

To whom: just for HIV?

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No conflicts

Menu for today

- Generalities
- Who
- Start
- How Follow- When to Stop
- Conclusions

Guidelines: cervical cancer screening



Morbidity and Mortality Weekly Report

TABLE 1. Cervical cancer screening and surveillance recommendations

		Guideline group, yr of recommendation				
Population	Screening specifics	USPSTF, 2018	ACOG, 2016	ACS, 2020		
Persons at average risk	Age to start screening	21 yrs	21 yrs	25 yrs		

Persons with an immunocompromising medical condition[†] (e.g., HIV infection or solid organ transplantation) Age to start screening

Age to end screening

No specific recommendation Within 1 yr of onset of sexual activity or, if already sexually active, within the first year after HIV or other immunocompromising medical condition diagnosis but no later than age 21 yrs None; lifelong screening recommended

Persons who have received HPV vaccination

No changes to the screening approaches above



Este análisis indicó que, en las mujeres no vacunadas, resulta más coste-efectivo iniciar el cribado a los 30 años y finalizar a los 70 años, sustituyendo el cribado citológico por el cribado basado en la prueba VPH a los 35 años.

Los datos más recientes sugieren iniciar el cribado cervical a los 25 años⁽⁴⁸⁾. Generalmente se recomienda realizar una citología anual a partir de los 25 años. En el caso de

Guidelines: anal cancer screening



CLINICAL GUIDELINES PROGRAM

NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Screening for Anal Disease

- For all patients with HIV ≥35 years old, regardless of HPV vaccination status, clinicians should:
 - Inquire annually about anal symptoms, such as itching, bleeding, palpable masses or nodules, pain, tenesmus, or a feeling of rectal fullness. (A2)
 - o Perform a visual inspection of the perianal [a] region. (A3)
 - Provide information about anal cancer screening and engage the patient in shared decision-making regarding screening, including anal cytology before DARE. (A3)
 - Perform DARE annually and whenever anal symptoms are present. (A*)
- For adults ≥35 years old who have HIV and are men who have sex with men (A3), transgender women (A3), women (B3), or transgender men (B3), clinicians should perform or recommend annual (A3) anal Pap testing to identify potentially cancerous cytologic abnormalities.
- Clinicians should promote smoking cessation for all patients with HIV, especially those at increased risk for anal cancer. (A3)
- For all patients with HIV ≥35 years old, clinicians should recommend and perform annual DARE to screen for anal pathology. (B3)
- Clinicians should evaluate any patient with HIV <35 years old who presents with signs or symptoms that suggest anal dysplasia.
 (A3)
- Clinicians should conduct HRA and histology (via biopsy) for any patient with LSILs or HSILs or refer as needed. (A2)
- For patients with anal cytology results indicating ASC-US, clinicians should perform HPV testing (A2):
- o If HPV testing is available and results are negative, repeat anal cytology in 1 year. (A3)
- o If HPV testing is available but reflex testing is not available, perform HPV test at follow-up within 6 months. (B2)
- o If positive for high-risk HPV or if HPV testing is not available, refer for HRA. (B2)
- Clinicians should refer patients with suspected anal cancer determined by DARE or histology to an experienced specialist for evaluation and management. (A3)
- Clinicians should discontinue screening for anal cancer when life expectancy is less than 10 years and in individuals with 2 consecutive negative anal cytology specimens who are not currently sexually active. (B3)



July 23, 2021

Sexually Transmitted Infections Treatment Guidelines, 2021

Cancers and Precancers Associated with Human Papillomavirus

Persistent infection with high-risk (oncogenic) types of HPV has a causal role in approximately all cervical cancers and in certain vulvar, vaginal, penile, anal, and oropharyngeal cancers (1238). However, cervical cancer is the only HPV-associated cancer for which routine screening is recommended.

Anal cancer screening: who









Anal Cancer Screening and Prevention: Summary of Evidence Reviewed for the 2021 Centers for Disease Control and Prevention Sexually Transmitted Infection Guidelines

Luis F. Barroso II, Elizabeth A. Stier, Richard Hillman, and Joel Palefsky



KEY QUESTION: WHICH GROUPS HAVE SUFFICIENT ANAL CANCER RISK TO CONSIDER SCREENING?

