB, do Vale DBAP, Zanine RM, de Melo YLMF, Primo WQSP, et al. (2018). Guidelines for HPV-DNA testing for cervical cancer screening in Brazil. *Rev Bras Ginecol Obstet*. 40(6):360–8. doi:10.1055/s-0038-1657754 PMID:29874685

Zhao XL, Liu ZH, Zhao S, Hu SY, Muwonge R, Duan XZ, et al. (2020). Efficacy of point-of-care thermal ablation among high-risk human papillomavirus positive women in China. *Int J Cancer*. 148(6):1419–27. doi:10.1002/ijc.33290 PMID:32895912