Cost-effectiveness of screening and treating anal pre-cancerous lesions among gay, bisexual and other men who have sex with men living with HIV

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Summary

Background Gay, bisexual and other men who have sex with men (GBM) living with HIV have a substantially elevated risk of anal cancer (85 cases per 100,000 person-years vs 1–2 cases per 100,000 person-years in the general population). The precursor to anal cancer is high-grade squamous intraepithelial lesion (HSIL). Findings regarding the cost-effectiveness of HSIL screening and treatment in GBM are conflicting. Using recent data on HSIL natural history and treatment effectiveness, we aimed to improve upon earlier models.

Methods We developed a Markov cohort model populated using observational study data and published literature. Our study population was GBM living with HIV aged ≥35 years. We used a lifetime horizon and framed our model on the Australian healthcare perspective. The intervention was anal HSIL screening and treatment. Our primary outcome was the incremental cost-effectiveness ratio (ICER) as cost per quality-adjusted life-year (QALY) gained.

Findings Anal cancer incidence was estimated to decline by 44–70% following implementation of annual HSIL screening and treatment. However, for the most cost-effective screening method assessed, the ICER relative to current practice, Australian Dollar (AUD) 135,800 per QALY gained, remained higher than Australia's commonly accepted willingness-to-pay threshold of AUD 50,000 per QALY gained. In probabilistic sensitivity analyses, HSIL screening and treatment had a 20% probability of being cost-effective. When the sensitivity and specificity of HSIL screening were enhanced beyond the limits of current technology, without an increase in the cost of screening, ICERs improved but were still not cost-effective. Cost-effectiveness was achieved with a screening test that had 95% sensitivity, 95% specificity, and cost ≤ AUD 24 per test.

Interpretation Establishing highly sensitive and highly specific HSIL screening methods that cost less than currently available techniques remains a research priority.

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Keywords: Anal; Cancer; High-grade squamous intra-epithelial; HIV; Men

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Research in context

Evidence before this study

Gay, bisexual and other men who have sex with men (GBM) living with HIV have a substantially elevated risk of anal cancer (85 cases per 100,000 person-years vs 1–2 cases per 100,000 person-years in the general population). The precursor to anal cancer is high-grade squamous intraepithelial lesion (HSIL). Findings regarding the cost-effectiveness of HSIL screening and treatment in GBM are conflicting. However, the two key limitations to earlier work have been a lack of information on the natural history of HSIL, and uncertainty around the effectiveness of HSIL treatment for preventing anal cancer. In 2021, we reported findings from the Study of the Prevention of Anal Cancer on anal HSIL natural history among GBM. In 2022, a landmark clinical trial, the ANal Cancer/HSIL Outcomes Research (ANCHOR) study, showed that HSIL treatment reduces anal cancer incidence by 57% in people living with HIV.

Added value of this study

We used this new information to improve upon earlier models and estimate the cost-effectiveness of HSIL screening and treatment among GBM with HIV in Australia. We found that the most cost-effective screening method assessed had an incremental cost-effectiveness ratio of Australian Dollar (AUD) 135,800 per quality-adjusted life-year gained. This is substantially higher than Australia's commonly accepted willingness-to-pay threshold of AUD 50,000 per quality-adjusted life-year gained.

Implications of all the available evidence

Future research priorities should include establishing highly sensitive and highly specific HSIL screening methods that cost less than currently available techniques and identifying methods that reliably select for HSIL at high risk of progressing to anal cancer.

Introduction

Early-stage anal cancer is frequently asymptomatic or mildly symptomatic.[1] This, combined with the stigma associated with anal disease, leads to many newly diagnosed individuals presenting with an advanced stage of disease.[1] Treatment of anal cancer is unpleasant and toxicity can be long lasting, particularly for advanced tumors requiring high dose chemoradiation.[2,3] Although pooled data from around the world show anal cancer is rare in the general population (1–2 cases per 100,000 person-years[4]), gay, bisexual and other men who have sex with men (GBM) living with HIV have a substantially elevated risk (85 cases per 100,000 person-years[4]).

Chronic high-risk human papillomavirus (HPV) infection causes about 90% of anal squamous cell cancers[5,6] with HPV-16 responsible for approximately 70% of cases in GBM with HIV.[7] The precursor to anal cancer is high-grade squamous intraepithelial lesion (HSIL).[5,6] Although HSIL usually clears spontaneously or persists uneventfully, approximately 2 cases per 1000 per year progress to anal cancer.[8]

Earlier work from the US suggests that HSIL screening and treatment may be cost-effective in GBM.[9,10] Yet, similar studies from the UK indicate otherwise.[11,12] Costs and resource use are highly context specific. There is also no consensus on the optimal screening approach. Many potential anal HSIL screening methods and algorithms are available,[13] including experimental procedures that may reduce overtreatment of HSIL with a low cancer progression risk.[14] However, the two key limitations to earlier work have been a lack of information on the natural history of HSIL, and uncertainty around the effectiveness of HSIL treatment for preventing anal cancer.[15,16]

In 2021, we reported findings from the Study of the Prevention of Anal Cancer (SPANC) on anal HSIL natural history among GBM.[17] In 2022, results from a large multi-centre clinical trial in the US evaluating the efficacy of HSIL treatment, the ANal Cancer/HSIL Outcomes Research (ANCHOR) study, were published.[18] We aimed to use this new information to improve upon earlier models and estimate the cost-effectiveness of HSIL screening and treatment among GBM with HIV in Australia.

