WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention

Supplemental material: GRADE evidence-to-recommendation tables and evidence profiles for each recommendation

World Health Organization

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WHO/RHR/13.21

Contents

Introduction

This document includes the judgements and evidence for each recommendation as presented and used by the Guideline Development Group to make recommendations for the *WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention*.[1]

In each section and for each recommendation, we provide:

- recommendation and remarks, which relate to the strength of the recommendation and the quality of the evidence;
- an evidence-to-recommendation table, describing the judgements made by the Guideline Development Group;
- evidence for each recommendation, including:
  - flowchart for the screen-and-treat strategies that were compared;
  - evidence used for decision-making:
    1. diagnostic test accuracy evidence profile;
    2. GRADE evidence table for patient-important outcomes following different screen-and-treat strategies (based on model);
    3. GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age.
  - references.

[1] Available at: http://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/index.html

Acronyms and abbreviations

ASCUS	atypical squamous cells of undetermined significance
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CKC	cold knife conization
colp	colposcopic impression; women who have abnormal results on colposcopy would not be treated
cryo	cryotherapy
cyto	cytology, Papanicolaou test (using conventional or liquid-based cytology); cut-off for screen-positive test is ASCUS
DTA	diagnostic test accuracy
FN	false negative, calculated from sensitivity of screening test; women who receive FN screening test results will not receive the treatment they need (because their positive status was undetected)
FP	false positive, calculated from specificity of screening test; women who receive FP screening test results will receive unnecessary treatment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	human immunodeficiency virus
HPV test	human papillomavirus screening test; cut-off for screen-positive test is 1 pg/mL
HPV→VIA	a sequence of screening tests in which an HPV test is followed by VIA; the HPV test is used first and only those women who screen positive for HPV are screened with VIA as a second screening test; women who screen positive on VIA are then treated, while women who screen negative on VIA are not treated
HPV +/– CKC	strategy in which an HPV screening test is used and screen-positive women are treated with CKC, but screen-negative women are not treated; it should be noted that all screen-and-treat strategies follow this format (also HPV→VIA +/– LEEP)
LEEP	loop electrosurgical excision procedure (also LLETZ, large loop excision of the transformation zone)
QoE	quality of evidence
QUADAS	QUality Assessment for Diagnostic Accuracy Studies
TN	true negative, calculated from specificity of screening test; women who receive TN screening test results will not receive treatment and do not need treatment
TP	true positive, calculated from sensitivity of screening test; women who receive TP screening test results will receive the treatment they need
VIA	visual inspection (of the cervix) with acetic acid; can be used (i) as a cervical screening test; or (ii) to assess whether a patient is eligible for cryotherapy

Section A.

GRADE evidence-to-recommendation tables and evidence profiles for each recommendation (negative or unknown HIV status)

Recommendation 1

The expert panel recommends against the use of CKC as treatment in a screen-and-treat strategy (strong recommendation, ⊕⊖⊖⊖ evidence)

Remarks: The screen-and-treat strategies considered by the panel with CKC as treatment included an HPV test, VIA, or an HPV test followed by VIA as screening. Although the benefits were similar for CKC compared with cryotherapy or LEEP for all screen-and-treat strategies, the harms were greater with CKC. 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 high- to moderate-quality evidence for the diagnostic test accuracy data for VIA and HPV test. 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 screen-and-treat strategy (reduction in CIN recurrence, cervical cancer, and related mortality) may be greater than VIA, and the harms may be similar. There may also be slightly greater overtreatment and slightly fewer cancers detected with HPV test compared to 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 also placed on a reduction in cervical cancer and related mortality versus complications from treatment (e.g. major bleeding or infection requiring hospitalization). Low value was placed on minor infections or bleeding, and the small number of cancers detected at screening or of women overtreated.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☐ No ☒	HPV testing is resource-dependent. Where HPV testing is available, affordable and implementable, the overall net benefit over VIA is worth the resources. But where not available, HPV test may not be worth the benefits.

This recommendation was made using the data from recommendations 2 to 9, in which the outcomes after use of CKC were compared to LEEP and cryotherapy (e.g. HPV→CKC in evidence for recommendation 2). Refer to the following recommendations as presented in this section.

Recommendation 2

Where resources permit, the expert panel suggests a strategy of screen with an HPV test 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)

In resource-constrained settings, where screening with an HPV test is not feasible, the expert panel suggests a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible) over a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

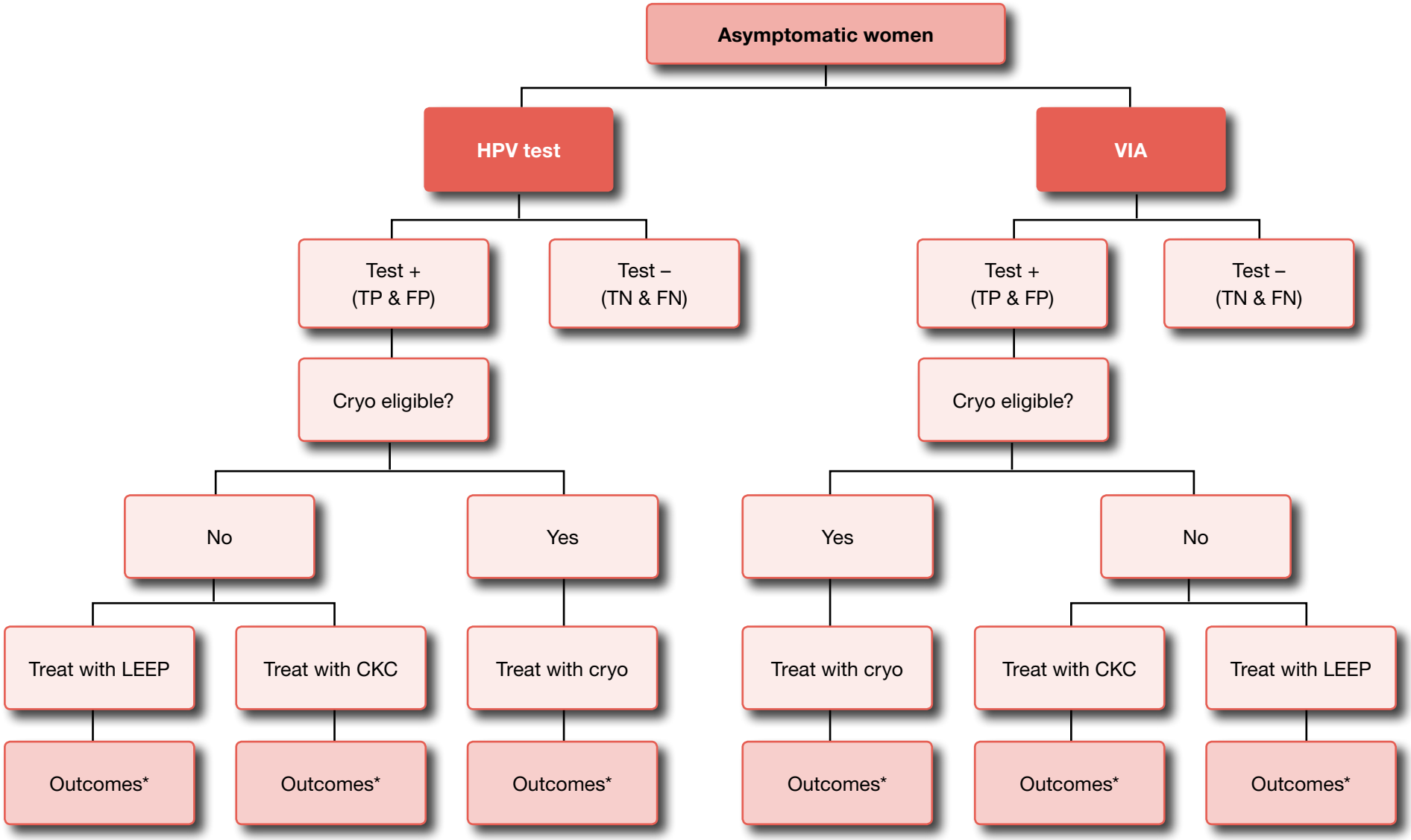
Remarks: The benefits of screen-and-treat with an HPV test or VIA, compared to no screening, outweighed the harms, but the reductions in cancer and related mortality were greater with an HPV test when compared to VIA. The availability of HPV testing is resource-dependent and, therefore, the expert panel suggests that an HPV test over VIA be provided where it is available, affordable, implementable, and sustainable over time. 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- to high-quality evidence for the diagnostic test accuracy data for all screen-and-treat strategies. 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 desirable effects of screen-and-treat strategies with cold knife conization may be greater than no screening, but may be similar to other screen-and-treat strategies with cryotherapy or LEEP. However, the risk of major and minor harms was greater when compared to those strategies.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ / No ☐	A high value was placed on the complications (including risk of premature delivery) from treatment with cold knife conization after screening.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	Resources for cold knife conization are greater than for cryotherapy or LEEP.

Evidence for HPV test compared to VIA to screen for CIN2+

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 compared to VIA to screen for CIN2+

Diagnostic test accuracy

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

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 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test	VIA	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None	None[b]	None	Undetected	⊕⊕⊕⊕ high	19 (17 to 20)	14 (11 to 16)	CRITICAL
TP absolute difference									5 more		
True negatives (patients without CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None	Serious[b]	None[c]	Undetected	⊕⊕⊕⊖ moderate	823 (706 to 892)	853 (774 to 902)	CRITICAL
TP absolute difference									30 fewer		
False positives (patients incorrectly classified as having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None	Serious[b]	None[c]	Undetected	⊕⊕⊕⊖ moderate	157 (88 to 274)	127 (78 to 206)	CRITICAL
FP absolute difference									30 more		
False negatives (patients incorrectly classified as not having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None	None[b]	None	Undetected	⊕⊕⊕⊕ high	1 (0 to 3)	6 (4 to 9)	CRITICAL
FP absolute difference									5 fewer		

Footnotes:

[a] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. This was not downgraded and this was a borderline judgement.

[b] Estimates of HPV test and VIA sensitivity and specificity were variable despite similar cut-off values, and could not be explained by the quality of studies. For TP and FN this was a borderline judgement. We downgraded TN and FP and considered this in the context of other factors, in particular imprecision.

[c] Wide CI for TN and FP that may lead to different decisions depending on which of the confidence limits is assumed.

2.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test compared to VIA

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV +/– CKC	HPV +/–LEEP	HPV +/– cryo	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	No screen[10]
Mortality from cervical cancer[1]	20	30	30	81	88	88	250
Cervical cancer incidence[2]	28	43	43	112	124	124	350
CIN2+ recurrence[3]	1088	1677	1677	4328	4762	4762	13 400
Undetected CIN2+ (FN)	1000			6000			–
Major bleeding[4]	1511	397	60	1210	318	48	0
Premature delivery[5]	712	575	610	670	560	588	500
Infertility[6]	–	–	–	–	–	–	0
Major infections[7]	156	225	24	125	180	19	0
Minor infections[8]	1649	1061	1139	1321	850	913	0
Unnecessarily treated (FP)	157 000			127 000			–
Cancer found at first-time screening[9]	2454			3168			–

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 2%
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

2.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	6	9	9	23	25	25	71
Cervical cancer incidence	8	12	12	32	35	35	100
CIN2+ recurrence	1109	1698	1698	4457	4891	4891	13 829
40–49 years[a]							
Mortality from cervical cancer	37	57	57	150	164	164	464
Cervical cancer incidence	52	79	79	209	229	229	650
CIN2+ recurrence	1062	1651	1651	4174	4608	4608	12 886
50–74 years[a]							
Mortality from cervical cancer	68	105	105	276	303	303	857
Cervical cancer incidence	96	146	146	386	424	424	1200
CIN2+ recurrence	1015	1604	1604	3891	4325	4325	11 943
Complications (same across all groups)							
Major bleeding[4]	1511	397	60	1210	318	48	0
Premature delivery[5]	712	575	610	670	560	588	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	156	225	24	125	180	19	0
Minor infections[8]	1649	1061	1139	1321	850	913	0

Footnotes:

[a] Events were calculated in a similar way to that used for Table 2.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 2.2.

3. 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. *Gynecologic 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.

Shastri SS et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bulletin of the World Health Organization*, 2005, 83(3):186–194.

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.

Recommendation 3

The expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

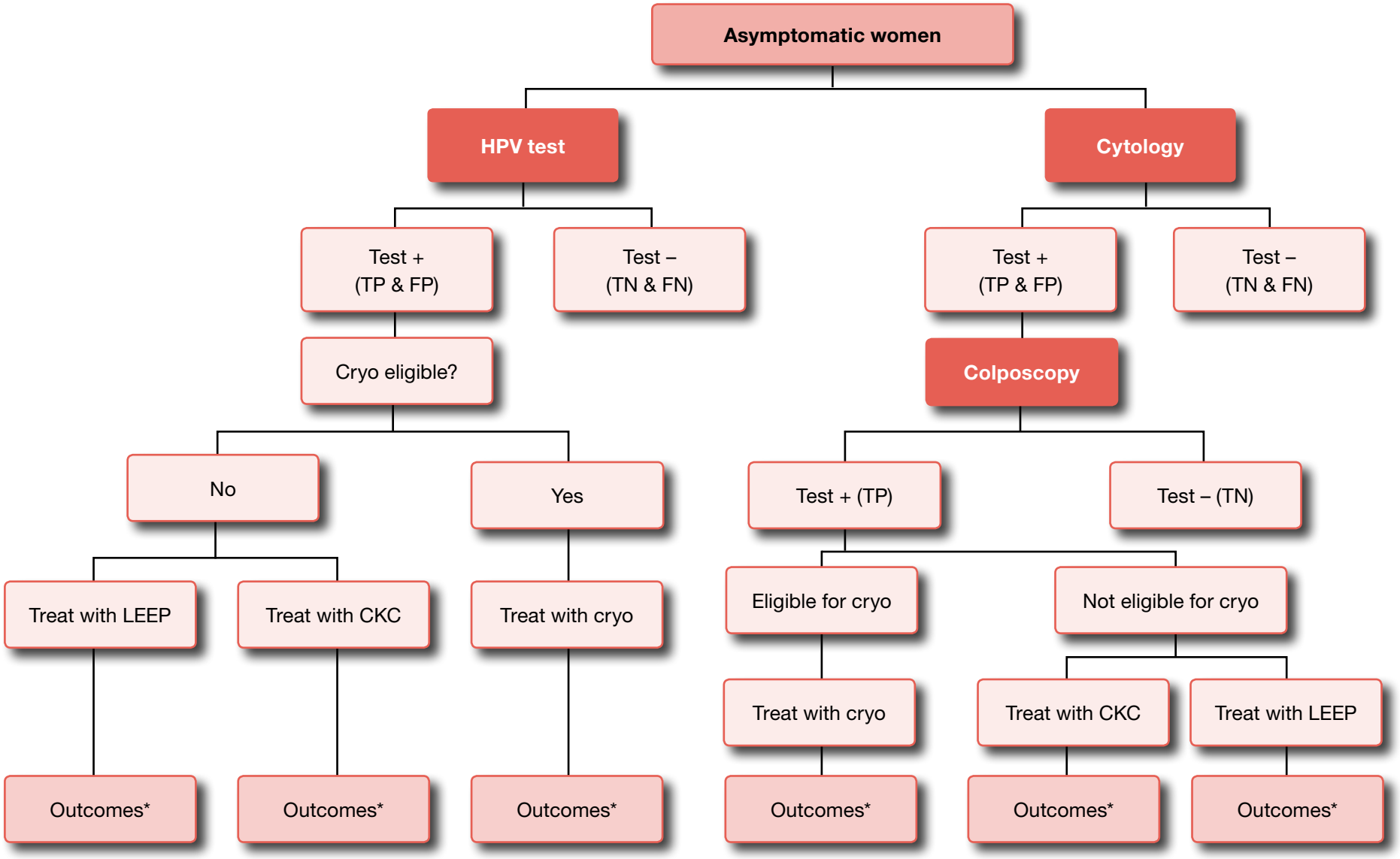
Remarks: The reductions in cancer and related mortality were slightly greater with an HPV test only compared to cytology followed by colposcopy. Although there may be overtreatment of populations with high HPV prevalence and consequently more harms, as well as fewer cancers seen at first-time screening with an HPV test, there are greater resources required in cytology programmes due to quality control, training, and waiting time. The addition of colposcopy also requires a second visit. However, in countries where an appropriate/high-quality screening strategy with cytology (referring women with ASCUS or greater results) followed by colposcopy already exists, either an HPV test or cytology followed by colposcopy could be used.

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 cytology followed by colposcopy 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: ☒	The benefits of HPV test alone were greater than with cytology followed by colposcopy. However, there may be greater harms with HPV test alone (due to overtreatment with HPV test alone) and fewer cancers detected with HPV test.
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 resources required and lower value on the harms.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes: ☒ No: ☐	There may be additional resources required in cytology programmes due to increased training of providers, quality control, and waiting time. Colposcopy following cytology also requires a second visit. However, in countries where an appropriate/high-quality screening strategy with cytology exists, resources would be required to change over to HPV test.

Evidence for HPV test compared to cytology followed by colposcopy to screen for CIN2+

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 compared to cytology (ASCUS) followed by colposcopic impression to screen for CIN2+

Diagnostic test accuracy

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)	Pooled sensitivity colposcopic impresssion	95% (95% CI: 86 to 98)
Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity cytology (ASCUS)	95% (95% CI: 92 to 97)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

2.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to cytology (ASCUS) followed by colposcopic impression

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test	Cytology followed by colposcopic impression	
True positives (patients with CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	19 (18 to 19)	13	CRITICAL
TP absolute difference									6 more		
True negatives (patients without CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	882 (843 to 911)	952	CRITICAL
TP absolute difference									70 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	98 (69 to 137)	28	CRITICAL
FP absolute difference									70 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious [b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	1 (1 to 2)	7	CRITICAL
FP absolute difference									6 fewer		

Footnotes:

[a] This is the number of studies that assessed data for HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of the studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] Estimates of HPV test, cytology (ASCUS) and colposcopy sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of cytology followed by colposcopy 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: HPV test compared to cytology (ASCUS) followed by colposcopic impression

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	Cyto→colp imp +/– CKC	Cyto→colp imp +/– LEEP	Cyto→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	20	30	30	89	96	96	250
Cervical cancer incidence[2]	28	20	43	125	135	135	350
CIN2+ recurrence[3]	1088	1677	1677	4782	5194	5194	13 400
Undetected CIN2+ (FN)	1000			7000			–
Major bleeding[4]	1004	264	40	358	94	14	0
Premature delivery[5]	641	550	573	550	518	520	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	104	150	16	37	53	6	0
Minor infections[8]	1096	705	757	391	251	270	0
Unnecessarily treated (FP)	98 000			28 000			–
Cancer found at first-time screening[9]	2454			4794			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 2%
- HPV test: pooled sensitivity 94% (95% CI: 89 to 97), pooled specificity 90% (95% CI: 86 to 93)
- Cytology (ASCUS): pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
- Colposcopic impression: pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

2.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	Cyto→colp imp +/– CKC	Cyto→colp imp +/–LEEP	Cyto→colp imp +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	6	9	9	25	28	28	71
Cervical cancer incidence	8	12	12	36	39	39	100
CIN2+ recurrence	1109	1698	1698	4925	5337	5337	13 829
40–49 years[a]							
Mortality from cervical cancer	37	57	57	165	179	179	464
Cervical cancer incidence	52	79	79	231	250	250	650
CIN2+ recurrence	1062	1651	1651	4609	5022	5022	12 886
50–74 years[a]							
Mortality from cervical cancer	68	105	105	305	330	330	857
Cervical cancer incidence	96	146	146	427	462	462	1200
CIN2+ recurrence	1015	1604	1604	4293	4706	4706	11 943
Complications (same across all groups)							
Major bleeding[4]	1004	264	40	358	94	14	0
Premature delivery[5]	641	550	573	550	518	520	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	104	150	16	37	53	6	0
Minor infections[8]	1096	705	757	391	251	270	0

Footnotes:

[a] Events were calculated similar to Table 2.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 2.2.

