Should all people living with HIV above 45 years old receive an annual digital anorectal examination for anal cancer screening?

The issue:

- The current Australian guidelines recommend an annual DARE for MSM living with HIV aged 50 and above.
    - The incidence of anal cancer in MSM living with HIV is 50-100 times higher than the general population.
    - Anal cancer diagnosis and treatment can have significant effects on quality of life and detecting cancer at an earlier stage can reduce morbidity and mortality.
    - Anal cancer survival outcomes are related to stage at presentation and hence early detection is a priority.
- ASHM has received a request to amend this recommendation so that DARE is extended to all people living with HIV aged 45 and above.
    - i.e. include men who have sex with women, and women who have sex with men (in addition to men having sex with men), and is trans-inclusive.

Options for the ASHM HIV Subcommittee to consider:

1) Change guidelines so that the starting age of screening **begins from 45 years old for all MSM living with HIV**
    a. There is an issue of equity here whereby non-MSM (with a 22-32 times higher incidence of anal cancer compared to people without HIV) may find this difficult to accept if the recommendation is only for MSM (85 times higher incidence).
2) Starting age of screening to begin from **45 years old for all people living with HIV**
    a. This solves the equity concern but major gaps exist for the acceptability, feasibility and cost-effectiveness of anal cancer using DARE among non-MSM.
    b. The committee could consider stating that there is less evidence for non-MSM for screening using DARE, but might be beneficial considering the increased incidence of anal cancer in these populations and that early detection of anal cancers lead to better outcomes.
    c. Provide the evidence review included below as a weblink.

Scoping review was performed by QiRui Soh, Melissa Shi and Emma Sivewright under the guidance of Jason Ong.
The document was reviewed by Prof. Christopher Fairley, Prof. Andrew Grulich, A/Prof Richard Hillman, Dr. Mary Poynten, Dr. Jeff Jin and Dr. Nicholas Comninos.

Methods
We conducted a scoping review of the evidence for screening for anal cancer using DARE for all people living with HIV aged 45 and above. We searched for relevant papers on 27th December 2020 in Medline OVID and Econlit (for economic evaluations) using concepts of anal cancer, HIV and screening, with no publication date restrictions. Details of the search strategy are found in Appendix 1.

Results
A summary of the findings is presented in the table below.

Summary of evidence (in terms of Wilson and Junger's criteria)[1]**:**

Anal cancer should be an important health problem	
Anal cancer should have an early symptomatic stage	
Natural history of anal cancer should be understood	
DARE is simple, safe, precise and validated	
DARE is acceptable to the target population	
Early treatment leads to better outcomes	
Agreed policy on who should be treated and how	
Facilities for diagnosis and treatment should be available	
The cost of case findings should be economically balanced in relation to possible expenditure on medical care as a whole	
Case findings should be a continuing process and not a "once for all" project	
Agreed policy on who should be treated and how	

Green = sufficient evidence
Orange = limited evidence
Red = no evidence found

1) The condition sought should be an important health problem

Anal cancer is defined as a cancer arising from either the squamous or glandular epithelia of the anus. The majority of anal cancer is squamous cell carcinoma [2]. They are divided into two groups based on where they originate: cancers of the anal canal (above the anal verge) and cancers of the perianal skin (below the anal verge).

Anal cancers are rare when compared to other cancers but are steadily increasing [2]. In a study on anal cancer trends in Australia, the age-adjusted annual incidence rates of anal squamous cell carcinoma increased from 0.65 per 100,000 person-years in 1982-1987 to 1 per 100,000 person-years in the 2000-2005 period [2]. Internationally, anal cancer rates are also on the rise with incidences increasing in both men and women, especially in the Americas, Northern and Western Europe, and Australia [3].

Specific population such as people living with HIV are at risk of anal cancer much more commonly [4]. Among people living with HIV, the crude incidence in Australia rose from 14.8 per 100,000 person-years (1982-1995) to 62.1 per 100,000 per-years (2009-2012).[5] In particular, MSM living with HIV have the highest risk of being affected by HPV with subsequent higher incidence of anal cancer [6]. In the United States, the proportion of anal

cancer cases that were HIV-infected has risen from 1.1% among males (1980-1984) to 28.4% (2001-2005), and 0% among females (1980-1984) to 1.2% (2001-2005) [7].

Anal cancer compares poorly to other HPV-related cancers in terms of quality of life valuations (where 0 equates to the equivalence of death and 1 equates to perfect health) with anal cancer scored at 0.57 [8]. In comparison, oropharyngeal cancer scored 0.58, vaginal cancer scored 0.59, vulval cancer scored 0.65 and penile cancer scored 0.79 [8].