Methods

Target population

Our target population was GBM with HIV aged ≥35 years and living in Australia. Thirty-five years of age is approximately when anal cancer incidence among GBM living with HIV begins to diverge from that of GBM without HIV.[4]

Screening and treatment for anal HSIL in GBM with HIV

Currently, HSIL screening and treatment is not routinely conducted in Australia. Therefore, we assumed low HSIL screening and treatment proportions in our modelled control group. Annual screening was split into two stages: i) initial screening to assess the likelihood of anal HSIL being present and 2) confirmatory diagnosis of anal HSIL in those with a positive initial screening result. Initial screening strategies evaluated are described in Table 1. Briefly, we assessed a method with high sensitivity for detecting anal HSIL

	Test sensitivity, %	Test specificity, %
High-risk HPV DNA testing	96.3	41.8
High-risk HPV mRNA	75.4	69.4
High HPV16/18 viral load	28.9	94.0

Sensitivity and specificity estimates taken from Jin et al.[13] High-risk HPV genotypes include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. High viral load defined as above 66th percentile. HPV, Human papillomavirus.

Table 1: **Sensitivity and specificity of modelled screening methods.**

(high-risk HPV DNA testing), a method with high specificity (HPV16/18 viral load testing), and a method with moderate sensitivity and specificity (high-risk HPV mRNA testing).[13] Confirmatory diagnosis involved high resolution anoscopy and a biopsy to identify HSIL histologically. HSIL treatment was modelled as ablation by electrocautery.

Decision analytic modelling

A Markov model with an annual cycle was developed to compare the costs and health outcomes associated with implementing alternative screening and treatment options for anal HSIL. The model consisted of mutually exclusive health states that reflect the natural history of progressing from no HSIL to anal cancer (Fig. 1). TNM cancer staging was used to categorise anal cancer as local (N = 0 and M = 0), regional (N ≥ 1 and M = 0), or distal (M ≥ 1).[19] The main parameters used to inform this model are shown in Table 2. Individuals entered the model from a 'No HSIL' or 'HSIL' health state. They could either move to an adjacent health state, remain in their current health state, or die. For those in the 'HSIL' state, we assigned probabilities for remaining in the current state, natural regression, progression to localised anal cancer, and death. Localised and regional anal cancers could be detected and treated, undetected without progression, or undetected and progress to next stage (i.e., regional and distal, respectively). Distal anal cancers could be detected and treated, or remain undetected. Once cancer treatment was initiated, the probability of progressing to a more advanced cancer stage was reduced substantially.

We assumed that all anal cancers would be detected among patients who underwent screening. The probability of anal cancer being detected was substantially lower in those who did not undergo screening. The probabilities of progressing to a more advanced stage of anal cancer were calculated using the probability of cancer being undetected and the distribution of anal cancer by stage at diagnosis.[23] Unpublished data on mortality rates for males enrolled in the Australian HIV Observational Database up to March 2022[29] were used as the background all-cause mortality. Mortality following anal cancer diagnosis was informed by survival data from the US Surveillance, Epidemiology, and End Results program.[23] Australian estimates are lacking. However, given the similarly high quality of healthcare in Australia and the US, anal cancer survival rates are likely to be comparable. Survival probability plotted against age follows an exponential distribution, therefore exponential distributions were fitted to the survival data assuming a constant hazard (death) rate. The death rate was calculated from the fitted distribution and transformed to a probability for each age group and cancer stage.

We ran the model with a lifetime horizon. Both costs and quality-adjusted life-years (QALYs) were discounted at 5% per year in line with Australian government guidelines.[30,31] The model was validated by ensuring our modelled anal cancer incidence rates without screening were comparable to recent empirical estimates.[4] The main model outputs were the expected costs and QALYs per person under different screening strategies. Our primary outcome was the incremental cost-effectiveness ratio (ICER). A willingness-to-pay threshold of Australian Dollar (AUD) 50,000 per QALY gained was used as this is commonly considered an approximate threshold beyond which new medical interventions are less likely to be supported by the Australian government.[32,33]

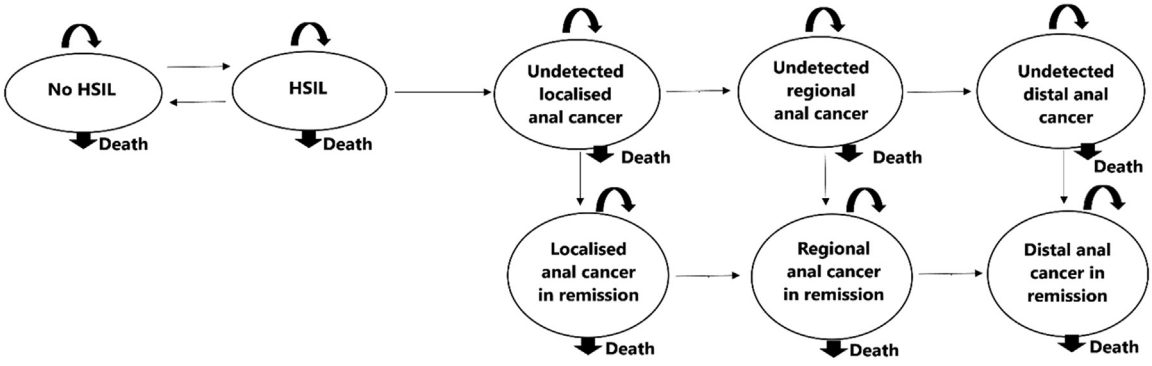

Fig. 1: **Markov model structure**. HSIL, High-grade squamous intraepithelial lesion.

