

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	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																								
<ul style="list-style-type: none"> ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know 	<p>From Jiang 2017 systematic review of comparative non-randomised studies.</p> <table border="1"> <thead> <tr> <th>Outcomes</th> <th>With CKC</th> <th>With LLETZ/LEEP</th> <th>Difference</th> <th>Relative effect (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Recurrence rate of AIS follow up: 2 years</td> <td>6 per 100</td> <td>6 per 100 (3 to 16)</td> <td>1 more per 100 (3 fewer to 10 more)</td> <td>RR 1.13 (0.46 to 2.79)</td> </tr> <tr> <td>Residual rate follow up: 12 years</td> <td>11 per 100</td> <td>11 per 100 (7 to 19)</td> <td>0 fewer per 100 (4 fewer to 8 more)</td> <td>RR 1.02 (0.60 to 1.72)</td> </tr> <tr> <td>Positive margin rates follow up: 12 years</td> <td>29 per 100</td> <td>45 per 100 (39 to 52)</td> <td>16 more per 100 (10 more to 23 more)</td> <td>RR 1.55 (1.34 to 1.80)</td> </tr> <tr> <td>Major bleeding</td> <td>2 per 100</td> <td>0 per 100 (0 to 0)</td> <td>2 fewer per 100 (2 fewer to 2 fewer)</td> <td>not estimable</td> </tr> <tr> <td>Major infection</td> <td>0 per 100</td> <td>0 per 100 (0 to 0)</td> <td>0 fewer per 100 (0 fewer to 0 fewer)</td> <td>not estimable</td> </tr> <tr> <td>Premature delivery LLETZ/LEEP compared to no treatment assessed with: <37 weeks</td> <td>5 per 100</td> <td>8 per 100 (7 to 9)</td> <td>3 more per 100 (2 more to 4 more)</td> <td>RR 1.58 (1.37 to 1.81)</td> </tr> <tr> <td>Premature delivery CKC compared to no</td> <td>5 per 100</td> <td>14 per 100 (11 to 17)</td> <td>9 more per 100 (6 more to 12 more)</td> <td>RR 2.70 (2.14 to 3.40)</td> </tr> </tbody> </table>	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)	<p>The GDG agreed that the benefits (including recurrence rate and other surrogates) are similar between loop excision and CKC</p> <p>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.</p>
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Undesirable Effects

How substantial are the undesirable anticipated effects?

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

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies		

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input checked="" type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability	<p>Value of outcomes:</p> <ol style="list-style-type: none"> 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
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input checked="" type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> 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
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input checked="" type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>In most settings, CKC is performed in an operating theatre, and costs will likely be higher for CKC.</p> <p>Therefore moderate saving with loop excision</p>	
Certainty of evidence of required resources		
What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies 		
Cost effectiveness		
Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input checked="" type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies 		
Equity		
What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input checked="" type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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.</p>	
Acceptability		
Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>No research evidence found.</p>	<p>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.</p> <p>The GDG agreed that for health care providers: In public sector, providing outpatient treatment is a high priority meaning loop excision might be preferred.</p>

Feasibility		
Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	No research evidence found.	The GDG agreed that <ul style="list-style-type: none"> 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						
	Trivial	Small	Moderate	Large		Varies	Don't know
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 <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input checked="" type="radio"/>	Conditional recommendation for the intervention <input type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
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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.