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).