In a German study of 446 MSM living with HIV, six of the 11 participants with anal cancer were under the age of 50 at diagnosis. The age range for this subgroup was 41-69 (mean 50.6), which suggests anal cancer screening for MSM living with HIV under 50 years to be important [9]. The mean age for anal cancer diagnosis in people living with HIV was 49.9 years (SD 10.7) and median age was 49 (IQR 42-54) [5].

In a 2020 systematic review, anal cancer incidence rates among people living with HIV were: 85 per 100,000 person-years (PY) for MSM (95% CI: 82-89), 32 per 100,000 PY (95% CI: 30-35) for non-MSM males, and 22 per 100,000 PY (95% CI: 19-24) for females.[10] Similarly, a 2015 systematic review highlighted that women, especially those who were living with HIV or had a history of HPV-related lower genital tract pathology, as a population at risk of anal dysplasia [11].

The incidence of anal cancer in heterosexual men living with HIV has been reported as 45.1 per 100,000 person-years (95% CI: 28.9-61.2) in France [12] and 46 per 100,000 person-years (95% CI:25-77) in North America [13]. The incidence of anal cancer in WLHIV has been reported in these regions as 18.3 per 100,000 person-years (95% CI:8.0-28.7) [12] and 30 per 100,000 person-years (95% CI:17-50) [13].

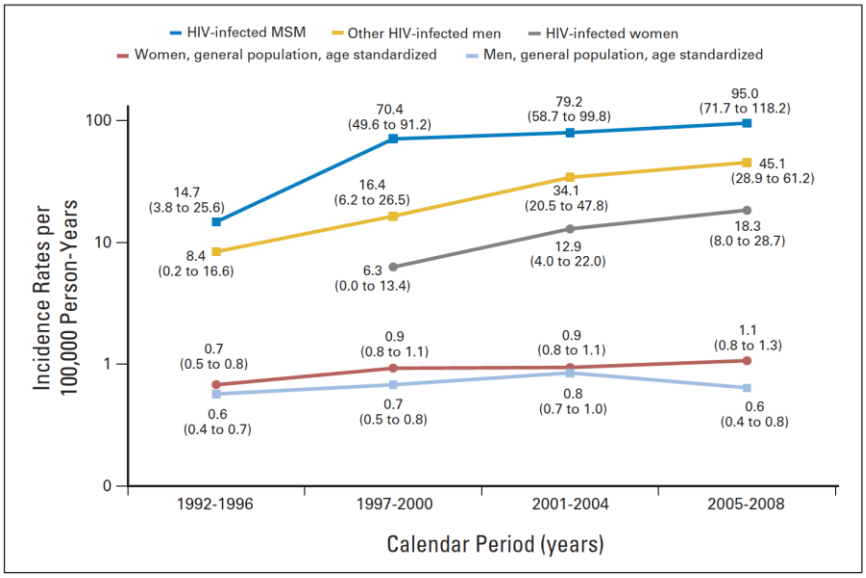

Fig 2. Incidence of anal cancer according to sex, HIV transmission group, and calendar period. For the general population, incidence rates were standardized by 5-year age groups on the basis of the age and sex distribution of the HIV-infected population in the French Hospital Database on HIV in the combined antiretroviral treatment period (1997-2008). Incidence rates are expressed per 100,000 person-years with 95% CIs in brackets. MSM, men who have sex with men.

Figure 1 [12]

Table 1[13]

Table 1. Baseline Characteristics, Anal Cancer Rates, and Rate Ratios by HIV Status, Men Who Have Sex With Men, and Sex, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), Years 1996–2007