Model parameters	Baseline	Lower estimate	Upper estimate	Source
Starting distribution				
HSIL	0.4730			[20]
No HSIL	0.5270			[20]
Annual HSIL screening and treatment uptake				
Screening - control	0.0500	0.0000	0.1000	Expert opinion[a]
Screening - intervention	0.6000	0.4000	0.8000	[17,21]
Treatment - control	0.1000	0.0000	0.2000	Expert opinion[a]
Treatment - intervention	0.7500	0.5000	1.0000	Expert opinion[a]
Annual transition probabilities				
Natural regression from HSIL to no HSIL	0.1870	0.1471	0.2336	[17]
Develop localised cancer from HSIL - control	0.0040	0.0036	0.0044	[17,18]
Develop localised cancer from HSIL - intervention	0.0017	0.0015	0.0020	[18]
Progress from no HSIL to HSIL	0.1306	0.0976	0.1696	[17]
Localised anal cancer detection without screening	0.2000	0.1500	0.2500	[22], Expert opinion[a]
Regional anal cancer detection without screening	0.2500	0.2000	0.3000	[22], Expert opinion[a]
Distal anal cancer detection without screening	0.3000	0.2500	0.3500	[22], Expert opinion[a]
Undetected localised anal cancer progressing to regional anal cancer	0.1000	0.0700	0.1400	Expert opinion[a]
Undetected regional anal cancer progressing to distal anal cancer	0.1500	0.1000	0.2000	Expert opinion[a]
Treated localised anal cancer progressing to regional anal cancer	0.0200	0.0024	0.0697	St Vincent's Hospital, Sydney – Local data
Treated regional anal cancer progressing to distal anal cancer	0.0410	0.0108	0.0973	St Vincent's Hospital, Sydney – Local data
Distribution of anal cancer by stage at diagnosis				[23]
Local	0.5293			
Regional	0.3472			
Distal	0.1234			
Annual mortality rate (HIV+)				**AHOD 2022 – unpublished data**
age, years				
35–39	0.0016			
40–44	0.0015			
45–49	0.0024			
50–54	0.0042			
55–59	0.0055			
60–64	0.0082			
65–69	0.0116			
70–74	0.0177			
75–79	0.0334			
80–84	0.0575			
85+	0.1306			
Annual mortality rate (anal cancer)				[23]
Local cancer				
age, years				
35–39	0.0246			
40–64	0.0365			
65–74	0.0423			
75+	0.0584			
Regional cancer				
age, years				
35–39	0.0857			
40–64	0.0795			
65–74	0.0754			
75+	0.1236			
Distal cancer				
age, years				
35–39	0.2318			
40–64	0.2302			
65–74	0.2585			
75+	0.3717			

(Table 2 continues on next page)

Model parameters	Baseline	Lower estimate	Upper estimate	Source
(Continued from previous page)				
Transition costs (2020 AUD)				
HSIL screening				[24], Expert opinion[a]
High-risk HPV DNA testing	125	60	250	
High-risk HPV mRNA	150	75	300	
High HPV 16/18 viral load	152	75	300	
Confirmatory high-resolution anoscopy	266	100	500	[24], Expert opinion[a]
HSIL electrocautery	66.55	30	130	[24], Expert opinion[a]
Workup	1827	900	3600	[24]
Localised cancer treatment	7825	4000	16,000	[24,25], Expert opinion[a]
Regional cancer treatment	9014	5000	18,000	[24,25], Expert opinion[a]
Distal cancer treatment	14,232	7000	28,000	[24,25], Expert opinion[a]
Annual health state costs (2020 AUD)				
No HSIL	15,228	7500	30,000	[26]
HSIL	15,228	7500	30,000	[26]
Undetected localised cancer	15,228	7500	30,000	[26]
Undetected regional cancer	15,228	7500	30,000	[26]
Undetected distal cancer	15,228	7500	30,000	[26]
Treated localised cancer	17,540	9000	35,000	[24], Expert opinion[a]
Treated regional cancer	17,467	9000	35,000	[24], Expert opinion[a]
Treated distal cancer	16,670	9000	35,000	[24], Expert opinion[a]
Health state utility				
No HSIL/HSIL/Undetected localised cancer	0.75	0.6	0.9	SPANC - unpublished data
Undetected regional cancer	0.66	0.5	0.75	[27]
Undetected distal cancer	0.52	0.4	0.65	[27]
Remission	0.71	0.6	0.8	[22]
Disutility				
Screening for HSIL	0.001	0.0005	0.002	[28], Expert opinion[a]
Treating HSIL	0.005	0.001	0.040	[28], Expert opinion[a]
Treating anal cancer	0.007	0.003	0.012	[28]

HSIL, High-grade squamous intraepithelial lesion; AHOD, Australian HIV Observational Database; AUD, Australian Dollar; HPV, Human papillomavirus; SPANC, Study of the Prevention of Anal Cancer.
[a]Where we were lacking data on which to base a model parameter, we relied on the clinical (JJO, RJH, GH), epidemiologic (IMP, FJ, AG, DCB), and health economic (QC, JJO, KH, AN, DCB) expertise of our authorship group to establish an expert opinion.

