EVIDENCE TO DECISION TABLE: PICO 3,4,5,6,7 GENERAL POPULATION AND WOMEN LIVING WITH HIV

Should we follow-up 12 and/or 24 months, or 3, 5 or 10 years after a negative screening test, a positive screening test and negative triage, or a positive test and treatment, with the same or different test(s)?	
POPULATION:	General population of women and WLHIV
INTERVENTION:	12 and/or 24 months, or 3, 5 or 10 years with same test
COMPARISON:	12 and/or 24 months, or 3, 5 or 10 years with different test
MAIN OUTCOMES:	•Cervical cancer •Mortality •CIN 2+ •HPV infection •Preterm birth (early/late) •Acceptability (to all stakeholders) •Pre-cancer treatments •Adverse events related to pre-cancer treatments - Major infections or bleeding, Procedure associated pain, Cervical stenosis, Infertility, Spontaneous abortions (1st trimester/ 2nd trimester), Perinatal deaths, Premature rupture of membrane, Unnecessary interventions, Increased viral shedding in HIV infected women and, costs (number of tests), feasibility (Coverage of treatment, Coverage of screening), acceptability (stigmatization), equity
SETTING:	outpatient
PERSPECTIVE:	Population
BACKGROUND:	In 2014, the World Health Organization (WHO) published recommendations for screening and treatment of precancerous lesions and indicated different follow up times after screening negative or positive or after treatment using the same test. WHO also provided guidance that screening even once in a lifetime would be beneficial.
CONFLICT OF INTERESTS:	

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	We conducted a systematic search up to August 2020 but did not find primary studies that compared different follow-up periods using the 7 priority algorithms, or non-comparative studies using the same algorithm but at different follow-up periods. **Follow-up and type of test after negative screening test** Evidence from modelling was used in which outcomes (cervical cancer and related death, and number of treatments) were calculated for follow-up after 3, 5 or 10 years for the priority algorithms (see Evidence to Decision table PICO 1 and 2 general population and WLHIV) **Follow-up and type of test after positive screening test and negative triage test** Evidence from modelling was used in which outcomes (cervical cancer and related death, and number of treatments) were calculated for follow-up at 12 months or 24 months, and at both 12 and 24 months with HPV test GENERAL POPULATION Results compared to baseline of 12 months versus 24 months and versus both 12 and 24 months in general population:	

Summary table - General population screened 5-yearly ages 30-50 (PICO4)

Flowchart	PICO variation	Cervical cancer cases* (% change)	Cervical cancer deaths* (% change)	Pre-cancer treatments*	NNT to avert a cervical cancer death	Discounted lifetime cost ($)
No Screening	-	1,950 (-)	1,456 (-)	0	-	3
Primary HPV	Baseline (HPV at 12m)	851 (-56%)	572 (-61%)	50,179	57	52
HPV, 16/18 triage	Baseline (HPV at 12m)	877 (-55%)	591 (-59%)	34,408	40	51
	Triage negative follow-up: HPV test at 12 and 24m Difference c/f baseline (HPV at 12m)	863 (-56%) -14 (-1%)	581 (-60%) -10 (-1%)	35,543 +1,136 (+3%)	41 +1 (+2%)	52 +1 (+2%)
	Triage negative follow-up: HPV test at 24m Difference c/f baseline (HPV at 12m)	893 (-54%) +16 (+1%)	603 (-58%) +11 (+1%)	28,497 -5,911 (-17%)	33 -6 (-16%)	49 -2 (-4%)
HPV, VIA triage	Baseline (HPV at 12m)	940 (-52%)	638 (-56%)	30,186	37	51
	Triage negative follow-up: HPV test at 12 and 24m Difference c/f baseline (HPV at 12m)	909 (-53%) -31 (-2%)	615 (-58%) -23 (-2%)	31,900 +1,714 (+6%)	38 +1 (+3%)	53 +1 (+2%)
	Triage negative follow-up: HPV test at 24m Difference c/f baseline (HPV at 12m)	*1,012 (-48%)* *+73 (+4%)*	*696 (-52%)* *+58 (+4%)*	22,111 -8,074 (-27%)	29 -8 (-21%)	48 -3 (-6%)
HPV, colposcopy triage	Baseline (HPV at 12m)	940 (-52%)	625 (-57%)	33,265	40	57
	Triage negative follow-up: HPV test at 12 and 24m Difference c/f baseline (HPV at 12m)	924 (-53%) -16 (-1%)	613 (-58%) -11 (-1%)	34,008 +743 (+2%)	40 +0 (+1%)	58 +1 (+2%)
	Triage negative follow-up: HPV test at 24m Difference c/f baseline (HPV at 12m)	952 (-51%) +12 (+1%)	635 (-56%) +10 (+1%)	30,847 -2,418 (-7%)	38 -2 (-6%)	55 -2 (-3%)
HPV, cytology triage	Baseline (HPV at 12m)	966 (-50%)	648 (-56%)	22,352	28	61
	Triage negative follow-up: HPV test at 12 and 24m Difference c/f baseline (HPV at 12m)	946 (-52%) -21 (-1%)	632 (-57%) -16 (-1%)	23,429 +1,077 (+5%)	28 +1 (+3%)	62 +1 (+2%)
	Triage negative follow-up: HPV test at 24m Difference c/f baseline (HPV at 12m)	*1,003 (-49%)* *+37 (+2%)*	*678 (-53%)* *+30 (+2%)*	*17,719* *-4,633 (-21%)*	23 -5 (-19%)	*57* *-4 (-6%)*