	HIV-Infected			HIV-Uninfected	
	MSM	Other Men	Women	Men	Women
Baseline characteristics					
No.	18 855[a]	6492[a]	8842	102 607	11 653
Median age (IQR)	38 (33–44)	40 (35–46)	36 (30–43)	40 (34–47)	37 (31–44)
Race/ethnicity					
Black	3383 (18%)	3360 (52%)	4770 (54%)	6153 (6%)	1678 (14%)
White	11 951 (63%)	1773 (27%)	2051 (23%)	32 915 (32%)	4306 (37%)
Other[b]	1946 (10%)	732 (11%)	1269 (14%)	19 631 (19%)	3201 (27%)
Unknown	1575 (8%)	627 (10%)	752 (9%)	43 908 (43%)	2468 (21%)
HIV risk group					
MSM	18 855 (100%)	0 (0%)	0 (0%)	…	…
IDU	0 (0%)	2225 (34%)	1595 (18%)	…	…
Heterosexual	0 (0%)	3820 (59%)	5433 (61%)	…	…
Other	0 (0%)	447 (7%)	464 (5%)	…	…
Unknown	0 (0%)	0 (0%)	1355 (15%)	…	…
Median year start of follow-up (IQR)	2000 (1997–2004)	2000 (1997–2003)	2000 (1996–2003)	1998 (1996–2003)	1998 (1996–2003)
Median baseline CD4 cells/μL (IQR)[c]	320 (140–505)	225 (65–418)	336 (155–538)	…	…
Anal cancer rates and rate ratios					
Cases	122	14	15	13	0
Person-years	93 063	30 570	49 676	585 049	67 942
Median years follow-up (IQR)	4.0 (1.6–7.8)	3.9 (1.6–7.2)	5.3 (2.0–8.8)	4.7 (2.0–10.0)	5.0 (2.1–9.9)
Incidence rate per 100 000 person-years (95% CI)	131 (109–157)	46 (25–77)	30 (17–50)	2 (1–4)	0 (0–5)
Rate ratio (95% CI)	80.3 (42.7–151.1)[d]	26.7 (11.5–61.7)[d]	Undefined[e]	Reference	Undefined[e]

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men.

[a] Excludes 2280 HIV-infected men with missing or unknown HIV risk group.

[b] Other race/ethnicity category was predominantly Hispanic.

[c] Closest CD4 test result within 1 year of start of follow-up; 0.8% had missing baseline CD4.

[d] Rate ratios for HIV-infected MSM and other men compared with HIV-uninfected men from Poisson regression models adjusted for race/ethnicity, calendar era, age at entry into calendar era, and cohort.

[e] Zero cases of anal cancer among the reference group of HIV-uninfected females.

There is a higher burden of disease of anal cancer among people living with HIV regardless of gender or sexual orientation, when compared to their counterparts without HIV.
We found evidence that anal cancer can be detected in MSM living with HIV younger than 50 years, supporting the proposal to reduce the starting age for screening.

2) The condition should have an early symptomatic stage

Anal cancer may present as rectal bleeding, anal or perineal pain, a painful/hard/friable mass, pruritus ani, faecal incontinence, anal fistula, anal discharge and ulceration[14-18]. It is estimated that up to 80% of anal cancers may be symptomatic at the time of diagnosis [19]. However symptoms may be present with a mean of 22 weeks before diagnosis was made [15]. Rectal bleeding occurred in 45 percent of patients with anal squamous-cell carcinoma and is the most common initial symptom [17]. Other symptoms include pain or sensation of the rectal mass (occurring in about 30% of patients) and 20 percent have no rectal symptoms at all [17].

A 2013 Melbourne retrospective review suggests that a substantial proportion of anal squamous cell carcinoma is visible, palpable and even symptomatic for a time period before diagnosis [20]. Furthermore, more than 90% of anal squamous cell carcinomas were at least 1 centimetre during diagnosis with 50 percent being visible on external inspection of the anus [20]. Of particular note is that the mean estimated tumour size was 36mm at diagnosis (29 mm in HIV-positive and 38 mm in HIV-negative patients; p = 0.04) [20]. This is important because the most important prognostic factor for anal cancer is tumour size, with tumours more than 2 cm in size having a low prognosis of about 45 percent [21]

We found no evidence that early anal cancer may present differently according to age, gender or sexual orientation. There was one study that suggested that people living with HIV presented with a larger tumour size at the time of diagnosis but it is not clear if this was due to pathophysiological reasons, individual factors or structural barriers [22].

3) The natural history of the condition should be understood

Anal squamous cell carcinoma originates from a precursor lesion termed anal intraepithelial neoplasia (AIN) [23]. AIN is more commonly found in high-risk individuals (such as patients with HPV infection, those living with HIV and MSM) [24]. Tumour stage is directly linked to outcomes and staging factors are tumour diameter (T), nodal status (N) and detection of metastasis to other organs (M) [25]. Anal cancer is understood to progress from primary to nodal and metastatic stage.

We found no evidence of differences in the natural history of anal cancer related to age, gender or sexual orientation.

4) The test: Is the test simple, safe, precise and validated?