Table 2: **Markov model inputs.**

Resource use and costs

Our cost-effectiveness analysis was conducted from an Australian healthcare system perspective where only direct medical costs were considered. Societal or indirect costs, such as those associated with productivity losses due to work absenteeism, were not included. Table 2 shows that unit costs were extracted from a range of sources including the Medicare Benefits Schedule,[24] Pharmaceutical Benefits Scheme,[25] and published literature.[26] Costs for HSIL screening, HSIL treatment, anal cancer workup, and anal cancer treatment were considered transition or one-off costs. The cost of HSIL screening included the cost of medical consultations with a specialist and the cost of testing. HSIL treatment costs were based on the current cost of cervical cauterisation in Australia under the Medicare Benefits Schedule.[24] The costs of cancer workup and treatment consisted of a series of medical consultations, tests and medical procedures, consistent with earlier work.[22] For individuals in 'No HSIL', 'HSIL' and undetected anal cancer health states, the annual cost of managing HIV was used as the health state cost.[26] Health state costs for treated anal cancer included the cost of managing HIV plus the cost of continued post-treatment monitoring. The cost of being in a treated anal cancer state accounted for the costs associated with a small proportion of people experiencing recurrence.[2] All cost items were in 2020 Australian dollars.

Health outcomes

QALYs were calculated by multiplying the utility weight associated with a health state by the number of years lived in that state. Utility weights range between 0 and 1, with 0 representing death and 1 representing full health. The utility weights for individuals with and without HSIL were informed by unpublished analyses from SPANC which involved study participants completing SF-36 quality of life questionnaires[34] and the SF-36 scores

converted to SF-6D utility weights.[35,36] As HSIL and localised anal cancer are generally asymptomatic, we assumed these states had the same utility weight as being in the 'No HSIL' state.[1] Evidence is lacking on the utility weights of more advanced anal cancers therefore we assumed utility weights for colorectal cancer.[27] Individuals were assumed to experience a disutility (i.e., a transient drop in QALYs) associated with the discomfort of procedures for detecting and treating HSIL and anal cancer. Each instance of HSIL screening was assumed to result in a loss of 0.001 QALYs, and each instance of HSIL treatment was assumed to result in a loss of 0.005 QALYs. The QALY reduction associated with cancer treatment (0.007 QALYs per treatment) was informed by a recent systematic review on the disutility of radiotherapy.[28]

Sensitivity analyses

Multiple one-way sensitivity analyses were conducted by varying the values of key model inputs within their lower to upper range. In probabilistic sensitivity analyses, we varied multiple key input parameters simultaneously across prespecified distributions over 10,000 simulations.

Scenario analysis

Improving HSIL screening technology is an active area of investigation.[13,14] We explored the likely impact of improving the sensitivity and specificity of the HSIL screening methods used in our base-case analyses. This involved assuming a screening test sensitivity of 95% and varying specificity (between 55 and 95%) and cost (between AUD 75–300 per test). We also assumed a screening test specificity of 95% and varied sensitivity (between 55 and 95%) and cost (between AUD 75–300 per test).

Software

Modelling was performed in TreeAge Pro 2021 Version R2.1 (TreeAge Software, Williamstown, Massachusetts).

IRB approval

This project has been approved by UNSW Sydney Human Research Ethics Committee (Approval number HC200365).

Role of the funding source

No specific funding was received for this analysis.

Results

Model validation

Our modelled anal cancer incidence rate without routine HSIL screening was 231 per 100,000 person years. This is comparable to recent empirical estimates of anal cancer incidence among GBM with HIV which range between 18 and 271 per 100,000 person years.[4] Given anal cancer incidence increases sharply with age among GBM with HIV,[4] the HIV population in Australia is rapidly aging,[37] and our study population excluded GBM with HIV aged <35 years, we considered it appropriate that our baseline incidence rate was towards the higher end of this range.

Base-case analyses

Modelled anal cancer incidence rates were greatly reduced following implementation of HSIL screening and treatment, with higher sensitivity HSIL screening methods leading to lower incidence rates (Table 1 and Supplementary Table S1). The costs and QALYs associated with each HSIL screening strategy are presented in Table 3. With a willingness-to-pay threshold at AUD 50,000 per QALY gained, screening and treating HSIL was not cost-effective with any screening method modelled. Relative to no screening, high-risk HPV mRNA testing had an ICER of AUD 135,800 per QALY gained. High-risk HPV mRNA testing dominated both high HPV16/18 viral load (extended dominance) and high-risk HPV DNA testing (absolute dominance).