Summary

- Men who have Sex with Men (MSM) living with HIV have the highest anal squamous cell carcinoma (aSCC) incidence and represent the best studied high-risk group.
- All people living with HIV (PLWH) ≥ 35 years old have a substantially elevated aSCC risk and should be considered for anal cancer prevention interventions.
- Other risk groups include: Women with a history of HPVassociated genital cancers, solid organ transplant recipients, HIV negative MSM, and other immunocompromised persons without HIV infection.
- Anal cancer incidence increases as a function of age in all of the described groups.
- Patients who do not fall into an increased risk category should not be screened for anal cancer.



Current guidelines recommendations for anal HPV-related disease screening



There is no consensus in national and international guidelines regarding anal HPV-related disease screening.

Recommendations can be conflicting and with low strength of evidence (expert opinion in many cases).

H NYSDHAI 2020 ⁴ In C: F: H A	Anal cancer screening* annually for all HIV ≥ 35 years old, regardless HPV vaccine status. Informed and shared decision-making with patient regarding anal cytology. For HIV <35 years old only if anal signs/symptoms. HRA and biopsy if abnormal anal cytology. Annual DARE. Annual DARE.	A2 (inquiring), A3 (inspection), B3 (DARE) A3 A3 A2	
c; Fi H	cytology. For HIV <35 years old only if anal signs/symptoms. HRA and biopsy if abnormal anal cytology. Annual DARE.	A3	
H A	HRA and biopsy if abnormal anal cytology. Annual DARE.	7.77	
A	Annual DARE.	A2	
	A STATE OF THE PROPERTY OF THE		
HIVMA/IDSA 2020 ⁷	People with receptive anal intercourse Abnormal cervical Pap test Genital warts	Weak recommendation Moderate quality evidence.	
H	HRA if abnormal cytology.		
N	No recommendation regarding periodicity.		
	No national recommendations exist for routine screening for anal cancer.		
DHHS Nov 20188 S	Some experts recommend anal cytology or HRA for PLWH.	C3	
A	Annual DARE.	B3	
If	f abnormal anal cytology HRA + biopsy if visible lesions.	B3	
EACS 10.1 October 2020°	Expert opinion.		
	Screening interval: 1-3 years.	A3	

ASCRS 2018 ¹³	Anal cytology may be considered in high-risk population: PLWH, MSM, history of cervical dysplasia. HPV testing may be used as an adjunct to screening for anal cancer. HRA may be considered as a screening option for patients at high risk for cancer.	Weak recommendation. Moderate quality evidence.
ASTIDCP 2019 ¹²	Anal cytology in solid-organ transplant recipients if history of receptive anal intercourse, history of cervical dysplasia. HRA if abnormal cytology.	
	Normal cytology repeated every 1-3 years	evidence.

B3

Consensus or expert opinion.

Not reported.

AIN: Anal Intraepithelial Neoplasia; HIV: human immunodeficiency virus; HPV: human papillomavirus; HRA: high-resolution anoscopy; MSM: men who have sex with men; PLWH: people living with HIV; DARE: digital anorectal examination.

Legend for Evidence Column:

A. Strong evidence, should always be offered. B. Moderate evidence, in general should be offered. C. Weak evidence, must be offered optionally. 1. Data from randomized clinical trials or metaanalysis; 2. Data from non-randomized trials or observational cohorts; 3. Expert opinion.

THE LANCET

RESEARCH ARTICLE VOLUME 343, ISSUE 8898, P636-639, MARCH 12, 1994

High incidence of anal cancer among AIDS patients

M Melbye, MD • T.R Coté, MD A • R.J Biggar, MD • L Kessler, ScD • M Gail, MD • AlDS:Cancer Working Group • Show footnotes

Published: March 12, 1994 • DOI: https://doi.org/10.1016/S0140-6736(94)92636-0

RESEARCH SUMMARY

Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

Palefsky JM et al. DOI: 10.1056/NEJMoa2201048

CLINICAL PROBLEM

Anal cancer is caused by human papillomavirus infection and is preceded by high-grade squamous intraepithelial lesions (HSIL). Whether treatment of anal HSIL reduces progression to anal cancer is unknown.

CLINICAL TRIAL

Design: A multisite, randomized, U.S. trial examined the efficacy and safety of HSIL treatment for the prevention of anal cancer in adults living with HIV, a group disproportionately affected by anal cancer.