A Digital Ano-Rectal Examination (DARE) is similar to a Digital Rectal Examination (DRE), which is used primarily for prostate examination. DARE, however, involves thorough palpation of the anal canal, distal rectum, and the rectovaginal septum in women, as well as palpation and visualization of the perianus to a distance of 5cm from the anal verge [26]. In a German study of 446 MSM living with HIV, 11 were found to have anal cancer. Including visualization of the perianal area, 100% (n=11) of anal cancers in this group were detectable using DARE [9], suggesting the sensitivity of DARE to be reasonably high. In a phase II clinical study in the US, 200 MSM living with HIV were taught to perform self- or partner-DARE. DARE was shown to detect 3mm lesions with 71-80% sensitivity and 92-100% specificity [27]. This is of notable significance as a French retrospective study of 69 patients with anal cancer showed there is a high cure rate (>90%) for anal cancers diagnosed at a size less than 1cm [28].

DARE data related to whether it is simple, safe, precise and validated could not be found specifically for heterosexual men, or transgender and gender diverse people living with HIV. One study among a prospective cohort of 124 women living with HIV, reported that the median pain score for DARE out of 10 (0=no pain, 10=worst pain ever felt) was 1 out of 10, compared to screening using high resolution anoscopy (HRA) with a median score of 5 [29].

We did not find evidence of DARE's safety, precision and validation in heterosexual men or transgender and gender diverse people living with HIV. One small study reports the experience of DARE among heterosexual women living with HIV.

5) The test: acceptable to the population

In a Canadian prospective cohort study of 124 women living with HIV, the acceptability of DARE was compared with Pap smears and considered acceptable at all proposed frequencies of yearly, every 2 years, and every 5 years [29]. Almost all women living with HIV who participated in the study believed that anal cancer screening for their demographic is an "absolute necessity", with most (87%) describing DARE as "very acceptable". Acceptability of DARE increased further as proposed screening frequency decreased: 95% for 2-yearly DARE and 96% for 5-yearly DARE [29]. Reasons for some participants rating lower acceptability for DARE included pain (n=5) and duration of the procedure (n=1) [29].

Routine anal cancer screening via DARE in MSM aged 35 years have also been reported to have high acceptability and minimal adverse effects [30-32]. However, we were not able to find any studies that looked at the acceptability of DARE in heterosexual men living with HIV.

There is limited evidence for the acceptability of DARE for women living with HIV and younger MSM, but no evidence was found for heterosexual men or trans and gender diverse people living with HIV.

6) The treatment: effective treatment for those identified with evidence that early treatment leads to better outcomes

The gold standard of treatment for stage I to III anal squamous cell carcinoma is chemo-radiation [33]. There are no differences in treatment between males and females.

A division between anal canal cancers and anal margin cancers exist. This distinction is important due to the difference in treatment. Early anal margin cancer can be locally excised while anal canal cancer is treated by chemoradiation [34]. Localized and smaller anal canal cancers (T1N0) are treated mainly with exclusive radiation therapy while anal margin cancers of similar staging are treated by surgery [35]. Locally advanced tumours (T2-T4, N0-N2) are preferentially treated by definitive concomitant chemoradiation [35]. Nonoperative treatments for anal cancer include surveillance and topical imiquimod/5-fluorouracil [34].

Prognosis has a direct correlation with tumour size at diagnosis. Data released by the US National Cancer Institute shows that tumours less than 2cm have an 80% five-year survival rate whereas tumours larger than 2cm had prognoses as low as 45% [21]. The five-year survival falls to 20% in metastatic tumours [21]. Currently, most tumours detected have a mean size of 3-4 cm [21]. The average size of anal squamous cell carcinoma in patients living

with HIV is 2.9cm [20]. Furthermore, a French retrospective survey of 69 patients with anal cancers of less than 1cm showed a 100% 5-year survival [36].

This further highlights the importance of earlier diagnosis to ensure better prognosis.

We did not find evidence that anal cancer treatment outcomes differed according to age, gender or sexual orientation.

7) The screening program: agreed policy on who should be treated and how

There are clear guidelines defining the most efficacious treatment of intracanal and perianal anal cancer [37, 38]. The current standard treatment for anal cancer comprises primarily chemoradiation with treatment related to stage at presentation. New studies are looking at integrating modern radiation techniques and de-escalating early stage cancers with the aim of similar cure rates but less long term toxicities [39]. Some expert groups recommend that local excision alone for well differentiated T1 cancers [37]. If more small asymptomatic cancers were detected earlier by clinicians with DARE, more patients may avoid the potential acute and late toxicities of chemoradiation [40].

We did not find evidence regarding who should be treated for anal cancer differed according to age, gender or sexual orientation.

