WHO guidelines for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition

Web Annex B: Evidence to Decision Tables

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WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition. Web Annex B. Evidence-to-decision tables

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EVIDENCE TO DECISION TABLE (ETD) PICO 1 AND 2 GENERAL POPULATION

Should HPV DNA detection algorithms vs. other algorithms be used for screening (triage) and treating women in the general population?

POPULATION:	screening (triage) and treating women in the general population
INTERVENTION:	HPV DNA detection algorithms
COMPARISON:	other algorithms
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:	
PERSPECTIVE:	Population
BACKGROUND:	There are many strategies (algorithms) that can be used to screen, triage and treat women to prevent cervical cancer. The GDG prioritised the following algorithms to evaluate (other algorithms will be assessed in future): 1.VIA 2.HPV DNA (self or clinician) 3.Cytology then colposcopy 4.HPV DNA then HPV 16/18 (only when already part of the HPV test) and VIA 5.HPV DNA then VIA triage 6.HPV DNA then colposcopy (triage) 7.HPV DNA then cytology (triage) – colposcopy [full description of algorithms is available at
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	**REVIEWS OF LONGITUDINAL STUDIES** were conducted by IARC: HPV versus VIA: HPV-and-treat approach achieved greater reduction on the prevalent CIN2+ at 6 months of follow-up compared with VIA-and-treat (77% vs 37%) based on the RCT conducted in South Africa (Denny 2005). Greater reduction of cervical cancer incidence and mortality of a single round of screening with HPV DNA test compared with VIA has been identified at the Osmanabad India RCT (age-standardized incidence [ASR]: 47.4 vs 58.7 per 100 000 person-year, age-standardized mortality: 12.7 vs 20.9 per 100 000 person-year) (Sankaranarayanan 2005, 2009). In addition, HPV DNA test has dramatically reduced the incidence of stage II or higher cervical cancer compared to VIA in the trial (ASR 14.5 vs 32.2 per 100 000 person-year). Regarding diagnostic harms, no absolute trend of higher or lower colposcopy referral rate and PPV were identified between the two screening modalities across different studies. HPV versus cytology: Eight out of nine randomized controlled trials (Ronco 2008, Ogilvie 2018, leinonen 2012, Canfell 2017, Rijkaart 2012, Naucler 2007, Kitchener 2009, Chan 2020) have shown that HPV-based screening by HPV alone, or followed by triage with cytology or colposcopy, or co-testing detects more CIN2+ in screening than cytology, and five out of six trials have shown a decrease in CIN2+ in the next screening round. In a pooled analysis of four of these randomized trials with a median follow-up of 6.5 years, cervical cancer risk was 40% lower in the HPV-based testing arm (Ronco 2014). In one other randomized trial in a previously unscreened population, cervical cancer mortality was 41% lower in the HPV-based testing arm than in the cytological screening arm after a cumulative follow-up of 8 years. The increased CIN2+ detection of HPV-based screening was confirmed in twelve real-world HPV implementation cohorts. These studies evaluated different HPV DNA screening with or without triage (including cytology, co-testing with cytology, and/or colposcopy). These studies also observed an	The GDG agreed on the following based on the modelling: • Primary HPV testing every 5-years from ages 30-50 years, regardless of triaging strategy, resulted in the largest reductions in cervical cancer incidence and mortality rates, with >50% reduction in cervical cancer incidence and >55% reduction in cervical cancer mortality. • Primary VIA testing could reduce cervical cancer incidence rates by up to 46% but required more frequent testing (3-yearly intervals) and high test performance (sustained, population-level sensitivity to CIN2+ of 60%).

increase in the number of screen positives and colposcopy referrals in the HPV screening arm, but the effect on the positive predictive value of CIN3+ was limited.

REVIEWS OF REVIEWS in LMICs for loss to follow-up, triage, treatment

'loss to triage'

- systematic review of *VIA* screening programmes in India
- large variation in loss from 10 to 70% when colposcopy used as triage
- less loss (0 to 1.4%) when colposcopy offered same day

'loss to active surveillance'

- systematic review measuring follow-up after *histological confirmation* - 19% loss at 6 months, 15% loss at 12 months

'loss to treatment'

- systematic review of studies in women with *histological confirmation* - variation in loss from 58 to 100%
- systematic review of *HPV* screening - follow-up may be hindered by access to health care

REVIEWS OF THE ACCURACY OF SCREENING AND TRIAGE TESTS were conducted:

VIA for CIN2+: sensitivity 66%; specificity 87%; extreme heterogeneity (variability) in studies, likely due to subjectivity of interpretation

HPV compared to cytology for CIN2+: relative sensitivity 1.35 [HPV has greater sensitivity); relative specificity 0.94 (HPV slightly lower specificity)

HPV vaginal self versus cervical clinician samples: self PCR similar sensitivity and specificity; self signal amplification lower sensitivity and specificity; self mRNA HPV lower sensitivity but similar specificity

Cytology (ASCUS+) as triage after HPV for CIN2+: sensitivity 71%; specificity 75%

VIA as triage after HPV for CIN2+: sensitivity 65%; specificity 73%

HPV 16/18 (and VIA for negative) as triage for CIN2+: sensitivity 53%; specificity 75%

Colposcopy as triage for CIN2+: sensitivity 83%; specificity 75%

MODELLING was conducted to calculate benefits and harms of different algorithms starting at different ages and with different frequency intervals:

Summary table: General population

	Screening ages	Cervical Cx cases* (% reduction)	Cervical Cx deaths* (% reduction)	Pre-cancer treatments*	Additional pre-term deliveries due to pre-cancer treatment*	NNT to avert a cervical cancer death	Discounted lifetime cost (2019 $US)
No Screening	-	1,950 (-)	1,456 (-)	0	0	-	$3
Primary VIA (high sens)	3yrly, 30-50 yrs (7X)	1,046 (46%)	714 (51%)	147,349	180	199	$54
	5yrly, 30-50 yrs (5X)	1,181 (39%)	803 (45%)	120,442	139	184	$41
Primary VIA	3yrly, 30-50 yrs (7X)	1,194 (39%)	838 (42%)	137,172	167	222	$51
	5yrly, 30-50 yrs (5X)	1,351 (31%)	949 (35%)	111,915	127	221	$39
Primary HPV	5yrly, 30-50 yrs (5X)	851 (56%)	572 (61%)	50,179	88	57	$52
	10yrly, 30-50 yrs (3X)	1,048 (46%)	720 (51%)	40,090	74	54	$35
	10yrly, 35-45 yrs (2X)	1,237 (37%)	883 (39%)	18,528	28	32	$21
Cytology, HPV triage	3yrly, 30-50 yrs (7X)	1,101 (44%)	756 (48%)	20,922	43	30	$60
	5yrly, 30-50 yrs (5X)	1,200 (38%)	822 (44%)	18,516	34	29	$59
HPV, 16/18 triage	5yrly, 30-50 yrs (5X)	877 (55%)	591 (59%)	34,408	67	40	$51
	10yrly, 30-50 yrs (3X)	1,069 (45%)	737 (49%)	27,880	56	39	$34
	10yrly, 35-45 yrs (2X)	1,253 (36%)	897 (38%)	13,119	21	23	$21
HPV, VIA triage	5yrly, 30-50 yrs (5X)	940 (52%)	638 (56%)	30,186	61	37	$51
	10yrly, 30-50 yrs (3X)	1,144 (41%)	792 (46%)	24,239	51	37	$35
	10yrly, 35-45 yrs (2X)	1,318 (32%)	945 (35%)	11,621	18	23	$21
HPV, colp triage	5yrly, 30-50 yrs (5X)	940 (52%)	625 (57%)	33,265	64	40	$57
	10yrly, 30-50 yrs (3X)	1,141 (41%)	779 (47%)	26,633	54	39	$39
	10yrly, 35-45 yrs (2X)	1,308 (33%)	929 (36%)	12,398	20	24	$23
HPV, cytology triage	5yrly, 30-50 yrs (5X)	966 (50%)	648 (56%)	22,352	48	28	$61
	10yrly, 30-50 yrs (3X)	1,166 (40%)	799 (45%)	18,075	40	27	$42
	10yrly, 35-45 yrs (2X)	1,329 (32%)	947 (35%)	8,693	15	17	$25

*Outcomes represent total events over the lifetime of a cohort of 100,000 women

Note: costs of preterm deliveries with thermal ablation was estimated from the risk after ablation from systematic review by Kyrgiou 2017.

- Primary HPV testing approaches resulted in substantially fewer precancer treatment events and fewer adverse obstetric outcomes when compared to primary VIA strategies, even when we assume favourable VIA test performance.
- Of the Primary HPV approaches, no triage (where visual assessment is used to determine eligibility for ablative treatment) had the highest reduction in incidence of cervical cancer (56% reduction). Different triaging options resulted in similar reductions in cervical cancer rates (range 50-55% reduction in incidence), and at least 31% fewer precancer treatment events when compared with no triage.
- Although, not modelled, the sensitivity and specificity of clinically validated PCR-based high risk HPV DNA for detection of CIN2+ on self-collected upper vaginal versus health provider-taken cervical samples are likely similar.
- A 5-year screening interval resulted in greater benefits, fewer harms and lower costs than 10 years when providing HPV DNA testing with or without triage. These effects were similar to cytology (followed by colposcopy) every 3 years, but better than every 5 years; and better than VIA every 5 years.
- Previous modelling for the WHO Global Strategy towards the elimination of cervical cancer demonstrated benefits with screening twice in a lifetime compared to once.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**See above.**	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 HPV DNA based testing compared to VIA or cytology based screening is from longitudinal studies and modelling. The evidence from longitudinal studies was reviewed in the IARC Handbook and found moderate certainty evidence when HPV DNA based testing (with or without triage) was used. The modelled evidence provided low certainty evidence and supported the effects from the longitudinal studies: 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).	