Intervention: 4446 participants 35 years of age or older with HSIL and without a history of anal cancer received either HSIL treatment until complete resolution (e.g., office-based ablation, ablation or excision under anesthesia, or topical therapies) or active monitoring without treatment. Participants in the treatment group returned for high-resolution anoscopy at least every 6 months, suspicious lesions were biopsied, and recurrences were treated. Participants in the active-monitoring group underwent anoscopy every 6 months, and visible lesions were biopsied annually. The primary outcome was progression to anal cancer in a time-to-event analysis.

RESULTS

Efficacy: During a median follow-up of roughly 26 months, the rate of progression to anal cancer was significantly lower in the treatment group than in the active-monitoring group.

Safety: Trial-related serious adverse events were uncommon.

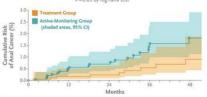
LIMITATIONS AND REMAINING QUESTIONS

- HSIL treatment did not prevent all cancers, which underscores the need for close follow-up and for more effective treatments.
- The results may not be generalizable to settings in which high-resolution anoscopy and treatment are performed by clinicians with less training and support.
- Additional research is warranted to improve screening algorithms for identifying anal HSIL.

Links: Full Article | NEJM Quick Take

Time to Progression to Anal Cancer

P=0.03 by log-rank test



Invasive Anal Cancer (Median Follow-up, 25.8 Mo)



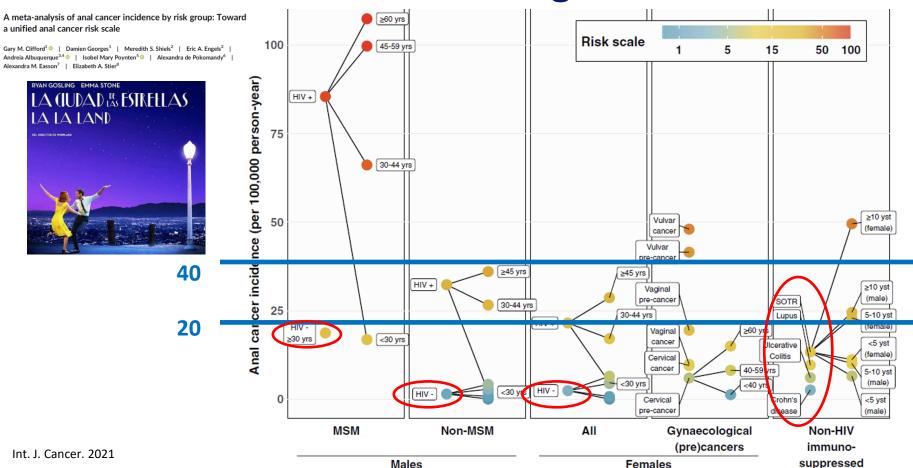
Trial-Related Serious Adverse Events



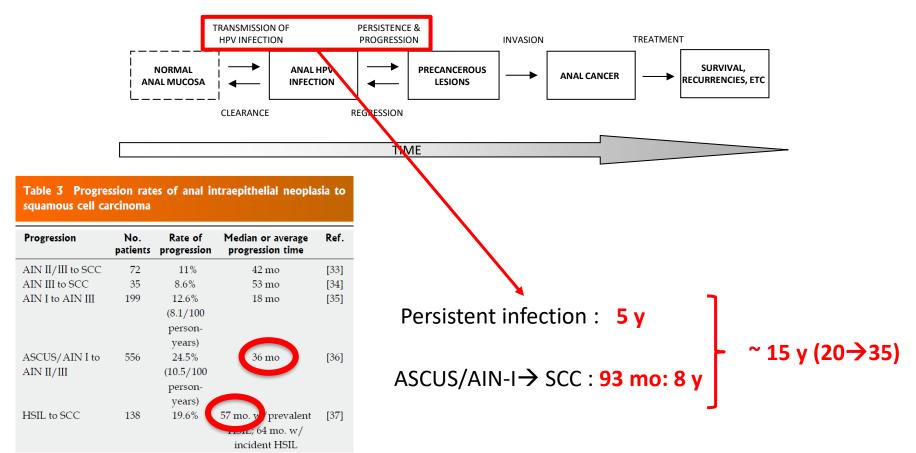
CONCLUSIONS

Among adults living with HIV who had anal HSIL, treatment of HSIL reduced the risk of progression to anal cancer, with a low incidence of serious adverse events.

