Recommendation 6

The expert panel suggests either a strategy of screen with an HPV test followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) or a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

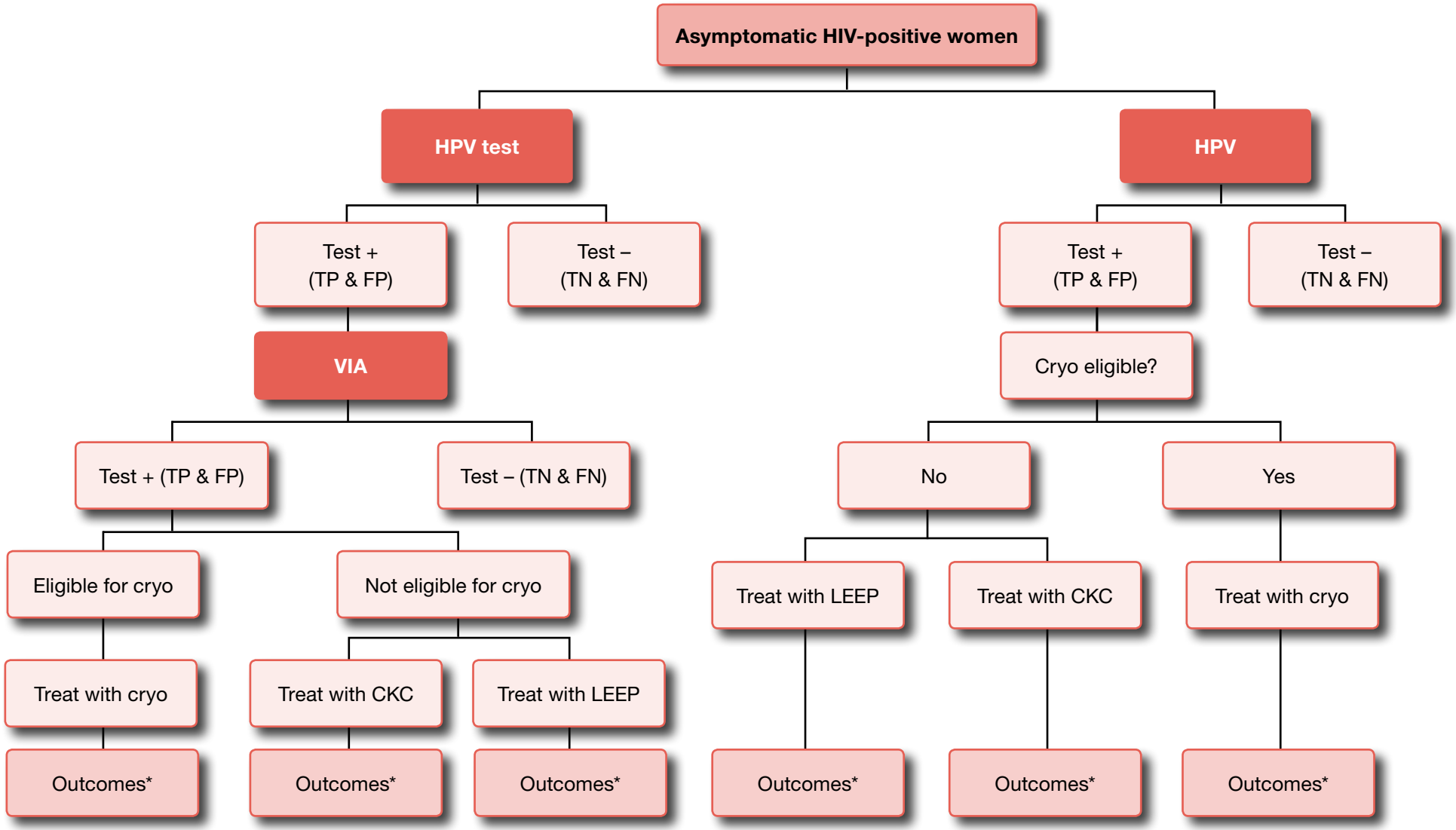
Remarks: The reductions in cancer and related mortality were greater with an HPV test used as a single screening test than with an HPV test followed by VIA, and this reduction was even greater in women of HIV-positive status. However, there may be overtreatment, and thus potentially greater harms with screen-and-treat when using an HPV test as a single test. There is also some uncertainty about the effects of an HPV test followed by VIA and how VIA performs after a positive HPV test because there was no direct evidence about this strategy. There is also the potential for additional resources that are required to refer women for VIA testing after a positive HPV test, the need for a second visit to perform VIA, and increased training to perform both tests. For these reasons, the recommendation is for either an HPV test followed by VIA or an HPV test only, and it is conditional. It is to be noted that benefits are more pronounced compared to 'harms' in women of HIV-positive status when using an HPV test only.