3. Evidence used for decision-making: HPV test compared to cytology (ASCUS) followed by colposcopic impression and biopsy when indicated to screen for CIN2+

Diagnostic test accuracy

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)
Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity cytology (ASCUS)	95% (95% CI: 92 to 97)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to cytology (ASCUS) followed by colposcopic impressed and biopsy when indicated

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test	Cytology followed by colposcopy with biopsy	
True positives (patients with CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	19 (18 to 19)	14	CRITICAL
TP absolute difference									5 more		
True negatives (patients without CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	882 (843 to 911)	980	CRITICAL
TP absolute difference									98 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	98 (69 to 137)	0	CRITICAL
FP absolute difference									98 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	1 (1 to 2)	6	CRITICAL
FP absolute difference									5 fewer		

Footnotes:

[a] This is the number of studies that assessed data for HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for cytology followed by colposcopy +/– biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] Estimates of HPV test and cytology (ASCUS) sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of cytology followed by colposcopy and therefore wide CI for TP, TN, FP, FN, may lead to different decisions depending on which confidence limits are assumed.

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test compared to cytology (ASCUS) followed by colposcopy impressed and biopsy when indicated

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/–LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
Mortality from cervical cancer[1]	20	30	30	81	88	88	250
Cervical cancer incidence[2]	28	20	43	113	124	124	350
CIN2+ recurrence[3]	1088	1677	1677	4328	4762	4762	13 400
Undetected CIN2+ (FN)	1000			6000			–
Major bleeding[4]	1004	264	40	120	32	5	0
Premature delivery[5]	641	550	573	517	506	509	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	104	150	16	12	18	2	0
Minor infections[8]	1096	705	757	131	84	91	0
Unnecessarily treated (FP)	98 000			0			–
Cancer found at first-time screening[9]	2454			4794			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 2%
- HPV test: pooled sensitivity 94% (95% CI: 89 to 97), pooled specificity 90% (95% CI: 86 to 93)
- Cytology (ASCUS): Pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

3.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/–LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	6	9	9	23	25	25	71
Cervical cancer incidence	8	12	12	32	35	35	100
CIN2+ recurrence	1109	1698	1698	4457	4891	4891	13 829
40–49 years[a]							
Mortality from cervical cancer	37	57	57	150	164	164	464
Cervical cancer incidence	52	79	79	209	229	229	650
CIN2+ recurrence	1062	1651	1651	4174	4608	4608	12 886
50–74 years[a]							
Mortality from cervical cancer	68	105	105	276	303	303	857
Cervical cancer incidence	96	146	146	386	424	424	1200
CIN2+ recurrence	1015	1604	1604	3891	4325	4325	11 943
Complications (same across all groups)							
Major bleeding[4]	1004	264	40	120	32	5	0
Premature delivery[5]	641	550	573	517	506	509	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	104	150	16	12	18	2	0
Minor infections[8]	1096	705	757	131	84	91	0

Footnotes:

[a] Events were calculated similar to Table 3.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 3.2.

4. References

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

Agorastos T et al. Human papillomavirus testing for primary screening in women at low risk of developing cervical cancer. The Greek experience. *Gynecologic Oncology*, 2005, 96(3):714–720.

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4.2 References to studies included for diagnostic test accuracy of colposcopic impression

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Recommendation 4

The expert panel recommends a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (strong recommendation, ⊕⊖⊖⊖ evidence)

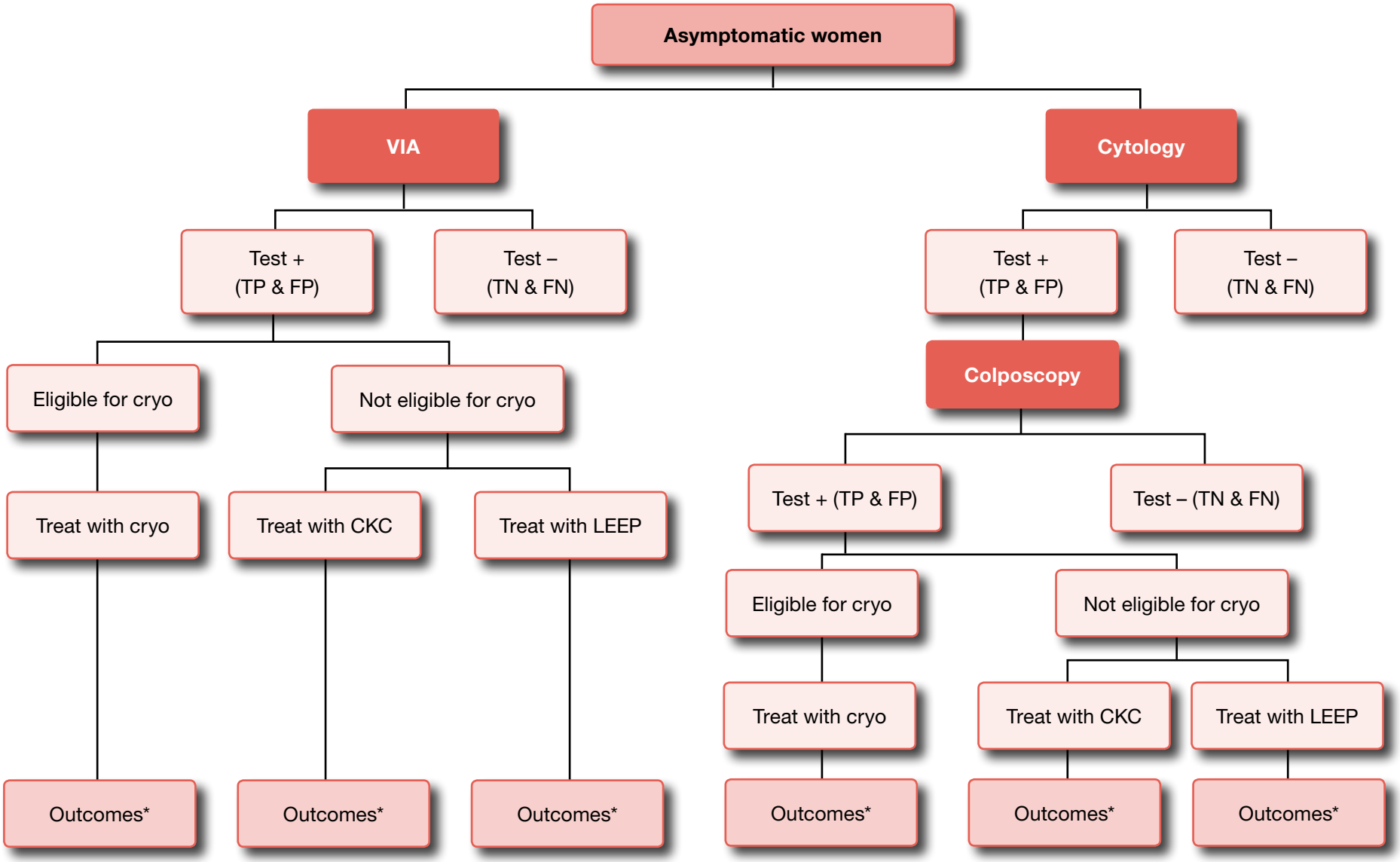
Remarks: The benefits and harms of the two screen-and-treat strategies are similar, but there are fewer harms with cytology followed by colposcopy with biopsy when indicated. Despite overtreatment with VIA and fewer cancers detected at first-time screening, more resources are required for cytology programmes with colposcopy (with or without biopsy) due to quality control, training, and waiting time, as well as a second visit. The recommendation for VIA over cytology followed by colposcopy can be applied in countries that are currently considering either strategy or countries that currently have both strategies available. 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 of cytology followed by colposcopy compared 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. Also 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 cytology followed by colposcopy and VIA alone may be similar. However, there may be slightly greater harms with VIA alone (due to overtreatment with HPV test alone) and slightly fewer cancers detected with 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 resources required and lower value on the harms.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	Fewer resources are required for VIA. There may be additional resources required in cytology programmes due to increased training of providers, quality control, and waiting time. Colposcopy following cytology also requires a second visit.

Evidence for VIA compared to cytology followed by colposcopy to screen for CIN2+

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: VIA compared to cytology followed by colposcopic impression

Diagnostic test accuracy

Pooled sensitivity VIA	77% (95% CI: 65 to 85)	Pooled sensitivity cytology (ASCUS)	84% (95% CI: 76 to 90)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity VIA	82% (95% CI: 67 to 91)	Pooled specificity cytology (ASCUS)	88% (95% CI: 79 to 93)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

2.1 Diagnostic test accuracy (DTA) evidence profile: VIA compared to cytology followed by colposcopic impression

Outcome	No. of studies (No. of patients) [a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		VIA	Cytology followed by colposcopic impression	
True positives (patients with CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	15 (13 to 17)	16	CRITICAL
TP absolute difference									1 fewer		
True negatives (patients without CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	804 (657 to 892)	912	CRITICAL
TN absolute difference									108 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	176 (88 to 323)	68	CRITICAL
FP absolute difference									108 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	5 (3 to 7)	4	CRITICAL
FN absolute difference									1 more		

Footnotes:

[a] This is the number of studies that assessed data for HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] Estimates of VIA, cytology (ASCUS) and colposcopy sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of cytology followed by colposcopy 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: VIA compared to cytology followed by colposcopic impression

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	Cyto→colp imp +/– CKC	Cyto→colp imp +/–LEEP	Cyto→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	44	54	54	54	63	63	250
Cervical cancer incidence[2]	62	75	75	76	89	89	350
CIN2+ recurrence[3]	2384	2911	2911	2935	3435	3435	13 400
Undetected CIN2+ (FN)	5000			4000			–
Major bleeding[4]	901	237	36	726	191	29	0
Premature delivery[5]	627	545	566	602	536	553	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	93	134	14	75	108	11	0
Minor infections[8]	984	633	680	792	510	548	0
Unnecessarily treated (FP)	176 000			68 000			–
Cancer found at first-time screening[9]	3168			4794			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 2%
- VIA: pooled sensitivity 77% (95% CI: 66 to 85), pooled specificity 82% (95% CI: 67 to 91)
- Cytology (ASCUS): Pooled sensitivity 84% (95% CI: 76 to 90), pooled specificity 88% (95% CI: 79 to 93)
- Colposcopic impression: Pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

2.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	Cyto→colp imp +/– CKC	Cyto→colp imp +/–LEEP	Cyto→colp imp +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	13	16	15	15	18	18	71
Cervical cancer incidence	18	22	21	21	25	25	100
CIN2+ recurrence	2448	3017	2975	2975	3518	3518	13 829
40–49 years[a]							
Mortality from cervical cancer	82	101	100	100	118	118	464
Cervical cancer incidence	115	142	139	139	165	165	650
CIN2+ recurrence	2307	2836	2834	2834	3336	3336	12 886
50–74 years[a]							
Mortality from cervical cancer	151	187	184	184	217	217	857
Cervical cancer incidence	212	261	257	257	304	304	1200
CIN2+ recurrence	2165	2692	2692	2654	3155	3155	11 943
Complications (same across all groups)							
Major bleeding[4]	901	237	36	726	191	29	0
Premature delivery[5]	627	545	566	602	536	553	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	93	134	14	75	108	11	0
Minor infections[8]	984	633	680	792	510	548	0

Footnotes:

[a] Events were calculated similar to Table 2.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 2.2.

3. Evidence used for decision-making: VIA compared to cytology followed by colposcopic impression and biopsy when indicated

Diagnostic test accuracy

Pooled sensitivity VIA	77% (95% CI: 66 to 85)	Pooled sensitivity cytology (ASCUS)	84% (95% CI: 76 to 90)
Pooled specificity VIA	82% (95% CI: 67 to 91)	Pooled specificity cytology (ASCUS)	88% (95% CI: 79 to 93)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: VIA compared to cytology followed by colposcopic impression and biopsy when indicated

Outcome	No. of studies (No. of patients) [a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		VIA	Cytology followed by colposcopy with biopsy	
True positives (patients with CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	15 (13 to 17)	17	CRITICAL
TP absolute difference									2 fewer		
True negatives (patients without CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	804 (657 to 892)	980	CRITICAL
TN absolute difference									176 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	176 (88 to 323)	0	CRITICAL
FP absolute difference									176 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	5 (3 to 7)	3	CRITICAL
FN absolute difference									2 more		

Footnotes:

[a] This is the number of studies that assessed data for HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for cytology followed by colposcopy +/– biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] Estimates of VIA and cytology (ASCUS) sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of cytology followed by colposcopy and therefore wide CI for TP, TN, FP, FN, may lead to different decisions depending on which confidence limits are assumed.

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: VIA compared to cytology followed by colposcopic impression and biopsy when indicated

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/–LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
Mortality from cervical cancer[1]	44	54	54	44	54	54	250
Cervical cancer incidence[2]	62	75	75	62	75	75	350
CIN2+ recurrence[3]	2384	2911	2911	2384	2911	2911	13 400
Undetected CIN2+ (FN)	5000			3000			–
Major bleeding[4]	901	237	36	146	38	6	0
Premature delivery[5]	627	545	566	520	507	511	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	93	134	14	15	22	2	0
Minor infections[8]	984	633	680	159	102	110	0
Unnecessarily treated (FP)	176 000			0			–
Cancer found at first-time screening[9]	3168			4794			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 2%
- VIA: pooled sensitivity 77% (95% CI: 66 to 85), pooled specificity 83% (95% CI: 68 to 92)
- Cytology (ASCUS): Pooled sensitivity 84% (95% CI: 76 to 90), pooled specificity 88% (95% CI: 79 to 93)
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see previously for calculations). 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 tests 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 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.

3.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/–LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	13	16	15	13	15	15	71
Cervical cancer incidence	18	22	21	18	21	21	100
CIN2+ recurrence	2448	3017	2975	2448	2975	2975	13 829
40–49 years[a]							
Mortality from cervical cancer	82	101	100	82	100	100	464
Cervical cancer incidence	115	142	139	115	139	139	650
CIN2+ recurrence	2307	2836	2834	2307	2834	2834	12 886
50–74 years[a]							
Mortality from cervical cancer	151	187	184	151	184	184	857
Cervical cancer incidence	212	261	257	212	257	257	1200
CIN2+ recurrence	2165	2692	2692	2165	2692	2692	11 943
Complications (same across all groups)							
Major bleeding[4]	901	237	36	146	38	6	0
Premature delivery[5]	627	545	566	520	507	511	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	93	134	14	15	22	2	0
Minor infections[8]	984	633	680	159	102	110	0

Footnotes:

[a] Events were calculated similar to Table 3.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 3.2.

4. References

4.1 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. *Gynecologic Oncology*, 2001, 83(2):439–444.

Cremer M et al. Adequacy of visual inspection with acetic acid in women of advancing age. *International Journal of Gynaecology & Obstetrics*, 2011, 113(1):68–71.

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Sahasrabuddhe VV et al. Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among HIV-infected women in India. *International Journal of Cancer*, 2012, 130(1):234–240.

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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.

4.2 References to studies included for diagnostic test accuracy of colposcopic impression

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Cantor SB et al. Accuracy of colposcopy in the diagnostic setting compared with the screening setting. *Obstetrics & Gynecology*, 2008, 111(1):7–14.

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Cristoforoni PM et al. Computerized colposcopy: results of a pilot study and analysis of its clinical relevance. *Obstetrics & Gynecology*, 1995, 85(6):1011–1016.

Durdi GS et al. Correlation of colposcopy using Reid colposcopic index with histopathology – a prospective study. *Journal of the Turkish German Gynecology Association*, 2009, 10(4):205–207.