Anal cancer screening: who



Anal cancer/HPV → natural history HIV-MSM→ 35 y

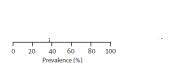


HPV anal infection in MSM prevalence& several hr-HPV

Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis



В	Sample size (n)		Prevalence of any high-risk HPV type (% [95% CI])
HIV-positive			
Conley et al (2010)26	379	-	88-7 (85-5-91-9)
Damay et al (2010)25	67	⊢∎∔	68-7 (57-6-79-8)
Milosevic et al (2010) ²⁸	20	ı ! ■	85.0 (69.4-100)
Berry et al (2009)30	32	⊢	71.9 (56.3-87.5)
Salit et al (2009)31	224	i -	79-5 (74-2-84-8)
Vajdic et al (2009) ²⁴	36	⊢ ■-	94-4 (87-0-100)
Chin-Hong et al (2008) ³⁴	38	⊢ ■	71.1 (56.6-85.5)
Piketty et al (2004)37	45	⊢ ■→	48-9 (34-3-63-5)
Lacey et al (1999) ⁴⁰	54	⊢ ■	85-2 (75-7-94-7)
Critchlow et al (1998) ⁴²	322	HIIIH	55-9 (50-5-61-3)
Friedman et al (1998)43	135	⊢■ -1	56-6 (47-9-64-7)
Overall	1352	\Diamond	73.5 (63.9-83.0);
		Y	l2=94·2%; p<0·000



RESEARCH ARTICLE

Open Access

Multiple human papillomavirus infections are highly prevalent in the anal canal of human immunodeficiency virus-positive men who have sex with men

Table 2 Summary of HPV

TOTAL (n)	HPV (n)	HPV16/HPV18* (N)	HPV16-HPV18 - (N)	HPV16+ (n)	HPV18+ (n)	HPV-
100% (324)	86.1% (279)	27.5% (89)	58.6% (190)	23.8% (77)**	7.4% (24)	13.9% (45)

Notes: *Patients were positive for HPV16 and/or HPV18. **There were 12 patients that were doubly infected by HPV type 16 and 18.

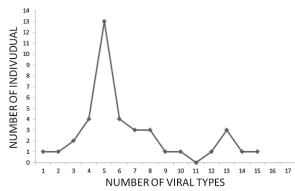


Figure 3 More than half of the patients have between 4 and 6 different viral types. The number of different viral types among individuals was datarminad as described in Mathods

Lancet Oncol 2012; 13: 487-500 BMC Infect Dis 2014

Anal cancer screening: MSM no HIV

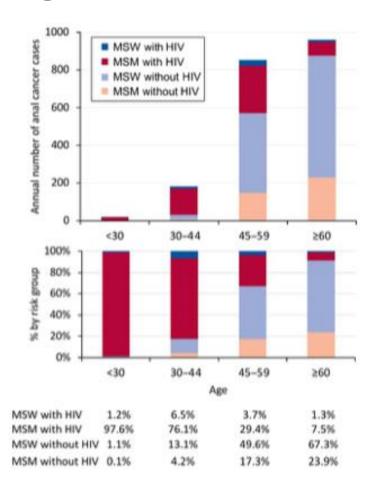
Human Papillomavirus-Associated Anal Cancer Incidence and Burden Among US Men, According to Sexual Orientation, Human Immunodeficiency Virus Status, and Age

Ashish A. Deshmukh,^{1,a} Haluk Damgacioglu,^{1,a} Damien Georges,² Kalyani Sonawane,^{1,a} and Gary M. Clifford²

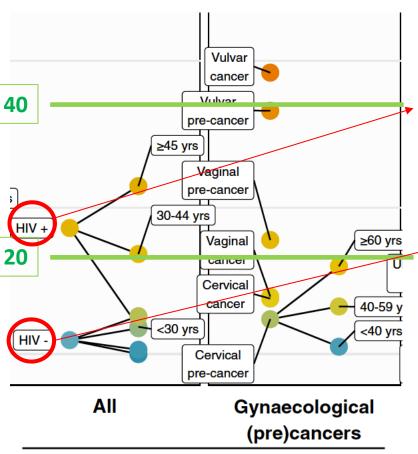
Age matters...