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	The GDG agreed that • HPV DNA as a primary test is favoured over VIA or cytology as a primary test. • HPV DNA testing alone or followed by a triage test are similarly favoured. • HPV DNA testing every 5 or 10 years is probably favoured over every 3 years, and every 3 years with cytology or VIA.	

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: **Summary of aggregate costs (average across all 78 LMIC+)** Event / Cost (US$ 2019) 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) 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. Additional costs considered: - 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	

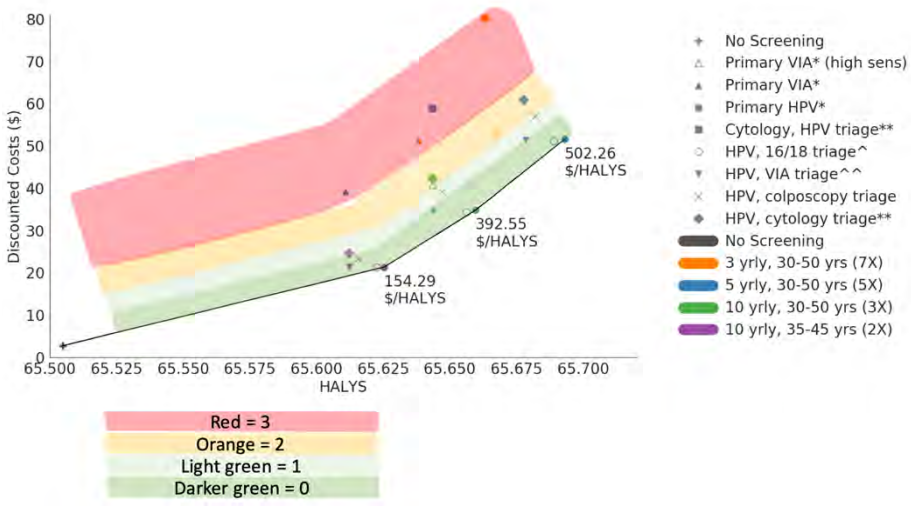
Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Based on modelling.	

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. Figure below illustrates where each algorithm falls when comparing Health Adjusted Life Years (HALYs, a combination of mortality and morbidity) against discounted costs:  	The GDG agreed about the following when comparing HPV testing to VIA or cytology testing: Primary HPV testing without triage was on the cost-effectiveness frontier: ● 10-yearly intervals at ages 35-45 (ICER =$154/HALY saved), ● 10-yearly intervals at ages 30-50 (ICER = $393/HALY saved), ● 5-yearly intervals at ages 30-50 ($502/HALY saved) Primary HPV 16/18 triage had similar costs and effects and could be considered to have similar cost-effectiveness outcomes. As a reference point for a potential willingness-to-pay

		(WTP) threshold in this population, the population-weighted average GDP per capita (pc) for 2019 across the 78-LMIC is US$1,999. Also, 68 of 78 LMIC (87%) had a GDP/pc >$500. The findings were robust to lower compliance assumptions. The GDG noted that the costs of HPV alone and HPV with HPV 16/18 triage were similar. The reason for this is greater treatments with HPV alone but fewer treatments with HPV 16/18 triage but greater cost of additional testing with triage.

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	No research evidence found	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 GDG members** was conducted to explore concern for costs and integration of different algorithms: • respondents were moderately to very concerned about the ability to finance ALL algorithms (cyto>HPV>VIA) for scale-up and sustainability • more were very concerned about ability to minimize cost to patient for HPV and cytology algorithms **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 • most women (82.56%) in the general population stated that they would not face problems in attending a screening program • clear and strong preference for immediate treatment following a diagnosis of a cervical intraepithelial lesion (78%) among all women • follow-up visits after treatment for a cervical lesion were likely to cause difficulties to the respondents • aversion for the use of a speculum during screening • request from the community for better counselling, patient education, availability of choices of treatment and screening tests A systematic review of qualitative studies was conducted and included 43 studies. The results showed that the studies consistently demonstrate very high acceptability (70% or higher, several with 90%) across the studies for self-sampling, VIA, HPV DNA tests or a triage-based method. Studies also showed that women desired to decide whether to receive treatment, few said they would prefer to consult with their partner and few felt that they felt obligated to consult prior to treatment. Factors lowering acceptability included lack of reminders, payment of test, no tertiary education, no children, recent HIV diagnosis, poor awareness of cervical cancer, poor provider patient relationships. **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 • perceived incompetency – standardised training needed • lack of criteria for VIA positive	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

	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 • Self-sampling could reduce opportunities to see women for other care	

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 the intervention or the 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 the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**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

Recommendation

1. WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV.*
[Strong recommendation, moderate certainty of evidence in effects]

Remarks: Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance.

2. WHO suggests using an HPV DNA primary screening test either **with triage or without triage** to prevent cervical cancer among the general population of women.
[Conditional recommendation, moderate certainty of evidence in effects]

3a. **In a screen-and-treat approach** using HPV DNA detection as the primary screening test, WHO suggests treating women who test positive for HPV DNA among the general population of women.
3b. **In a screen, triage and treat approach** using HPV DNA detection as the primary screening test among the general population of women, WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women after a positive HPV DNA test (Annex 4).
[Conditional recommendation, moderate certainty of evidence in effects]

Remarks: The benefits, harms and programmatic costs of the triage options are similar; therefore, the choice of triage method will be dependent on feasibility, training, programme quality assurance and resources in countries. HPV16/18 genotyping could be integrated into the HPV DNA test (refer to Annex 4 for specific details of the algorithms).

4. When providing HPV DNA testing, WHO suggests using either samples taken by a health-care provider or self-collected samples among both the general population of women and women living with HIV.*
[Conditional recommendation, low-certainty evidence in effects]

8. WHO suggests a regular screening interval of every 5 to 10 years when using HPV DNA detection as the primary screening test among the general population of women.
[Conditional recommendation, low-certainty evidence in effects]

9. Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every 3 years when using VIA or cytology as the primary screening test among both the general population of women and women living with HIV.*
[Conditional recommendation, low-certainty evidence in effects]

10. While transitioning to a programme with a recommended regular screening interval, screening even just twice in a lifetime is beneficial among both the general population of women and women living with HIV.*
[Good-practice statement]

Justification

A strong recommendation was made for using HPV DNA detection as a primary screening test when part of a screen-and-treat approach or a screen, triage and treat approach because a higher value was placed on the greater reductions in cervical cancer and deaths that are likely with HPV DNA detection compared with using VIA or cytology as a primary screening test (moderate-certainty evidence). There may also be fewer harms, such as preterm deliveries, when screening with an HPV DNA test compared with VIA. HPV DNA testing by the provider or by self-sampling may have similar effects, so either method of testing was suggested (low-certainty evidence). HPV DNA testing is largely acceptable to women and providers, is feasible and is more likely to lead to more equitable access to screening.

A conditional recommendation was made to use either HPV DNA detection followed by treatment or HPV DNA detection with a triage test because the balance of benefits and harms may be similar for either approach (moderate-certainty evidence). The benefits and harms may also be similar with any of the triage tests considered (moderate-certainty evidence), but the choice of approach should be made depending on context, because the feasibility and the resources needed for triage tests vary across settings.

Conditional recommendations were made on the screening intervals and the age at which to stop screening based on modelled evidence showing greater benefits and fewer harms with 5- to 10-year screening intervals with HPV DNA testing, compared with more frequent screening or similar intervals using cytology or VIA (low-certainty evidence).

EVIDENCE TO DECISION TABLE (ETD) PICO 1 AND 2 WOMEN LIVING WITH HIV

Should HPV DNA detection algorithms vs. another algorithm be used for screening (triage) and treating women living with HIV?