When triage is VIA or cytology, triage-negative women returning for HPV test at 24 months instead of 12 months can result in a loss in effectiveness

When triage is 16/18 genotyping, triage-negative women returning for HPV test at 24 months instead of 12 months can result in a reduction in precancer treatments with a minor loss of effectiveness

The first set of numbers in each box represents the % change versus no screening; the second line in each box represents the difference versus the baseline scenarios (12m follow-up with HPV). Note that for cervical cancer cases and deaths, the % in brackets in the second line is difference in the % change versus no screening; for precancer treatment, NNT and cost columns, it is the % difference versus the baseline for that flowchart. *Outcomes represent total events over the lifetime of a cohort of 100,000 women.

WLHIV
Results compared to baseline 12 months versus 24 months and versus 12 and 24 months:

Summary table – WLHIV population screened 3-yearly ages 25-50 (PICO4)
ART uptake=47%

	PICO variation	Cervical cancer cases* (% reduction)	Cervical cancer deaths* (% reduction)	Pre-cancer treatments*	NNT to avert a cervical cancer death
No Screening	-	5921 (0%)	5296 (0%)	0	0
Primary VIA	Baseline (HPV at 12m)	3138 (46%)	2682 (49%)	158,478	62
Prim VIA (high sens)	Baseline (HPV at 12m)	2569 (56%)	2080 (62%)	173,[illegible]	53
Prim HPV	Baseline (HPV at 12m)	1772 (70%)	1379 (74%)	193,838	40
HPV, 16/18 triage	Baseline (HPV at 12m)	1898 (68%)	1452 (72%)	129907	34
	Triage negative follow-up: HPV test at 12 and 24m Difference c/f baseline (HPV at 12m)	1898 (68%) +0 (+0%)	1452 (72%) 16 (+0%)	129905 -2 (0%)	34 0 (0%)
	Triage negative follow-up: HPV test at 24m Difference c/f baseline (HPV at 12m)	2221 (62%) +330 (+6%)	1758 (67%) +307 (+5%)	114970 -14937 (-11%)	32 -1 (-3%)
HPV, VIA triage	Baseline (HPV at 12m)	2106 (64%)	1587 (70%)	99385	27
	Triage negative follow-up: HPV test at 12 and 24m Difference c/f baseline (HPV at 12m)	2106 (64%) +0 (+0%)	1587 (70%) +0 (+0%)	99384 -1 (0%)	27 0 (0%)
	Triage negative follow-up: HPV test at 24m Difference c/f baseline (HPV at 12m)	2526 (57%) +420 (+7%)	2004 (62%) +417 (+8%)	79809 -19576 (-20%)	25 -2 (-7%)
HPV, colp triage	Baseline (HPV at 12m)	1908 (67%)	1488 (72%)	122419	32
	Triage negative follow-up: HPV test at 12 and 24m Difference c/f baseline (HPV at 12m)	1908 (67%) +0 (+0%)	1488 (72%) +0 (+0%)	122417 -2 (0%)	32 0 (0%)
	Triage negative follow-up: HPV test at 24m Difference c/f baseline (HPV at 12m)	2029 (65%) +121 (+2%)	1611 (69%) +123 (+3%)	113377 -9042 (-7%)	31 -1 (-3%)