Anal cancer incidence (per 100 000) among MSM without HIV

- 1.4 (0.6 to 2.3) \rightarrow 30–44
- 17.6 (13.8–23.5) → 45–59
- 33.9 (28.3–42.3) \rightarrow ≥60 years



Anal cancer screening: Women & gynecological HPV



→ KEY POINT

 The absence of HPV-related cervical disease in the genital tract does not eliminate the need to screen for anal dysplasia in women with HIV who are ≥35 years old.



A ...L: -1 -

Natural History of Anal HPV Infection in Women Treated for Cervical Intraepithelial Neoplasia

Marta del Pino ^{1,2,*}, Isabel Matas ¹, Pilar Carrillo ¹, Cristina Martí ¹, Ariel Glickman ¹, Núria Carreras-Dieguez ^{1,3}, Lorena Marimon ^{3,4}, Adela Saco ^{3,4}, Natalia Rakislova ^{3,4}, Aureli Torné ^{1,2} and Jaume Ordi ^{3,4}

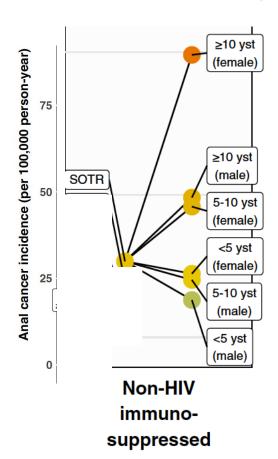
68 w non-HIV, treated HSIL/CIN

Persistent Anal HPV: 43%→ Anal HSIL: 34%

Females

Cancer 2023. 2021

Factors to consider: SOT time: matters



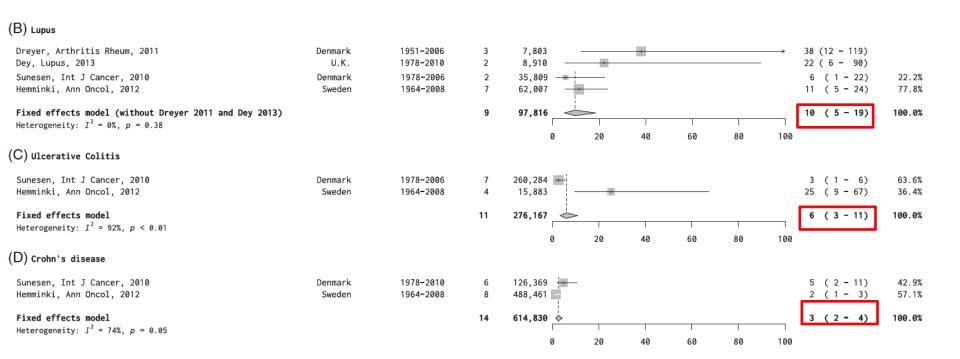
Consider YST and age for screening??

	Males			Females				
	Cases	Person-years	IR per 100 000 person-years (95% CI)	Cases	Person-years	IR per 100 000 person-years (95% CI)		
All	99	1 050 327	9.4 (7.7-11.5)	128	676 462	18.9 (15.8-22.5)		
Age group (y)								
<30	0	116 804	0.0 (0.0-3.2)	3	97 399	3.1 (0.6-9.0)		
30-44	9	194 004	4.6 (2.1-8.8)	19	145 121	13.1 (7.9-20.4)		
45-59	42	403 603	10.4 (7.5-14.1)	56	240 592	23.3 (17.6-30.2)		
≥60	48	335 916	14.3 (10.5-18.9)	50	193 350	25.9 (19.2-34.1)		
Years since tra	nspla t					•		
<5	3	657 746	6.5 (4.7-8.8)	46	412 509	11.2 (8.2-14.9)		
5-9	!8	278 346	10.1 (6.7-14.5)	42	183 231	22.9 (16.5-31.0)		
≥10	.8	114 235	24.5 (16.3-35.4)	40	80 722	49.6 (35.4-67.5)		

Abbreviations: CI, confidence interval; IR, incidence rate.

Anal cancer screening: others... IBD, LES...

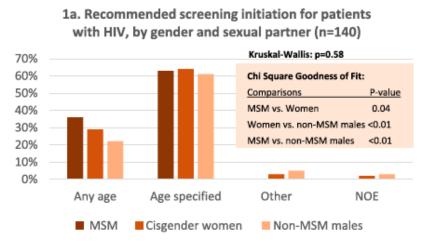
Few data to recommend routine screening?? → only if symptoms??