Sensitivity analyses

The tornado diagram in Fig. 2 displays the results for our one-way sensitivity analyses. The base-case ICER assumed the same sensitivity and specificity as high-risk HPV mRNA screening (75.4% and 69.4%, respectively). None of our parameters, when varied within their sensitivity analysis range, lead to the ICER dropping below AUD 50,000 per QALY gained. The parameter that influenced the ICER most was the initial screening test sensitivity. Higher sensitivity led to improved cost-effectiveness. The utility of no HSIL/HSIL/localized

Screening method	Cost, AUD	QALYs	Incremental Cost, AUD	Incremental QALYs	ICER – AUD/QALY gained[a]
No routine screening	258,763	12.6860			
Annual HSIL screening and treatment - High HPV16/18 viral load	261,288	12.7031	Dominated (extended dominance[b])		
Annual HSIL screening and treatment - High-risk HPV mRNA	262,485	12.7134	3722	0.0274	135,800
Annual HSIL screening and treatment - High-risk HPV DNA testing	263,061	12.7067	Dominated (absolute dominance[c])		

ICER, Incremental cost-effectiveness ratio; AUD, Australian dollar; QALY, Quality adjusted life-year; HPV, Human papillomavirus; HSIL, High-grade squamous intraepithelial lesion. [a]Rounded to nearest hundred. [b]Extended dominance occurs when an intervention is less effective and has a higher ICER than an alternative intervention. [c]Absolute dominance occurs when an intervention is less effective and more costly than an alternative intervention.

Table 3: **ICERs (AUD per QALY gained) for base-case analyses.**

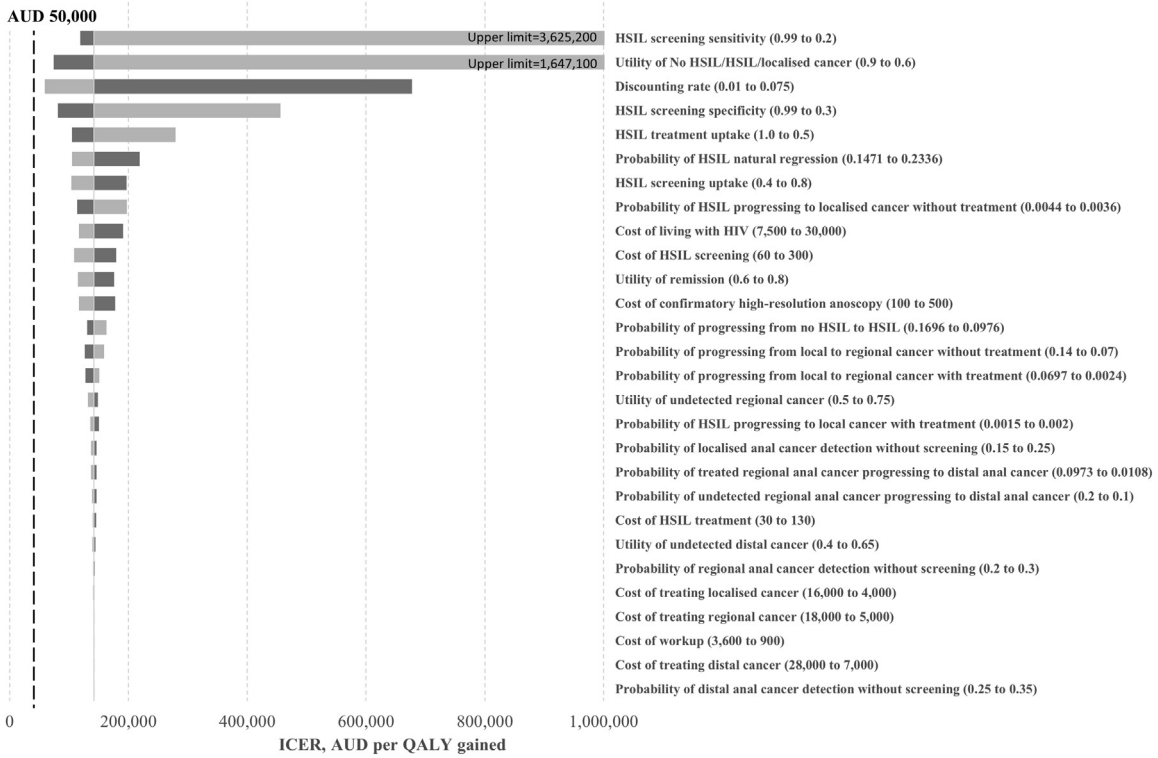

***Fig. 2:* Tornado diagram for one-way sensitivity analyses of key model parameters**. The base-case ICER assumed the sensitivity and specificity of high-risk HPV mRNA screening (75.4% and 69.4%, respectively). Light/dark grey bars indicative of sensitivity values below/above base-case. AUD, Australian dollar; HSIL, High-grade squamous intraepithelial lesion; ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life-year.

anal cancer stages also had a substantial impact on the ICER with higher estimated utility leading to HSIL screening and treatment being more cost-effective. Other parameters had a smaller impact on the ICER.

The probability that HSIL screening and treatment would be cost-effective at different willingness-to-pay thresholds is presented in Supplementary Fig. S1. The probability of being cost-effective at a willingness-to-pay threshold of AUD 50,000 per QALY gained was 20%. Although our key model inputs could vary within wide ranges, HSIL screening and treatment had a low (<30%) probability of being cost-effective even at willingness-to-pay thresholds substantially higher than AUD 50,000 per QALY gained.

Scenario analyses

Fig. 3 illustrates our scenario analysis results. In the best-case scenario, initial HSIL screening had a sensitivity of 95%, a specificity of 95%, and a cost of AUD 75 per test (while holding all other parameters at their base-case value). Under this scenario, the ICER remained above AUD 50,000 per QALY gained (AUD 61,500 per QALY gained). Only with a sensitivity of 95%, specificity of 95%, and cost ≤ AUD 24 per test did HSIL screening and treatment become cost-effective.