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Recommendation 5

The expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

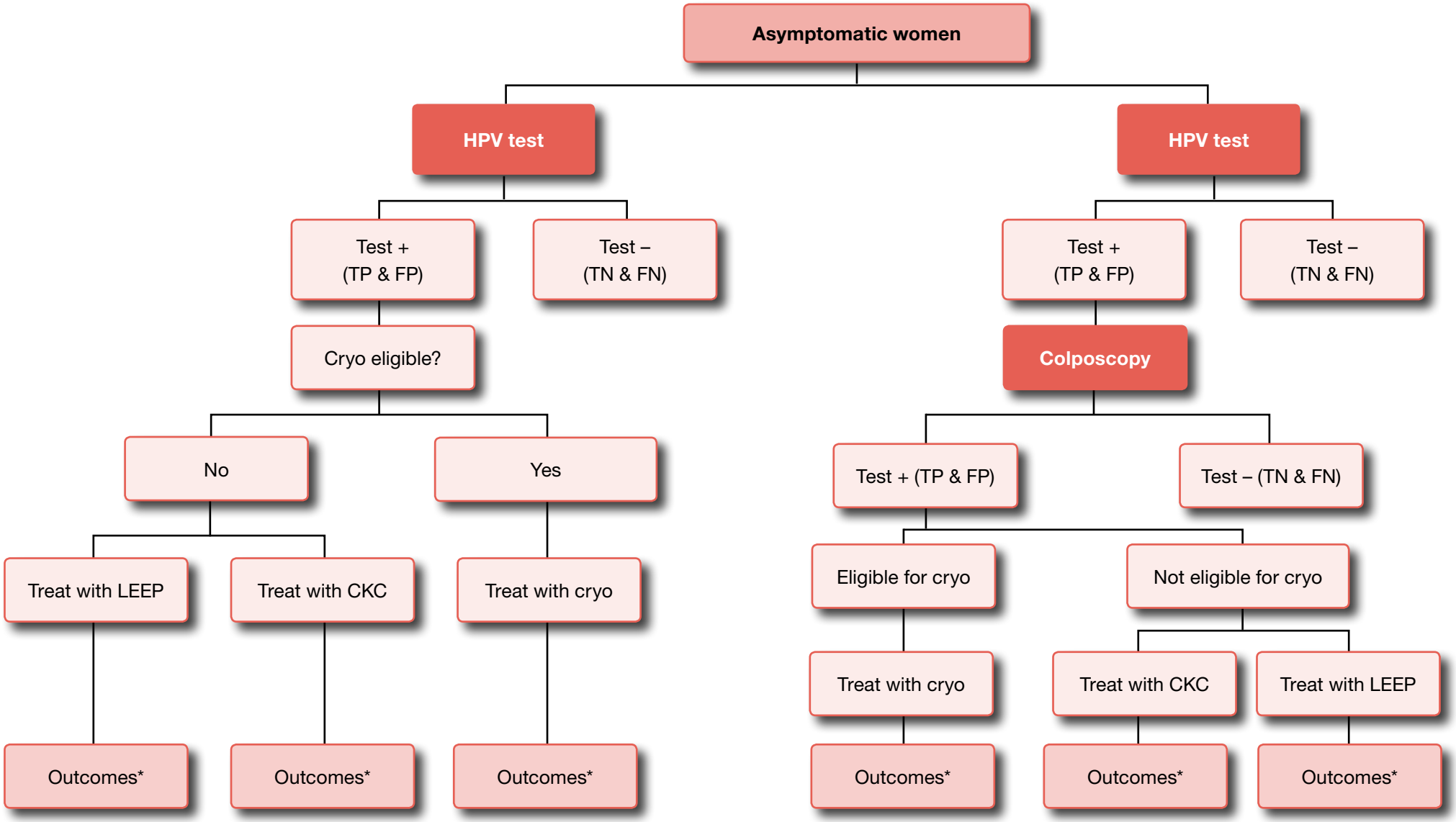
Remarks: The reductions in cancer and related mortality with either strategy outweigh the harms and costs of no screening, and were similar between the two strategies. Although overtreatment and, consequently, harms are reduced with the addition of colposcopy (with or without biopsy), there are more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and the potential for more women to be lost to follow-up. The addition of colposcopy to an HPV test would also require a second visit. In countries without an existing screening strategy, an HPV test followed by colposcopy is not recommended. 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 of HPV test followed by colposcopy and we did not have a direct comparison of this triage test 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: ☒	The benefits of HPV test followed by colposcopy and HPV test alone may be similar. However, there were greater harms with HPV test alone (due to overtreatment with HPV test alone). There may also be slightly fewer cancers detected with HPV test followed by colposcopy.
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 resources required and lower value on the harms.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes: ☒ No: ☐	There may be additional resources required with the addition of colposcopy (with or without biopsy), there are more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and potential for more women lost to follow up. The addition of colposcopy to HPV test would also require a second visit.

Evidence for HPV test compared to HPV test followed by colposcopy to screen for CIN2+

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 compared to HPV test followed by colposcopic impression

Diagnostic test accuracy

Pooled sensitivity HPV test	93% (95% CI: 87 to 96)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity HPV test	88% (95% CI: 82 to 91)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

2.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to HPV test followed by colposcopic impression

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test	HPV test followed by colposcopic impression	
True positives (patients with CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	19 (17 to 19)	18	CRITICAL
TP absolute difference									1 more		
True negatives (patients without CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	862 (813 to 892)	911	CRITICAL
TN absolute difference									49 fewer		
False positives (patients incorrectly classified as having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	118 (88 to 167)	68	CRITICAL
FP absolute difference									50 more		
False negatives (patients incorrectly classified as not having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	1 (1 to 3)	2	CRITICAL
FN absolute difference									1 fewer		

Footnotes:

[a] This is the number of studies that assessed data for HPV test.

[b] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] 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.

[e] Few participants contributed to colposcopy data. Therefore there are wide confidence intervals for colposcopy specificity, which 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: HPV test compared to HPV test followed by colposcopic impression

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	HPV→colp imp +/– CKC	HPV→colp imp +/–LEEP	HPV→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	20	30	30	31	41	41	250
Cervical cancer incidence[2]	28	43	43	44	58	58	350
CIN2+ recurrence[3]	1088	1677	1677	1704	2263	2263	13 400
Undetected CIN2+ (FN)	1000			2000			–
Major bleeding[4]	1176	309	46	743	195	29	0
Premature delivery[5]	665	558	586	604	537	554	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	122	175	18	77	111	12	0
Minor infections[8]	1283	826	887	810	521	560	0
Unnecessarily treated (FP)	118 000			68 000			–
Cancer found at first-time screening[9]	2454			3545			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 2%
- HPV test: pooled sensitivity 93% (95% CI: 87 to 96), pooled specificity 88% (95% CI: 82 to 91)
- Colposcopic impression: pooled sensitivity 95% (95% CI: 82 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

2.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	HPV→colp imp +/– CKC	HPV→colp imp +/–LEEP	HPV→colp imp +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	6	9	9	9	12	12	71
Cervical cancer incidence	8	13	12	12	17	17	100
CIN2+ recurrence	1109	1745	1698	1698	2305	2305	13 829
40–49 years[a]							
Mortality from cervical cancer	37	58	57	57	77	77	464
Cervical cancer incidence	52	82	79	79	108	108	650
CIN2+ recurrence	1062	1653	1651	1651	2213	2213	12 886
50–74 years[a]							
Mortality from cervical cancer	68	108	105	105	142	142	857
Cervical cancer incidence	96	199	151	146	146	199	1200
CIN2+ recurrence	1015	1604	1604	1562	2121	2121	11 943
Complications (same across all groups)							
Major bleeding[4]	1176	309	46	743	195	29	0
Premature delivery[5]	665	558	586	604	537	554	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	122	175	18	77	111	12	0
Minor infections[8]	1283	826	887	810	521	560	0

Footnotes:

[a] Events were calculated similar to Table 2.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 2.2.

3. Evidence used for decision-making: HPV test compared to HPV test followed by colposcopic impression

Diagnostic test accuracy

Pooled sensitivity HPV test	93% (95% CI: 87 to 96)	Pooled specificity HPV test	88% (95% CI: 82 to 91)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to HPV test followed by colposcopic impression

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test	HPV test followed by colposcopy with biopsy	
True positives (patients with CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	19 (17 to 19)	19	CRITICAL
TP absolute difference									0 more		
True negatives (patients without CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	862 (804 to 892)	980	CRITICAL
TN absolute difference									118 fewer		
False positives (patients incorrectly classified as having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	118 (88 to 176)	0	CRITICAL
FP absolute difference									118 more		
False negatives (patients incorrectly classified as not having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	1 (1 to 3)	1	CRITICAL
FN absolute difference									0		

Footnotes:

[a] This is the number of studies that assessed data for HPV test.

[b] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by colposcopy +/– biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] 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.

[e] Few participants contributed to colposcopy data. Therefore there are wide confidence intervals for colposcopy specificity, which may lead to different decisions depending on which confidence limits are assumed.

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test compared to HPV test followed by colposcopic impression

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	HPV→colp biopsy +/– CKC	HPV→colp biopsy +/–LEEP	HPV→colp biopsy +/– cryo	No screen[10]
Mortality from cervical cancer[1]	20	30	30	20	30	30	250
Cervical cancer incidence[2]	28	43	43	28	43	43	350
CIN2+ recurrence[3]	1088	1677	1677	1088	1677	1677	13 400
Undetected CIN2+ (FN)	1000			1000			–
Major bleeding[4]	1176	309	46	163	43	6	0
Premature delivery[5]	665	558	586	523	508	512	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	122	175	18	17	24	3	0
Minor infections[8]	1283	826	887	178	115	123	0
Unnecessarily treated (FP)	118 000			0			–
Cancer found at first-time screening[9]	2454			3545			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 2%
- HPV test: pooled sensitivity 93% (95% CI: 87 to 96), pooled specificity 88% (95% CI: 82 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

3.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV +/– CKC	HPV +/– LEEP	HPV +/– Cryo	HPV→colp biopsy +/– CKC	HPV→colp biopsy +/–LEEP	HPV→colp biopsy +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	6	9	9	6	9	9	71
Cervical cancer incidence	8	12	12	8	12	12	100
CIN2+ recurrence	1109	1698	1698	1109	1698	1698	13 829
40–49 years[a]							
Mortality from cervical cancer	37	57	57	37	57	57	464
Cervical cancer incidence	52	79	79	52	79	79	650
CIN2+ recurrence	1062	1651	1651	1062	1651	1651	12 886
50–74 years[a]							
Mortality from cervical cancer	68	105	105	68	105	105	857
Cervical cancer incidence	96	146	146	96	146	146	1200
CIN2+ recurrence	1015	1604	1604	1015	1604	1604	11 943
Complications (same across all groups)							
Major bleeding[4]	1176	309	46	163	43	6	0
Premature delivery[5]	665	558	586	523	508	512	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	122	175	18	17	24	3	0
Minor infections[8]	1283	826	887	178	115	123	0

Footnotes:

[a] Events were calculated similar to Table 3.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 3.2.

4. References

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

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4.2 References to studies included for diagnostic test accuracy of colposcopic impression

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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)**

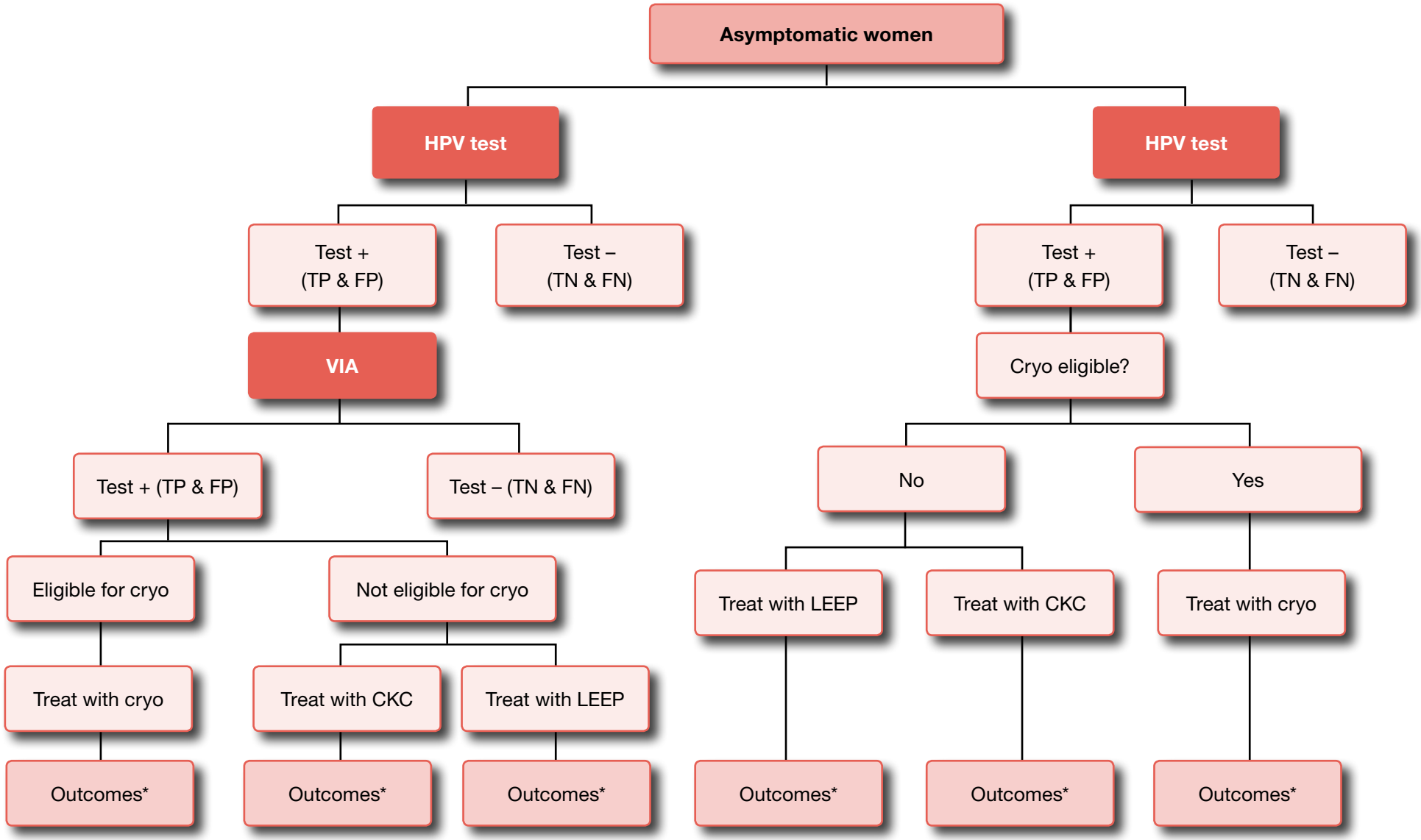
Remarks: The reductions in cancer and related mortality were greater with an HPV test used as a single screening test than with an HPV test followed by VIA, and this reduction was even greater in women of HIV-positive status. However, there may be overtreatment, and thus potentially greater harms with 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+

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 HPV test

Diagnostic test accuracy

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

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 5%		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	13	19 (17 to 20)	CRITICAL
TP absolute difference									6 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	960	823 (706 to 892)	CRITICAL
TN absolute difference									137 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	20	157 (88 to 274)	CRITICAL
FP absolute difference									137 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	7	1 (0 to 3)	CRITICAL
FN absolute difference									6 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.

[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: HPV test followed by VIA compared to HPV test

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]	91	99	99	20	30	30	250
Cervical cancer incidence[2]	128	138	138	28	43	43	350
CIN2+ recurrence[3]	4905	5311	5311	1088	1677	1677	13 400
Undetected CIN2+ (FN)	7000			1000			–
Major bleeding[4]	288	76	11	1511	397	60	0
Premature delivery[5]	540	514	521	712	575	610	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	30	43	5	156	225	24	0
Minor infections[8]	314	202	217	1649	1061	1139	0
Unnecessarily treated (FP)	20 000			157 000			–
Cancer found at first-time screening[9]	3168			2454			0

Footnotes:

*The colours in the table: I*n 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 2%
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 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.

2.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV→VIA +/– CKC	HPV→VIA +/– LEEP	HPV→VIA +/– cryo	HPV +/– CKC	HPV +/–LEEP	HPV +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	26	28	28	6	9	9	71
Cervical cancer incidence	37	39	39	8	12	12	100
CIN2+ recurrence	5052	5459	5459	1109	1698	1698	13 829
40–49 years[a]							
Mortality from cervical cancer	170	183	183	37	57	57	464
Cervical cancer incidence	237	256	256	52	79	79	650
CIN2+ recurrence	4728	5134	5134	1062	1651	1651	12 886
50–74 years[a]							
Mortality from cervical cancer	313	338	338	68	105	105	857
Cervical cancer incidence	438	473	473	96	146	146	1200
CIN2+ recurrence	4403	4809	4809	1015	1604	1604	11 943
Complications (same across all groups)							
Major bleeding[4]	288	76	11	1511	397	60	0
Premature delivery[5]	540	514	521	712	575	610	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	30	43	5	156	225	24	0
Minor infections[8]	314	202	217	1649	1061	1139	0

Footnotes:

[a] Events were calculated similar to Table 2.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 2.2.

3. 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. *Gynecologic 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.

Shastri SS et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bulletin of the World Health Organization*, 2005, 83(3):186–194.

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.

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)**

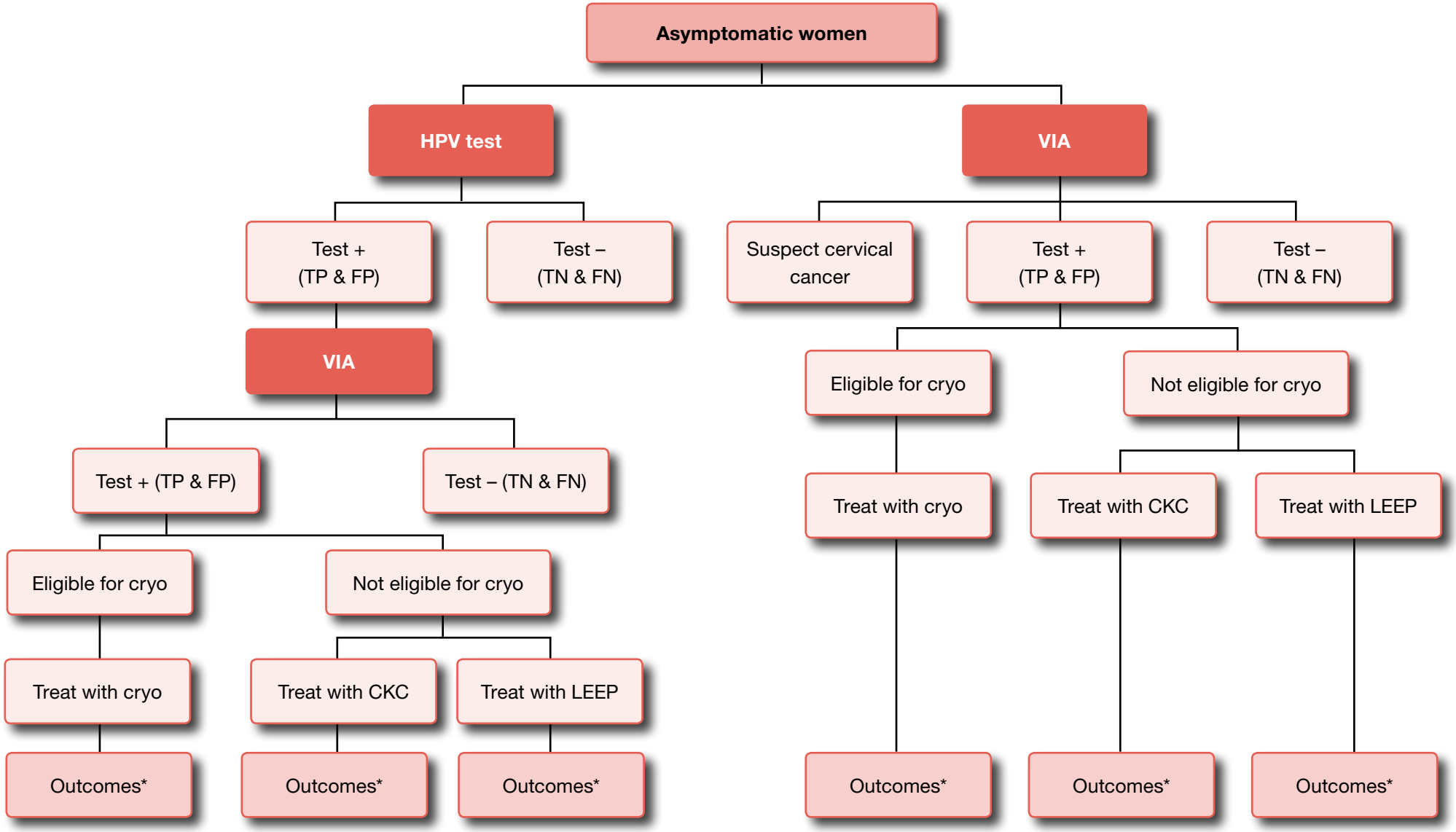
Remarks: The reductions in cancer and related mortality with an HPV test followed by VIA or with VIA alone outweighed the harms. However, the harms may be greater when using VIA only, which is likely due to overtreatment. Although, a slightly larger number of cancers may be detected on initial screen 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 an 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 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 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 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+

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

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

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 5%		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	13	14 (16 to 41)	CRITICAL
TP absolute difference									1 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	960	853 (774 to 902)	CRITICAL
TN absolute difference									107 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	20	127 (78 to 206)	CRITICAL
FP absolute difference									107 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	7	6 (4 to 9)	CRITICAL
FN absolute difference									1 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.