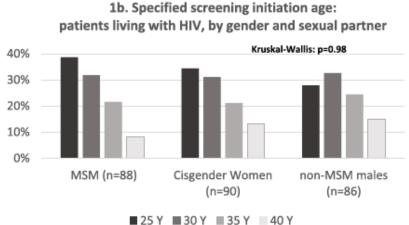


Preferences for anal cancer screening initiation age

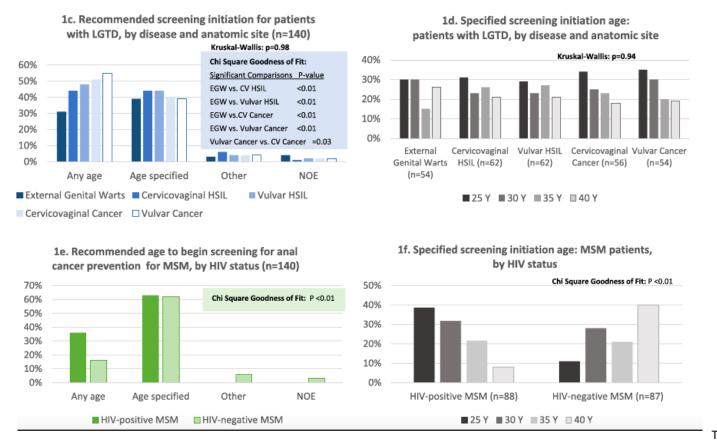
Provider preferences for anal cancer prevention screening: Results of the International Anal Neoplasia Society survey

Rosalyn E. Plotzker ^{a,*}, Gregory M. Barnell ^b, Dorothy J. Wiley ^c, Elizabeth A. Stier ^d, Naomi Jay ^a

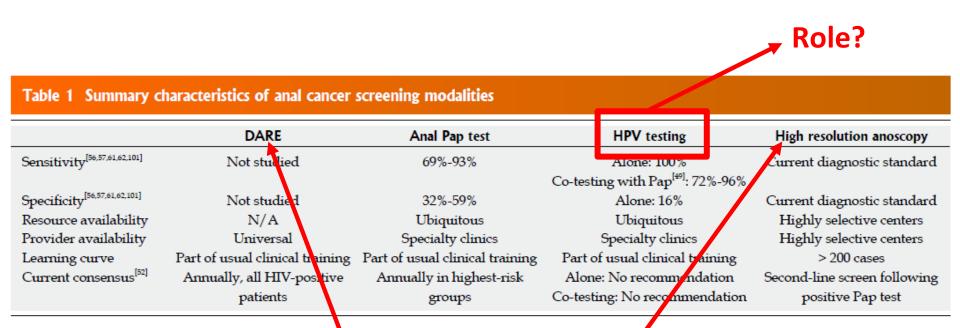




Preferences for anal cancer screening initiation age



Anal cancer screening/follow up in low risk SCCA population



DARE: Digital anorectal exam; HPV: Human papillom, virus; N/A: Not applicable; HIV: Human immunodeficiency virus; Pap: Papanicolaou.

Anal cancer

s HSIL

always DARE + anamnesis of symptoms

Populations & Factors to consider... (start)

• MSM +/- HIV

HPV infection& natural history

- Women +/- HIV
 Immunodepression
- SOT

RAI&sexual partners

Others

- Gynecologic HPV disease
- Vaccination

Factors to consider: HPV16?







Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide

Laia Alemany^{1,2}, Maëlie Saunier¹, Isabel Alvarado-Calvero¹, Beatriz Quiros¹, Ingres Salmeron¹, Hai-Rim Shin⁴, Edyla C. Pirog², Winti Guilmer², Gustavo Hemanders Sauer², Ana Felk², Omar Clawer³, Belen Lloveras², Elena Kasamatsui¹⁰, Marc T. Goodman^{1,1,2}, Brenda Y. Hemander^{1,1}, Jan Laco¹¹, Leopoldo Tinoco^{1,2}, Daan T. Geraets⁴, Chafies F. Lynch⁵, Yadori Manghes³, Manlo Poljaki², Robert Jach^{1,2}, Goop Yeage², Christine Clawei², Cathy Midaye²1, JoEllen Klaustermeier^{1,2}, Antonio Cubillai⁹, Xavier Castellsague³, Ignacio G. Brav³, Michael Pawilia^{2,2}, William G. Quint⁴, Mulla Müllor^{2,2}, Frances X. Bosch¹, and Silvia de Saniose^{5,4} on behalf of the HPV WOP Study Group