POPULATION:	screening (triage) and treating WOMEN LIVING WITH HIV (WLHIV)
INTERVENTION:	HPV DNA detection algorithms
COMPARISON:	another algorithm
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:	
PERSPECTIVE:	Population
BACKGROUND:	There are many strategies (algorithms) that can be used to screen, triage and treat women to prevent cervical cancer. The GDG prioritised the following algorithms to evaluate (other algorithms will be assessed in future): 1.VIA 2.HPV DNA (self or clinician) 3.Cytology then colposcopy 4.HPV DNA then HPV 16/18 (only when already part of the HPV test) and VIA 5.HPV DNA then VIA triage 6.HPV DNA then colposcopy (triage) 7.HPV DNA then cytology (triage) – colposcopy [Full description of algorithms is available]
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	**REVIEWS OF LONGITUDINAL STUDIES** HPV versus VIA (Denny 2005 and Kuhn 2010): After 36 months approximately 7.5% had CIN2+ after screening with VIA, and 3% with HPV (control 15%) Prospective studies following women who were screened negative Johannesburg, South Africa, 688 WLHIV incident CIN2+ at 12 months (Firnhaber 2016) •VIA negative: 4.4%, •HPV negative: 2.1% • Cytology (<ASCUS): 2.5% A multi-site study in Johannesburg, South Africa and Ouagadougou, Burkina Faso; CIN2+ over 16 months (Segondy 2016) •VIA negative: 2.2%, •HPV negative: 0.5% • Cytology (<ASCUS): 0.5% A prospective study among 688 WLHIV in India; CIN 2+ over median 3 years (Joshi 2019) •VIA negative: 0.5%, •HPV negative: 0.0% • Cytology (<ASCUS): 0.5% **REVIEWS OF THE ACCURACY OF TESTS** VIA for CIN2+: sensitivity ranged from 43.8–86.6%; specificity ranged from 47.3-96.7 HPV for CIN2+: sensitivity 92%; Specificity 55.2% (increase with high CD4+ count, and effective ART); HPV by genotype: Specificity of a restricted genotype approach 8-HR* vs 13-HR= 65.6% vs. 56.5% Cytology (ASCUS+) for CIN 2+: Sensitivity variable 57.5% to 100%; specificity ranged from 8.5% to 94.5%	The GDG agreed that from prospective studies that HPV may result in reduced CIN 2+ lesions over time. The GDG agreed there is greater variability in specificity and sensitivity of VIA test compared to HPV or cytology. The GDG agreed based on the modelling that • although screening started earlier in WLHIV in the model, the results followed similar pattern as in general population

HPV followed by VIA for CIN 2+: Sensitivity range: 45.2% to 84.2%; specificity: 44.8% to 94.5%; similar for HPV followed by cytology

HPV provider versus self collected samples: From the general population of women, self PCR similar sensitivity and specificity; self signal amplification lower sensitivity and specificity; self mRNA HPV lower sensitivity but similar specificity

Relative sensitivity and specificity between tests

	CIN2+		
	N studies	Relative Sensitivity (95%CI)	Relative Specificity (95%CI)
HPV vs. VIA	9	1.41 (1.27-1.58)	0.73 (0.68-0.79)
HPV vs. Cytology ASCUS+*	9	0.99 (0.96-1.02)	0.81 (0.73-0.89)
HPV vs. Cytology LSIL+	6	0.98 (0.95-1.01)	0.74 (0.65-0.85)
HPV vs. Cytology HSIL+	7	1.44 (1.28-1.62)	0.62 (0.54-0.72)
HPV vs. HPV -> VIA triage	6	1.33 (1.18-1.49)	

MODELLING was conducted for benefits and harms of algorithms in WLHIV (followed by ablative treatment if eligible, and LLETZ if not eligible) . *Outcomes represent total events over the lifetime of a cohort of 100 000

	Screening ages	Cervical Cx cases* (% reduction)	Cervical Cx deaths* (% reduction)	Pre-cancer treatments*	NNT to avert a cervical Cx death
No Screening	-	0%	0%	-	-
Primary VIA	3 yrly, 25-50 yrs	43%	60%	735,891	581
Prim VIA* (high sens)	3 yrly, 25-50 yrs	52%	71%	824,010	553
Prim HPV*	3 yrly, 25-50 yrs	74%	82%	671,862	327
	5 yrly, 25-50 yrs	69%	78%	558,035	284
	10 yrly, 25-50 yrs	50%	58%	464,960	318
	10 yrly, 30-50 yrs	46%	57%	155,341	109
	10 yrly, 35-45 yrs	37%	45%	74,318	66
Cyto, HPV triage**	3 yrly, 25-50 yrs	50%	69%	97,450	56
HPV, 16/18 triage^	3 yrly, 25-50 yrs	70%	79%	382,628	191
	5 yrly, 25-50 yrs	64%	75%	302,180	159
	10 yrly, 25-50 yrs	45%	55%	229,431	165
	10 yrly, 30-50 yrs	42%	54%	120,710	90
	10 yrly, 35-45 yrs	34%	42%	59,138	55
HPV, VIA triage^^	3 yrly, 25-50 yrs	70%	80%	443,301	221
	5 yrly, 25-50 yrs	65%	75%	351,189	185
	10 yrly, 25-50 yrs	46%	55%	270,536	194
	10 yrly, 30-50 yrs	42%	54%	132,527	98
	10 yrly, 35-45 yrs	34%	43%	64,521	60
HPV, colp triage	3 yrly, 25-50 yrs	69%	81%	198,944	98
	5 yrly, 25-50 yrs	64%	77%	164,214	84
	10 yrly, 25-50 yrs	46%	58%	128,116	88
	10 yrly, 30-50 yrs	41%	55%	71,106	51
	10 yrly, 35-45 yrs	32%	44%	37,638	34
HPV, cyto triage **	3 yrly, 25-50 yrs	68%	80%	283,709	142
	5 yrly, 25-50 yrs	63%	76%	220,462	116
	10 yrly, 25-50 yrs	44%	56%	160,847	114
	10 yrly, 30-50 yrs	40%	54%	99,126	73
	10 yrly, 35-45 yrs	32%	43%	48,413	45

- Primary HPV testing strategies every 3 or 5 years resulted in the largest reduction in cervical cancer incidence. Primary HPV testing every 5 years for ages 25-50, regardless of triaging strategy, resulted in >62% reduction in cervical cancer incidence. Primary HPV testing every 3 years resulted in >67% reduction in cervical cancer incidence, and generally added 4-6% to the reduction in cancer incidence across the different triaging approaches.
- Primary VIA testing every 3 years had a lower impact on cervical cancer incidence rates when compared to Primary HPV testing every 5 years, even when assuming sustained, population-level sensitivity to CIN2+ of 60%. Primary VIA testing also resulted in more precancer treatment events, and the number needed to treat to avert a cervical cancer death for Primary VIA strategies was over 550 (compared to <250 for Primary HPV strategies which triaged women before treatment)
- Although, not modelled, the sensitivity and specificity of clinically validated PCR-based high risk HPV DNA for detection of CIN2+ on self-collected upper vaginal versus health provider-taken cervical samples are likely similar.

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 HPV DNA based testing compared to VIA or cytology based screening is from longitudinal studies and modelling. The evidence from longitudinal studies was reviewed in the IARC Handbook and found moderate certainty evidence for greater benefits than harms when providing HPV DNA testing. The modelled evidence provided low certainty evidence and supported the effects from the longitudinal studies: 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), and most of the model inputs were of moderate or low certainty evidence (e.g., diagnostic accuracy of HPV). Evidence for the use of different triage tests and versus HPV DNA testing alone was informed by evidence from the general population and the model. The moderate certainty evidence reviewed in the IARC Handbook found that there are likely similar benefits and but more referral or treatments without triage when using different triage tests and compared to HPV DNA testing alone in a general population. The modelling evidence also found there may be greater treatments without triaging.	

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).	While there was little data specific to women living with HIV, the Guideline Development Group agreed that the values placed on outcomes would be similar to women in the general population: 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	The GDG agreed that • HPV DNA as a primary test is favoured over VIA or cytology as a primary test. • HPV DNA testing with a triage test is probably favoured over HPV DNA testing alone (although less value was placed on the number of treatments, there were greater treatments with HPV alone which therefore favoured triage) • HPV DNA testing every 3 or 5 years is probably favoured over every 10 years, and VIA or cytology every 3 years	

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	See resources listed and modelling for general population: EtD PICO 1 and 2 (general population)	

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	Based on modelling for general population: EtD PICO 1 and 2 (general population)	

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	Cost-effectiveness based on general population modelling: EtD PICO 1 and 2 (general population)	From the modelling in the general population: The GDG agreed about the following: Primary HPV testing without triage was on the cost-effectiveness frontier: • 10-yearly intervals at ages 35-45 (ICER =$154/HALY saved), • 10-yearly intervals at ages 30-50 (ICER = $393/HALY saved), • 5-yearly intervals at ages 30-50 ($502/HALY saved) Primary HPV 16/18 triage had similar costs and effects and could be considered to have similar cost-effectiveness outcomes. As a reference point for a potential willingness-to-pay (WTP) threshold in this population, the population-weighted average GDP per capita (pc) for 2019 across the 78-LMIC is US$1,999. Also, 68 of 78 LMIC (87%) had a GDP/pc >$500. The findings were robust to lower compliance assumptions.

		The GDG noted that the costs of HPV alone and HPV with HPV 16/18 triage were similar. The reason for this is greater treatments with HPV alone but fewer treatments with HPV 16/18 triage but greater cost of additional testing with triage.