[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: HPV test followed by VIA compared to VIA

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]	91	99	99	81	88	88	250
Cervical cancer incidence[2]	128	138	138	113	124	124	350
CIN2+ recurrence[3]	4905	5311	5311	4328	4762	4762	13 400
Undetected CIN2+ (FN)	7000			6000			–
Major bleeding[4]	288	76	11	1210	318	48	0
Premature delivery[5]	540	514	521	670	560	588	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	30	43	5	125	180	19	0
Minor infections[8]	314	202	217	1321	850	913	0
Unnecessarily treated (FP)	20 000			127 000			–
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 2%
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 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.

2.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV→VIA +/– CKC	HPV→VIA +/– LEEP	HPV→VIA +/– cryo	VIA +/– CKC	VIA +/–LEEP	VIA +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	26	28	28	23	25	25	71
Cervical cancer incidence	37	39	39	32	35	35	100
CIN2+ recurrence	5052	5459	5459	4457	4891	4891	13 829
40–49 years[a]							
Mortality from cervical cancer	170	183	183	150	164	164	464
Cervical cancer incidence	237	256	256	209	229	229	650
CIN2+ recurrence	4728	5134	5134	4174	4608	4608	12 886
50–74 years[a]							
Mortality from cervical cancer	313	338	338	276	303	303	857
Cervical cancer incidence	438	473	473	386	424	424	1200
CIN2+ recurrence	4403	4809	4809	3891	4325	4325	11 943
Complications (same across all groups)							
Major bleeding[4]	288	76	11	1210	318	48	0
Premature delivery[5]	540	514	521	670	560	588	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	30	43	5	125	180	19	0
Minor infections[8]	314	202	217	1321	850	913	0

Footnotes:

[a] Events were calculated similar to Table 2.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 2.2.

3. 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. *Gynecologic 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 Gynaecology & 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.

Shastri SS et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bulletin of the World Health Organization*, 2005, 83(3):186–194.

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.

Recommendation 8

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 cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) **(conditional recommendation, ⊕⊖⊖⊖ evidence)**

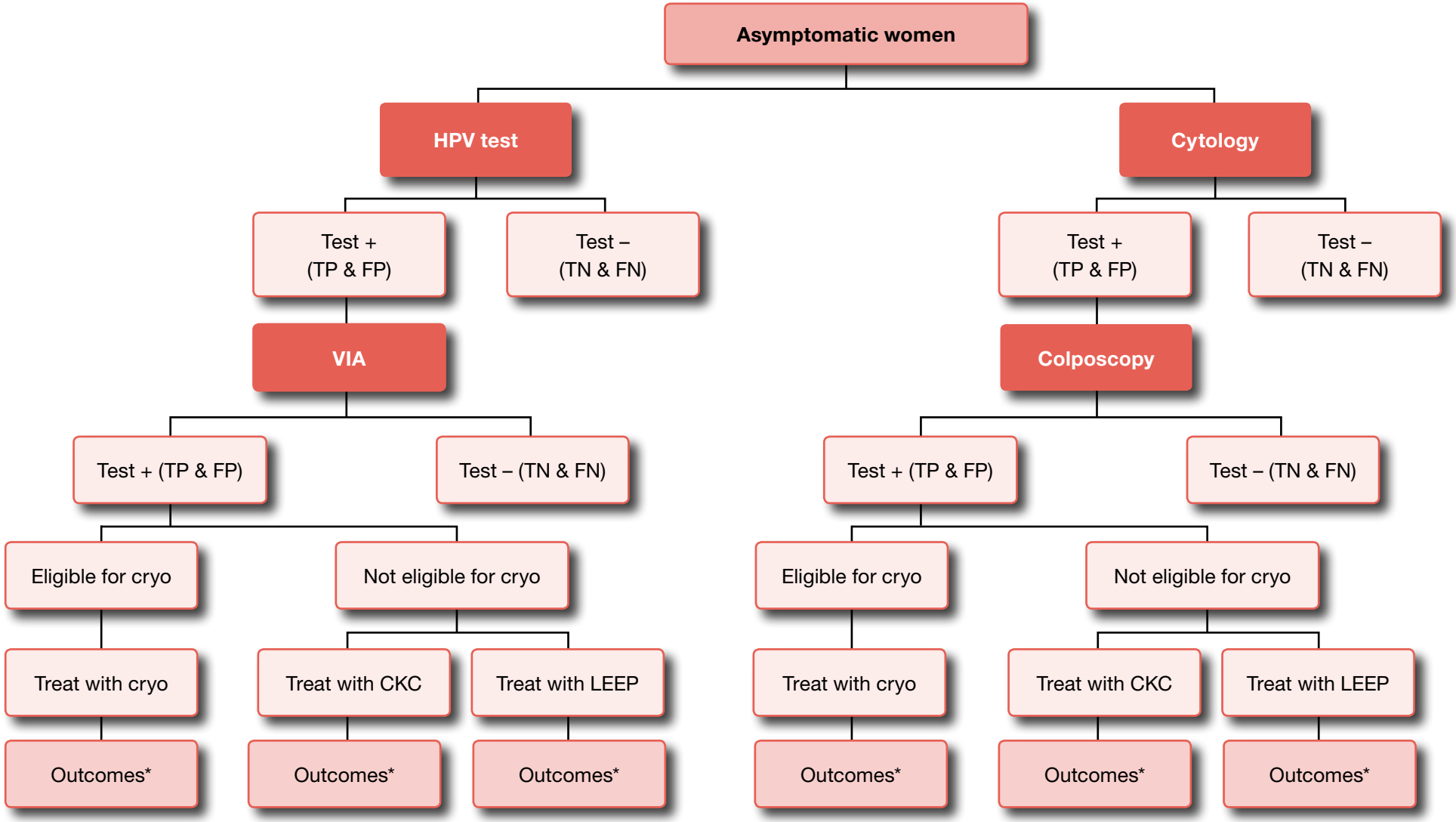
Remarks: The benefits of the two screen-and-treat strategies are similar. However, there may be higher resources required in cytology programmes due to quality control, training, and waiting time. The addition of colposcopy requires a second visit. This recommendation applies to women regardless of HIV 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 compared to cytology followed by colposcopy. 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 and harms of HPV test followed by VIA and cytology followed by colposcopy may be similar. However, 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 resources required.
Resource implications Is the cost small relative to the net benefits for the recommended strategy?	Yes ☒ / No ☐	Fewer resources may be required for HPV test followed by VIA as there may be additional resources required in cytology programmes due to increased training of providers, quality control, and waiting time. Colposcopy following cytology also requires a second visit.

Evidence for an HPV test followed by VIA compared to cytology followed by colposcopy to screen for CIN2+

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 cytology (ASCUS) and colposcopic impression

Diagnostic test accuracy

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity VIA	69% (95% CI: 54 to 81)
Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity VIA	87% (95% CI: 79 to 92)
Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity cytology (ASCUS)	95% (95% CI: 92 to 97)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

2.1 Diagnostic test accuracy (DTA) evidence profile: HPV test followed by VIA compared to cytology (ASCUS) and colposcopic impression

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test followed by VIA	Cytology followed by colposcopic impression	
True positives (patients with CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	13	13	CRITICAL
TP absolute difference									0		
True negatives (patients without CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	967	952	CRITICAL
TN absolute difference									15 more		
False positives (patients incorrectly classified as having CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	13	28	CRITICAL
FP absolute difference									15 fewer		
False negatives (patients incorrectly classified as not having CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	7	7	CRITICAL
FN absolute difference									0		

Footnotes:

[a] This is the number of studies that assessed DTA data for: 1. HPV test and VIA; and 2. HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by VIA and cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] Estimates of HPV test, VIA, cytology (ASCUS) and colposcopy sensitivity/specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of HPV test followed by VIA and cytology followed by colposcopy 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: HPV test followed by VIA compared to cytology (ASCUS) and colposcopic impression

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	Cyto→colp imp +/– CKC	Cyto→colp imp +/– LEEP	Cyto→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	91	99	99	89	96	96	250
Cervical cancer incidence[2]	128	138	138	125	135	135	350
CIN2+ recurrence[3]	4905	5311	5311	4782	5194	5194	13 400
Undetected CIN2+ (FN)	7000			7000			–
Major bleeding[4]	222	58	9	358	94	14	0
Premature delivery[5]	531	511	516	550	518	526	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	23	33	3	37	53	6	0
Minor infections[8]	242	156	167	391	251	270	0
Unnecessarily treated (FP)	13 000			28 000			–
Cancer found at first-time screening[9]	3168			4794			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 2%
- VIA: Pooled sensitivity 69% (95% CI: 54 to 81), pooled specificity 87% (95% CI: 79 to 92)
- Cytology (ASCUS): Pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
- Colposcopy: Pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

2.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV→VIA +/– CKC	HPV→VIA +/– LEEP	HPV→VIA +/– cryo	Cyto→colp imp +/– CKC	Cyto→colp imp +/–LEEP	Cyto→colp imp +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	26	28	28	25	28	28	71
Cervical cancer incidence	37	39	39	36	39	39	100
CIN2+ recurrence	5052	5459	5459	4925	5337	5337	13 829
40–49 years[a]							
Mortality from cervical cancer	170	183	183	165	179	179	464
Cervical cancer incidence	237	256	256	231	250	250	650
CIN2+ recurrence	4728	5134	5134	4609	5022	5022	12 886
50–74 years[a]							
Mortality from cervical cancer	313	338	338	305	330	330	857
Cervical cancer incidence	438	473	473	427	462	462	1200
CIN2+ recurrence	4403	4809	4809	4293	4706	4706	11 943
Complications (same across all groups)							
Major bleeding[4]	222	58	9	358	94	14	0
Premature delivery[5]	531	511	516	550	518	526	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	23	33	3	37	53	6	0
Minor infections[8]	242	156	167	391	251	270	0

Footnotes:

[a] Events were calculated similar to Table 2.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 2.2.

3. Evidence used for decision-making: HPV test followed by VIA compared to cytology (ASCUS) and colposcopic impression with biopsy when indicated

Diagnostic test accuracy

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity VIA	69% (95% CI: 54 to 81)	Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)
Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity VIA	87% (95% CI: 79 to 92)	Pooled specificity cytology (ASCUS)	95% (95% CI: 92 to 97)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: HPV test followed by VIA compared to cytology (ASCUS) and colposcopy with biopsy when indicated

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test followed by VIA	Cytology followed by colposcopy with biopsy	
True positives (patients with CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	13	14	CRITICAL
TP absolute difference									1 fewer		
True negatives (patients without CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	967	980	CRITICAL
TN absolute difference									13 fewer		
False positives (patients incorrectly classified as having CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	13	0	CRITICAL
FP absolute difference									13 more		
False negatives (patients incorrectly classified as not having CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	7	6	CRITICAL
FN absolute difference									1 more		

Footnotes:

[a] This is the number of studies that assessed DTA data for: 1. HPV test and VIA, and 2. HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by VIA and cytology followed by colposcopy +/– biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] Estimates of HPV test, VIA and cytology (ASCUS) sensitivity/specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

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

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test followed by VIA compared to cytology (ASCUS) and colposcopy with biopsy when indicated

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	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/–LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
Mortality from cervical cancer[1]	91	99	99	81	88	88	250
Cervical cancer incidence[2]	128	138	138	113	124	124	350
CIN2+ recurrence[3]	4905	5311	5311	4328	4762	4762	13 400
Undetected CIN2+ (FN)	7000			6000			–
Major bleeding[4]	222	58	9	120	32	5	0
Premature delivery[5]	531	511	516	517	506	509	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	23	33	3	12	18	2	0
Minor infections[8]	242	156	167	131	84	91	0
Unnecessarily treated (FP)	13 000			0			–
Cancer found at first-time screening[9]	3168			3545			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 2%
- HPV test: Pooled sensitivity 94% (95% CI: 89 to 97), pooled specificity 90% (95% CI: 86 to 93)
- VIA: Pooled sensitivity 69% (95% CI: 54 to 81), pooled specificity 87% (95% CI: 79 to 92)
- Cytology (ASCUS): Pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

3.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV→VIA +/– CKC	HPV→VIA +/– LEEP	HPV→VIA +/– cryo	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/– LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	26	28	28	23	25	25	71
Cervical cancer incidence	37	39	39	32	35	35	100
CIN2+ recurrence	5052	5459	5459	4457	4891	4891	13 829
40–49 years[a]							
Mortality from cervical cancer	170	183	183	150	164	164	464
Cervical cancer incidence	237	256	256	209	229	229	650
CIN2+ recurrence	4728	5134	5134	4174	4608	4608	12 886
50–74 years[a]							
Mortality from cervical cancer	313	338	338	276	303	303	857
Cervical cancer incidence	438	473	473	386	424	424	1200
CIN2+ recurrence	4403	4809	4809	3891	4325	4325	11 943
Complications (same across all groups)							
Major bleeding[4]	222	58	9	120	32	5	0
Premature delivery[5]	531	511	516	517	506	509	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	23	33	3	12	18	2	0
Minor infections[8]	242	156	167	131	84	91	0

Footnotes:

[a] Events were calculated similar to Table 3.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 3.2.

4. References

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

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4.2 References to studies included for diagnostic test accuracy of colposcopic impression

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Recommendation 9

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 an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible)
(conditional recommendation, ⊕⊖⊖⊖ evidence)

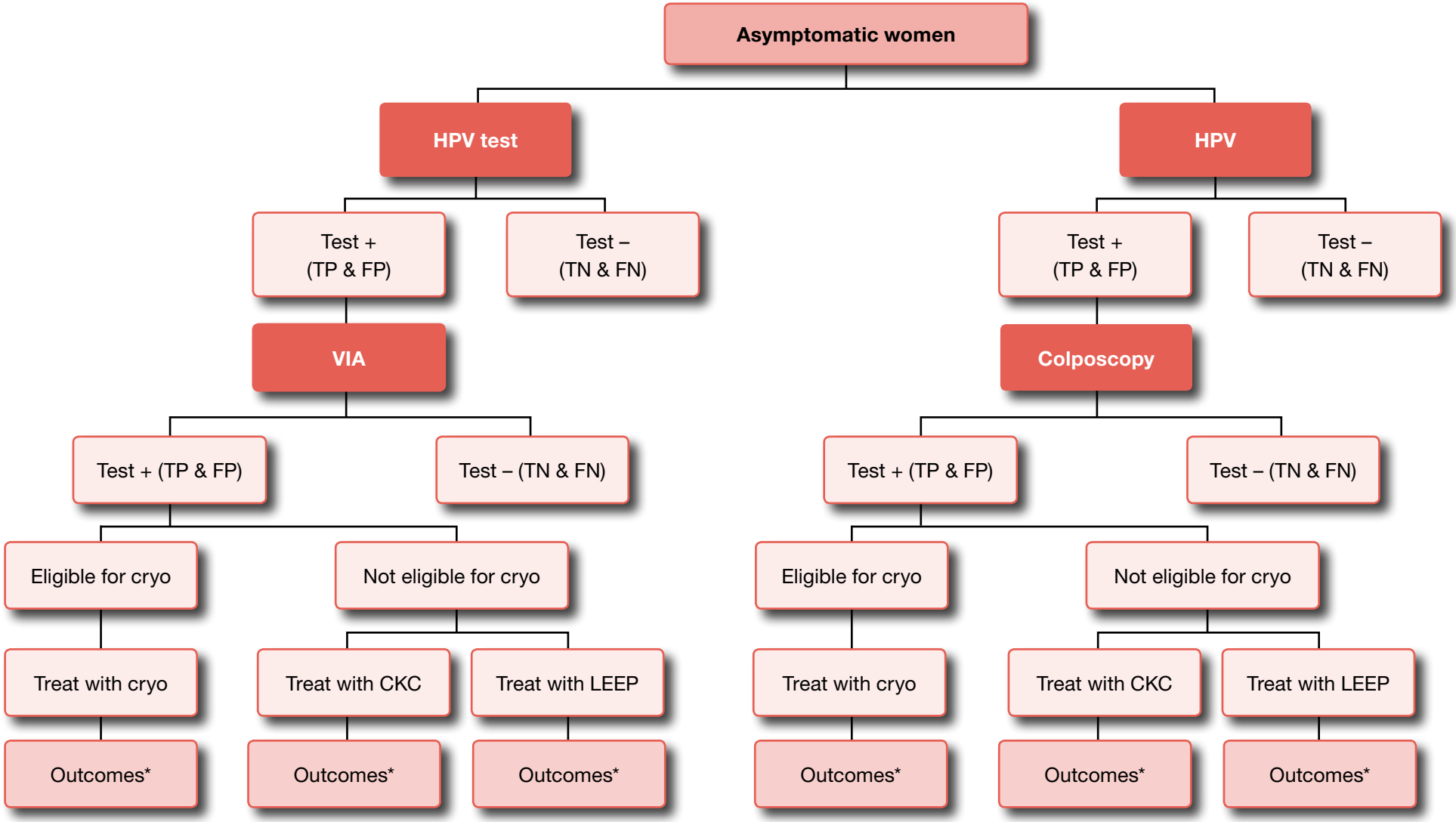
Remarks: The reductions in cancer and related mortality of screen-and-treat with an HPV test followed by colposcopy (with or without biopsy) may be slightly greater compared to an HPV test followed by VIA. The panel agreed that the benefits of either strategy outweigh the harms and costs; however, the difference in costs between the strategies is uncertain. There may be more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and the potential for more women to be lost to follow-up. It is also unclear whether women would perceive a difference between VIA and colposcopy; however, a biopsy during colposcopy may be less acceptable than VIA. 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 of both triage tests and a comparison between the strategies. 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. Also 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 colposcopy (reduction in CIN recurrence, cervical cancer, and related mortality) may be greater than with HPV test followed by VIA. But there may be greater overtreatment with HPV test followed by colposcopy without biopsy. Little or no difference in cancers detected.
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 women overtreated and potential complications. High value was placed on women finding a biopsy less acceptable than visual inspection.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☐ / No ☒	There may be greater resource implications by adding colposcopy than with adding VIA to the HPV test due to increased training of providers, quality control, waiting time, and potential for more women lost to follow up.