8) The screening program: facilities for diagnosis and treatment should be available

Most HIV patients in high income countries see a HIV physician at least annually for management [41]. DARE is a short procedure, taking less than 1 minute to perform[42], and is estimated to extend a routine HIV consultation by less than 5 minutes [32, 41]. Since Nov 2016, ASHM guidelines recommend that MSM living with HIV aged 50 years and above should receive DARE annually as part of their routine HIV care[43], however in Australia there are no guidelines for other people living with HIV despite women and heterosexual men living with HIV still being at increased risk of anal cancer compared to their counterparts not living with HIV [6, 12, 13]. If the recommendation is for annual DARE to be extended to all people living with HIV aged 45 years and above, we expect that no additional facilities for screening is required as screening for anal cancer with DARE will be incorporated into routine HIV care.

It was estimated that in 2017, MSM accounted for 77.4% of the Australian population of people living with HIV. Furthermore, 48.1% of Australian males living with HIV were aged 50 years and above [44]. Given that the majority of PLHIV aged 45 years and above in Australia are MSM aged 50 years and above and already recommended to be receiving annual DARE for cancer screening, we expect that if we were to recommend annual DARE to all PLWHIV aged 45 years and above, the addition burden on the health care system will be marginal.

It is possible that increased screening for anal cancer via DARE may necessitate additional training for performing DARE. In 2013, a Melbourne study surveyed 36 physicians (sexual health, infectious disease, and general practitioners- all with considerable experience in managing PLHIV) about their confidence in performing DARE for anal cancer screening in MSM living with HIV. While 67% of these physicians were confident in performing DARE, only 22% were confident in recognising anal cancer via DARE [45]. A later prospective cohort study (the ACE study) published by the same group in 2018 recruited a similar group of 31 physicians to perform annual DARE in 327 MSM living with HIV. Here, prior to commencement of the study, 90% of physicians were confident in performing DARE and 75% of those were confident in their ability to recognise an anal cancer via DARE. During the study, physicians were given training on screening for anal cancer via DARE, and at conclusion of the study, 95% of physicians were confident in performing DARE and 85% were confident in ability to recognise an anal cancer [46]. While this improvement in confidence is encouraging, it should be noted that these studies were confined to inner city clinics in Melbourne, and physicians had considerable experience managing PLHIV. Currently, no training syllabus exists for DARE [42] and it is unclear what level of confidence and experience physicians in other settings have in performing DARE.

In the same ACE study where DARE was used for anal cancer screening in 327 MSM living with HIV who were age 35 years and over, 862 DAREs were performed over 3 years. Following DARE, 33 of patients (3.8%) were referred to colorectal surgeon for management, and one case was anal cancer [46]. We did not find any equivalent studies that evaluated the referral rate to a colorectal surgeon following DARE in heterosexuals or trans-people.

We did not find evidence regarding who should be treated for anal cancer differed according to age, gender or sexual orientation.

2.9 The screening program: is the cost of case finding (including diagnosis and treatment of patients diagnosed) economically balanced in relation to possible expenditure on medical care as a whole?

There is evidence for the cost-effectiveness of regular anal cancer screening via DARE in MSM living with HIV in Australia [41]. In this modelling study, the factor that had the most significant impact on cost-effectiveness was the cost of referrals for anal lesions that were not cancer. Thus, by increasing physician training and experience in recognising anal cancer via DARE, the an anal cancer screening program can potentially be more cost-effective[41]. It was noted in the ACE study that the proportion of referrals following DARE from the sexual health centre was 10 fold lower compared to the tertiary hospital with HIV clinic (1.6/100 DARE) vs (16.1/100 DARE). This may in part be influenced by differences in physician's experience in performing DARE for the detection of anal cancer vs other anorectal conditions [31, 46].

We were not able to find any cost-effectiveness studies looking at the use of DARE in PLHIV who were not MSM aged 50 years and above. As the incidence of anal cancer is lower in non-MSM vs MSM living with HIV, we anticipate that the incremental cost-effectiveness ratio (ICER) will be higher (i.e. less cost-effective) for non-MSM living with HIV compared with MSM living with HIV. This is because of the need to screen more people to detect an anal cancer.

However, it must be borne in mind that in Australia, the national cervical screening program (NCSP) began in 1981, with the recommendation for women aged 20-69 to be screened for cervical abnormalities via pap smear biennially. In 1982, the incidence of cervical cancer in this population in Australia was 19.0/100,000 person-years[47]. This is comparable to the estimated incidence of anal cancer in men who have sex with women (32/100,000 person-years) and women living with HIV (22/100,000 person-years).[10]

We did not find evidence regarding the cost-effectiveness of DARE for non-MSM populations. We recommend a cost effectiveness study for all people living with HIV to be performed, which takes into consideration at what starting age and how often screening via DARE should occur among non-MSM living with HIV.