Discussion

Despite the ANCHOR study demonstrating that HSIL treatment effectively reduces anal cancer incidence in people living with HIV,[18] our analysis shows that HSIL screening and treatment in GBM with HIV ≥35-years-old is not likely to be a cost-effective in Australia using currently available screening tests. This result was consistent across a broad range of sensitivity analyses. Scenarios that assumed greater sensitivity and specificity of HSIL screening than currently available methods improved the cost-effectiveness of routine HSIL screening and treatment but still did not achieve cost-effectiveness. We estimate that an initial screening approach with 95% sensitivity and 95% specificity would become cost-effective at a cost of ≤ AUD 24 per test.

Our findings align with studies on the cost-effectiveness of HSIL screening and treatment among GBM with HIV in the UK.[11,12] US studies have found contrasting results. This is probably because they assumed much higher rates of HSIL progression to cancer.[9,10] All models published to date, including our own, have shown that HSIL screening and treatment is not cost-effective when low rates of HSIL progression are assumed. Goldie et al.[9] and Deshmukh et al.[10] based their core estimates of HSIL progression (approximately

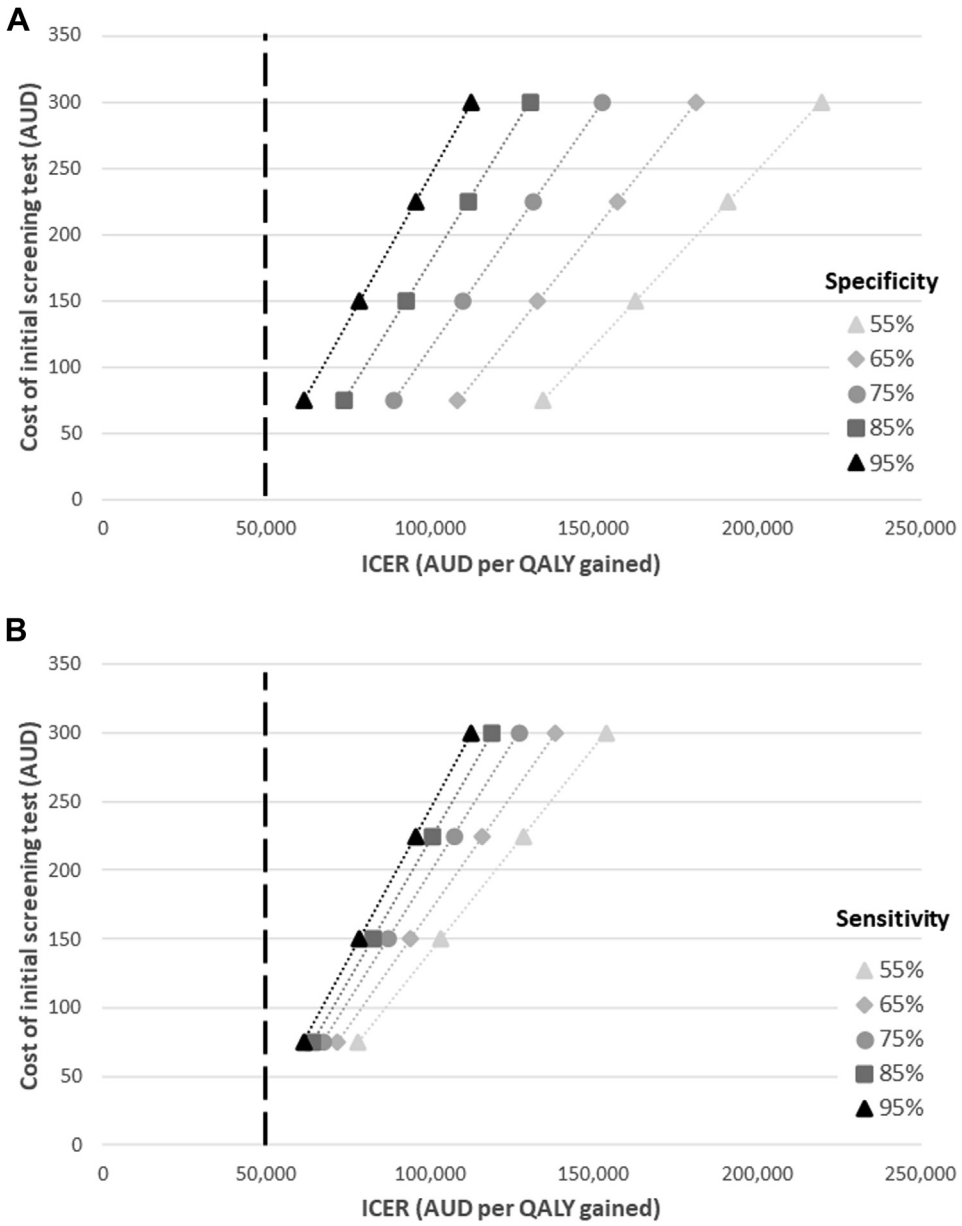

***Fig. 3*: ICERs under various scenarios for initial screening test sensitivity, specificity, and cost: A) assumes 95% sensitivity and B) assumes 95% specificity**. Vertical dashed line represents our assumed willingness-to-pay threshold (AUD 50,000 per QALY gained). AUD, Australian dollar; ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life-year.