Evidence for an HPV test followed by VIA compared to an HPV test followed by colposcopy to screen for CIN2+

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 HPV test followed by colposcopic impression

Diagnostic test accuracy

Pooled sensitivity HPV test	95% (95% CI: 84 to 98)	Pooled sensitivity VIA	69% (95% CI: 54 to 81)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity HPV test	84% (95% CI: 72 to 91)	Pooled specificity VIA	87% (95% CI: 79 to 92)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

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

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test followed by VIA	HPV test followed by colposcopic impression	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	13	18	CRITICAL
TP absolute difference									5 fewer		
True negatives (patients without CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	960	889	CRITICAL
TN absolute difference									71 more		
False positives (patients incorrectly classified as having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	20	91	CRITICAL
FP absolute difference									71 fewer		
False negatives (patients incorrectly classified as not having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	7	2	CRITICAL
FN absolute difference									5 more		

Footnotes:

[a] This is the number of studies that assessed DTA data for HPV test and VIA.

[b] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by VIA and for HPV test followed by colposcopic impression were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] 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.

[e] 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: HPV test followed by VIA compared to HPV test followed by colposcopic impression

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→colp imp +/– CKC	HPV→colp imp +/–LEEP	HPV→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	91	99	99	31	41	42	250
Cervical cancer incidence[2]	128	138	138	44	58	58	350
CIN2+ recurrence[3]	4905	5311	5311	1704	2263	2263	13 400
Undetected CIN2+ (FN)	7000			2000			
Major bleeding[4]	288	76	11	937	246	37	0
Premature delivery[5]	540	514	521	631	546	568	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	30	43	5	97	140	15	0
Minor infections[8]	314	202	217	1022	658	706	0
Unnecessarily treated (FP)	20 000			91 000			–
Cancer found at first-time screening[9]	3168			3545			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 2%
- 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)
- Colposcopy: pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

2.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV→VIA +/– CKC	HPV→VIA +/– LEEP	HPV→VIA +/– cryo	HPV→colp imp +/– CKC	HPV→colp imp +/– LEEP	HPV→colp imp +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	26	28	28	9	12	12	71
Cervical cancer incidence	37	39	39	13	17	17	100
CIN2+ recurrence	5052	5459	5459	1745	2305	2305	13 829
40–49 years[a]							
Mortality from cervical cancer	170	183	183	58	77	77	464
Cervical cancer incidence	237	256	256	82	108	108	650
CIN2+ recurrence	4728	5134	5134	1653	2213	2213	12 886
50–74 years[a]							
Mortality from cervical cancer	313	338	338	108	142	142	857
Cervical cancer incidence	438	473	473	151	199	199	1200
CIN2+ recurrence	4403	4809	4809	1562	2121	2121	11 943
Complications (same across all groups)							
Major bleeding[4]	288	76	11	937	246	37	0
Premature delivery[5]	540	514	521	631	546	568	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	30	43	5	97	140	15	0
Minor infections[8]	314	202	217	1022	658	706	0

Footnotes:

[a] Events were calculated similar to Table 2.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 2.2.

3. Evidence used for decision-making: HPV test followed by VIA compared to HPV test followed by colposcopy with biopsy

Diagnostic test accuracy

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)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: HPV test followed by VIA vs HPV test followed by colposcopy with biopsy

Outcome	No. of studies (No. of patients)[a]	Study design	Factors that may decrease quality of evidence					DTA QoE	Effect per 1000 patients/year for pretest probability of 2%		Importance
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test followed by VIA	HPV test followed by colposcopy with biopsy	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	13	19	CRITICAL
TP absolute difference									6 fewer		
True negatives (patients without CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	960	980	CRITICAL
TN absolute difference									20 fewer		
False positives (patients incorrectly classified as having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	20	0	CRITICAL
FP absolute difference									20 more		
False negatives (patients incorrectly classified as not having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	7	1	CRITICAL
FN absolute difference									6 more		

Footnotes:

[a] This is the number of studies that assessed DTA data for HPV test and VIA.

[b] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by VIA and for HPV test followed by colposcopy with biopsy when indicated were calculated based on sensitivity and specificity of the two tests. Direct data were not available.

[d] 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.

[e] 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.

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test followed by VIA compared to HPV test followed by colposcopy with biopsy

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→colp biopsy +/– CKC	HPV→colp biopsy +/–LEEP	HPV→colp biopsy +/– cryo	No screen[10]
Mortality from cervical cancer[1]	91	99	99	20	30	31	250
Cervical cancer incidence[2]	128	138	138	28	43	43	350
CIN2+ recurrence[3]	4905	5311	5311	1088	1677	1677	13 400
Undetected CIN2+ (FN)	7000			1000			
Major bleeding[4]	288	76	11	163	43	6	0
Premature delivery[5]	540	514	521	523	508	512	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	30	43	5	17	24	3	0
Minor infections[8]	314	202	217	178	115	123	0
Unnecessarily treated (FP)	20 000			0			–
Cancer found at first-time screening[9]	3168			3545			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 2%
- 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, we assumed 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. To calculate cervical cancer incidence in women with persistent CIN2+, 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 70% natural persistence of CIN2+ with no treatment (30% regression) in FN. The incidence of cervical cancer and mortality are also subtracted from the CIN2+ in FN (see above for calculations). 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 tests 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 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.

3.3 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies by age

	HPV→VIA +/– CKC	HPV→VIA +/– LEEP	HPV→VIA +/– cryo	HPV→colp biopsy +/– CKC	HPV→colp biopsy +/–LEEP	HPV→colp biopsy +/– cryo	No screen[10]
15–39 years[a]							
Mortality from cervical cancer	26	28	28	6	9	9	71
Cervical cancer incidence	37	39	39	8	12	12	100
CIN2+ recurrence	5052	5459	5459	1109	1698	1698	13 829
40–49 years[a]							
Mortality from cervical cancer	170	183	183	37	57	57	464
Cervical cancer incidence	237	256	256	52	79	79	650
CIN2+ recurrence	4728	5134	5134	1062	1651	1651	12 886
50–74 years[a]							
Mortality from cervical cancer	313	338	338	68	105	105	857
Cervical cancer incidence	438	473	473	96	146	146	1200
CIN2+ recurrence	4403	4809	4809	1015	1604	1604	11 943
Complications (same across all groups)							
Major bleeding[4]	288	76	11	163	43	6	0
Premature delivery[5]	540	514	521	523	508	512	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	30	43	5	17	24	3	0
Minor infections[8]	314	202	217	178	115	123	0

Footnotes:

[a] Events were calculated similar to Table 3.2. However, events for cervical cancer are based on incidence of cervical cancer in Eastern Africa of 100/1 000 000 cervical cancers per year in women age 15–39 years; 650 for age 40–49 years; and 1200 for age 50–74 years, provided by WHO (http://globocan.iarc.fr/, accessed 30 October 2012). It is assumed that the recurrence of CIN is constant across age groups but the incidence of cervical cancer and associated mortality increases, thus reducing the overall recurrence of CIN (a proportion of those with CIN will develop cancer or die). These data should be used primarily to make comparisons across screen-and-treat strategies, not within columns for different age groups.

[4,5,6,7,8,10] See footnotes for Table 3.2.

4. References

4.1 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. *Gynecologic 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.

Shastri SS et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bulletin of the World Health Organization*, 2005, 83(3):186–194.

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.

4.2 References to studies included for diagnostic test accuracy of colposcopic impression

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

Cantor SB et al. Accuracy of colposcopy in the diagnostic setting compared with the screening setting. *Obstetrics & Gynecology*, 2008, 111(1):7–14.

Cremer ML et al. Digital assessment of the reproductive tract versus colposcopy for directing biopsies in women with abnormal Pap smears. *Journal of Lower Genital Tract Disease*, 2010, 14(1):5–10.

Cristoforoni PM et al. Computerized colposcopy: results of a pilot study and analysis of its clinical relevance. *Obstetrics & Gynecology*, 1995, 85(6):1011–1016.

Durdi GS et al. Correlation of colposcopy using Reid colposcopic index with histopathology – a prospective study. *Journal of the Turkish German Gynecology Association*, 2009, 10(4):205–207.

Ferris DG, Miller MD. Colposcopic accuracy in a residency training program: defining competency and proficiency. *Journal of Family Practice*, 1993, 36(5):515–520.

Homesley HD, Jobson VW, Reish RL. Use of colposcopically directed, four-quadrant cervical biopsy by the colposcopy trainee. *Journal of Reproductive Medicine*, 1984, 29(5):311–316.

Jones DE et al. Evaluation of the atypical Pap smear. *American Journal of Obstetric Gynecology*, 1987, 157(3):544–549.

Kierkegaard O et al. Diagnostic accuracy of cytology and colposcopy in cervical squamous intraepithelial lesions. *Acta Obstetricia et Gynecologica Scandinavica*, 1994, 73(8):648–651.

Mousavi AS et al. A prospective study to evaluate the correlation between Reid colposcopic index impression and biopsy histology. *Journal of Lower Genital Tract Disease*, 2007, 11(3):147–150.

Patil K et al. Comparison of diagnostic efficacy of visual inspection of cervix with acetic acid and Pap smear for prevention of cervical cancer: Is VIA superseding Pap smear? *Journal of SAFOG*, 2011, 3(3):131–134.

Section B.

GRADE evidence-to-recommendation tables and evidence profiles for each recommendation (HIV-positive status or unknown HIV status in areas with high endemic HIV infection)

Recommendation 1

The expert panel recommends against the use of CKC as treatment in a screen-and-treat strategy (strong recommendation, ⊕⊖⊖⊖ evidence)

Remarks: The screen-and-treat strategies considered by the panel with CKC as treatment included the HPV test, VIA, or an HPV test followed by VIA as screening. Although the benefits were similar for CKC compared with cryotherapy or LEEP for all screen-and-treat strategies, the harms were greater with CKC. 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- to high-quality evidence for the diagnostic test accuracy data for all screen-and-treat strategies. 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 desirable effects of screen-and-treat strategies with cold knife conization may be greater than no screening, but may be similar to other screen-and-treat strategies with cryotherapy or LEEP. However, the risk of major and minor harms was greater when compared to those strategies.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ / No ☐	A high value was placed on the complications (including risk of premature delivery) from treatment with cold knife conization after screening.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	Resources for cold knife conization are greater than for cryotherapy or LEEP.

This recommendation was made using the data from recommendations 1 to 8, in which the outcomes after use of CKC were compared to LEEP and cyrotherapy. Refer to the following recommendations as presented in this section.

Recommendation 2

Where resources permit, the expert panel suggests a strategy of screen with an HPV test 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)

In resource-constrained settings, where screening with an HPV test is not feasible, the expert panel suggests a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible) over a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

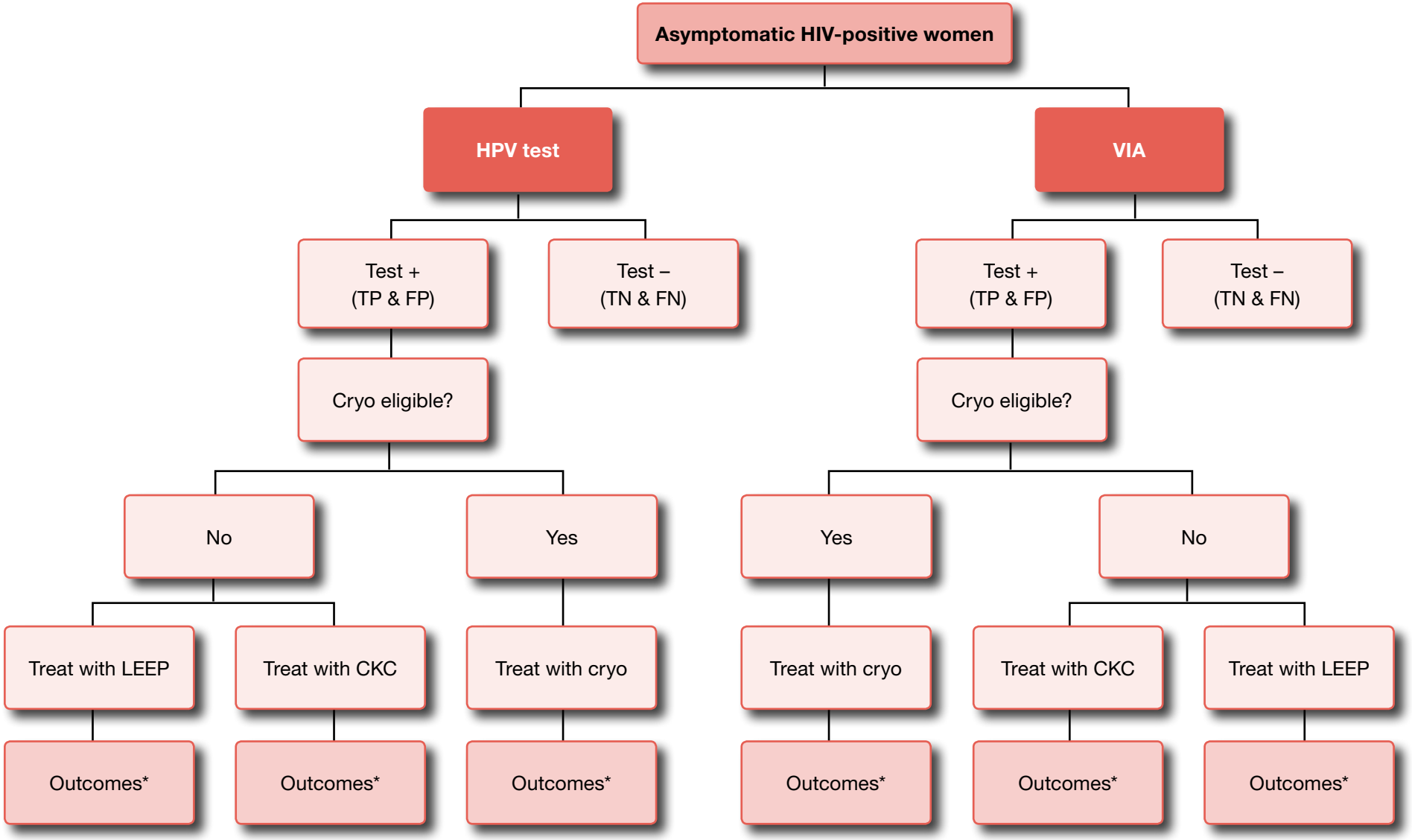
Remarks: The benefits of screen-and-treat with an HPV test or VIA, compared to no screening, outweighed the harms, but the reductions in cancer and related mortality were greater with an HPV test when compared to VIA. The availability of HPV testing is resource-dependent and, therefore, the expert panel suggests that an HPV test over VIA be provided where it is available, affordable, implementable, and sustainable over time. 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 high- to moderate-quality evidence for the diagnostic test accuracy data for VIA and the HPV test. 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 screen-and-treat strategy (reduction in CIN recurrence, cervical cancer, and related mortality) may be greater than VIA, and the harms may be similar. There may also be slightly greater overtreatment and slightly fewer cancers detected with an HPV test compared to 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 also placed on a reduction in cervical cancer and related mortality versus complications from treatment (e.g. major bleeding or infection requiring hospitalization). Low value was placed on minor infections or bleeding, and the small number of cancers detected at screening or of women overtreated.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☐ / No ☒	HPV testing is resource dependent. Where HPV testing is available, affordable and implementable, the overall net benefit over VIA is worth the resources. But where not available, an HPV test may not be worth the benefits.

Evidence for an HPV test 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 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 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	VIA	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None[b]	None[c]	None	Undetected	⊕⊕⊕⊕ high	95 (84 to 98)	69 (11 to 81)	CRITICAL
TP absolute difference									26 more		
True negatives (patients without CIN2+)	5 studies 8921 patients)	Cross-sectional and cohort studies	None[a]	None[b]	Serious[c]	None[d]	Undetected	⊕⊕⊕⊖ moderate	756 (648 to 819)	783 (711 to 828)	CRITICAL
TP absolute difference									27 fewer		
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	144 (81 to 252)	117 (72 to 189)	CRITICAL
FP absolute difference									27 more		
False negatives (patients incorrectly classified as not having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	None[a]	None[b]	None[c]	None	Undetected	⊕⊕⊕⊕ high	5 (2 to 16)	31 (19 to 46)	CRITICAL
FP absolute difference									26 fewer		

Footnotes:

[a] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. The decision not to downgrade this was a borderline judgement.

[b] 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 and VIA sensitivity and specificity were variable despite similar cut-off values; and could not be explained by quality of studies. For TP and FN this was a borderline judgement. We downgraded TN and FP and considered this in the context of other factors, in particular, imprecision.

[d] Wide CI for TN and FP that may lead to different decisions depending on which of the confidence limits is assumed.

2.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test compared to VIA

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV +/– CKC	HPV +/–LEEP	HPV +/– cryo	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	No screen[10]
Mortality from cervical cancer[1]	318	460	460	1481	1521	1521	4350
Cervical cancer incidence[2]	445	644	644	1986	2130	2130	6075
CIN2+ recurrence[3]	6069	9014	9014	26 190	28 329	28 329	79 575
Undetected CIN2+ (FN)	5000			31 000			–
Major bleeding[4]	2052	539	81	1597	420	63	0
Premature delivery[5]	788	602	649	724	579	616	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	212	306	32	165	238	25	0
Minor infections[8]	2239	1440	1547	1742	1121	1204	0
Unnecessarily treated (FP)	144 000			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+.

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[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

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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

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Zhang HY et al. HPV prevalence and cervical intraepithelial neoplasia among HIV-infected women in Yunnan Province, China: a pilot study. *Asian Pacific Journal of Cancer Prevention*, 2012, 13(1):91–96.