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	No research evidence found. The GDG agreed that there would probably be no impact.	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	Surveys and systematic reviews were conducted in GDG members and women. However, there is no data specifically related to women living with HIV. Below we present the results from the general population which the GDG agreed would apply: **A survey of GDG members** was conducted to explore concern for costs and integration of different algorithms: • respondents were moderately to very concerned about the ability to finance ALL algorithms (cyto>HPV>VIA) for scale-up and sustainability • more were very concerned about ability to minimize cost to patient for HPV and cytology algorithms **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 • most women (82.56%) in the general population stated that they would not face problems in attending a screening program • clear and strong preference for immediate treatment following a diagnosis of a cervical intraepithelial lesion (78%) among all women • follow-up visits after treatment for a cervical lesion were likely to cause difficulties to the respondents • aversion for the use of a speculum during screening • request from the community for better counselling, patient education, availability of choices of treatment and screening tests A systematic review of qualitative studies was conducted and included 43 studies. The results showed that the studies consistently demonstrate very high acceptability (70% or higher, several with 90%) across the studies for self-sampling, VIA, HPV DNA tests or a triage-based method. Studies also showed that women desired to decide whether to receive treatment, few said they would prefer to consult with their partner and few felt that they felt obligated to consult prior to treatment. Factors lowering acceptability included lack of reminders, payment of test, no tertiary education, no children, recent HIV diagnosis, poor awareness of cervical cancer, poor provider patient relationships. **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 • perceived incompetency – standardised training needed • lack of criteria for VIA positive <u>HPV</u> • 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 • Self-sampling could reduce opportunities to see women for other care	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

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. The following results are not specific to WLHIV but the GDG agreed would apply: • >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 the intervention or the 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 the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	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

Recommendation

21. WHO recommends using HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women and women living with HIV.*
[Strong recommendation, moderate certainty of evidence in effects]

Remarks: Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of inherent challenges with quality assurance.

22. WHO suggests using an HPV DNA primary screening test **with triage** rather than without triage to prevent cervical cancer among women living with HIV.
[Conditional recommendation, moderate certainty of evidence in effects]

23. **In a screen, triage and treat approach** using HPV DNA detection as the primary screening test among women living with HIV, WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women after a positive HPV DNA test (Annex 4).
[Conditional recommendation, moderate certainty of evidence in effects]

Remarks: The benefits, harms and programmatic costs of the triage options are similar; therefore, the choice of triage method will be dependent on feasibility, training, programme quality assurance and resources in countries. HPV16/18 genotyping could be integrated into the HPV DNA test (refer to Annex 4 for specific details of the algorithms).

24. When providing HPV DNA testing, WHO suggests using either samples taken by a health-care provider or self-collected samples among both the general population of women and women living with HIV.*
[Conditional recommendation, low-certainty evidence in effects]

28. WHO suggests a regular screening interval of every 3 to 5 years when using HPV DNA detection as the primary screening test among women living with HIV.
[Conditional recommendation, low-certainty evidence in effects]

29. Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every 3 years when using VIA or cytology as the primary screening test among both the general population of women and women living with HIV.*
[Conditional recommendation, low-certainty evidence in effects.

30. When transitioning to a programme with a recommended regular screening interval, screening even just twice in a lifetime is beneficial among both the general population of women and women living with HIV.*
[Good practice statement]

Justification

For women living with HIV, a strong recommendation was made for using HPV DNA testing as a primary screening test because a higher value was placed on the reductions in cervical cancer and deaths that are likely with this approach than on the potential harm that may occur, such as preterm deliveries (moderate-certainty evidence). When compared with VIA or cytology as a primary screening test, greater benefits are also more likely with HPV DNA testing. HPV DNA testing is acceptable to women and providers, is feasible and is not likely to lead to inequities. In some settings, HPV DNA testing is not yet available, though, and there will be a period when existing quality-assured programmes will need to remain until HPV DNA testing becomes operational.

A conditional recommendation was made to use HPV DNA testing with a triage test rather than HPV DNA testing followed by treatment because providing a triage test may lead to reduced potential harms, with minimal change in benefits (moderate-certainty evidence). The feasibility and resources needed to provide different triage tests vary across settings, thus influencing which test is chosen.

Overall, with all screening and treatment strategies, there are greater reductions in cervical cancer, deaths and CIN2/3 lesions for women living with HIV compared with the general population of women. For women living with HIV on antiretroviral therapy (ART), there were few data regarding the impact of ART on HPV-associated lesions, although the evidence is growing; therefore, recommendations based on use of antiretrovirals were not made.

Conditional recommendations were made for screening intervals based on modelled evidence showing greater benefits may occur with three- to five-year screening intervals with HPV DNA testing (or cytology or VIA), though there may be more treatments and therefore harms compared with a longer interval (low-certainty evidence).

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%)	604 (-58%) +13 (+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	-	[illegible] (0%)	[illegible] (0%)	0	0
Primary VIA	Baseline (HPV at 12m)	3138 (46%)	2682 (49%)	[illegible]	[illegible]
Prim VIA (high sens)	Baseline (HPV at 12m)	2569 (56%)	2080 (60%)	[illegible]	[illegible]
Prim HPV	Baseline (HPV at 12m)	1772 (69%)	1379 (74%)	[illegible]	[illegible]
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%) [illegible]	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%)	1597 (70%)	99385	27
	Triage negative follow-up: HPV test at 12 and 24m Difference c/f baseline (HPV at 12m)	2106 (64%) +0 (+0%)	1597 (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%) +407 (+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%)	[illegible] [illegible]

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

	Sensitivity ratio estimate	(95% CI)	Specificity ratio estimate	(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%)

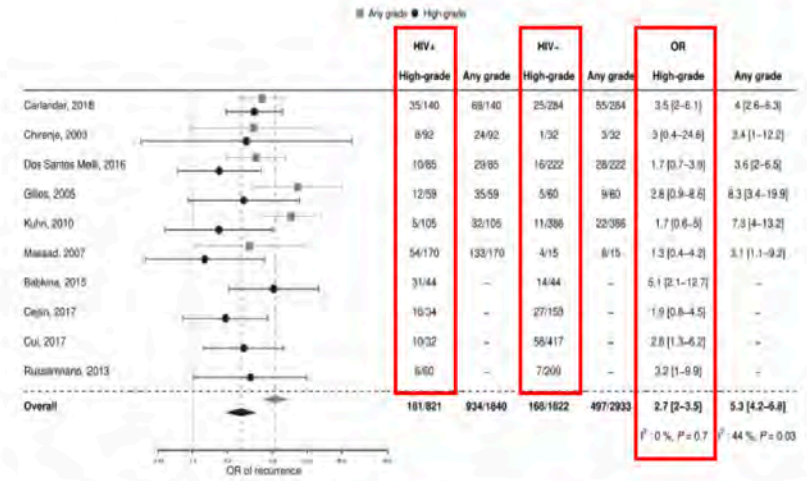


Figure 5. Meta-analysis of the risk of post treatment lesions after first treatment in HIV-infected versus uninfected women. Abbreviations: +, positive; -, negative; HIV, human immunodeficiency virus; OR, odds ratio

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)
---	---
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)
---	---
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	

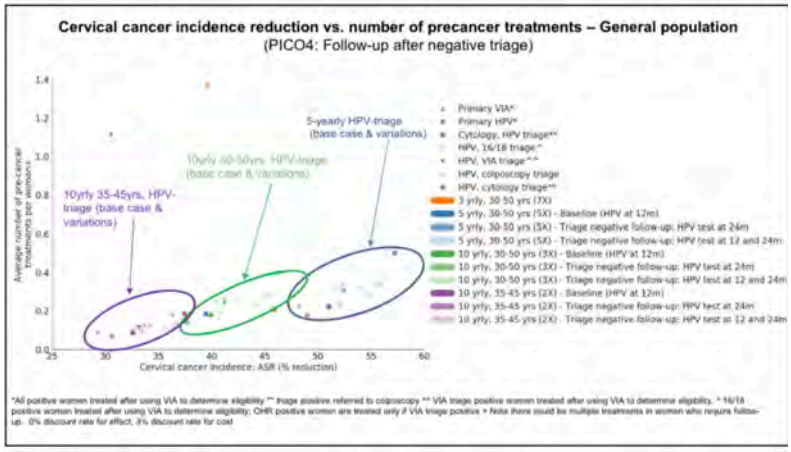
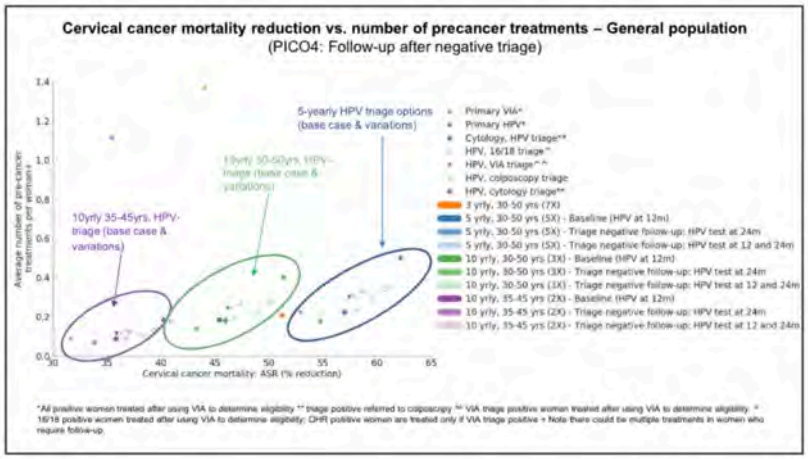
Certainty of evidence of required resources

