

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 <i>Is there high- or moderate-quality evidence?</i>	<table border="1"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input checked="" type="checkbox"/>	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.
Yes	No					
<input type="checkbox"/>	<input checked="" type="checkbox"/>					
Balance of benefits versus harms and burdens <i>Are you confident that the benefits outweigh the harms and burdens for the recommended strategy?</i>	<table border="1"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input checked="" type="checkbox"/>	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.
Yes	No					
<input type="checkbox"/>	<input checked="" type="checkbox"/>					
Values and preferences <i>Are you confident about the assumed or identified relative values and are they similar across the target population?</i>	<table border="1"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Yes	No	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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.
Yes	No					
<input checked="" type="checkbox"/>	<input type="checkbox"/>					
Resource implications <i>Is the cost small relative to the net benefits for the recommended strategy?</i>	<table border="1"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Yes	No	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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.
Yes	No					
<input checked="" type="checkbox"/>	<input type="checkbox"/>					

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 cancer¹	44	54	54	54	63	63	250
Cervical cancer incidence²	62	75	75	76	89	89	350
CIN2+ recurrence³	2384	2911	2911	2935	3435	3435	13 400
Undetected CIN2+ (FN)	5000			4000			–
Major bleeding⁴	901	237	36	726	191	29	0
Premature delivery⁵	627	545	566	602	536	553	500
Infertility⁶	–	–	–	–	–	–	–
Major infections⁷	93	134	14	75	108	11	0
Minor infections⁸	984	633	680	792	510	548	0
Unnecessarily treated (FP)	176 000			68 000			–
Cancer found at first-time screening⁹	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 bleeding⁴	901	237	36	726	191	29	0
Premature delivery⁵	627	545	566	602	536	553	500
Infertility⁶	–	–	–	–	–	–	–
Major infections⁷	93	134	14	75	108	11	0
Minor infections⁸	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)

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			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		

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- ^c Data for cytology followed by colposcopy +/- biopsy were calculated based on sensitivity and specificity of the two tests. Direct data were not available.
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CIN2+ recurrence³	2384	2911	2911	2384	2911	2911	13 400
Undetected CIN2+ (FN)	5000			3000			–
Major bleeding⁴	901	237	36	146	38	6	0
Premature delivery⁵	627	545	566	520	507	511	500
Infertility⁶	–	–	–	–	–	–	–
Major infections⁷	93	134	14	15	22	2	0
Minor infections⁸	984	633	680	159	102	110	0
Unnecessarily treated (FP)	176 000			0			–
Cancer found at first-time screening⁹	3168			4794			0

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Major infections ⁷	93	134	14	15	22	2	0
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^{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.

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.

Elit L et al. Assessment of 2 cervical screening methods in Mongolia: cervical cytology and visual inspection with acetic acid. *Journal of Lower Genital Tract Disease*, 2006, 10(2):83–88.

Ghaemmaghami F et al. Visual inspection with acetic acid as a feasible screening test for cervical neoplasia in Iran. *International Journal of Gynecological Cancer*, 2004, 14(3):465–469.

Goel A et al. Visual inspection of the cervix with acetic acid for cervical intraepithelial lesions. *International Journal of Gynaecology & Obstetrics*, 2005, 88(1):25–30.

Hedge D et al. Diagnostic value of acetic acid comparing with conventional Pap smear in the detection of colposcopic biopsy-proved CIN. *Journal of Cancer Research & Therapeutics*, 2011, 7(4):454–458.

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.

Sahasrabudde 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.

Sankaranarayanan R et al. Test characteristics of visual inspection with 4% acetic acid (VIA) and Lugol's iodine (VILI) in cervical cancer screening in Kerala, India. *International Journal of Cancer*, 2003, 106(3):404–408.

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 Obstetrics & Gynecology*, 1987, 157(3):544–549.
- Kierkegaard O et al. Diagnostic accuracy of cytology and colposcopy in cervical squamous intraepithelial lesions. *Acta Obstetrica 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.