2.10 The screening program: case findings should be a continuing process and not a "once for all" project

The rate of anal cancer progression cannot be accurately determined as it is unethical to observe the natural progression of cancer [41, 48]. Thus, no published studies exist on which to base recommendations of the optimal frequency of anal cancer screening via DARE. However experts propose that it is plausible for anal cancer to progress from local to regional to distal cancer over one-year periods [41].

Hillman et al. [42] recommend a minimum DARE frequency of at least annually in all MSM living with HIV aged 35 years and above and all people living with HIV aged 50 years and above. These suggestions are based on the frequency of anal cancer in those populations. The European AIDS Clinical Society Guidelines recommend that MSM should have 'a digital rectal exam +/- a Papanicolau test every one to three years' [49]. Moscicki et al.[48] recommend that routine screening for anal cancer with DARE should be performed in all women living with HIV. These suggestions were all developed based on expert opinion.

Considering that tumour size is linked to overall prognosis[30], there is value in recommending regular routine DARE for all PLHIV aged 45 years and above, in order to increase chances of early detection of anal abnormalities and therefore better treatment outcomes.

Bibliography

1. Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. Bol Oficina Sanit Panam. 1968;65(4):281-393.
2. Jin F, Stein AN, Conway EL, Regan DG, Law M, Brotherton JM, et al. Trends in anal cancer in Australia, 1982-2005. Vaccine. 2011;29(12):2322-7.
3. Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. International Journal of Epidemiology. 2016;46(3):924-38.
4. Nyitray AG, Chiao EY. Re: Cui T, Kovell RC, Terlecki RP. Is it time to abandon the digital rectal examination? Lessons from the PLCO Cancer Screening Trial and peer-reviewed literature. Curr Med Res Opin 2016;32:1-7. Current Medical Research and Opinion. 2017;33(2):315-6.

5. Jin F, Vajdic CM, Law M, Amin J, van Leeuwen M, McGregor S, et al. Incidence and time trends of anal cancer among people living with HIV in Australia. Aids. 2019;33(8):1361-8.
6. Machalek DA, Poynten M, Jin F, Fairley CK, Farnsworth A, Garland SM, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol. 2012;13(5):487-500.
7. Shiels MS, Pfeiffer RM, Chaturvedi AK, Kreimer AR, Engels EA. Impact of the HIV epidemic on the incidence rates of anal cancer in the United States. J Natl Cancer Inst. 2012;104(20):1591-8.
8. Conway EL, Farmer KC, Lynch WJ, Rees GL, Wain G, Adams J. Quality of life valuations of HPV-associated cancer health states by the general population. Sexually Transmitted Infections. 2012;88(7):517-21.
9. Kreuter A, Potthoff A, Brockmeyer NH, Gambichler T, Swoboda J, Stücker M, et al. Anal carcinoma in human immunodeficiency virus-positive men: results of a prospective study from Germany. British Journal of Dermatology. 2010;162(6):1269-77.
10. Clifford GM, Georges D, Shiels MS, Engels EA, Albuquerque A, Poynten IM, 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.
11. Stier EA, Sebring MC, Mendez AE, Ba FS, Trimble DD, Chiao EY. Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review. Am J Obstet Gynecol. 2015;213(3):278-309.
12. Piketty C, Selinger-Leneman H, Bouvier AM, Belot A, Mary-Krause M, Duvivier C, et al. Incidence of HIV-related anal cancer remains increased despite long-term combined antiretroviral treatment: results from the french hospital database on HIV. J Clin Oncol. 2012;30(35):4360-6.
13. Silverberg MJ, Lau B, Justice AC, Engels E, Gill MJ, Goedert JJ, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis. 2012;54(7):1026-34.
14. Szmulowicz UM, Wu JS. Squamous cell carcinoma of the anal canal: a review of the aetiology, presentation, staging, prognosis and methods available for treatment. Sex Health. 2012;9(6):593-609.
15. Read T, Huson K, Millar J, Haydon A, Porter I, Grulich A, et al. Size of anal squamous cell carcinomas at diagnosis: a retrospective case series. Int J STD AIDS. 2013;24(11):879-82.
16. Tanum G, Tveit K, Karlsen KO. Diagnosis of anal carcinoma--doctor's finger still the best? Oncology. 1991;48(5):383-6.
17. Ryan DP, Compton CC, Mayer RJ. Carcinoma of the anal canal. N Engl J Med. 2000;342(11):792-800.
18. Palefsky JM. Practising high-resolution anoscopy. Sex Health. 2012;9(6):580-6.
19. Fleshner PR, Chalasani S, Chang GJ, Levien DH, Hyman NH, Buie WD, et al. Practice parameters for anal squamous neoplasms. Dis Colon Rectum. 2008;51(1):2-9.
20. Read TR, Huson KL, Millar JL, Haydon A, Porter IW, Grulich AE, et al. Size of anal squamous cell carcinomas at diagnosis: a retrospective case series. Int J STD AIDS. 2013;24(11):879-82.
21. Lewis T, Samraj S, Patel R, Sundaram SS. Acceptability of digital anal cancer screening in HIV-positive men who have sex with men attending a UK Sexual Health service. Int J STD AIDS. 2016;27(12):1138-40.