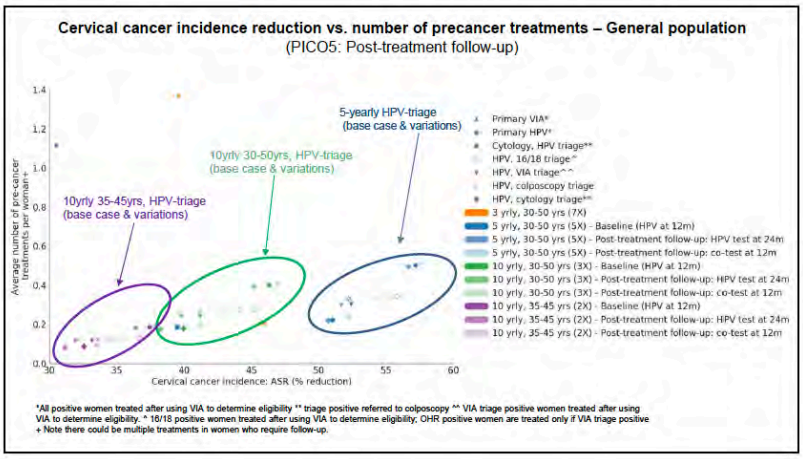
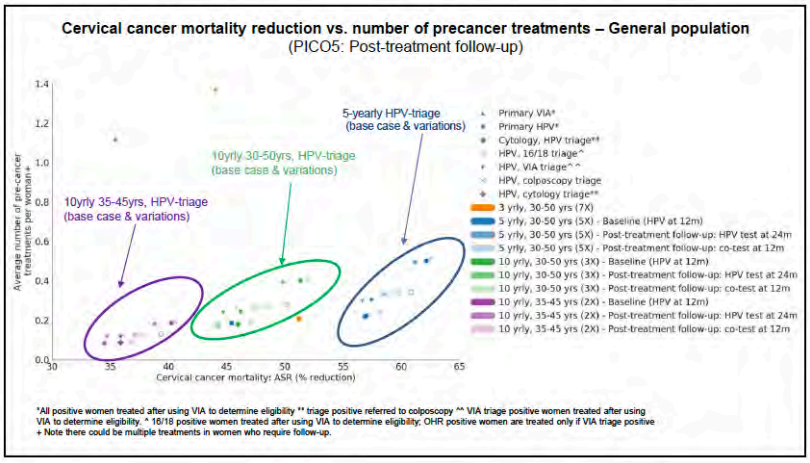
What is the certainty of the evidence of resource requirements (costs)?

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).

EVIDENCE TO DECISION TABLE: PICO 8 AGE AT INITIATION GENERAL POPULATION

Should age 30 years vs. another age be used for a threshold to initiate cervical cancer screening in the general population?

POPULATION:	a threshold to initiate cervical cancer screening in the general population
INTERVENTION:	age 30 years
COMPARISON:	another age
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 that the age to start screening is 30 years. There are also other recommendations from WHO that may not be consistent with age 30.
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 literature search from 1996 to August 2020 for systematic reviews of studies that report age stratified data for cervical cancer, histologically confirmed cervical precancer lesions, HSIL and ACIS, and/or HPV (any type). **Prevalence CIN 2, CIN 3** Zhao 2012 (pooled analysis of 17 population-based studies in China) of 30,207 women primarily in rural areas and never screened before; screened with VIA, HPV or cytology and histologically confirmed <u>Prevalence of CIN 2 by age</u> At 15-29: 1.4% At 30-34: 1.2% At 35-39: 1.5% At 40-44: 1.8% <u>Prevalence of CIN 3+ (including cervical cancer)</u> At 15-29: 0.7% At 30-34: 0.9% At 35-39: 1.3% At 40-44: 2.1% At 45-49: 2.4% At 50-59: 1.5% <u>Prevalence of Invasive Cancer</u> Arbyn 2020 (worldwide analysis from 185 countries from the Global Cancer Observatory 2018 database; ~570 000 cases of cervical cancer and ~311 000 deaths from disease in 2018. Cases per 100 000 women years by world At 20 years: 3 At 25 years: 5 At 30 years: 12 At 35 years: 19 At 40 years: 26 At 55 years: 36	The GDG agreed that the prevalence of histologically confirmed CIN 2 or CIN 3 before age 30 years may be lower or similar, but regression of CIN 2 before age 30 was higher than after age 30. Therefore the benefits of screening before age 30 for prevention of cervical cancer or histologically confirmed CIN 2/3 lesions was small.

At 60 years: 35 (then decreasing)

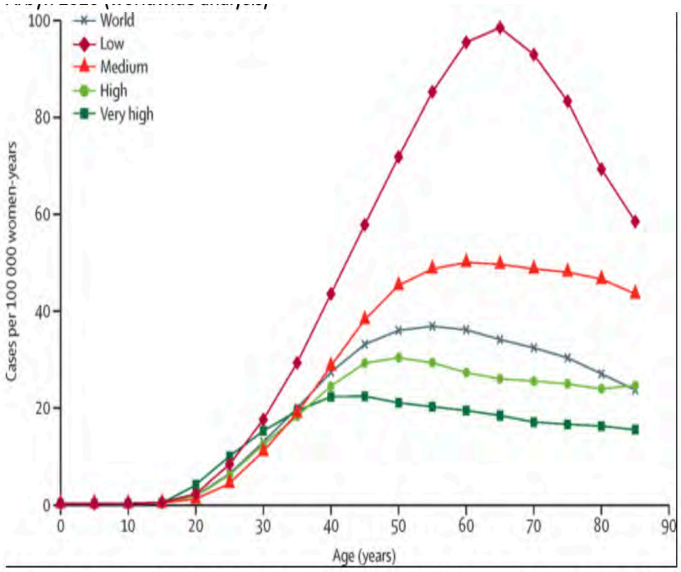
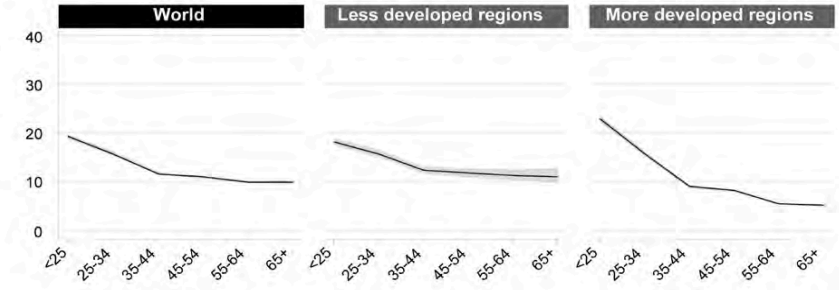


Figure 5: **Age-specific incidence of cervical cancer worldwide and in terms of the four-tier HDI**
The four tiers of HDI are the following: very high (HDI ≥0·8), high (HDI <0·8 to ≥0·7), medium (HDI <0·7 to ≥0·55), and low (HDI <0·55). HDI=Human Development Index.

Prevalence of HPV
Bruni 2010 (review of 114 studies of women with normal cytological findings)

Variable	Women, no.		HPV prevalence, % (95% CI)	
	Total tested	HPV positive	Crude	Adjusted[a]
Mean age of enrolled women				
<25 years	27,343	5960	21.8 (21.3–22.3)	24.0 (23.5–24.5)
25–34 years	60,475	8901	14.7 (14.4–15.0)	13.9 (13.6–14.1)
35–44 years	263,740	27,962	10.6 (10.5–10.7)	9.1 (9.0–9.2)
45–54 years	658,695	28,691	4.4 (4.3–4.4)	4.2 (4.2–4.3)
≥55 years	328	44	13.4 (9.9–17.6)	7.5 (5.0–11.0)

By less and more developed regions



Progression of CIN 2 and Regression of CIN 2
Analysis from 2 sysetmatic reviews

Age group (years)	No. participants	Regression rate	No. studies	Population	Length of follow-up	Source
< 25	754	44.7%	7	Women with CIN I, II, and III	28 to 30 months	Bekos 2018
<30	1069	60.0%	4	Non-pregnancy women with CIN II	24 months	Tianio 2018
<30	938	52.8%	7	Women with CIN I, II, and III	28 to 30 months	Bekos 2019
<30	131	70.0%	2	Non-pregnancy women with CIN II	36 months	Tianio 2018
>30	401	44.0%	7	Non-pregnancy women with CIN II	24 months	Tianio 2018
<35	1,058	51.9%	7	Women with CIN I, II, and III	28 to 30 months	Bekos 2020
>=35	172	46.2%	7	Women with CIN I, II, and III	28 to 30 months	Bekos 2021

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	Although there was no evidence comparing different age groups at initiation of screening, we had evidence from systematic reviews of large databases and primary studies of incidence and prevalence of cervical cancer and CIN at different age groups provided moderate certainty evidence. Modelling at different age groups was also available.	

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 (43 studies), but there was very little data reporting the value of outcomes (data was primarily for acceptability of tests/treatments – see below). **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 from 275 respondents found that some of the key concerns from women who had never been screened before were fear of the test itself higher costs of test(22.91%) and the fear of having cancer(22.91%).	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		

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	No research evidence was found. However, there was evidence from modelling showing that the differences in cost when starting screening later than age 30 were small to negligible.	