5% of cases per year progressing to anal cancer) on simulation models derived on what would be required given documented HSIL prevalence and anal cancer incidence rates. Karnon et al.[11] and Czoski-Murray et al.,[12] on the other hand, used observational data to estimate progression rates of 0.14% per year for men aged 36–45 years and 0.45% per year for men aged greater than 45 years. We used an estimated progression rate of 0.4% per year in our study based on the control group in the ANCHOR trial,[18] which was consistent with data from SPANC.[17] When we used a progression rate of 5% per year in our models, ICERs for all the screening approaches we tested dropped below AUD 50,000 per QALY gained compared with no intervention (results not shown).

Despite the poor cost-effectiveness of HSIL screening and treatment for preventing anal cancer, there is reason to be optimistic about the future health

burden of anal cancer among GBM. Firstly, evidence suggests that HPV genotyping and evaluation of methylation markers may help identify HSIL at high risk of cancer progression.[8,14] This could lead to substantially reduced overtreatment of HSIL in a screening program leading to a more favourable cost-effectiveness equation. Secondly, HPV vaccination for boys was added to Australia's national vaccination program in 2013.[38] Vaccination against HPV 6/11/16/18 has been shown to reduce rates of anal intraepithelial neoplasia by more than 50% among GBM aged 16–26 years.[39] It is anticipated that routine vaccination against high-risk HPV genotypes in boys will begin to substantially reduce anal cancer rates within the next 20 years, similar to what has been predicted for routine HPV vaccination in girls and future cervical cancer rates.[40]

An important limitation of this study was the lack of supporting evidence for some of our transition probabilities, quality-of-life weights, and costs. We had to make several assumptions, usually based on local unpublished data, extrapolation from other patient populations (e.g., patients with colorectal cancer), or expert opinion. Although our ICERs were not overly sensitive to variation in these parameters, stronger empirical data would increase confidence in our results. Further, strong empirical data stratified by age would allow more detailed modelling of HSIL screening and treatment. It is likely that HSIL screening and treatment is more cost-effective in older GBM with HIV due to their increased risk of anal cancer.

HSIL screening and treatment in GBM living with HIV is not likely to be a cost-effective means of preventing anal cancer in Australia with current screening technology. Our model findings are consistent with those from other high-income settings when comparable estimates of HSIL progression to cancer are used. Future research priorities should include establishing highly sensitive and highly specific HSIL screening methods that cost less than currently available techniques and identifying methods that reliably select for HSIL at high risk of progressing to anal cancer. Accurate surveillance of anal cancer rates must also continue as it is expected there will be an HPV-vaccine associated decline in incidence within the next 20 years.

Contributors

QC and DCB undertook the literature search, designed and carried out the analysis, and drafted the manuscript; IMP, FJ, AG, JJO, RJH, GH, KH, and AN provided critical input to the design of the analysis; DCB oversaw the project; All authors helped draft the manuscript and have read and approved the final submission.

Declaration of interests

None to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2022.100676.

References

1 Sauter M, Keilholz G, Kranzbuhler H, et al. Presenting symptoms predict local staging of anal cancer: a retrospective analysis of 86 patients. *BMC Gastroenterol*. 2016;16:46.
2 Yates A, Carroll S, Kneebone A, et al. Implementing intensity-modulated radiotherapy with simultaneous integrated boost for anal cancer: 3 Year outcomes at two Sydney institutions. *Clin Oncol*. 2015;27(12):700–707.
3 Koerber SA, Slynko A, Haefner MF, et al. Efficacy and toxicity of chemoradiation in patients with anal cancer–a retrospective analysis. *Radiat Oncol*. 2014;9:113.
4 Clifford GM, Georges D, Shiels MS, et al. A meta-analysis of anal cancer incidence by risk group: toward a unified anal cancer risk scale. *Int J Cancer*. 2021;148(1):38–47.
5 De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer*. 2009;124(7):1626–1636.
6 Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. *Int J Cancer*. 2009;124(10):2375–2383.
7 Lin C, Franceschi S, Clifford GM. Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis. *Lancet Infect Dis*. 2018;18(2):198–206.
8 Poynten IM, Jin F, Roberts JM, et al. The natural history of anal high-grade squamous intraepithelial lesions in gay and bisexual men. *Clin Infect Dis*. 2021;72(5):853–861.
9 Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA, J Am Med Assoc*. 1999;281(19):1822–1829.
10 Deshmukh AA, Chiao EY, Cantor SB, et al. Management of precancerous anal intraepithelial lesions in human immunodeficiency virus-positive men who have sex with men: clinical effectiveness and cost-effectiveness. *Cancer*. 2017;123(23):4709–4719.
11 Karnon J, Jones R, Czoski-Murray C, Smith KJ. Cost-utility analysis of screening high-risk groups for anal cancer. *J Public Health*. 2008;30(3):293–304.
12 Czoski-Murray C, Karnon J, Jones R, Smith K, Kinghorn G. Cost-effectiveness of screening high-risk HIV-positive men who have sex with men (MSM) and HIV-positive women for anal cancer. *Health Technol Assess*. 2010;14(53):1–101. iii-iv, ix-x.
13 Jin F, Roberts JM, Grulich AE, et al. The performance of human papillomavirus biomarkers in predicting anal high-grade squamous intraepithelial lesions in gay and bisexual men. *Aids*. 2017;31(9):1303–1311.
14 van der Zee RP, Richel O, van Noesel CJM, et al. Cancer risk stratification of anal intraepithelial neoplasia in human immunodeficiency virus-positive men by validated methylation markers associated with progression to cancer. *Clin Infect Dis*. 2021;72(12):2154–2163.