Triage-negative women returning for HPV test at 24 months instead of 12 months can result in loss in effectiveness

The first set of numbers in each box represents the % change versus no screening; the second line in each box represents the difference versus the baseline scenarios (12m follow-up with HPV). Note that for cervical cancer cases and deaths, the % in brackets in the second line is difference in the % change versus no screening; for precancer treatment and NNT columns, it is the % difference versus the baseline for that flowchart. *Outcomes represent total events over the lifetime of a cohort of 100,000 women.

Follow up after positive test and treatment

Evidence from systematic reviews of the recurrence of cervical intraepithelial neoplasia (CIN 2/3) after treatment were used to inform this recommendation and sensitivity and specificity of tests (see Supplementary Material 3).

GENERAL POPULATION:

Recurrence or treatment failure after ablative treatment: CIN 2/3 (many studies follow-up at 2 to 3 years)

Approximately 10% recurrence/failure at 2 to 3 years follow-up

Not enough data to analyse changes in percentage over time

Outcome Nº of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects	
		Risk with cryotherapy	Risk with thermal ablation
Cure Nº of participants: 85 (1 RCT)	RR 1.14 (0.89 to 1.46)		Moderate
		90.0%	100.0% (80.1 to 100.0)
Cure Nº of participants: 157 (1 observational study)	RR 1.01 (0.89 to 1.14)		Moderate
		90.0%	90.9% (80.1 to 100.0)
Cure Nº of participants: (23 case series)	not estimable		Moderate
		90.0% (87 to 93)	92% (90 to 95) 2 probe: 95 (93 to 98) Not 2 probe: 85 (80 to 90)

	Sensitivity ratio estimate	Sensitivity ratio (95% CI)	Specificity ratio estimate	Specificity ratio (95% CI)
HPV / Cyto	1.29	(1.18-1.40)	0.94	(0.90-0.99)
HPV&Cyto / HPV	1.07	(0.97-1.17)	0.93	(0.88-0.97)

HPV more likely to find more CIN recurrence, but slightly more likely to include more women who do not have recurrence

HPV & Cyto slightly more likely to include more women who do not have recurrence

WLHIV (supplementary material 2):
Risk of CIN 2/3 recurrence greater in WLHIV compared to general population (10%)

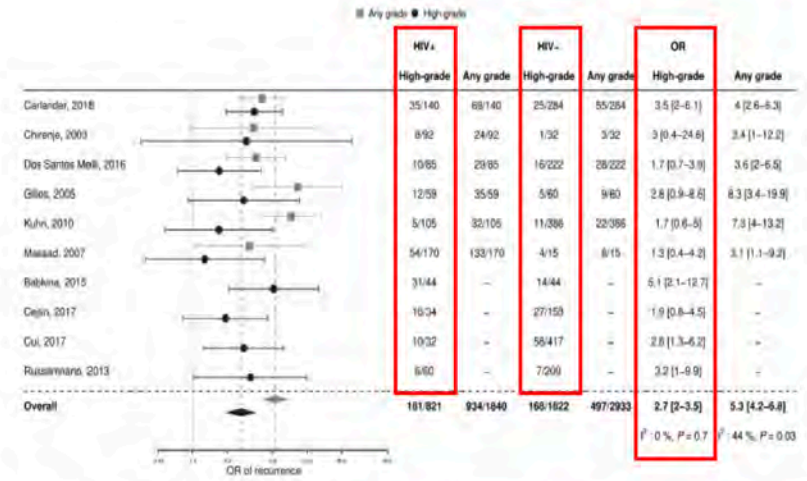

Figure 5. Meta-analysis of the risk of post treatment lesions after first treatment in HIV-infected versus uninfected women. Abbreviations: +, positive; -, negative; HIV, human immunodeficiency virus; OR, odds ratio

DeBeaudrap et al, 2019 Clin Inf Dis;69(9)

Evidence from modelling was also used in which outcomes (cervical cancer and related death, and number of treatments) were calculated for follow-up at 12 months with HPV or HPV and cytology cotesting or at 24 months with HPV using the recommended routine screening interval of 5 years.