Anal HPV16 → 75-80%

Persistent anal HPV16: 25-35%

Table 3. HPV type specific relative contribution among HPV DNA-positive AIN 2/3 and invasive anal cancer cases

	AIN 2/3 (HPV+, n=41)			Invasive anal cancer (HPV+, n=438)							
	Single		Single + multiple ¹		Si	Single		Single + multiple ¹		Relative contribution ratio (cancer:AIN) ²	
HPV type	n	%	n	%	n	%	n	%	Ratio	95% CI	
HPV6	-	-	-	-	8	(1.8)	8	(1.8)	-	-	
HPV11	2	(4.9)	2	(5.0)	4	(0.9)	5	(1.1)	0.21	(0.04-1.06)	
HPV16	27	(65.9)	31	(75.4)	332	(75.8)	354	(80.7)	1.07	(0.89-1.28	
HPV18	-	-	-	-	15	(3.4)	16	(3.6)	-	-	
HPV30	-	-	-	-	1	(0.2)	1	(0.2)	-	-	
HPV31	1	(2.4)	2	(3.7)	5	(1.1)	8	(1.9)	0.51	(0.09-2.83)	
HPV33	-	-	-	-	10	(2.3)	12	(2.7)	-	-	
HPV35	-	-	-	-	7	(1.6)	7	(1.6)	-	-	
HPV39	-	-	-	-	1	(0.2)	2	(0.5)	-	-	
HPV42	-	-	-	-	1	(0.2)	1	(0.2)	-	-	
HPV45	1	(2.4)	1	(2.4)	4	(0.9)	4	(0.9)	0.37	(0.04-3.27)	
HPV51	1	(2.4)	2	(3.7)	-	-	-	-	-	-	
HPV52	-	-	-	-	2	(0.5)	3	(0.7)	-	-	
HPV56	-	-	-	-	2	(0.5)	2	(0.5)	-	-	
HPV58	-	-	-	-	8	(1.8)	8	(1.8)	-	-	
HPV59	-	-	-	-	1	(0.2)	2	(0.5)	-	-	
HPV67	-	-	-	-	1	(0.2)	1	(0.2)	-	-	
HPV68	-	-	-	-	1	(0.2)	1	(0.3)	-	-	
HPV97	-	-	-	-	1	(0.2)	1	(0.2)			
HPV undetermined	-	-	-	-	2	(0.5)	2	(0.5)	-	-	
Multiple infections	9	(22.0)	-	-	32	(7.3)	-	-	0.33	(0.17-0.65)	

Factors to consider: Receptive anal intercourse?

RAI → ↑↑Risk for anal HPV infection

Anal HPV infection is not always associated with RAI

♂10 %

♀27 %

- Passive anal infection in sexual intercourse
- Front-to-back & dabbing wiping behaviour post-toilet

RAI→ consider in screening??

Guidelines: when stop cervical cancer screening



TABLE 1. Cervical cancer screening and surveillance recommendations

		Guideline group, yr of recommendation				
Population	Screening specifics	USPSTF, 2018	ACOG, 2016	ACS, 2020		
Persons at average risk	Age to start screening Age to end screening	21 yrs 65 yrs	21 yrs 65 yrs	25 yrs 65 yrs		

If three consecutive negative cytology tests or two negative cytology plus HPV tests or two negative HPV tests (ACS) with the most recent within the previous 5 yrs and no abnormal tests within the previous 10 yrs (ACS) and no CIN 2 or CIN 3 within the previous 25 yrs

Persons with an immunocompromising medical condition[†] (e.g., HIV infection or solid organ transplantation)

Age to start screening

No specific recommendation Within 1 vr of onset of sexual activity or, if already sexually active. within the first year after HIV or other immunocompromising medical condition diagnosis but no later than age 21 yrs None; lifelong screening recommended

Age to end screening



No data

Guidelines: when stop anal cancer screening



STOP

Clinicians should discontinue screening for anal cancer when life expectancy is less than 10 years and in individuals
with 2 consecutive negative anal cytology specimens who are not currently sexually active. (B3)

