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.

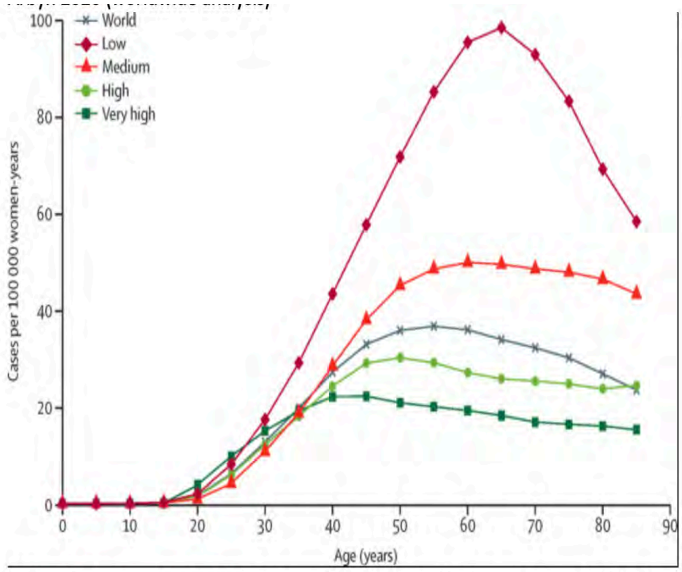
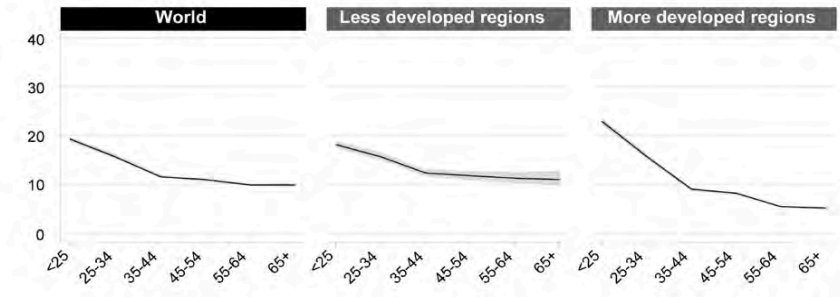


Figure 5: Age-specific incidence of cervical cancer worldwide and in terms of the four-tier HDI
The four tiers of HDI are the following: very high (HDI ≥0·8), high (HDI <0·8 to ≥0·7), medium (HDI <0·7 to ≥0·55), and low (HDI <0·55). HDI=Human Development Index.

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)

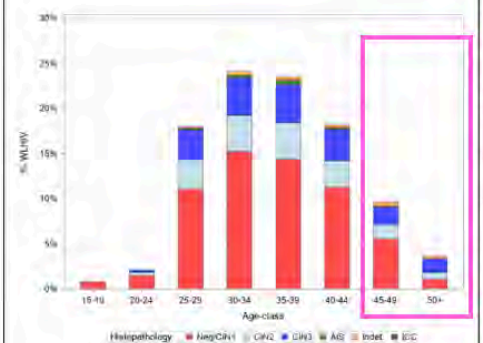
By less and more developed regions



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.