Recommendation 3

The expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

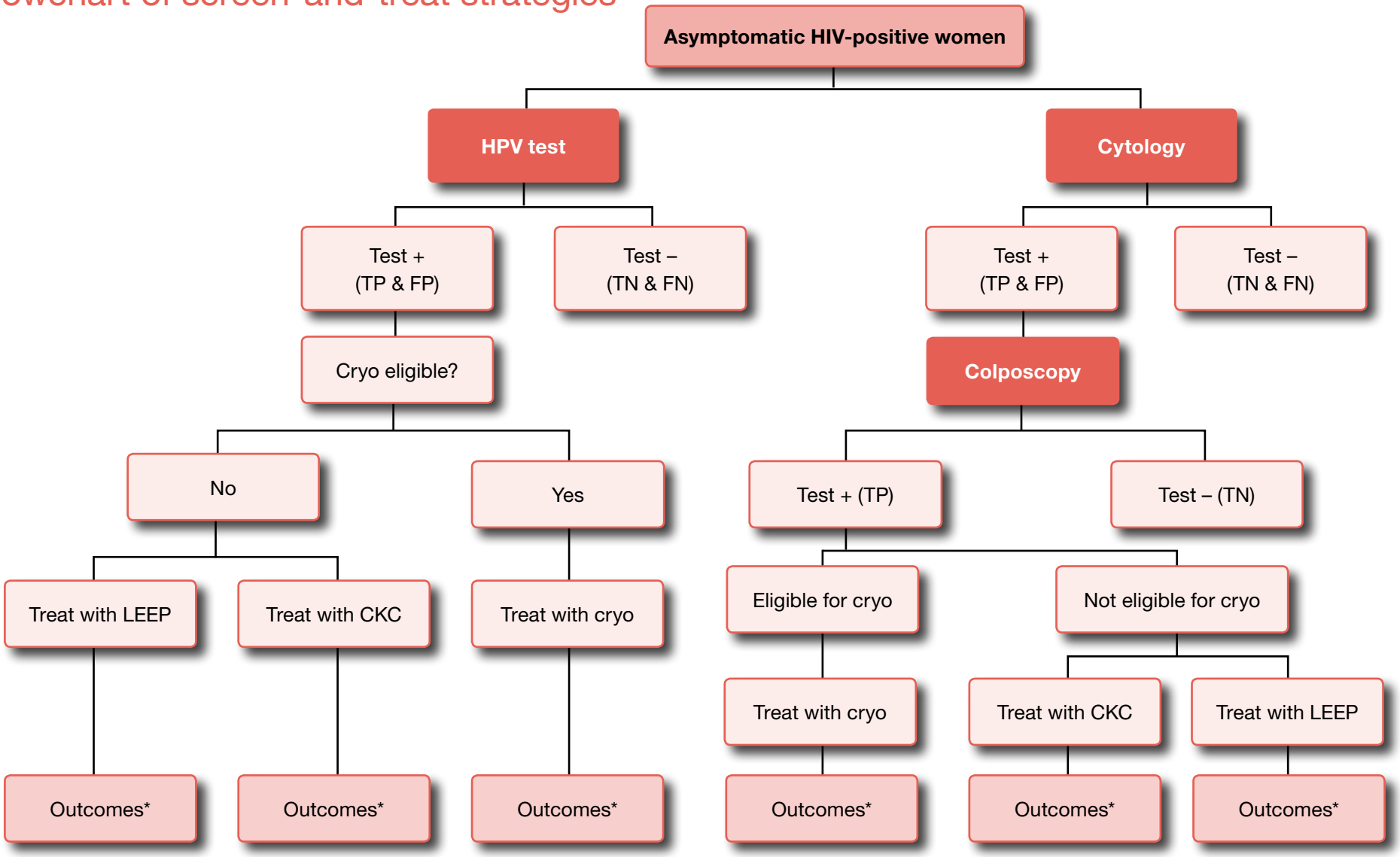
Remarks: The reductions in cancer and related mortality were slightly greater with an HPV test only compared to cytology followed by colposcopy. Although there may be overtreatment of populations with high HPV prevalence and consequently more harms, as well as fewer cancers seen at first-time screening with an HPV test, there are greater resources required in cytology programmes due to quality control, training, and waiting time. The addition of colposcopy also requires a second visit. However, in countries where an appropriate/high-quality screening strategy with cytology (referring women with ASCUS or greater results) followed by colposcopy already exists, either an HPV test or cytology followed by colposcopy could be used.

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 cytology followed by colposcopy 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: ☒	The benefits of HPV test alone were greater than with cytology followed by colposcopy. However, there may be greater harms with HPV test alone (due to overtreatment with HPV test alone) and fewer cancers detected with HPV test.
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 resources required and lower value on the harms.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes: ☒ No: ☐	There may be additional resources required in cytology programmes due to increased training of providers, quality control, and waiting time. Colposcopy following cytology also requires a second visit. However, in countries where an appropriate/high-quality screening strategy with cytology exists, resources would be required to change over to HPV test.

Evidence for an HPV test compared to cytology followed by colposcopy 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 compared to cytology (ASCUS) and colposcopic impression

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

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)	Pooled sensitivity colposcopic impresssion	95% (95% CI: 86 to 98)
Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity cytology (ASCUS)	95% (95% CI: 92 to 97)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

2.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to cytology (ASCUS) and colposcopic impression

Outcome	No. of studies (No. of patients)[a]	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	Cytology followed by colposcopic impression	
True positives (patients with CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	94 (89 to 97)	67	CRITICAL
TP absolute difference									27 more		
True negatives (patients without CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	810 (774 to 837)	874	CRITICAL
TP absolute difference									64 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	90 (63 to 126)	26	CRITICAL
FP absolute difference									64 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	6 (3 to 11)	34	CRITICAL
FP absolute difference									28 fewer		

Footnotes:

[a] This is the number of studies that assessed data for HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available. 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.

[d] Estimates of HPV test, cytology (ASCUS) and colposcopy sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of cytology followed by colposcopy 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: HPV test compared to cytology (ASCUS) and colposcopic impression

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	Cyto→colp imp +/– CKC	Cyto→colp imp +/– LEEP	Cyto→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	360	501	501	1524	1624	1624	4350
Cervical cancer incidence[2]	504	701	701	2134	2273	2273	6075
CIN2+ recurrence[3]	6843	9757	9757	28 124	30 186	30 186	79 575
Undetected CIN2+ (FN)	6000			34 000			–
Major bleeding[4]	1580	415	62	795	209	31	0
Premature delivery[5]	722	578	615	612	539	558	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	163	235	25	82	118	13	0
Minor infections[8]	1724	1109	1191	867	558	599	0
Unnecessarily treated (FP)	90 000			26 000			–
Cancer found at first-time screening[9]	2454			4794			–

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% of women of HIV-positive status (Denny et al., 2008; De Vuyst et al., 2012; Joshi et al., 2012; Zhang et al., 2012)
- HPV test: pooled sensitivity 94% (95% CI: 89 to 97), pooled specificity 90% (95% CI: 86 to 93)
- Cytology (ASCUS): pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
- Colposcopic impression: pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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.

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[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. Evidence used for decision-making: HPV test compared to cytology (ASCUS) and colposcopic impression with biopsy when indicated

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

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)
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			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		HPV test	Cytology followed by colposcopy with biopsy	
True positives (patients with CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	94 (89 to 97)	70	CRITICAL
TP absolute difference									24 more		
True negatives (patients without CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	810 (774 to 837)	900	CRITICAL
TP absolute difference									90 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	90 (63 to 126)	0	CRITICAL
FP absolute difference									90 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (39 050 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	6 (3 to 11)	30	CRITICAL
FP absolute difference									24 fewer		

Footnotes:

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[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. This was downgraded one level in the context of other factors, in particular indirectness.

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Major infections[7]	163	235	25	62	90	9	0
Minor infections[8]	1724	1109	1191	656	422	453	0
Unnecessarily treated (FP)	90 000			0			–
Cancer found at first-time screening[9]	2454			4794			0

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[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.

4. References

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

Agorastos T et al. Human papillomavirus testing for primary screening in women at low risk of developing cervical cancer. The Greek experience. *Gynecologic Oncology*, 2005, 96(3):714–720.

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

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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.

Petry KU et al. Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. *British Journal of Cancer*, 2003, 88(10):1570–1577.

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.

4.2 References to studies included for diagnostic test accuracy of colposcopic impression

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

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Durdi GS et al. Correlation of colposcopy using Reid colposcopic index with histopathology – a prospective study. *Journal of the Turkish German Gynecology Association*, 2009, 10(4):205–207.

Ferris DG, Miller MD. Colposcopic accuracy in a residency training program: defining competency and proficiency. *Journal of Family Practice*, 1993, 36(5):515–520.

Homesley HD, Jobson VW, Reish RL. Use of colposcopically directed, four-quadrant cervical biopsy by the colposcopy trainee. *Journal of Reproductive Medicine*, 1984, 29(5):311–316.

Jones DE et al. Evaluation of the atypical Pap smear. *American Journal of Obstetrics & Gynecology*, 1987, 157(3):544–549.

Kierkegaard O et al. Diagnostic accuracy of cytology and colposcopy in cervical squamous intraepithelial lesions. *Acta Obstetricia et Gynecologica Scandinavica*, 1994, 73(8):648–651.

Mousavi AS et al. A prospective study to evaluate the correlation between Reid colposcopic index impression and biopsy histology. *Journal of Lower Genital Tract Disease*, 2007, 11(3):147–150.

Patil K et al. Comparison of diagnostic efficacy of visual inspection of cervix with acetic acid and Pap smear for prevention of cervical cancer: is VIA superseding Pap smear? *Journal of SAFOG*, 2011, 3(3):131–134.

4.3 References to studies included for diagnostic test accuracy of colposcopic impression

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.

De Vuyst H et al. Prevalence and determinants of human papillomavirus infection and cervical lesions in HIV-positive women in Kenya. *British Journal of Cancer*, 2012, 107(9):1624–1630.

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.

Zhang HY et al. HPV prevalence and cervical intraepithelial neoplasia among HIV-infected women in Yunnan Province, China: a pilot study. *Asian Pacific Journal of Cancer Prevention*, 2012, 13(1):91–96.

Recommendation 4

The expert panel recommends a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (strong recommendation, ⊕⊖⊖⊖ evidence)

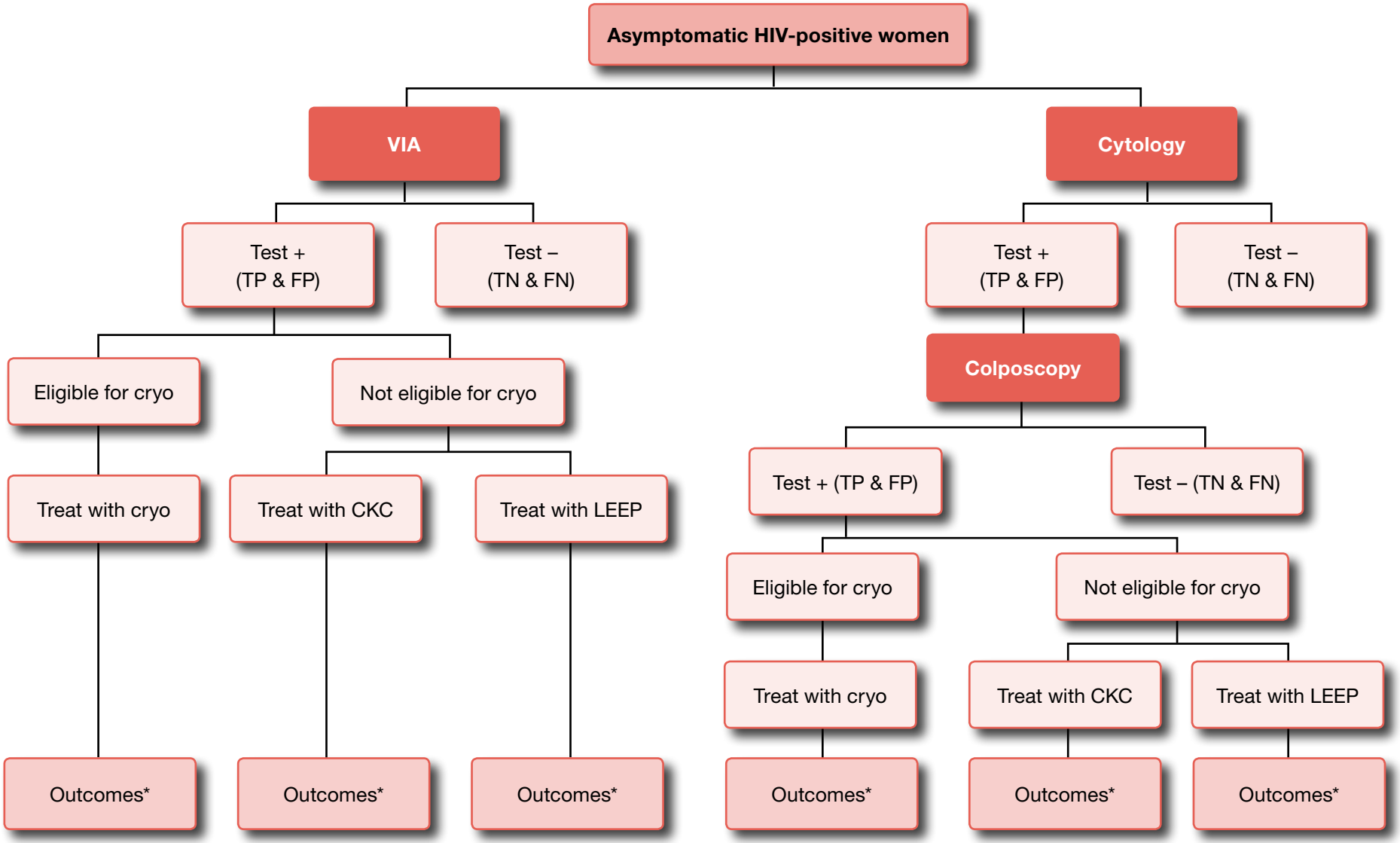
Remarks: The benefits and harms of the two screen-and-treat strategies are similar, but there are fewer harms with cytology followed by colposcopy with biopsy when indicated. Despite overtreatment with VIA and fewer cancers detected at first-time screening, more resources are required for cytology programmes with colposcopy (with or without biopsy) due to quality control, training, and waiting time, as well as a second visit. The recommendation for VIA over cytology followed by colposcopy can be applied in countries that are currently considering either strategy or countries that currently have both strategies available. 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 of cytology followed by colposcopy compared 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. Also 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 cytology followed by colposcopy and VIA alone may be similar. However, there may be slightly greater harms with VIA alone (due to overtreatment with HPV test alone) and slightly fewer cancers detected with 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 resources required and lower value on the harms.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	Fewer resources are required for VIA. There may be additional resources required in cytology programmes due to increased training of providers, quality control, and waiting time. Colposcopy following cytology also requires a second visit.

Evidence for VIA compared to cytology followed by colposcopy 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: VIA compared to cytology (ASCUS) followed by colposcopic impression

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

Pooled sensitivity VIA	77% (95% CI: 65 to 85)	Pooled sensitivity cytology (ASCUS)	84% (95% CI: 76 to 90)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity VIA	82% (95% CI: 67 to 91)	Pooled specificity cytology (ASCUS)	88% (95% CI: 79 to 93)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

2.1 Diagnostic Test Accuracy (DTA) evidence profile: VIA compared to cytology (ASCUS) followed by colposcopic impression

Outcome	No. of studies (No. of patients) [a]	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		VIA	Cytology followed by colposcopic impression	
True positives (patients with CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	77 (65 to 85)	80	CRITICAL
TP absolute difference									3 fewer		
True negatives (patients without CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	738 (603 to 819)	837	CRITICAL
TN absolute difference									99 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	162 (81 to 297)	63	CRITICAL
FP absolute difference									99 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	23 (15 to 35)	20	CRITICAL
FN absolute difference									3 more		

Footnotes:

[a] This is the number of studies that assessed data for HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available. 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.

[d] Estimates of VIA, cytology (ASCUS) and colposcopy sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of cytology followed by colposcopy 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: VIA compared to cytology (ASCUS) followed by colposcopic impression

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	Cyto→colp imp +/– CKC	Cyto→colp imp +/–LEEP	Cyto→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	1080	1195	1195	961	1080	1080	4350
Cervical cancer incidence[2]	1512	1673	1673	1346	1513	1513	6075
CIN2+ recurrence[3]	19 999	22 386	22 386	17832	20 306	20 306	79 575
Undetected CIN2+ (FN)	23 000			20 000			–
Major bleeding[4]	2052	539	81	1223	321	48	0
Premature delivery[5]	788	602	649	672	561	589	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	212	306	32	126	182	19	0
Minor infections[8]	2239	1440	1547	1334	858	922	0
Unnecessarily treated (FP)	162 000			63 000			–
Cancer found at first-time screening[9]	3168			4794			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 77% (95% CI: 66 to 85), pooled specificity 82% (95% CI: 67 to 91)
- Cytology (ASCUS): Pooled sensitivity 84% (95% CI: 76 to 90), pooled specificity 88% (95% CI: 79 to 93)
- Colposcopic impression: Pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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. Evidence used for decision-making: VIA compared to cytology (ASCUS) followed by colposcopic impression and biopsy when indicated

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

Pooled sensitivity VIA	77% (95% CI: 66 to 85)	Pooled sensitivity cytology (ASCUS)	84% (95% CI: 76 to 90)
Pooled specificity VIA	82% (95% CI: 67 to 91)	Pooled specificity cytology (ASCUS)	88% (95% CI: 79 to 93)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: VIA compared to cytology (ASCUS) followed by colposcopic impression and biopsy when indicated

Outcome	No. of studies (No. of patients) [a]	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		VIA	Cytology followed by colposcopy with biopsy	
True positives (patients with CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	77 (65 to 85)	84	CRITICAL
TP absolute difference									7 fewer		
True negatives (patients without CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	738 (603 to 819)	900	CRITICAL
TN absolute difference									162 fewer		
False positives (patients incorrectly classified as having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	162 (81 to 297)	0	CRITICAL
FP absolute difference									162 more		
False negatives (patients incorrectly classified as not having CIN2+)	11 studies (12 089 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	23 (15 to 35)	16	CRITICAL
FN absolute difference									7 more		

Footnotes:

[a] This is the number of studies that assessed data for HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for cytology followed by colposcopy +/– biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available. 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.

[d] Estimates of VIA and cytology (ASCUS) sensitivity and specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of cytology followed by colposcopy and therefore wide CI for TP, TN, FP, FN, may lead to different decisions depending on which confidence limits are assumed.

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: VIA compared to cytology (ASCUS) followed by colposcopic impression and biopsy when indicated

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	VIA +/– CKC	VIA +/– LEEP	VIA +/– cryo	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/–LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
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Undetected CIN2+ (FN)	23 000			16 000			–
Major bleeding[4]	2052	539	81	721	190	28	0
Premature delivery[5]	788	602	649	601	536	553	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	212	306	32	75	107	11	0
Minor infections[8]	2239	1440	1547	787	506	544	0
Unnecessarily treated (FP)	162 000			0			–
Cancer found at first-time screening[9]	3168			4794			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

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- 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.

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[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.

4. References

4.1 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. *Gynecologic Oncology*, 2001, 83(2):439–444.

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4.2 References to studies included for diagnostic test accuracy of colposcopic impression

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4.3 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.