Summary table - General population screened 5-yearly ages 30-50 (PICO5)

Flowchart	PICO variation	Cervical cancer cases* (% change)	Cervical cancer deaths* (% change)	Pre-cancer treatments*	NNT to avert a cervical cancer death	Discounted lifetime cost ($)
No Screening	-	1,950 (-)	1,456 (-)	0	-	0
Primary HPV	Baseline (HPV at 12m)	851 (-56%)	571 (-61%)	50,179	57	52
	Post-treatment follow-up: co-test at 12m	844 (-57%)	567 (-61%)	51,323	58	57
	Difference c/f baseline (HPV at 12m)	-7 (-0%)	-5 (-0%)	+1,144 (+2%)	+1 (+2%)	+5 (+10%)
	Post-treatment follow-up: HPV test at 24m	860 (-56%)	583 (-60%)	49,547	57	49
	Difference c/f baseline (HPV at 12m)	+9 (+0%)	+11 (+1%)	-633 (-1%)	+0 (+0%)	-2 (-4%)
HPV, 16/18 triage	Baseline (HPV at 12m)	877 (-55%)	591 (-59%)	34,408	40	51
	Post-treatment follow-up: co-test at 12m	861 (-56%)	579 (-60%)	36,362	41	56
	Difference c/f baseline (HPV at 12m)	-16 (-1%)	-12 (-1%)	+1,954 (+6%)	+2 (+4%)	+5 (+9%)
	Post-treatment follow-up: HPV test at 24m	888 (-54%)	602 (-59%)	33,969	40	50
	Difference c/f baseline (HPV at 12m)	+11 (+1%)	+11 (+1%)	-439 (-1%)	-0 (-0%)	-1 (-3%)
HPV, VIA triage	Baseline (HPV at 12m)	940 (-52%)	638 (-56%)	30,186	37	51
	Post-treatment follow-up: co-test at 12m	904 (-54%)	612 (-58%)	32,646	39	56
	Difference c/f baseline (HPV at 12m)	-36 (-2%)	-26 (-2%)	+2,460 (+8%)	+2 (+5%)	+5 (+9%)
	Post-treatment follow-up: HPV test at 24m	953 (-51%)	648 (-56%)	29,858	37	50
	Difference c/f baseline (HPV at 12m)	+13 (+1%)	+10 (+1%)	-328 (-1%)	+0 (+0%)	-1 (-2%)
HPV, colposcopy triage	Baseline (HPV at 12m)	940 (-52%)	625 (-57%)	33,265	40	57
	Post-treatment follow-up: co-test at 12m	918 (-53%)	609 (-58%)	34,740	41	62
	Difference c/f baseline (HPV at 12m)	-22 (-1%)	-16 (-1%)	+1,476 (+4%)	+1 (+2%)	+5 (+8%)
	Post-treatment follow-up: HPV test at 24m	944 (-52%)	628 (-57%)	32,878	40	56
	Difference c/f baseline (HPV at 12m)	+4 (+0%)	+3 (+0%)	-387 (-1%)	-0 (-1%)	-1 (-2%)
HPV, cytology triage	Baseline (HPV at 12m)	966 (-50%)	648 (-56%)	22,352	28	61
	Post-treatment follow-up: co-test at 12m	942 (-52%)	630 (-57%)	23,932	29	65
	Difference c/f baseline (HPV at 12m)	-24 (-1%)	-18 (-1%)	+1,580 (+7%)	+1 (+5%)	+4 (+6%)
	Post-treatment follow-up: HPV test at 24m	972 (-50%)	650 (-55%)	22,040	27	60
	Difference c/f baseline (HPV at 12m)	+6 (+0%)	+3 (+0%)	-312 (-1%)	-0 (-1%)	-1 (-1%)

Strategies have similar effectiveness (<5% difference) in incidence and mortality reductions for variations of test-of-cure management, within the same primary test-triage group