Anal cancer/HPV → natural history HIV-MSM. stop

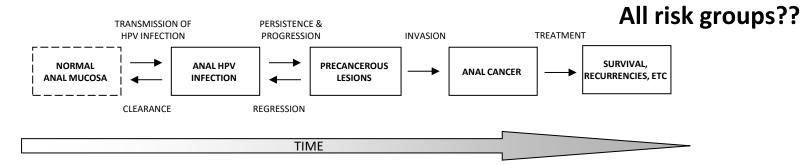


Table 3 Progression rates of anal intraepithelial neoplasia to squamous cell carcinoma

Progression	No. patients	Rate of progression	Median or average progression time	Ref.
AIN II/III to SCC	72	11%	42 mo	[33]
AIN III to SCC	35	8.6%	53 mo	[34]
AIN I to AIN III	199	12.6%	18 mo	[35]
		(8.1/100)		
		person-		
		years)		
ASCUS/AIN I to	556	24.5%	36 mo	[36]
AIN II/III		(10.5/100)		
		person-		
		years)		
HSIL to SCC	138	19.6%	57 mo. v prevalent	[37]
			1101L; 64 mo. w/	
			incident HSIL	

according to life expectancy?

ASCUS/AINI→ SCC : 93 mo: ~ 8 y

Populations & Factors to consider... (stop)

• MSM +/- HIV

HPV infection

- Women +/- HIV
- SOT
- Others

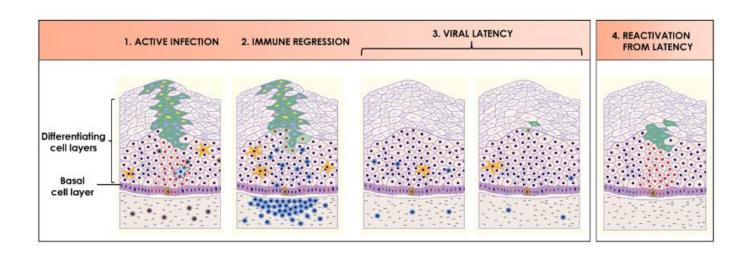
- Immunodepression → while it lasts...??
- RAI&new sexual partners →...
- Gynecologic HPV disease →??
- Vaccination →??

HPV clearance: ID → no presence is enough?? Reactivation from latency!!

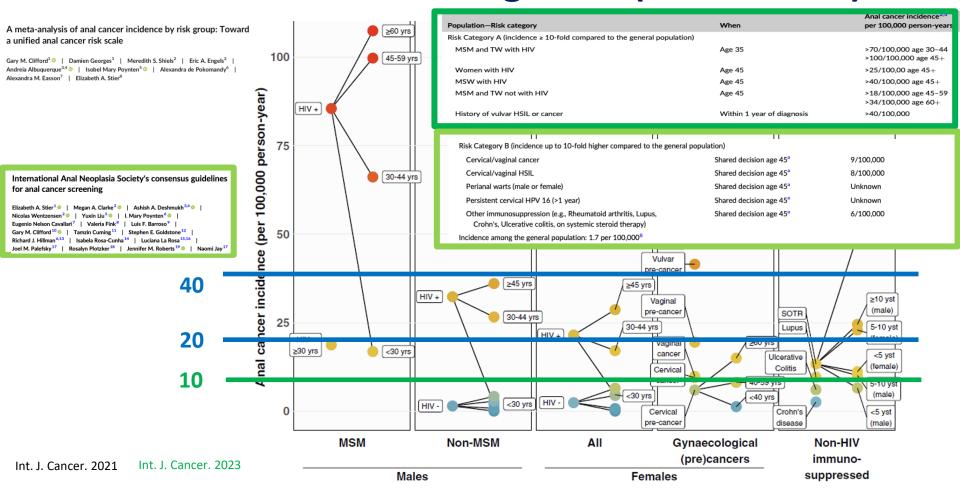
Review

The Biology and Life-Cycle of Human Papillomaviruses

John Doorbar^{a,*}, Wim Quint^b, Lawrence Banks^c, Ignacio G. Bravo^d, Mark Stoler^e, Tom R. Broker^f, Margaret A. Stanley^g



Anal cancer screening: who (conclusions)



Conclusions

- We need to generate more data to change what guidelines say: start&stop screening and type of screening)
- Screening in MSM-HIV should start at 35 y
- Screening start in other ID (SOT, QT,...) will depend on age/IS treatment initio (and probably type of IS treatment)
- Screening stop will depend on HPV persistence infection
- HPV vaccination (probably) will change...everything

Muchas gracias