Recommendation 7

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

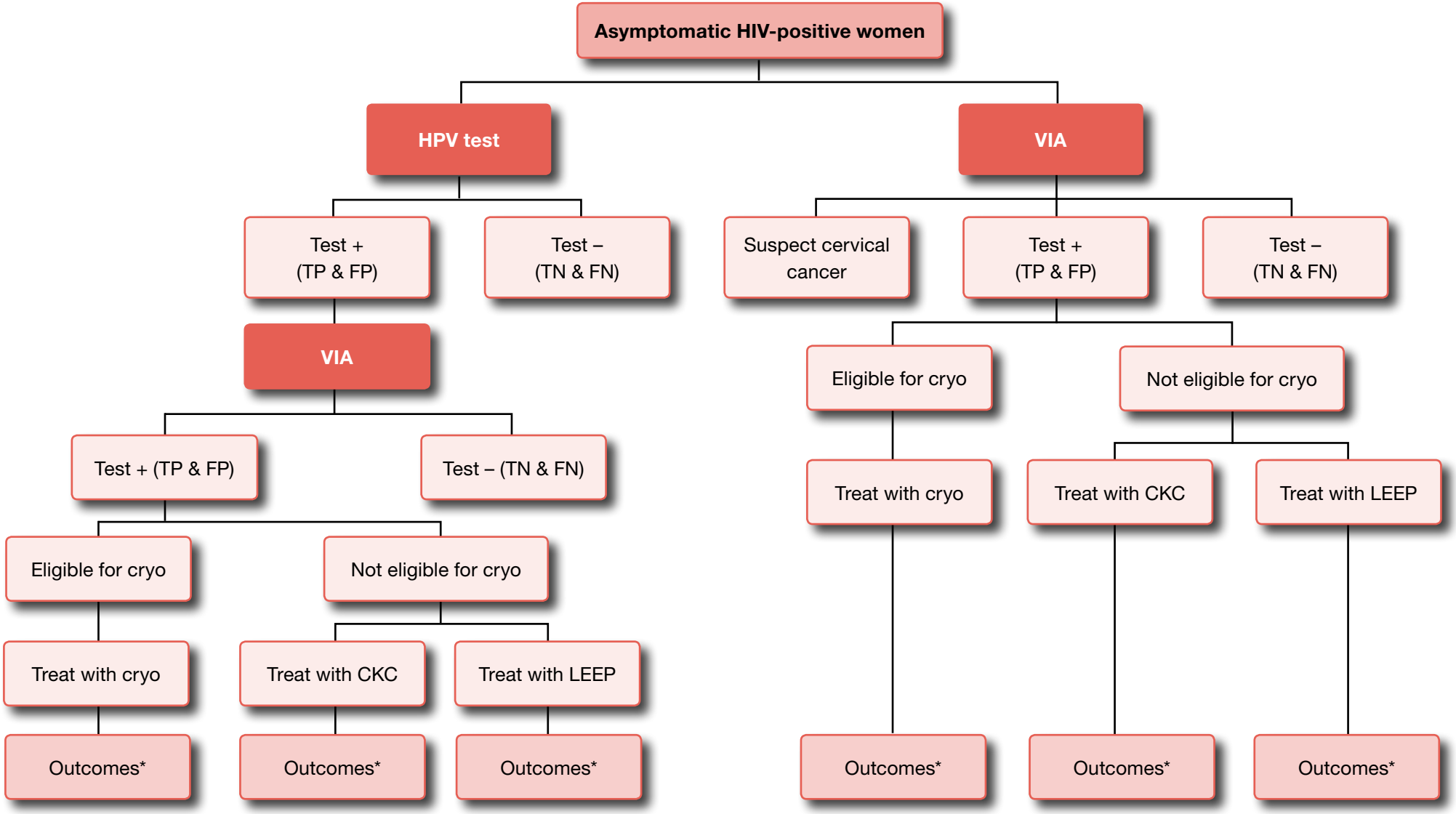
Remarks: The reductions in cancer and related mortality with an HPV test followed by VIA or with VIA alone outweighed the harms. However, the harms may be greater when using VIA only, which is likely due to overtreatment. Although, a slightly larger number of cancers may be detected on initial screen with VIA only. This recommendation is conditional due to the uncertain costs of providing the sequence of two tests (HPV test followed by VIA) over the single VIA test. In countries where HPV test is not available, we suggest screening with VIA only. This recommendation applies to women regardless of HIV status.

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 data for HPV test followed by VIA and we did not have a direct comparison of this triage test to VIA 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 ☐	The benefits of HPV test followed by VIA and VIA alone may be similar. However, there may be greater harms with VIA alone (due to overtreatment with VIA alone). There may be slightly fewer cancers detected with HPV test followed by VIA.
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 placed on the greater number of complications and the number of women overtreated.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☐ / No ☒	Greater resources with overtreatment with VIA alone. However there may be additional resources required to refer women for VIA testing after a positive HPV test, the need for a second visit, and increased training to perform both tests.

Evidence for an HPV test followed by VIA compared to VIA 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 VIA

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 VIA

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	VIA	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None[b]	Serious[c]	None[d]	Undetected	⊕⊕⊕⊖ moderate	66	69 (11 to 81)	CRITICAL
TP absolute difference									3 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	783 (711 to 828)	CRITICAL
TN absolute difference									98 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	117 (72 to 189)	CRITICAL
FP absolute difference									98 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[d]	Undetected	⊕⊕⊕⊖ moderate	34	31 (19 to 46)	CRITICAL
FN absolute difference									3 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	VIA +/– CKC	VIA +/–LEEP	VIA +/– cryo	No screen[10]
Mortality from cervical cancer[1]	1564	1662	1662	1481	1521	1521	4350
Cervical cancer incidence[2]	2190	2327	2327	1986	2130	2130	6075
CIN2+ recurrence[3]	28 859	30 891	30 891	26 190	28 329	28 329	79 575
Undetected CIN2+ (FN)	34 000			31 000			–
Major bleeding[4]	723	190	29	1597	420	63	0
Premature delivery[5]	602	536	553	724	579	616	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	75	108	11	165	238	25	0
Minor infections[8]	789	508	545	1742	1121	1204	0
Unnecessarily treated (FP)	19 000			117 000			–
Cancer found at first-time screening[9]	2454			3168			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

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

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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.

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Sodhani P et al. Test characteristics of various screening modalities for cervical cancer: a feasibility study to develop an alternative strategy for resource-limited settings. *Cytopathology*, 2006, 17(6):348–352.

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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