Using cytology and HPV co-testing for post-treatment follow-up increases precancer treatments, NNT and costs

The first set of numbers in each box represents the % change versus no screening; the second line in each box represents the difference versus the baseline scenarios (12m follow-up with HPV). Note that for cervical cancer cases and deaths, the % in brackets in the second line is difference in the % change versus no screening; for precancer treatment, NNT and cost columns, it is the % difference versus the baseline for that flowchart. *Outcomes represent total events over the lifetime of a cohort of 100,000 women.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	See above.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Evidence for the desirable and undesirable effects of repeat screening and follow-up is based on modelling. The modelled evidence provided low certainty evidence: there was some concern for risk of bias in the credibility of the model (e.g., assumptions of adherence and lost to follow-up after screening), but most of the model inputs were of moderate or high certainty evidence (e.g., diagnostic accuracy of HPV) for the general population, but moderate or low certainty for WLHIV.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The outcomes previously identified in the 2014 screening and treatment guidelines, using methods from the WHO Handbook for Guideline Development were agreed on by the GDG as the outcomes of importance for these new PICO questions. The importance of the outcomes was identified as: •Cervical cancer •Mortality •Preterm birth (early/late) •Pre-cancer treatments (and related adverse events, see below) •CIN 2+ •HPV infection •Adverse events related to pre-cancer treatments - Major infections or bleeding, Procedure associated pain, Cervical stenosis, Infertility, Spontaneous abortions (1st trimester/ 2nd trimester), Perinatal deaths, Premature rupture of membrane, Unnecessary interventions, Increased viral shedding in HIV infected women •Acceptability (to all stakeholders) A systematic review of qualitative research was conducted and included 43 studies. There was however very little data reporting the value of the outcomes (data was primarily about the acceptability of the different tests and treatments – see below).	The Guideline Development Group agreed that greater value should be placed on cervical cancer incidence and mortality, and less value on treatment of CIN (and subsequent harms) and reproductive outcomes. However, in young women of reproductive age, although more value is placed on reproductive outcomes, there was still greater value placed on cervical cancer and mortality.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know	**Follow-up after positive screening test and negative triage test** The GDG agreed that when triage is with VIA or cytology, women returning for an HPV test at 24 months instead of 12 months can result in slightly more cervical cancers and death. The GDG agreed that when triage is with HPV 16/18 genotyping, if women return at 24 months instead of 12 months there may be a reduction in treatments but little to no differences in cervical cancer and deaths. The GDG agreed that when comparing to screening at both 12 and 24 months, there were only slightly greater reductions and cervical cancer and deaths and slight worsening of harms from more treatments. The GDG agreed that in WLHIV that rescreening at 24 instead of 12 months can increase the number of cervical cancers and related deaths. **Follow-up after positive screening and/or triage and treated** The GDG agreed that women who returned for HPV and cytology co-testing 12 months after treatment (for all triage methods) compared to HPV only - had similar cervical cancer incidence and mortality - had omewhat more precancer treatment events The GDG agreed that for women who returned for HPV at 24 months after treatment (for all triage methods) compared to HPV at 12 months - had slightly larger reductions in cervical cancer incidence and mortality - had slightly fewer precancer treatment events For WLHIV, modelling was not performed. The GDG agreed that the results would likely be similar to the general population but that testing with HPV at 12 and 24 months would likely result in even greater reductions in cervical cancer incidence and mortality in this higher risk group.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Modelling** of outcomes was conducted and the following costs were used: Additional costs: - programmatic costs - cancer specific equipment - variations in health care worker wages and training (but not staff turnover) - HPV and thermal ablation costs are based on recently negotiated prices	