15 Brogden DRL, Walsh U, Pellino G, Kontovounisios C, Tekkis P, Mills SC. Evaluating the efficacy of treatment options for anal intraepithelial neoplasia: a systematic review. *Int J Colorectal Dis*. 2021;36(2):213–226.
16 Richel O, de Vries HJ, van Noesel CJ, Dijkgraaf MG, Prins JM. Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. *Lancet Oncol*. 2013;14(4):346–353.
17 Poynten IM, Jin F, Roberts JM, et al. The natural history of anal high-grade squamous intraepithelial lesions in gay and bisexual men. *Clin Infect Dis*. 2020;72(5).
18 Palefsky JM, Lee JY, Jay N, et al. Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer. *N Engl J Med*. 2022;386(24):2273–2282.
19 Rosen RD, Sapra A. TNM Classification. Treasure Island (FL): StatPearls; 2022.
20 Machalek DA, Jin F, Poynten IM, et al. Prevalence and risk factors associated with high-grade anal squamous intraepithelial lesions (HSIL)-AIN2 and HSIL-AIN3 in homosexual men. *Papillomavirus Res*. 2016;2:97–105.
21 Machalek DA, Grulich AE, Hillman RJ, et al. The Study of the Prevention of Anal Cancer (SPANC): design and methods of a three-year prospective cohort study. *BMC Publ Health*. 2013;13:946.
22 Ong JJ, Fairley CK, Carroll S, et al. Cost-effectiveness of screening for anal cancer using regular digital ano-rectal examinations in men who have sex with men living with HIV. *J Int AIDS Soc*. 2016;19(1):20514.
23 National Cancer Institute. Anus, anal canal & Anorectum cancer, stage distribution of SEER incidence cases. https://seer.cancer.gov/explorer/application.html; 2009-2018. Accessed July 1, 2019.
24 Australian Government. Medicare Benefits Schedule. http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home; 2020. Accessed July 15, 2020.
25 Australian Government. Pharmaceutical Benefits Scheme. https://www.pbs.gov.au/pbs/home. Accessed December 19, 2021.
26 Lim M, Devine A, Gray R, Kwon J, Hutchinson J, Ong JJ. Lifetime cost of HIV management in Australia: an economic model. https://doi.org/10.2139/ssrn.3868096; 2022. Accessed January 14, 2022.
27 Djalalov S, Rabeneck L, Tomlinson G, Bremner KE, Hilsden R, Hoch JS. A review and meta-analysis of colorectal cancer utilities. *Med Decis Making*. 2014;34(6):809–818.
28 Paracha N, Abdulla A, MacGilchrist KS. Systematic review of health state utility values in metastatic non-small cell lung cancer with a focus on previously treated patients. *Health Qual Life Outcomes*. 2018;16(1):179.
29 Australian HIV Observational Database. Rates of combination antiretroviral treatment change in Australia 1997-2000. *HIV Med*. 2002;3(1):28–36.
30 Pharmaceutical Benefits Advisory Committee. Guidelines for preparing submissions to the pharmaceutical benefits advisory committee (version 5.0). https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf; 2016. Accessed December 9, 2016.
31 Medical Services Advisory Committee Technical guidelines for preparing assessment reports for the medical services advisory committee – service type: Investigative (version 3.0). http://www.msac.gov.au/internet/msac/publishing.nsf/Content/0BD63667C984FEEACA25801000123AD8/$File/InvestigativeTechnicalGuidelines-December-2016-Version-3.0.pdf; 2017. Accessed September 1, 2017.
32 George B, Harris A, Mitchell A. Cost-effectiveness analysis and the consistency of decision making: evidence from pharmaceutical reimbursement in Australia (1991 to 1996). *Pharmacoeconomics*. 2001;19(11):1103–1109.
33 Raftery JP. Paying for costly pharmaceuticals: regulation of new drugs in Australia, England and New Zealand. *Med J Australia*. 2008;188(1):26–28.
34 Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473–483.
35 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21(2):271–292.
36 Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care*. 2004;42(9):851–859.
37 Jansson J, Wilson DP. Projected demographic profile of people living with HIV in Australia: planning for an older generation. *PLoS One*. 2012;7(8):e38334.
38 Cancer Council Australia. An Australian success story: the HPV vaccine. https://www.cancercouncil.com.au/news/australian-success-story-hpv-vaccine/?&utm_source=google&utm_content=1gsCCNSWAO2021&gclid=Cj0KCQiAip-PBhDVARIsAPP2xc0Bi6JwvSyS4MFvzzlifdRLFVTJyTVhU8EIRjBUYYNSMv0iziGQP-kaAny5EALw_wcB&gclsrc=aw.ds; 2022. Accessed January 20, 2022.
39 Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med*. 2011;365(17):1576–1585.
40 Simms KT, Steinberg J, Caruana M, et al. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. *Lancet Oncol*. 2019;20(3):394–407.