Evidence-to-recommendation table

Decision domain	Judgement	Summary of reason for judgement
Quality of evidence *Is there high- or moderate-quality evidence?*	Yes ☐ / No ☒	There is low-quality evidence for the diagnostic test accuracy of HPV test followed by VIA and compared to HPV test alone. There is low- to very-low-quality evidence for the effects of treatment and the natural progression of CIN from observational studies often with inconsistent results across studies. The link between test accuracy data and treatment effects is very uncertain.
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?*	Yes ☐ / No ☒	There may be fewer major harms with HPV test followed by VIA than with HPV test alone due to less overtreatment. There may also be slightly greater cancers detected with HPV test followed by VIA than with HPV test alone. However, there may be slightly greater CIN recurrence, cervical cancer, and related mortality with HPV test followed by VIA. In women of HIV-positive status, there were still fewer harms, less overtreatment and greater cancers detected at first-time screening. However, there was even greater CIN recurrence, cervical cancer and related mortality with HPV test followed by VIA in women of HIV-positive status than in women of unknown status.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ / No ☐	High value was placed on a screen-and-treat strategy versus no screening, since qualitative studies have shown that once women decide to be screened they find the screening tests and immediate treatment acceptable. High value was also placed on reducing overtreatment and resulting complications, and resource use.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☐ / No ☒	Greater resources may be required for HPV test followed by VIA due to adding on an additional test. However, there is less overtreatment (fewer treatments provided) and fewer complications requiring hospitalization.

Evidence for an HPV test followed by VIA compared to an HPV test to screen for CIN2+ in women of HIV-positive status

1. Flowchart of screen-and-treat strategies



* Outcomes are: mortality from cervical cancer, rate of cervical cancer detection, rate of CIN2+ detection, major bleeding, premature delivery, infertility, STI detection, major infections, and minor infections.

2. Evidence used for decision-making: HPV test followed by VIA compared to HIV

Diagnostic test accuracy (data based on women with unknown HIV status)

Pooled sensitivity HPV test	95% (95% CI: 84 to 98)	Pooled sensitivity VIA	69% (95% CI: 54 to 81)
Pooled specificity HPV test	84% (95% CI: 72 to 91)	Pooled specificity VIA	87% (95% CI: 79 to 92)

2.1 Diagnostic test accuracy (DTA) evidence profile: HPV test followed by VIA compared to HIV

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 10%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test followed by VIA	HPV test	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None[b]	Serious[c]	None	Undetected	⊕⊕⊕⊖ moderate	66	95 (84 to 98)	CRITICAL
TP absolute difference									29 fewer		
True negatives (patients without CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None[b]	Serious[c]	None[d]	Undetected	⊕⊕⊕⊖ moderate	881	756 (648 to 819)	CRITICAL
TN absolute difference									125 more		
False positives (patients incorrectly classified as having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None[b]	Serious[c]	None[d]	Undetected	⊕⊕⊕⊖ moderate	19	144 (81 to 252)	CRITICAL
FP absolute difference									125 fewer		
False negatives (patients incorrectly classified as not having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None[b]	Serious[c]	None	Undetected	⊕⊕⊕⊖ moderate	34	5 (2 to 16)	CRITICAL
FN absolute difference									29 more		

Footnotes:

[a] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. The decision to downgrade was a borderline judgement and was considered in the context of other factors.

[b] Data for HPV test followed by VIA were calculated based on sensitivity and specificity of the two tests. Direct data were unavailable. Diagnostic test accuracy data were based on women of unknown HIV status; the data were not considered indirect and so the quality of evidence was not downgraded.

[c] Estimates of HPV test and VIA sensitivity and specificity were variable despite similar cut-off values; inconsistency could not be explained by quality of studies. This was downgraded. This judgement was considered in the context of other factors, in particular imprecision.

[d] Wide CI for HPV test sensitivity and VIA specificity, and therefore wide CI for TP, TN, FP, FN, may lead to different decisions depending on which confidence limits are assumed.

2.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV→VIA +/– CKC	HPV→VIA +/– LEEP	HPV→VIA +/– cryo	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	No screen[10]
Mortality from cervical cancer[1]	1564	1662	1662	318	460	460	4350
Cervical cancer incidence[2]	2190	2327	2327	445	644	644	6075
CIN2+ recurrence[3]	28 859	30 891	30 891	6069	9014	9014	79 575
Undetected CIN2+ (FN)	34 000			5000			–
Major bleeding[4]	723	190	29	2052	539	81	0
Premature delivery[5]	602	536	553	788	602	649	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	75	108	11	212	306	32	0
Minor infections[8]	789	508	545	2239	1440	1547	0
Unnecessarily treated (FP)	19 000			144 000			–
Cancer found at first-time screening[9]	3168			2454			0

Footnotes:

The colours in the table: In each GRADE evidence table, colour-coding is used to highlight the 'desirability' of the effects for that outcome relative to other outcomes. The continuum runs from dark gray (desirable) through light gray and light pink to dark pink (least desirable).