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Recommendation 5

The expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

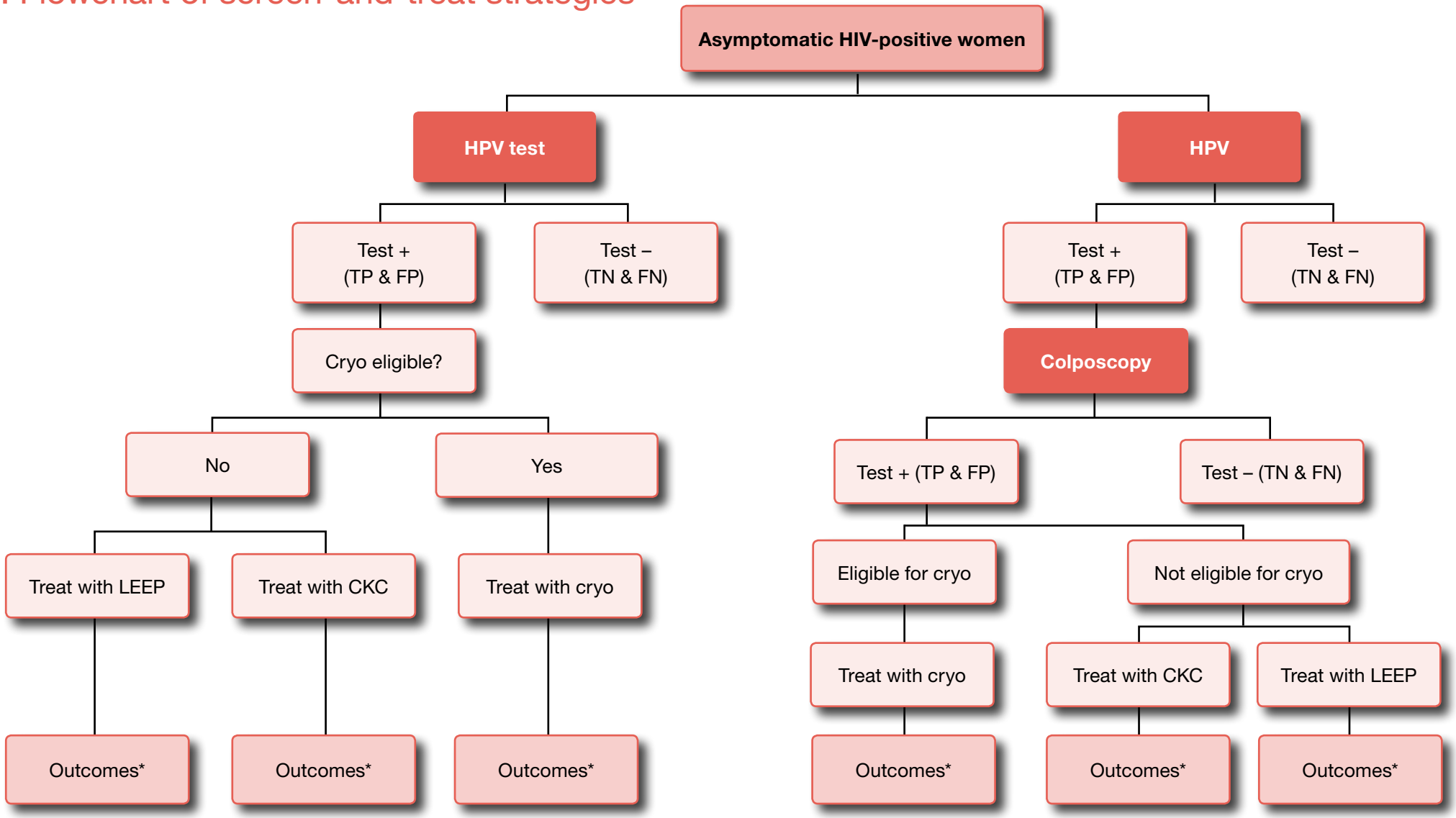
Remarks: The reductions in cancer and related mortality with either strategy outweigh the harms and costs of no screening, and were similar between the two strategies. Although overtreatment and, consequently, harms are reduced with the addition of colposcopy (with or without biopsy), there are more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and the potential for more women to be lost to follow-up. The addition of colposcopy to an HPV test would also require a second visit. In countries without an existing screening strategy, an HPV test followed by colposcopy is not recommended. 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 of HPV test followed by colposcopy and we did not have a direct comparison of this triage test 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: ☒	The benefits of HPV test followed by colposcopy and HPV test alone may be similar. However, there were greater harms with HPV test alone (due to overtreatment with HPV test alone). There may also be slightly fewer cancers detected with HPV test followed by colposcopy.
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 resources required and lower value on the harms.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes: ☒ No: ☐	There may be additional resources required with the addition of colposcopy (with or without biopsy), there are more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and potential for more women lost to follow-up. The addition of colposcopy to HPV test would also require a second visit.

Evidence for an HPV test compared to an HPV test followed by colposcopy 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 compared to HPV test followed by colposcopic impression

Diagnostic test accuracy

Pooled sensitivity HPV test	93% (95% CI: 87 to 96)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity HPV test	88% (95% CI: 82 to 91)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

2.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to HPV test followed by colposcopic impression

Outcome	No. of studies (No. of patients)[a]	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	HPV test followed by colposcopic impression	
True positives (patients with CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	93 (87 to 96)	88	CRITICAL
TP absolute difference									5 more		
True negatives (patients without CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	792 (738 to 819)	837	CRITICAL
TN absolute difference									55 fewer		
False positives (patients incorrectly classified as having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	108 (81 to 162)	63	CRITICAL
FP absolute difference									55 more		
False negatives (patients incorrectly classified as not having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	7 (4 to 13)	12	CRITICAL
FN absolute difference									5 fewer		

Footnotes:

[a] This is the number of studies that assessed data for HPV test.

[b] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available. 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.

[d] 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.

[e] Few participants contributed to colposcopy data. Therefore there were wide confidence intervals for colposcopy specificity, which 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: HPV test compared to HPV test followed by colposcopy

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
	HPV +/– CKC	HPV +/– LEEP	HPV +/– cryo	HPV→colp imp +/– CKC	HPV→colp imp +/–LEEP	HPV→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	402	541	541	599	731	731	4350
Cervical cancer incidence[2]	563	758	758	839	1024	1024	6075
CIN2+ recurrence[3]	7617	10 500	10 500	11 215	13 954	13 954	79 575
Undetected CIN2+ (FN)	7000			12 000			–
Major bleeding[4]	1726	454	68	1296	341	51	0
Premature delivery[5]	742	585	626	682	564	594	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	179	257	27	134	193	20	0
Minor infections[8]	1883	1211	1301	1414	910	977	0
Unnecessarily treated (FP)	108 000			63 000			–
Cancer found at first-time screening[9]	2454			3545			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)
- HPV test: pooled sensitivity 93% (95% CI: 87 to 96), pooled specificity 88% (95% CI: 82 to 91)
- Colposcopic impression: pooled sensitivity 95% (95% CI: 82 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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. Evidence used for decision-making: HPV test compared to HPV test followed by colposcopy with biopsy when indicated

Diagnostic test accuracy

Pooled sensitivity HPV test	93% (95% CI: 87 to 96)
Pooled specificity HPV test	88% (95% CI: 82 to 91)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: HPV test compared to HPV test followed by colposcopic impression

Outcome	No. of studies (No. of patients)[a]	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	HPV test followed by colposcopy with biopsy	
True positives (patients with CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	93 (87 to 96)	93	CRITICAL
TP absolute difference									0		
True negatives (patients without CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	792 (738 to 819)	900	CRITICAL
TN absolute difference									108 fewer		
False positives (patients incorrectly classified as having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	108 (81 to 162)	0	CRITICAL
FP absolute difference									108 more		
False negatives (patients incorrectly classified as not having CIN2+)	15 studies (45 783 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	7 (4 to 13)	7	CRITICAL
FN absolute difference									0		

Footnotes:

[a] This is the number of studies that assessed data for HPV test.

[b] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by colposcopy +/– biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available. 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.

[d] 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.

[e] Few participants contributed to colposcopy data. Therefore there were wide confidence intervals for colposcopy specificity, which may lead to different decisions depending on which confidence limits are assumed.

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test compared to HPV test followed by colposcopy with biopsy when indicated

Outcomes	Events in the screen-and-treat strategies for patient-important outcomes (numbers presented per 1 000 000 patients)						
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Cervical cancer incidence[2]	563	758	758	563	758	758	6075
CIN2+ recurrence[3]	7617	10 500	10 500	7617	10 500	10 500	79 575
Undetected CIN2+ (FN)	7000			7000			–
Major bleeding[4]	1726	454	68	798	210	32	0
Premature delivery[5]	742	585	626	612	540	558	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	179	257	27	83	119	13	0
Minor infections[8]	1883	1211	1301	871	561	602	0
Unnecessarily treated (FP)	108 000			0			–
Cancer found at first-time screening[9]	2454			3545			–

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)
- HPV test: pooled sensitivity 93% (95% CI: 87 to 96), pooled specificity 88% (95% CI: 82 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.

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[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.

4. References

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

Agorastos T et al. Human papillomavirus testing for primary screening in women at low risk of developing cervical cancer. The Greek experience. *Gynecologic Oncology*, 2005, 96(3):714–720.

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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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4.2 References to studies included for diagnostic test accuracy of colposcopic impression

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Patil K et al. Comparison of diagnostic efficacy of visual inspection of cervix with acetic acid and Pap smear for prevention of cervical cancer: Is VIA superseding Pap smear? *Journal of SAFOG*, 2011, 3(3):131–134.

4.3 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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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)

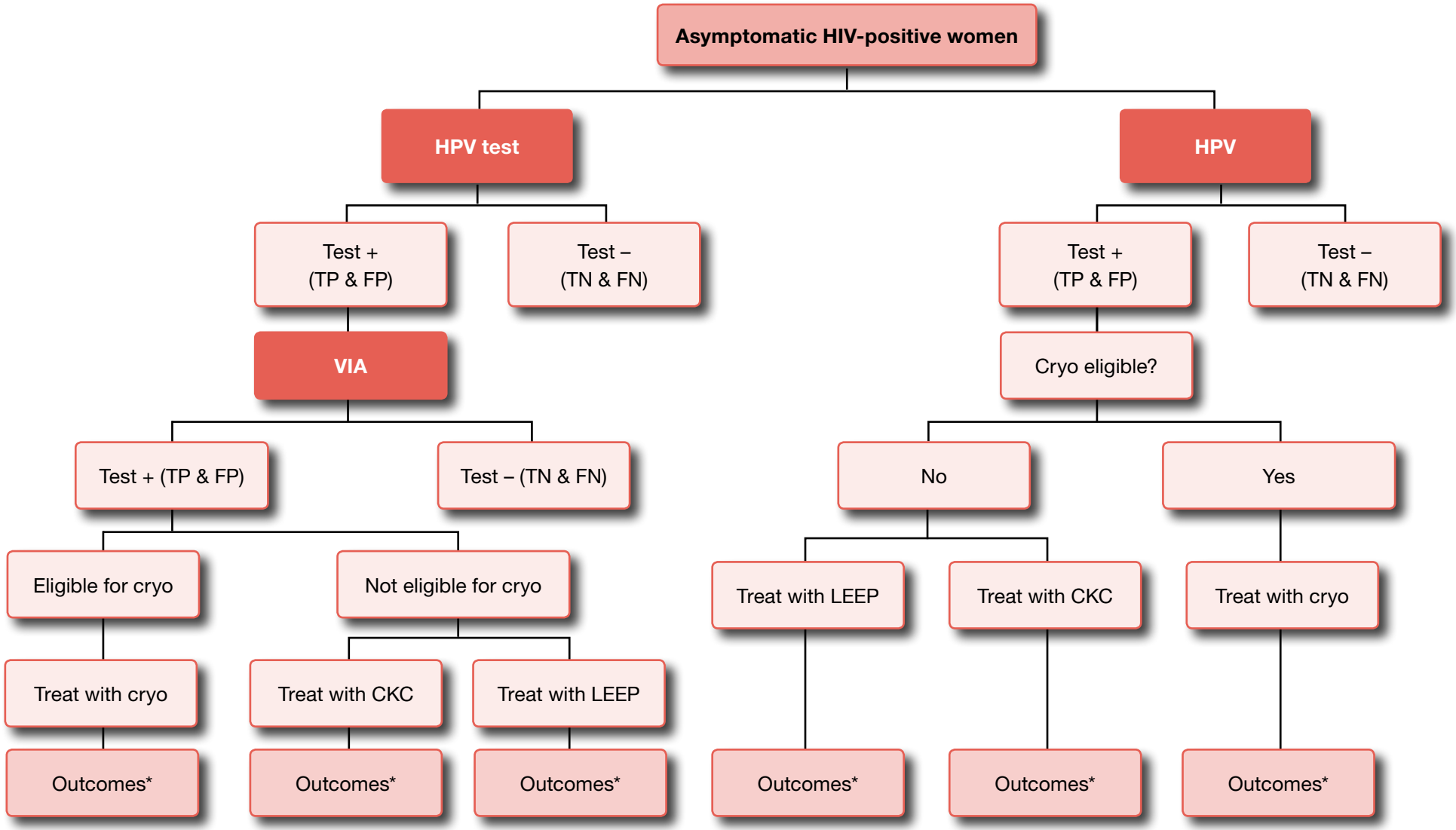
Remarks: The reductions in cancer and related mortality were greater with an HPV test used as a single screening test than with an HPV test followed by VIA, and this reduction was even greater in women of HIV-positive status. However, there may be overtreatment, and thus potentially greater harms with 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.

Shastri SS et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bulletin of the World Health Organization*, 2005, 83(3):186–194.

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.

De Vuyst H et al. Prevalence and determinants of human papillomavirus infection and cervical lesions in HIV-positive women in Kenya. *British Journal of Cancer*, 2012, 107(9):1624–1630.

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.

Zhang HY et al. HPV prevalence and cervical intraepithelial neoplasia among HIV-infected women in Yunnan Province, China: a pilot study. *Asian Pacific Journal of Cancer Prevention*, 2012, 13(1):91–96.

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)**

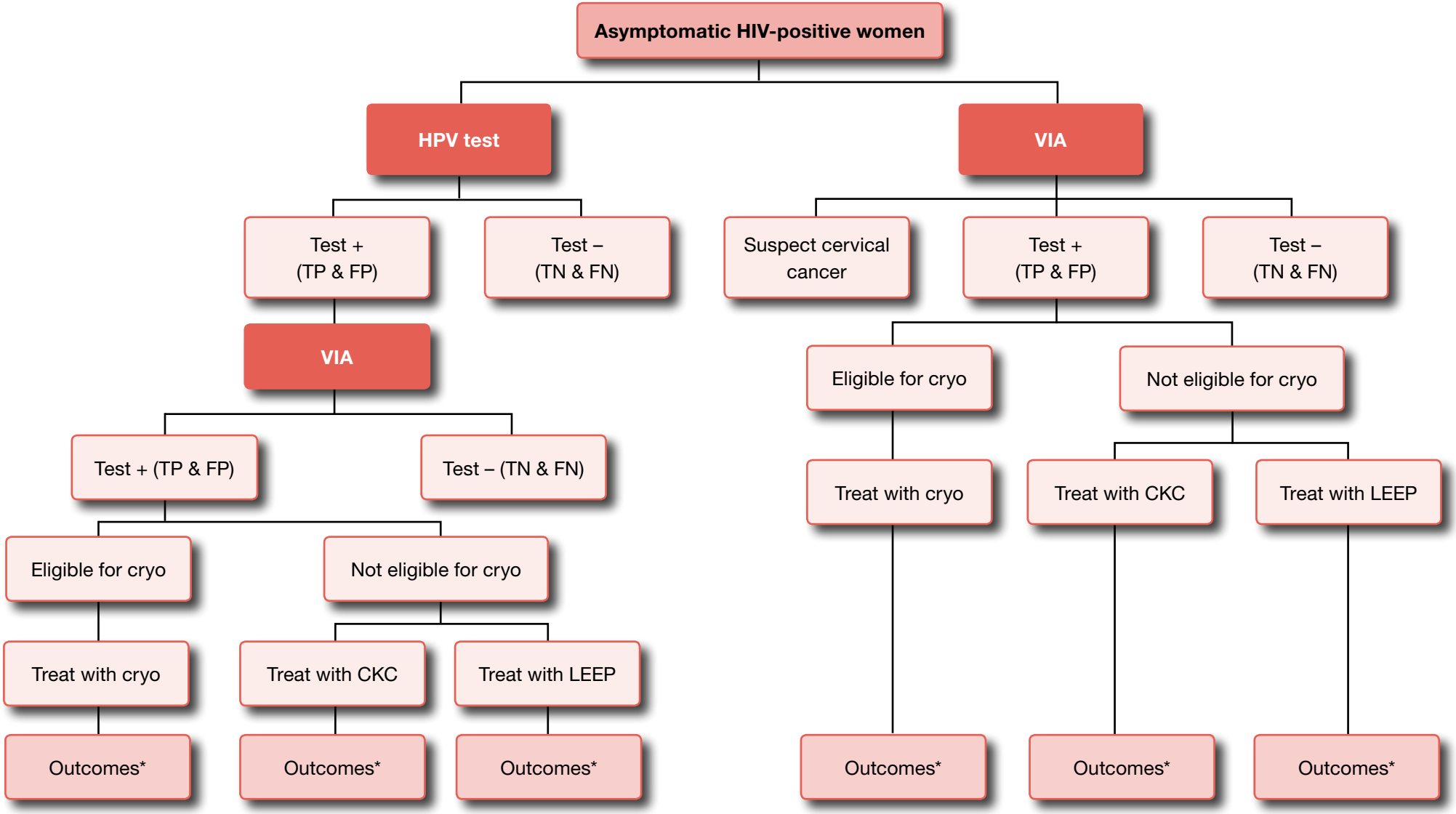
Remarks: The reductions in cancer and related mortality with an HPV test followed by VIA or with VIA alone outweighed the harms. However, the harms may be greater when using VIA only, which is likely due to overtreatment. Although, a slightly larger number of cancers may be detected on initial screen 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

Belinson J et al. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecologic 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.

Shastri SS et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bulletin of the World Health Organization*, 2005, 83(3):186–194.

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.

De Vuyst H et al. Prevalence and determinants of human papillomavirus infection and cervical lesions in HIV-positive women in Kenya. *British Journal of Cancer*, 2012, 107(9):1624–1630.

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.

Zhang HY et al. HPV prevalence and cervical intraepithelial neoplasia among HIV-infected women in Yunnan Province, China: a pilot study. *Asian Pacific Journal of Cancer Prevention*, 2012, 13(1):91–96.