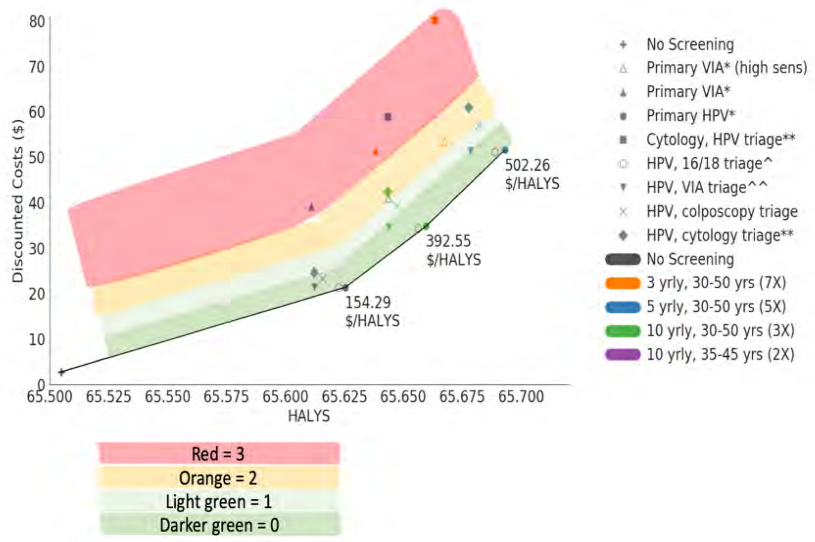
Certainty of evidence of required resources

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	From the modelling, strategies initiating at age 30 or 35 were on the cost-effectiveness frontier. 	

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	No research evidence. The GDG agreed that there would likely not be no impact on equity depending on age at screening.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence found. The GDG agreed that starting at any age would be acceptable to most women.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence found. However, the GDG agreed that the need for greater resources when starting at age 30 versus 35 may impact feasibility, but it is likely feasible in most settings.	

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 the intervention or the 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 the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	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

Recommendation

5. WHO recommends starting regular cervical cancer screening at the age of 30 years among the general population of women.
[Strong recommendation, moderate-certainty evidence in effects]

Justification

On the age at which to start screening, there is evidence from modelling and large databases measuring the incidence of cervical cancer and CIN that supports the initiation of screening at the age of 30 years (moderate-certainty evidence). Starting screening at this age is likely to be acceptable to stakeholders, is feasible and needs fewer resources than starting at an earlier age.

EVIDENCE TO DECISION TABLE (ETD): PICO 8 AGE AT INITIATION OF SCREENING WLHIV

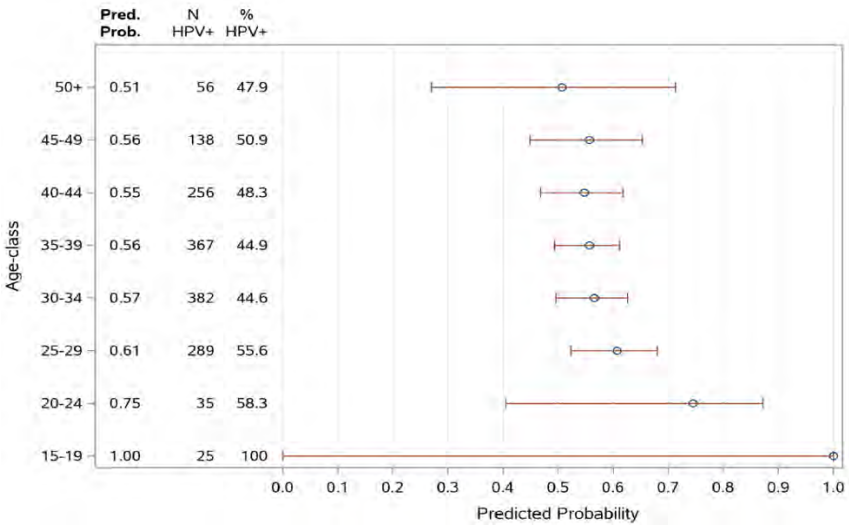
Should age 25 years vs. when tested positive for HIV be used for as a threshold to initiate cervical cancer screening in women living with HIV?	
POPULATION:	as a threshold to initiate cervical cancer screening in women living with HIV
INTERVENTION:	age 25 years
COMPARISON:	when tested positive for HIV
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 to prevent cervical cancer in all women including women living with HIV (WLHIV). In the context of the WHO strategy towards the elimination of cervical cancer, WHO is updating the current recommendation on screening and treatment of cervical cancer for all women, including for WLHIV. For the PICO questions related to WLHIV, the evidence is limited and the number of publications that present results by age at first screening are scarce.
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	**SYSTEMATIC REVIEW OF LITERATURE** We conducted a systematic literature search to October 2019 for studies comparing screening to prevent cervical cancer starting at different age groups and/or when individuals tested positive for HIV. Out of 1315 records, 12 studies were included. Studies used varying classification of histologically verified CIN grade as an outcome. It was possible to pool data from three studies by using the category CIN2/3, for a total of 390 cases in 2955 women. **Prevalence of CIN 2/3** Based on data from 2 studies, the pooled prevalence of CIN2/3 was 11.2% in WLHIV below the age of 30, and 11.5% in WLHIV above the age of 30 (De Vuyst et al, Swanepoel et al). Only one study showed a prevalence of CIN2/3 of 6.7% in WLHIV below 25 years of age, and 9.9% in WLHIV above 25 years of age, respectively (McDonald et al). **Prevalence of Invasive Cancer** One study reported no cases below 30 years of age (Swanepoel et al), and 3 studies reported a prevalence of 0.3-1.6% in WLHIV below the age of 35-40 (Abraham et al, Kapambwe et al, Swanepoel et al). **INDIVIDUAL PATIENT DATA META-ANALYSIS** We contacted authors of studies identified from the systematic review that included at least 40 women living with HIV who had CIN2+ and pooled the data from individual patients. **Probability of CIN 2/3 by age** The probability of having a confirmed diagnosis of CIN 2/3 15-19 years: 6% (total participants: 16) 20-24 years: 32% (total participants: 41) 25-29 years: 42% (total participants: 351) 30-34 years: 50% (total participants: 470)	The GDG agreed given the analyses that the group should focus on the numbers of histologically confirmed CIN 2/3. Based on the data, the evidence suggests similar and important numbers of women with CIN 2/3 at 25-29 years and 30-34 years. In addition, there may be lower numbers of CIN 2/3 in WLHIV at 20-24 or 15-19 years, but this is based on very small numbers of women in the analyses.

	Probability of HPV positive test by age  Little to no data available for perinatally HIV infected women or women infected in adolescents.	

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	A systematic review of primary studies and IPDMA were conducted, but there was little data available comparing the incidence of cervical cancer and CIN lesions resulting in low certainty evidence. There is also low certainty evidence from a large cohort study reporting the proportion of women with cervical cancer by age.	

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). **A survey of 561 women** (which included few women who are living with HIV) was conducted online via SurveyMonkey in 2020, and was completed anonymously. All women aged 15 years and older,	The GDG agreed that the data from the general population would apply to women living with HIV. 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.

	regardless of their prior cervical cancer screening or treatment status were eligible to participate. Survey results from 275 respondents found that some of the key concerns from women who had never been screened before were fear of the test itself higher costs of test(22.91%) and the fear of having cancer(22.91%).	

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	The GDG agreed that the benefits of screening at age 25 probably outweighs the harms of screening at age 20, 30 or 35.	

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	No research evidence was found about resources. There are likely greater costs when starting earlier than age 25 since more resources are needed for screening and treatment.	

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	Modelling was not conducted for women living with HIV, but the GDG agreed that the costs of screening and treating at age 25 would likely be higher due to the number of women screened positive, but based on the reduction in cervical cancer and related deaths, the costs would probably favour screening at age 25 versus 30 or 35.	

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	No research evidence found, but the GDG agreed that there is likely little impact on equity when initiating screening at different ages.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There was no research evidence for acceptability of initiating screening. The GDG agreed that age 25 is probably acceptable.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There was no research evidence. However, the GDG agreed that initiation of screening will depend on feasibility but initiating at 25 is probably feasible.	

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 no impact**	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

Recommendation

25. WHO suggests starting regular cervical cancer screening at the age of 25 years among women living with HIV.
[Conditional recommendation, low-certainty evidence in effects]

Justification

On the age at which to start screening, there was low-certainty evidence from an individual patient data meta-analysis (IPD-MA), mathematical modelling and studies about cervical cancer incidence and CIN by age that supported the initiation of screening at 25 years of age rather than at age 20 or 30. Starting at this age is likely to be acceptable to stakeholders, is feasible and needs fewer resources than starting screening at an earlier age.

EVIDENCE TO DECISION TABLE: PICO 8 AGE TO STOP IN GENERAL POPULATION AND WLHIV

Should age after 50 years vs. at age 50 be used for a threshold to stop cervical cancer screening in all women?