The numbers in the table are based on

- CIN2+ pretest probability 10% in women of HIV-positive status (Denny et al., 2008; De Vuyst et al., 2012; Joshi et al., 2012; Zhang et al., 2012)
- VIA: pooled sensitivity 69% (95% CI: 54 to 81), pooled specificity 87% (95% CI: 79 to 92)
- HPV test: pooled sensitivity 95% (95% CI: 84 to 98), pooled specificity 84% (95% CI: 72 to 91)
- The overall QoE for each of these outcomes is very low ⊕⊖⊖⊖. Our lack of confidence in these effect estimates stems mainly from very-low-quality evidence for treatment effects and natural progression/history data.

[1] We assume no mortality from cervical cancer in TN and FP. To calculate the mortality from cervical cancer in women of HIV-positive status, we assumed the same risk of mortality in women of unknown HIV status: 250 deaths per 350 women with cervical cancer. These numbers are based on Eastern Africa age-standardized rates of cervical cancer and mortality provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012).

[2] We assume no cervical cancer in TN or FP. The calculations for cervical cancer incidence in women of HIV-positive status with persistent CIN2+ are based on a 2.7 standardized Risk Ratio of cancer when compared to women with unknown HIV status (De Vuyst et al., 2008). For women of unknown status, we assumed 350 cervical cancers per 14 000 women who have persistent CIN2+ (i.e. FN). This incidence is based on Eastern Africa age-standardized rate of cervical cancer of 350 cervical cancers per 1 000 000 women, of whom 2% have CIN2+ (20 000 women with CIN2+, and a subsequent 30% regression for a total of 14 000 with persistent CIN2+). These data are available from WHO (http://globocan.iarc.fr/, accessed 30 October 2012).

[3] We assume no CIN2+ in TN and FP. Our calculations in the model are based on 90% natural persistence of CIN2+ with no treatment (10% regression) in FN. TP are treated and recurrence rates of CIN2+ are 5.3% in cryotherapy and LEEP, and 2.2% in CKC.

[4] We assumed major bleed would be 0 in TN and FN as they were not treated. We assumed 0.000339 of the population treated with cryotherapy, 0.002257 with LEEP, and 0.001705 with CKC, based on pooled proportions in observational studies with no independent controls, will have major bleeding.

[5] We assumed 5% population risk of premature delivery in 1% of women who become pregnant. Based on pooled meta-analysis of controlled observational studies, 0.001125 of the population treated with cryotherapy, 0.000925 with LEEP, and 0.001705 of the population treated with CKC will have premature delivery.

[6] We did not identify any data about the risk of infertility after treatment for CIN2+.

[7] We assumed major infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control, 0.000135 of the population treated with cryotherapy 0.001279 with LEEP, and 0.000888 with CKC will have major infection.

[8] We assumed minor infection would be 0 in TN and FN as they were not treated. Based on pooled proportions from studies with no independent control, 0.006473 of the population treated with cryotherapy, 0.006027 with LEEP, and 0.009368 with CKC will have minor infection.

[9] Cancers detected at first-time screening calculated from Sankaranarayanan et al. (2005). Numbers for single screening tests were calculated as 'screen-detected' cancers in women who participated in the screening programme; and numbers for test with colposcopy were calculated as 'screen-detected' plus 'clinically detected' cancers. For a sequence of tests (e.g. HPV test followed by VIA), the greater number of cancers detected between tests was used. No cancers would be found in the 'no screen' group. This is not the annual incidence of cervical cancer (which is shown in a row above). It represents the cumulative rate of cancer development before screening started (i.e. the prevalence of cancer at the time when screening is first conducted).

[10] 'No screen' numbers were calculated using the same assumptions above for FN, with the exception of premature delivery which was baseline risk in the population.

3. References to studies included in meta-analysis of diagnostic test accuracy

3.1 References to studies included in meta-analysis of diagnostic test accuracy

Belinson J et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecology Oncology*, 2001, 83(2):439–444.

De Vuyst H et al. Comparison of Pap smear, visual inspection with acetic acid, human papillomavirus DNA–PCR testing and cervicography. *International Journal of Gynecology & Obstetrics*, 2005, 89(2):120–126.

Pan Q et al. A thin-layer, liquid-based Pap test for mass screening in an area of China with a high incidence of cervical carcinoma: a cross-sectional, comparative study. *Acta Cytologica*, 2003, 47(1):45–50.

Qiao YL et al. A new HPV–DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncology*, 2008, 9(10):929–936.

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3.2 Additional references

Denny L et al. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. *Obstetrics & Gynecology*, 2008, 111(6):1380–1387.

De Vuyst H et al. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *European Journal of Cancer Prevention*, 2008, 17(6):545–554.

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Joshi S et al. Screening of cervical neoplasia in HIV-infected women in India, *AIDS*, 2013, 27(4):607–615.

Sankaranarayanan R et al.; Osmanabad District Cervical Screening Study Group. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *International Journal of Cancer*, 2005, 116(4):617–623.

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