	Summary of aggregate costs (average across all 78 LMIC+) | Event	Cost (US$ 2019)
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Primary VIA^	7.13
Primary HPV (+/- 16/18)*	15.20
Primary cytology^	18.13
VIA triage^{O}	3.03
Cytology triage^{O}	15.74
HPV triage^{O}	8.15
Colposcopy$^{O,\#}$	9.98
Ablative treatment	11.77
Excisional treatment	41.71 | | Event	Cost (US$ 2019)
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Histology @	18.14
Punch biopsy/Biopsy	11.67
Cancer diagnosis and treatment– FIGO 1[a]	263.23
Cancer diagnosis and treatment– FIGO 2[a]	546.28
Cancer diagnosis and treatment– FIGO 3[a]	683.08
Cancer diagnosis and treatment– FIGO 4[a]	312.77
Palliative care[a]	116.92
Yearly surveillance after treatment[a]	58.36 | ^ Includes workforce, consumables/equipment * Includes cost of test, sample drop-off and transport, laboratory staff time, lab supplies, general administration and overhead costs using WHO-CHOICE methodology and database ^{O} Same as primary, but includes a proportion of the labour, programmatic and utilisation costs from primary visits due to not requiring another visit. # Includes consumables/equipment, workforce @Includes consumables/equipment, workforce including pathologist and biomedical scientist [a]Cancer costs are only applied to the proportion of cancers that are treated, and assumed to apply to 90% of screen-detected cases. Yearly surveillance assumed to apply up to 10 years after diagnosis or death, whichever comes first. + The average across 78 LMIC sum the country-level costs weighted by the population of each country, and divides by the total population of those countries combined	

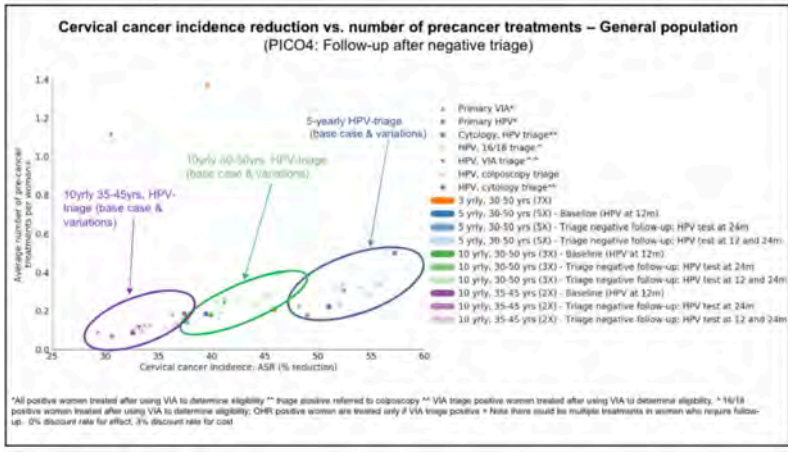
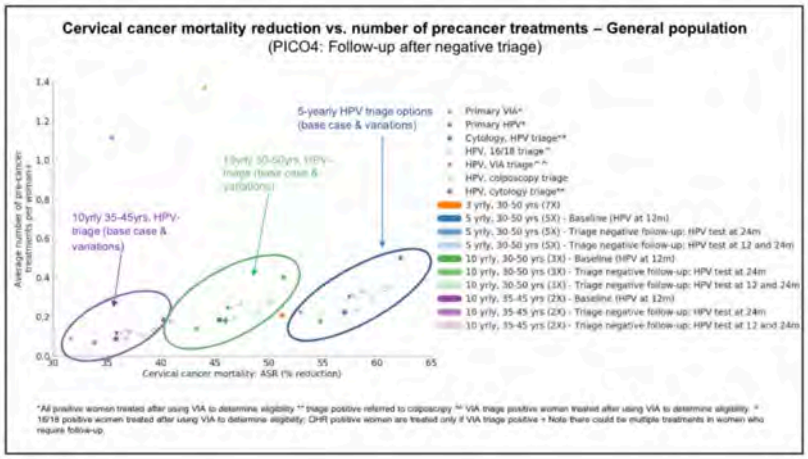
Certainty of evidence of required resources