POPULATION:	General population of women and women living with HIV (WLHIV)
INTERVENTION:	Stop screening after age 50 years
COMPARISON:	Stop screening at age 50 years
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 that the guideline applied "to women 30 years of age (recommended age to start screening) and older because of their higher risk of cervical cancer. However, the magnitude of the net benefit will differ among age groups and may extend to younger and older women depending on their baseline risk of CIN2+. Priority should be given to screening women aged 30–49 years, rather than maximizing the number of screening tests in a woman's lifetime. 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	**For general population** A review of the literature was conducted for the IARC Handbook for the age to stop screening. Three relevant studies reported the following [IARC Handbook]: Andrae 2008 (Swedish) - 32% of cervical cancer cases occurred in women >66 years and 92% had not been screened in the preceding interval Castañón 2014 (UK) - risk of developing ICC was almost twice in women who had their screening stopped at the age of 55 compared to women whose screening was stopped at 65 years of age (379 vs 208 ICC cases at age 55-84 years per 100 000 women) Lönnberg 2014 (Finland) - the odds of death from ICC was similar in women screened between 40-54 versus between 55-69 years We conducted a systematic literature search from 1996 to August 2020 for systematic reviews of studies that report age stratified data for cervical cancer, histologically confirmed cervical precancer lesions, HSIL and ACIS, and/or HPV (any type) [Supplementary Material 4]. **Prevalence CIN 2, CIN 3** Zhao 2012 (pooled analysis of 17 population-based studies in China) of 30,207 women primarily in rural areas and never screened before; screened with VIA, HPV or cytology and histologically confirmed Prevalence of CIN 2 by age At 40-44: 1.6% At 45-49: 1.3% At 50-59: 1.2%	The GDG agreed that the prevalence of histologically confirmed CIN 2 or CIN 3 may be slightly lower after age 50 compared to before, and potentially at high risk to age 65. Therefore the benefits of screening after age 50 for prevention of cervical cancer or histologically confirmed CIN 2/3 lesions could be moderate. There was some concern from the GDG to put a set age limit for screening given different screening intervals. There was also some concern about regions where screening has not occurred in women, in which case the GDG agreed that a women older than 50 should be

	Prevalence of CIN 3+ (including cervical cancer) At 40-44: 2.1% At 45-49: 2.4% At 50-59: 1.5% Prevalence of Invasive Cancer Arbyn 2020 (worldwide analysis from 185 countries from the Global Cancer Observatory 2018 database; ~570 000 cases of cervical cancer and ~311 000 deaths from disease in 2018. Cases per 100 000 women years by world At 40 years: 26 At 55 years: 36 At 60 years: 35 At 70 years: 33 At 80 years: 28	screened if she has not had regular screening.

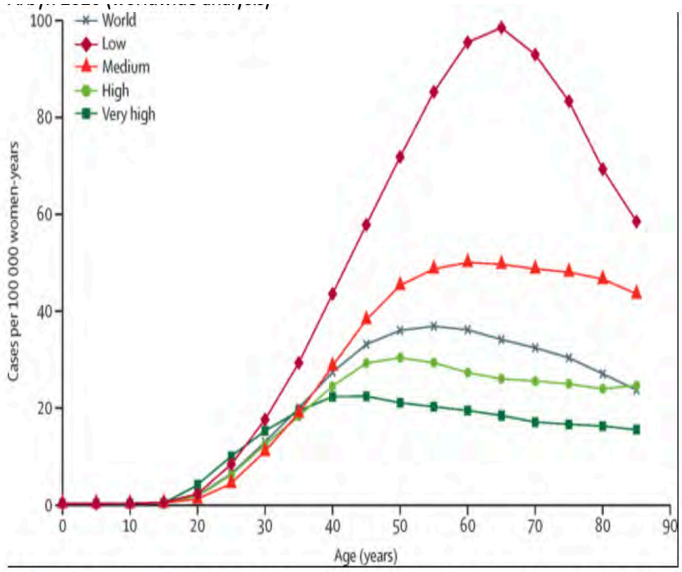
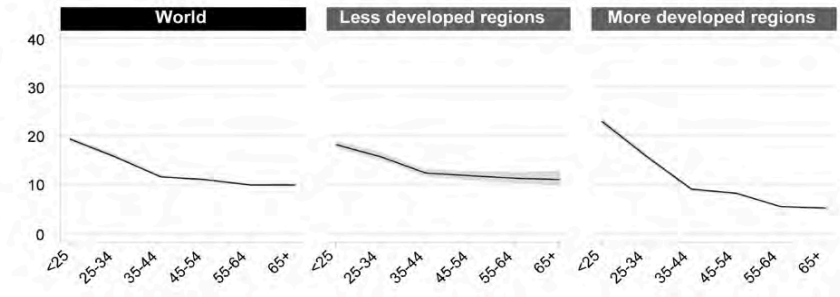


Figure 5: Age-specific incidence of cervical cancer worldwide and in terms of the four-tier HDI
The four tiers of HDI are the following: very high (HDI ≥0·8), high (HDI <0·8 to ≥0·7), medium (HDI <0·7 to ≥0·55), and low (HDI <0·55). HDI=Human Development Index.

Prevalence of HPV
Bruni 2010 (review of 114 studies of women with normal cytological findings)

Variable	Women, no.		HPV prevalence, % (95% CI)	
	Total tested	HPV positive	Crude	Adjusted[a]
Mean age of enrolled women				
<25 years	27,343	5960	21.8 (21.3–22.3)	24.0 (23.5–24.5)
25–34 years	60,475	8901	14.7 (14.4–15.0)	13.9 (13.6–14.1)
35–44 years	263,740	27,962	10.6 (10.5–10.7)	9.1 (9.0–9.2)
45–54 years	658,695	28,691	4.4 (4.3–4.4)	4.2 (4.2–4.3)
≥55 years	328	44	13.4 (9.9–17.6)	7.5 (5.0–11.0)

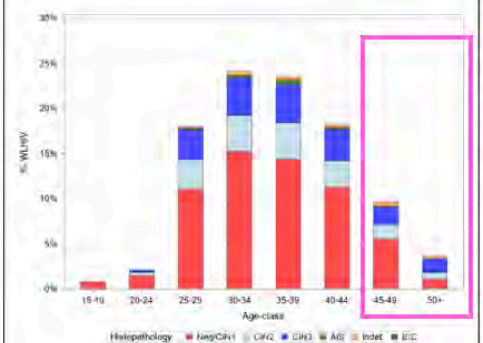
By less and more developed regions



We conducted a review of the literature and an Individual Patient Data Meta-Analysis for age to start and stop screening in women living with HIV [Supplementary Material 5 and 6].

Figure 1 and Table 1. Histopathology diagnoses by age among WLHIV

Panels age distribution and table of histopathology category distribution by age:



Age at screening	Histopathology n (row %)						
	Neg/CIN1	CIN2	CIN3	AIS	ICC	Indet.	T
15-19	15 (93.8)	1 (6.3)					
20-24	29 (70.7)	8 (19.5)	4 (9.8)				
25-29	216 (61.5)	64 (18.2)	65 (18.5)	4 (1.1)		2 (0.6)	
30-34	297 (63.2)	79 (16.8)	81 (17.2)	5 (1.1)	1 (0.2)	7 (1.5)	
35-39	281 (61.2)	79 (17.2)	83 (18.1)	7 (1.5)	2 (0.4)	7 (1.5)	
40-44	220 (62.0)	58 (16.3)	68 (19.2)	3 (0.9)	1 (0.3)	5 (1.4)	
45-49	108 (57.5)	32 (17.0)	38 (20.2)	2 (1.1)		8 (4.3)	
50+	21 (29.6)	15 (21.1)	30 (42.3)			5 (7.0)	
Total	1187	336	369	21	4	34	1

In addition, there was a summary of studies that reported the proportion of people with cervical cancer at different age groups.

TABLE 2: DISTRIBUTION OF CANCER CASES* IN WOMEN LIVING WITH HIV BY AGE AND BY STUDY

	Dhokotera et al n = 9321	van Aardt et al n = 77	Clifford et al** n = 20	Abraham et al n = 67		Mpunga et al n = 113		Kapambw n = 2
Age (years)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	Age (years)	% (95% CI)	Age (years)	% (95%
16-19	5							
	0.05 (0.01-0.1)							
20-29	485	12	3					
	5.2 (4.8-5.7)	15.7 (7.5-23.8)	**15.0 (-0.6-30.6)		25-34	8	<35	129
30-39	2864	25	8	33		7.1 (2.4-11.8)		49.2 (43.1-
	30.7 (29.8-31.7)	32.6 (22.1-43.1)	40.0 (18.5-61.5)	***49.3 (37.3-61.2)	35-44	40	35+	133
40-49	3441	25	9	25		35.4 (26.6-44.2)		50.8 (44.7-
	36.9 (35.9-37.9)	32.6 (22.1-43.1)	45.0 (23.2-66.8)	37.3 (25.7-48.9)	45-54	46		
50-59	1883	10		9		40.7 (31.7-49.8)		
	20.2 (19.4-21.0)	12.6 (5.3-20.3)		***13.4 (5.3-21.6)	55+	19		
60-69	520	3				16.8 (9.9 - 23.7)		
	5.6 (5.1-6.0)	3.4 (-0.7 - 7.5)						
70-79	113	1						
	1.2 (0.1-1.4)	1.3 (-1.2 -3.8)						
80-89	10	1						
	0.1 (0.0-0.1)	1.3 (-1.2-3.8)						

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	There was no direct evidence comparing different age groups at end of screening, but we had evidence from systematic reviews of large databases and primary studies of incidence and prevalence of cervical cancer and CIN at different age groups that provided low certainty evidence for the general population (indirect evidence for different age groups and non-randomised studies), and very low certainty evidence for women living with HIV (few women were greater than age 50). Modelling results were however only up to age 50.	