Recommendation 8

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 cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

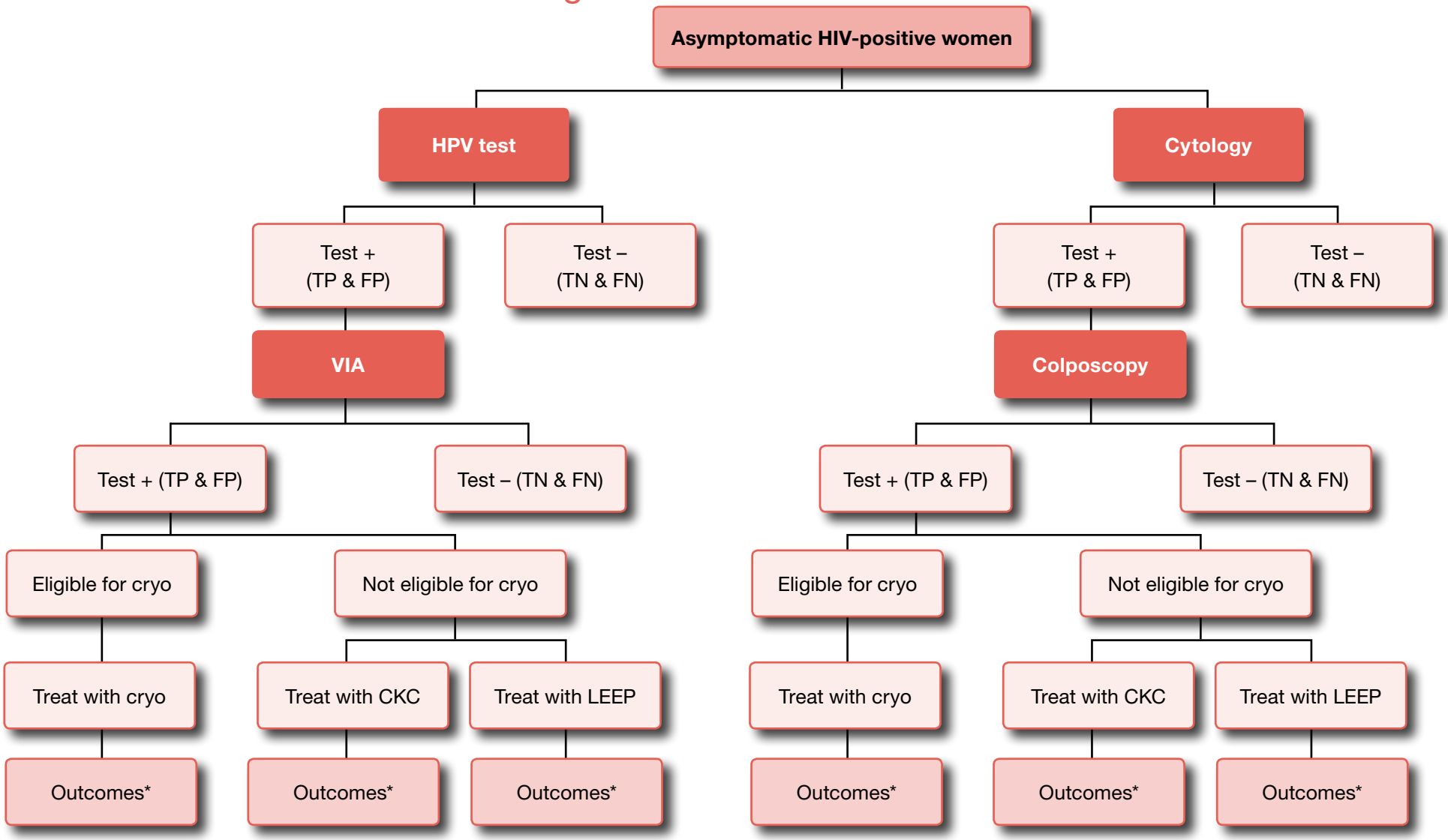
Remarks: The benefits of the two screen-and-treat strategies are similar. However, there may be higher resources required in cytology programmes due to quality control, training, and waiting time. The addition of colposcopy requires a second visit. This recommendation applies to women regardless of HIV 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 compared to cytology followed by colposcopy. 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 and harms of HPV test followed by VIA and cytology followed by colposcopy may be similar. However, 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 resources required.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☒ / No ☐	Fewer resources may be required for HPV test followed by VIA as there may be additional resources required in cytology programmes due to increased training of providers, quality control, and waiting time. Colposcopy following cytology also requires a second visit.

Evidence for an HPV test followed by VIA compared to cytology followed by colposcopy 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 cytology (ASCUS) and colposcopic impression

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

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity VIA	69% (95% CI: 54 to 81)
Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity VIA	87% (95% CI: 79 to 92)
Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity cytology (ASCUS)	95% (95% CI: 92 to 97)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

2.1 Diagnostic test accuracy (DTA) evidence profile: HPV test followed by VIA compared to cytology (ASCUS) and colposcopic impression

Outcome	No. of studies (No. of patients)[a]	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	Cytology followed by colposcopic impression	
True positives (patients with CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	65	67	CRITICAL
TP absolute difference									2 fewer		
True negatives (patients without CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	888	874	CRITICAL
TN absolute difference									14 more		
False positives (patients incorrectly classified as having CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	12	26	CRITICAL
FP absolute difference									14 fewer		
False negatives (patients incorrectly classified as not having CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	35	34	CRITICAL
FN absolute difference									1 more		

Footnotes:

[a] This is the number of studies that assessed DTA data for: 1. HPV test and VIA, and 2. HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by VIA and cytology followed by colposcopy were calculated based on sensitivity and specificity of the two tests. Direct data were not available. 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.

[d] Estimates of HPV test, VIA, cytology (ASCUS) and colposcopy sensitivity/specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

[e] Wide CI for sensitivity and specificity of HPV test followed by VIA and cytology followed by colposcopy 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: HPV test followed by VIA compared to cytology (ASCUS) and colposcopic impression

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	Cyto→colp imp +/– CKC	Cyto→colp imp +/– LEEP	Cyto→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	1594	1691	1691	1524	1624	1624	4350
Cervical cancer incidence[2]	2231	2367	2367	2134	1752	2273	6075
CIN2+ recurrence[3]	29 393	31 404	31 404	28 124	30 186	30 186	79 575
Undetected CIN2+ (FN)	35 000			34 000			–
Major bleeding[4]	657	173	26	795	209	31	0
Premature delivery[5]	612	539	558	592	533	548	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	82	118	13	68	98	10	0
Minor infections[8]	867	558	599	717	461	496	0
Unnecessarily treated (FP)	12 000			26 000			–
Cancer found at first-time screening[9]	3168			4794			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)
- Cytology (ASCUS): Pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
- Colposcopy: Pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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. Evidence used for decision-making: HPV test followed by VIA compared to cytology (ASCUS) and colposcopic impression and biopsy when indicated

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

Pooled sensitivity HPV test	94% (95% CI: 89 to 97)	Pooled sensitivity VIA	69% (95% CI: 54 to 81)	Pooled sensitivity cytology (ASCUS)	70% (95% CI: 57 to 81)
Pooled specificity HPV test	90% (95% CI: 86 to 93)	Pooled specificity VIA	87% (95% CI: 79 to 92)	Pooled specificity cytology (ASCUS)	95% (95% CI: 92 to 97)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: HPV test followed by VIA compared to cytology (ASCUS) and colposcopy with biopsy when indicated

Outcome	No. of studies (No. of patients)[a]	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	Cytology followed by colposcopy with biopsy	
True positives (patients with CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	65	70	CRITICAL
TP absolute difference									5 fewer		
True negatives (patients without CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	888	900	CRITICAL
TN absolute difference									12 fewer		
False positives (patients incorrectly classified as having CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	12	0	CRITICAL
FP absolute difference									12 more		
False negatives (patients incorrectly classified as not having CIN2+)	14 studies (34 584 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	35	30	CRITICAL
FN absolute difference									5 more		

Footnotes:

[a] This is the number of studies that assessed DTA data for: 1. HPV test and VIA, and 2. HPV test and cytology.

[b] We used QUADAS to assess risk of bias. Half of studies only performed one biopsy of an abnormal lesion and had unclear blinding of tests. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by VIA and cytology followed by colposcopy +/– biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available. 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.

[d] Estimates of HPV test, VIA and cytology (ASCUS) sensitivity/specificity were variable despite similar cut-off values; inconsistency was not explained by quality of studies. This was downgraded one level in the context of other factors, in particular imprecision.

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

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test followed by VIA and cytology (ASCUS) and colposcopy with biopsy when indicated

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	Cyto→colp biopsy +/– CKC	Cyto→colp biopsy +/–LEEP	Cyto→colp biopsy +/– cryo	No screen[10]
Mortality from cervical cancer[1]	1594	1691	1691	1376	1481	1481	4350
Cervical cancer incidence[2]	2231	2367	2367	1926	2073	2073	6075
CIN2+ recurrence[3]	29 393	31 404	31 404	25 416	27 586	27 586	79 575
Undetected CIN2+ (FN)	35 000			30 000			–
Major bleeding[4]	657	173	26	601	158	24	0
Premature delivery[5]	612	539	558	584	530	544	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	82	118	13	62	90	9	0
Minor infections[8]	867	558	599	656	422	453	0
Unnecessarily treated (FP)	12 000			0			–
Cancer found at first-time screening[9]	3168			3545			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)
- HPV test: Pooled sensitivity94% (95% CI: 89 to 97), pooled specificity 90% (95% CI: 86 to 93)
- VIA: Pooled sensitivity 69% (95% CI: 54 to 81), pooled specificity 87% (95% CI: 79 to 92)
- Cytology (ASCUS): Pooled sensitivity 70% (95% CI: 57 to 81), pooled specificity 95% (95% CI: 92 to 97)
- 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.

4. References

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

Agorastos T et al. Human papillomavirus testing for primary screening in women at low risk of developing cervical cancer. The Greek experience. Gynecologic Oncology, 2005, 96(3):714–720.

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

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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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4.2 References to studies included for diagnostic test accuracy of colposcopic impression

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

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Durdi GS et al. Correlation of colposcopy using Reid colposcopic index with histopathology – a prospective study. Journal of the Turkish German Gynecology Association, 2009, 10(4):205–207.

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Patil K et al. Comparison of diagnostic efficacy of visual inspection of cervix with acetic acid and Pap smear for prevention of cervical cancer: is VIA superseding Pap smear? Journal of SAFOG, 2011, 3(3):131–134.

4.3 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, Lillo F, Broutet N, Smith JS. 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 Maharashtra, 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.

Zhang HY et al. HPV prevalence and cervical intraepithelial neoplasia among HIV-infected women in Yunnan Province, China: a pilot study. Asian Pacific Journal of Cancer Prevention, 2012, 13(1):91–96..

Recommendation 9

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 HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

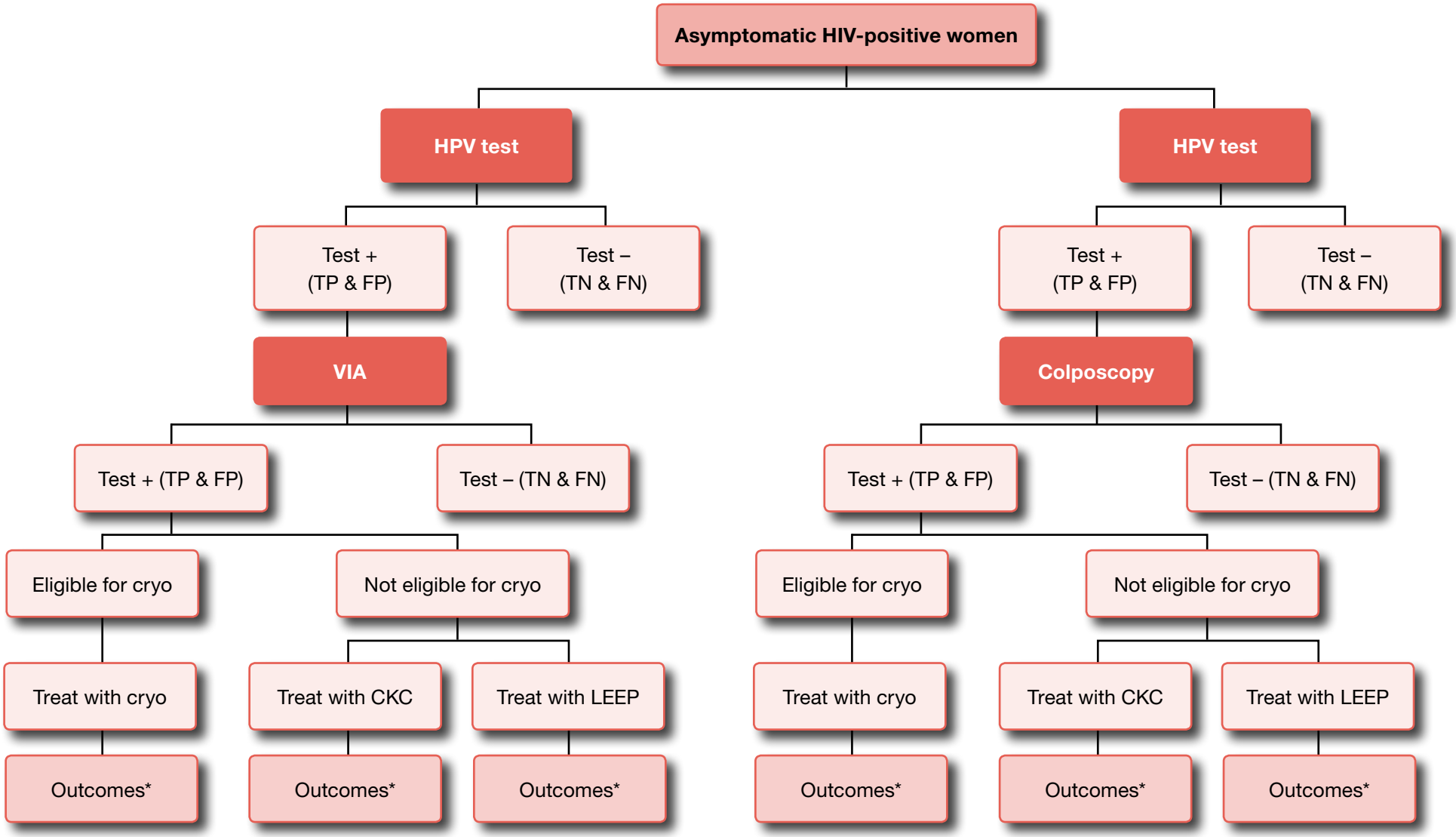
Remarks: The reductions in cancer and related mortality of screen-and-treat with an HPV test followed by colposcopy (with or without biopsy) may be slightly greater compared to an HPV test followed by VIA. The panel agreed that the benefits of either strategy outweigh the harms and costs; however, the difference in costs between the strategies is uncertain. There may be more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and the potential for more women to be lost to follow-up. It is also unclear whether women would perceive a difference between VIA and colposcopy; however, a biopsy during colposcopy may be less acceptable than VIA. 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 of both triage tests and a comparison between the strategies. 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. Also 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 colposcopy (reduction in CIN recurrence, cervical cancer, and related mortality) may be greater than with HPV test followed by VIA. But there may be greater overtreatment with HPV test followed by colposcopy without biopsy. Little or no difference in cancers detected.
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 women overtreated and potential complications. High value was placed on women finding a biopsy less acceptable than visual inspection.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☐ / No ☒	There may be greater resource implications by adding colposcopy then with adding VIA to the HPV test due to increased training of providers, quality control, waiting time, and potential for more women lost to follow-up.

Evidence for an HPV test followed by VIA compared to an HPV test followed by colposcopy 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 HPV test followed by colposcopic impression

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

Pooled sensitivity HPV test	95% (95% CI: 84 to 98)	Pooled sensitivity VIA	69% (95% CI: 54 to 81)	Pooled sensitivity colposcopic impression	95% (95% CI: 86 to 98)
Pooled specificity HPV test	84% (95% CI: 72 to 91)	Pooled specificity VIA	87% (95% CI: 79 to 92)	Pooled specificity colposcopic impression	42% (95% CI: 26 to 61)

(Reference standard: colposcopy with biopsy when indicated)

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

Outcome	No. of studies (No. of patients)[a]	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 followed by colposcopic impression	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	66	90	CRITICAL
TP absolute difference									24 fewer		
True negatives (patients without CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	881	816	CRITICAL
TN absolute difference									65 more		
False positives (patients incorrectly classified as having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	19	84	CRITICAL
FP absolute difference									65 fewer		
False negatives (patients incorrectly classified as not having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	34	10	CRITICAL
FN absolute difference									24 more		

Footnotes:

[a] This is the number of studies that assessed DTA data for HPV test and VIA.

[b] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. Colposcopy studies had unclear blinding of index test results. This was downgraded one level in the context of other factors, in particular indirectness.

[c] Data for HPV test followed by VIA and for HPV test followed by colposcopic impression were calculated based on sensitivity and specificity of the two tests. Direct data were not available. 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.

[d] 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.

[e] 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 HPV test followed by VIA compared to HPV test followed by colposcopic impression

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→colp imp +/– CKC	HPV→colp imp +/–LEEP	HPV→colp imp +/– cryo	No screen[10]
Mortality from cervical cancer[1]	1564	1662	1662	519	654	654	4350
Cervical cancer incidence[2]	2190	2327	2327	726	915	915	6075
CIN2+ recurrence[3]	28 859	30 891	30 891	9745	12 543	12 543	79 575
Undetected CIN2+ (FN)	34 000			10 000			–
Major bleeding[4]	723	190	29	1492	392	59	0
Premature delivery[5]	602	536	553	709	574	609	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	75	108	11	154	222	23	0
Minor infections[8]	789	508	545	1628	1047	1125	0
Unnecessarily treated (FP)	19 000			84 000			–
Cancer found at first-time screening[9]	3168			3545			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)
- Colposcopy: pooled sensitivity 95% (95% CI: 86 to 98), pooled specificity 42% (95% CI: 26 to 61)
- 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. Evidence used for decision-making: HPV test followed by VIA compared to HPV test followed by colposcopic impression and biopsy when indicated

Diagnostic test accuracy (data based on women of 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)

(Reference standard: colposcopy with biopsy when indicated)

3.1 Diagnostic test accuracy (DTA) evidence profile: HPV test followed by VIA compared to HPV test followed by colposcopic impression and biopsy when indicated

Outcome	No. of studies (No. of patients)[a]	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 followed by colposcopy with biopsy	
True positives (patients with CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	66	95	CRITICAL
TP absolute difference									29 fewer		
True negatives (patients without CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	881	900	CRITICAL
TN absolute difference									19 fewer		
False positives (patients incorrectly classified as having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	19	0	CRITICAL
FP absolute difference									19 more		
False negatives (patients incorrectly classified as not having CIN2+)	5 studies (8921 patients)	Cross-sectional and cohort studies	Serious[b]	None[c]	Serious[d]	None[e]	Undetected	⊕⊕⊖⊖ low	34	5	CRITICAL
FN absolute difference									29 more		

Footnotes:

[a] This is the number of studies that assessed DTA data for HPV test and VIA.

[b] We used QUADAS to assess risk of bias. Many studies only performed one biopsy of an abnormal lesion. This was downgraded one level in the context of other factors, in particular indirectness.

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

[d] 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.

[e] 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.

3.2 GRADE evidence table for patient-important outcomes following different screen-and-treat strategies: HPV test followed by VIA compared to HPV test followed by colposcopic impression and biopsy when indicated

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→colp biopsy +/– CKC	HPV→colp biopsy +/–LEEP	HPV→colp biopsy +/– 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	816	214	32	0
Premature delivery[5]	602	536	553	614	540	559	500
Infertility[6]	–	–	–	–	–	–	–
Major infections[7]	75	108	11	84	122	13	0
Minor infections[8]	789	508	545	890	573	615	0
Unnecessarily treated (FP)	19 000			0			–
Cancer found at first-time screening[9]	3168			3545			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)
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- 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.

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[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.

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[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.

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

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Editing, proofreading, design and layout: Green Ink (www.greenink.co.uk)


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