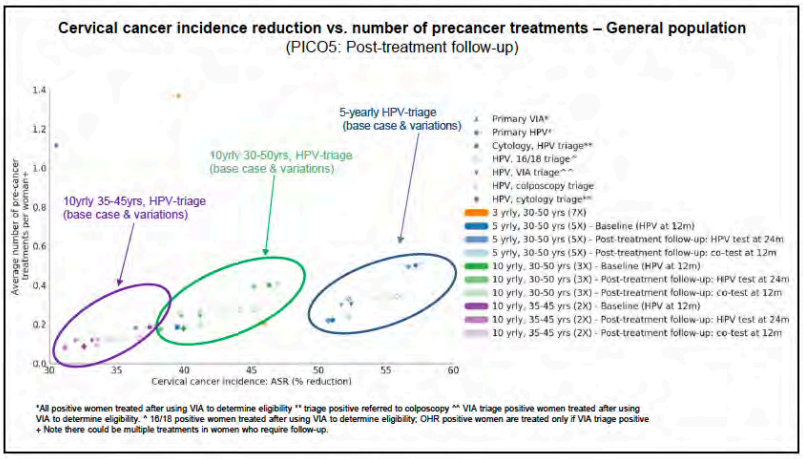
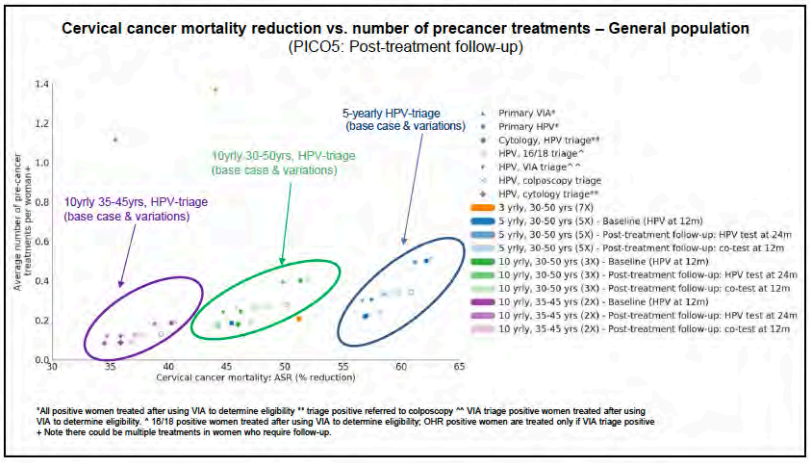
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	**Modelling** was conducted to compare cost-effectiveness. Figures below illustrate where each algorithm falls for cervical cancer incidence (first figure) AND mortality related to cervical cancer (second figure). Costs were not calculated for WLHIV, and results from the general population were directly applied to WLHIV. **Follow-up after positive screening test but negative triage test:**   	**Follow-up after positive screening test but negative triage test:** The GDG agreed that there were lower costs if women returned for HPV testing at 24 months when HPV based screening with triage was used. The GDG agreed that there were slightly greater costs when women returned for HPV testing at 12 AND 24 months.

	Follow-up after positive screening test or triage and treatment   	**Follow-up after positive screening test or triage and treatment** The GDG agreed that women who returned for HPV and cytology co-testing 12 months after treatment (for all triage methods) compared to HPV only - there are higher costs The GDG agreed that for women who returned for HPV at 24 months after treatment (for all triage methods) compared to HPV at 12 months - there are slightly lower costs

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		While there is no evidence yet, the GDG agreed that providing HPV DNA testing may lead to greater access to screening.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**A survey of 561 women** was conducted online via SurveyMonkey in 2020, and was completed anonymously. All women aged 15 years and older, regardless of their prior cervical cancer screening or treatment status were eligible to participate. Survey results found that • follow-up visits after treatment for a cervical lesion were likely to cause difficulties to the respondents • when participants were presented with several hypothetical scenarios, an important finding was that they found that repeat follow-up visits(>1) would be likely to cause problems for them at home. Nearly 46% said that it was very likely to be problematic, and 21% said it was likely. Only 24% reported that repeat visits were unlikely to be problematic. • these findings suggest that a greater emphasis placed on minimising the number of repeat visits following treatment for a precancer lesion. • written comments also accompany these findings, which include that they placed importance on what their healthcare provider told them, having a supportive partner. • COVID-19 was noted be a deterrent to repeat visits. **Systematic review of reviews of provider perspectives** was conducted <u>VIA</u> • perceived limitations of VIA – low sensitivity and specificity and subjectivity - leading to missed cases and unnecessary referral to colposcopy or treatment	The GDG also considered that it may be difficult to change perceptions of providers to NOT use cytology; however, there may be increasing positive attitudes to HPV