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). **A survey of 561 women** (which included few women who are living with HIV) 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 from 275 respondents found that some of the key concerns from women who had never been screened before were fear of the test itself higher costs of test(22.91%) and the fear of having cancer(22.91%).	The GDG agreed that the data from the general population would apply to women living with HIV. 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	The GDG agreed that the benefits of stopping screening after age 50 would probably outweigh the harms in women who have low risk of developing cervical cancer (e.g., women who have previously screened negative).	

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	No research evidence was found. Greater resources would be needed to screen for longer in women which result in higher costs than stopping earlier, but the GDG agreed it would be negligible.	

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	No research evidence or modelling available.	

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	No research evidence. The GDG agreed that there would likely not be no impact on equity depending on age to stop 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 review of reviews for the age to stop screening was conducted and information about age to stop screening was abstracted from relevant reviews: • Women were more likely to continue screening if had at any time had required further testing (Sirovich 2005) • Women in US survey – 44% said they might stop after age 80 years • Barriers for older women included embarrassment, lack of knowledge (in particular when no symptoms), fear of discomfort (Waller 2015, Hope 2017, Khodakarami 2012)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence found. However, the GDG agreed that the need for greater resources when stopping screening after age 50 versus at age 50 may impact feasibility, but it is likely feasible in most settings.	

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 the intervention or the 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 the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	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

Recommendation

General population

6. After the age of 50 years, WHO suggests screening is stopped after two consecutive negative screening results consistent with the recommended regular screening intervals among both the general population of women and women living with HIV.*
[Conditional recommendation, low-certainty evidence in effects]
Remarks: Neither VIA nor ablation treatment are suitable for screening or treatment of women in whom the transformation zone is not visible. Inadequate visualization is typical after the menopause.

7. Priority should be given to screening women aged 30–49 years in the general population of women. When tools are available to manage women aged 50–65 years, those in that age bracket who have never been screened should also be prioritized.
[Good-practice statement]

Women living with HIV

26. After the age of 50 years, WHO suggests screening is stopped after two consecutive negative screening results consistent with the recommended regular screening intervals among both the general population of women and women living with HIV.*
[Conditional recommendation, very low-certainty evidence in effects]
Remarks: Neither VIA nor ablation treatment are suitable for screening or treatment of women in whom the transformation zone is not visible. Inadequate visualization is typical after the menopause.

27. Priority should be given to screening women living with HIV aged 25–49 years. When tools are available to manage women, women living with HIV aged 50–65 years, those in the age bracket who have never been screened should also be prioritized.
[Good practice statement]

Justification

General population

There is low-certainty evidence from longitudinal studies of the benefits of screening and of the continued risk of CIN and cervical cancer after the age of 50 years; the evidence suggests there are benefits of continued screening, following regular screening intervals until there have been two consecutive negative screening results after the age of 50.

Women living with HIV

There was very low-certainty evidence from the studies mentioned above (given the small numbers of women followed and reporting cervical cancer or CIN lesions) that found that the risk of cervical cancer and lesions may continue. Screening was therefore suggested to continue at regular screening intervals, until there have been two consecutive negative screening results after the age of 50.

EVIDENCE TO DECISION TABLE (ETD): PICO 10 GENERAL POPULATION AND WOMEN LIVING WITH HIV

Should loop excision vs. cold knife conisation be used for women with adenocarcinoma in situ?

POPULATION:	women with adenocarcinoma in situ in general population and WLHIV
INTERVENTION:	loop excision
COMPARISON:	cold knife conisation
MAIN OUTCOMES:	1. CIN 1, 2-3 (cure/persistence/recurrence), 2. cervical cancer 3. mortality 4. HPV infection 5. Major infections (requiring hospital admission and antibiotics, e.g. pelvic inflammatory disease) 6. Major bleeding (requiring hospital admission, or blood transfusion) 7. Procedure associated pain 8. treatment-related social stigmatization 9. HIV shedding after treatment 10. Reproductive outcomes 11. Coverage of screening and treatment
SETTING:	
PERSPECTIVE:	Population
BACKGROUND:	Current recommendations indicate LLETZ or ablative treatment for women who have histologically confirmed CIN 2/3 or screened positive. There is a separate recommendation for CKC rather than LLETZ for AIS.
CONFLICT OF INTERESTS:	

ASSESSMENT

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

From Jiang 2017 systematic review of comparative non-randomised studies.

Outcomes	With CKC	With LLETZ/LEEP	Difference	Relative effect (95% CI)
Recurrence rate of AIS follow up: 2 years	6 per 100	**6 per 100** (3 to 16)	**1 more per 100** (3 fewer to 10 more)	**RR 1.13** (0.46 to 2.79)
Residual rate follow up: 12 years	11 per 100	**11 per 100** (7 to 19)	**0 fewer per 100** (4 fewer to 8 more)	**RR 1.02** (0.60 to 1.72)
Positive margin rates follow up: 12 years	29 per 100	**45 per 100** (39 to 52)	**16 more per 100** (10 more to 23 more)	**RR 1.55** (1.34 to 1.80)
Major bleeding	2 per 100	**0 per 100** (0 to 0)	**2 fewer per 100** (2 fewer to 2 fewer)	not estimable
Major infection	0 per 100	**0 per 100** (0 to 0)	**0 fewer per 100** (0 fewer to 0 fewer)	not estimable
Premature delivery LLETZ/LEEP compared to no treatment assessed with: <37 weeks	5 per 100	**8 per 100** (7 to 9)	**3 more per 100** (2 more to 4 more)	**RR 1.58** (1.37 to 1.81)
Premature delivery CKC compared to no	5 per 100	**14 per 100** (11 to 17)	**9 more per 100** (6 more to 12 more)	**RR 2.70** (2.14 to 3.40)

ADDITIONAL CONSIDERATIONS

The GDG agreed that the benefits (including recurrence rate and other surrogrates) are similar between loop excision and CKC

The evidence is low to very low certainty. The data is from retrospective comparative studies, therefore, women may have been chosen to receive either intervention based on their prognosis. In addition, it is unclear what type of loop excision was performed.

	treatment assessed with: <37 weeks					

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	See above.	Complications such as major bleeding and infections are likely similar However, the evidence suggests that 3 X more women with CKC had premature delivery Therefore, the undesirable effects with loop excision are trivial compared to CKC (and may be less with loop) This evidence is also of very low uncertainty.

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		

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	Value of outcomes: 1. Recurrence rate 2. Premature delivery and other harms 3. Residual rate 4. Positive margin rate	

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	Benefits appear similar, but may be more harms with CKC related to premature delivery. But evidence is low to very low certainty.	

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	In most settings, CKC is performed in an operating theatre, and costs will likely be higher for CKC. Therefore moderate saving with loop excision	

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		

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	CKC may be less available due to access to and availability of operating theatre. Therefore recommending loop excision could increase equity, however there is little information.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence found.	The GDG agreed that for women: Most women don't want to go to operating theatre and costs of CKC may be higher if women have to pay out of pocket for procedure, and loop excision more preferred. The GDG agreed that for health care providers: In public sector, providing outpatient treatment is a high priority meaning loop excision might be preferred.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence found.	The GDG agreed that • loop excision may be more feasible than CKC since there may be competition for operating theatre time, but loop is outpatient • however, health care providers may need more experience when performing loop excision for AIS

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 the intervention or the 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 the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**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

Recommendation

41. Once a decision to treat a woman is made – whether from the general population of women or women living with HIV – it is good practice to treat as soon as possible within six months, to reduce the risk of loss to follow-up. However, in women who are pregnant, good practice includes deferral until after pregnancy.

In circumstances when treatment is not provided within this time frame, it is good practice to re-evaluate the woman before treatment.
[Good-practice statement]

42. WHO suggests large-loop excision of the transformation zone (LLETZ) or cold knife conization (CKC) for women from the general population or women living with HIV who have histologically confirmed adenocarcinoma in situ (AIS).
[Conditional recommendation, low-certainty evidence for effects]

Remarks: Loop excision may be preferred in women of reproductive age, in settings with greater availability of LLETZ and by providers with greater expertise performing LLETZ. CKC may be preferred when interpretation of the margins of the histological specimen is imperative.

Justification

Low-certainty evidence from a systematic review of the literature found that there may be little to no difference in the recurrence rate of AIS with CKC or electrosurgical excision, or in the incidence of complications such as major infection and bleeding, and found that more women may have premature deliveries in subsequent pregnancies following a CKC compared with electrosurgical excision. The studies included in the systematic review did not confirm HIV status, but the GDG agreed that the data could be extrapolated to women living with HIV and applied directly. CKC is performed in the operating theatre, so access to CKC may be limited in some settings, more costly and less preferred by women compared with LLETZ. In addition, greater expertise may be needed for successful electrosurgical excision.

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