22. Bower M, Powles T, Newsom-Davis T, Thirlwell C, Stebbing J, Mandalia S, et al. HIV-associated anal cancer: has highly active antiretroviral therapy reduced the incidence or improved the outcome? J Acquir Immune Defic Syndr. 2004;37(5):1563-5.
23. Osborne MC, Maykel J, Johnson EK, Steele SR. Anal squamous cell carcinoma: an evolution in disease and management. World J Gastroenterol. 2014;20(36):13052-9.
24. Siddharthan RV, Lanciault C, Tsikitis VL. Anal intraepithelial neoplasia: diagnosis, screening, and treatment. Ann Gastroenterol. 2019;32(3):257-63.
25. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-4.
26. Hillman RJ, Berry-Lawhorn JM, Ong JJ, Cuming T, Nathan M, Goldstone S, et al. International Anal Neoplasia Society Guidelines for the Practice of Digital Anal Rectal Examination. Journal of Lower Genital Tract Disease. 2019;23(2):138-46.
27. Nyitray AG, Hicks JT, Hwang LY, Baraniuk S, White M, Millas S, et al. A phase II clinical study to assess the feasibility of self and partner anal examinations to detect anal canal abnormalities including anal cancer. Sex Transm Infect. 2018;94(2):124-30.
28. Ortholan C, Ramaioli A, Peiffert D, Lusinchi A, Romestaing P, Chauveinc L, et al. Anal canal carcinoma: Early-stage tumors ≤10 mm (T1 or Tis): Therapeutic options and original pattern of local failure after radiotherapy. International Journal of Radiation Oncology*Biology*Physics. 2005;62(2):479-85.
29. Kaufman E, de Castro C, Williamson T, Lessard B, Munoz M, Mayrand MH, et al. Acceptability of anal cancer screening tests for women living with HIV in the EVVA study. Curr. 2020;27(1):19-26.
30. Lewis T, Samraj S, Patel R, Sundaram SS. Acceptability of digital anal cancer screening in HIV-positive men who have sex with men attending a UK Sexual Health service. International Journal of STD & AIDS. 2016;27(12):1138-40.
31. Ong JJ, Grulich A, Walker S, Hoy J, Read T, Bradshaw C, et al. Baseline findings from the Anal Cancer Examination (ACE) study: screening using digital ano-rectal examination in HIV-positive men who have sex with men. Journal of Medical Screening. 2016;23(2):70-6.
32. Read TR, Vodstrcil L, Grulich AE, Farmer C, Bradshaw CS, Chen MY, et al. Acceptability of digital anal cancer screening examinations in HIV-positive homosexual men. HIV Medicine. 2013;14(8):491-6.
33. Morton M, Melnitchouk N, Bleday R. Squamous cell carcinoma of the anal canal. Current Problems in Cancer. 2018;42(5):486-92.
34. Kreuter A, Brockmeyer NH, Wieland U. [Anal intraepithelial neoplasia and anal carcinoma: an increasing problem in HIV patients]. Hautarzt. 2010;61(1):21-6.
35. Moureau-Zabotto L, Vendrely V, Abramowitz L, Borg C, Francois E, Goere D, et al. Anal cancer: French Intergroup Clinical Practice Guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SNFCP). Dig Liver Dis. 2017;49(8):831-40.
36. Ortholan C, Ramaioli A, Peiffert D, Lusinchi A, Romestaing P, Chauveinc L, et al. Anal canal carcinoma: early-stage tumors < or =10 mm (T1 or Tis): therapeutic options and original pattern of local failure after radiotherapy. Int J Radiat Oncol Biol Phys. 2005;62(2):479-85.
37. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version I.2015 2014 [Available from: www.nccn.org/professionals/physician_gls/pdf/anal.pdf

38. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, et al. Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii10-20.
39. Yates A, Carroll S, Kneebone A, Tse R, Horvath L, Byrne C, et al. Implementing Intensity-modulated Radiotherapy with Simultaneous Integrated Boost for Anal Cancer: 3 Year Outcomes at Two Sydney Institutions. Clin Oncol (R Coll Radiol). 2015.
40. Putta S, Andreyev HJ. Faecal incontinence: A late side-effect of pelvic radiotherapy. Clin Oncol (R Coll Radiol). 2005;17(6):469-77.
41. Ong JJ, Fairley CK, Carroll S, Walker S, Chen M, Read T, 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. Journal of the International AIDS Society. 2016;19(1):20514.
42. Hillman RJ, Berry-Lawhorn JM, Ong JJ, Cuming T, Nathan M, Goldstone S, et al. International Anal Neoplasia Society Guidelines for the Practice of Digital Anal Rectal Examination. J Low Genit Tract Dis. 2019;23(2):138-46.
43. Anal Cancer in Men Living With HIV ASHM 2016 [Available from: https://www.ashm.org.au/HIV/hiv-management/anal-cancer/.
44. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report. Kirby Institute, UNSW Sydney; 2018.
45. Ong J, Chen M, Temple-Smith M, Walker S, Hoy J, Woolley I, et al. The inside story. Physicians' views on digital ano-rectal examination for anal cancer screening of HIV positive men who have sex with men. Journal of Medical Screening. 2013;20(4):188-91.
46. Ong JJ, Walker S, Grulich A, Hoy J, Read TR, Bradshaw C, et al. Incorporating digital anorectal examinations for anal cancer screening into routine HIV care for men who have sex with men living with HIV: a prospective cohort study. Journal of the International AIDS Society. 2018;21(12):e25192.
47. Cervical screening in Australia 2012–2013. Canberra: Australian Institute of Health and Welfare; 2015.
48. Moscicki AB, Darragh TM, Berry-Lawhorn JM, Roberts JM, Khan MJ, Boardman LA, et al. Screening for Anal Cancer in Women. Journal of Lower Genital Tract Disease. 2015;19(3 Suppl 1):S27-42.
49. European AIDS Clinical Society: Guidelines 2015 [Available from: https://www.eacsociety.org/files/guidelines_8.0-english-revised_20160610.pdf.

Appendix 1

Medline Ovid – Searched on 27 December 2020
47 results

#	search	results
1	exp Anus Neoplasms/	6452
2	((Anal or anus or peri?anal or ano?rectal or anal?rectal) and (Cancer or neoplas* or maligan* or carcinoma or squamous cell carcinoma or adenocarcinoma or tumo?r or lesion or pre?cancer or pre?malignan* or dysplas*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	19718
3	((anal intraepithelial and (malign* or neoplas*)) or ASIL or ((anal or anus) and (LSIL or HSIL))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	737
4	exp HIV/	100085
5	(HIV or HIV-1 or HIV1 or HIV-2 or HIV2 or human immun* virus).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	375852
6	(Digit* and (Screen* or exam* or test)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	67056
7	1 or 2 or 3	19773
8	4 or 5	375852
9	6 and 7 and 8	47

Medline Ovid – 27 December 2020
47 results final

	Search terms	Results #
1	exp Anus Neoplasms/	6452
2	((Anal or anus or peri?anal or ano?rectal or anal?rectal) and (Cancer or neoplas* or maligan* or carcinoma or squamous cell carcinoma or adenocarcinoma or tumo?r or lesion or pre?cancer or pre?malignan* or dysplas*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	19718

3	((anal intraepithelial and (malign* or neoplas*)) or ASIL or ((anal or anus) and (LSIL or HSIL))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	737
4	exp HIV/	100085
5	(HIV or HIV-1 or HIV1 or HIV-2 or HIV2 or human immun* virus).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	375852
6	(Digit* and (Screen* or exam* or test)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	67056
7	(1 or 2 or 3) and (4 or 5) and 6	47

Econlit – 2021_01_13
2 results

1	exp Anus Neoplasms/
2	(Anal or anus or peri?anal or ano?rectal or anal?rectal) and (Cancer or neoplas* or maligan* or carcinoma or squamous cell carcinoma or adenocarcinoma or tumo?r or lesion or pre?cancer or pre?malignan* or dysplas*)
3	anal intraepithelial and (malign* or neoplas*) or ASIL or ((anal or anus) and (LSIL or HSIL))
4	HIV or HIV-1 or HIV1 or HIV-2 or HIV2 or human immun* virus
5	Digit* and (Screen* or exam* or test)
6	1 OR 2 OR 3 AND 4 AND 5