	• perceived incompetency – standardised training needed • lack of criteria for VIA positive HPV • Lack of understanding about HPV tests and meaning of positive result • In LMICs, perception that implementing HPV would increase uptake, lead to more treatment (if same day) and be more sensitive to detect precancerous lesions	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**A survey of GDG members** was conducted to explore feasibility/implementations issues: • >70% of respondents were moderately to very concerned about generating demand for screening for all algorithms; ~80% was the highest for VIA • more were very concerned about access to HPV or cytology screening (30-40%) compared with VIA • more were moderately or very concerned about scale-up and sustainability of maintaining a trained workforce for VIA and cytology (~90%) vs. HPV (~55%) • over 50% of respondents were moderately or very concerned about ability to meet infrastructural demands for HPV or cytology • ability to maintain registry (aggregate or patient level) was moderately or very concerning in all algorithms (>75%) • variable concerns about integration with other programs (by level of concern cyto>HPV>VIA)	The GDG also considered: • complexity of algorithm may mean difficulty implementing • multiple steps in algorithm and across health sectors may reduce feasibility • political will appears to be a large factor in implementation • training providers and sustaining a skilled workforce is a large factor

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either intervention or comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either intervention or comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced		**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendations

For general population:

11. WHO suggests that the general population of women who have screened positive on an HPV DNA primary screening test and then negative on a triage test are retested with HPV DNA testing at 24 months and, if negative, move to the recommended regular screening interval.
[Conditional recommendation, low-certainty evidence in effects]

12. WHO suggests that women from the general population and women living with HIV who have screened positive on a cytology primary screening test and then have normal results on colposcopy are retested with HPV DNA testing at 12 months and, if negative, move to the recommended regular screening interval.*
[Conditional recommendation, low-certainty evidence in effects]

13. WHO suggests that women from the general population who have been treated for histologically confirmed CIN2/3 or adenocarcinoma in situ (AIS), or treated as a result of a positive screening test are retested at 12 months with HPV DNA testing when available, rather than with cytology or VIA or co-testing and, if negative, move to the recommended regular screening interval.
[Conditional recommendation, low-certainty evidence in effects]

14. As programmes introduce HPV DNA testing, use this test at the woman's next routine screening date regardless of the test that was used at prior screening. In existing programmes with cytology or VIA as the primary screening test, rescreening with the same test should be continued until HPV DNA testing is operational among both the general population of women and women living with HIV.*
[Good-practice statement]

For Women living with HIV:

31. WHO suggests that women living with HIV who have screened positive on an HPV DNA primary screening test and then negative on a triage test, are retested with HPV DNA testing at 12 months and, if negative, move to the recommended regular screening interval.
[Conditional recommendation, low-certainty evidence in effects]

32. WHO suggests that women from the general population and women living with HIV who have screened positive on a cytology primary screening test and then have normal results on colposcopy are retested with HPV DNA testing at 12 months and, if negative, move to the recommended regular screening interval.*
[Conditional recommendation, low-certainty evidence in effects]

33. WHO suggests that women living with HIV who have been treated for histologically confirmed CIN2/3 or adenocarcinoma in situ (AIS), or treated as a result of a positive screening test are retested at 12 months with HPV DNA testing when available, rather than with cytology or VIA or co-testing, and, if negative, are retested again at 12 months and, if negative again, move to the recommended regular screening interval.
[Conditional recommendation, low-certainty evidence in effects]

34. As programmes introduce HPV DNA testing, use this test at the woman's next routine screening date regardless of the test that was used at prior screening. In existing programmes with cytology or VIA as the primary screening test, rescreening with the same test should be continued until HPV DNA testing is operational among both the general population of women and women living with HIV.*
[Good practice statement]

Justification

General population

Conditional recommendations were made for HPV DNA testing 12 months after treatment and 24 months after a negative triage test, if screened initially with an HPV DNA test, or 12 months after a positive cytology test (but negative colposcopy); this is because there may be greater benefits and fewer harms compared with alternative follow-up times (low-certainty evidence based on modelling).

Women living with HIV

Conditional recommendations were made for HPV DNA testing 12 months after treatment and after a negative triage test, regardless of initial screening test, as there may be greater benefits and fewer harms (low-certainty evidence based on modelling).