Seguimiento: qué hacer con los resultados. Algoritmo de manejo.

Jorge N. García
Servei M.Infeccioses
Hospital Vall d'Hebron
19/10/2022

CRIBADO DISPLASIA ANAL: Controversias

1) ¿Debemos hacer cribado?

2) Si la respuesta es sí… ¿Cómo debemos hacer cribado?

- ¿A quién debemos hacerlo?
- Herramientas de cribado
  - Citología anal
  - Anoscopia de alta resolución (AAR)
  - Determinación VPH
- ¿Cómo debemos hacerlo?
- ¿Cada cuánto debemos hacerlo?

Última consulta 08/10/22

GUIA	RECOMENDACION	GRADO
NY State AIDS Inst 2022	DARE a todos los pacientes Citología anal anual y AAR si alterado en **VIH+ >35a**: - **MSM y mujeres trans** - Mujeres cis y hombres trans	MSM A III Trans W A III Trans M BIII Cis W BIII
HIVMA/IDSA 2020	DARE anual. Citología anal y AAR si alterado en **Personas** VIH+: - Con historia de SAr - Citología genital anómala - Antecedentes de condilomas anogenitales	Recom. débil, evidencia moderada
GESIDA 2019	Citología anal anual y AAR si alterado en VIH+: **MSM**, mujeres CIN2+, o condilomas. Se podría valorar en HSM con condilomas.	B II-III
EACS 2022	DARE +/- citología anal (1-3 años) en pacientes HIV + **MSM y personas con HPV displasia**, y en caso de alteraciones, AAR	Opinión expertos
DHHS 2018	DARE Respecto citologia+/-AAR en personas VIH no recomendación nacional, algunos especialistas lo recomiendan Si cito alterada derivar a AAR+biopsia	DARE BIII Cito+/-AAR CIII
BHIVA 2014	The BHIVA guidelines for HIV-associated malignancies 2014 have been **archived**. Instead, more recent, evidence-based, pan-European guidelines are available.	

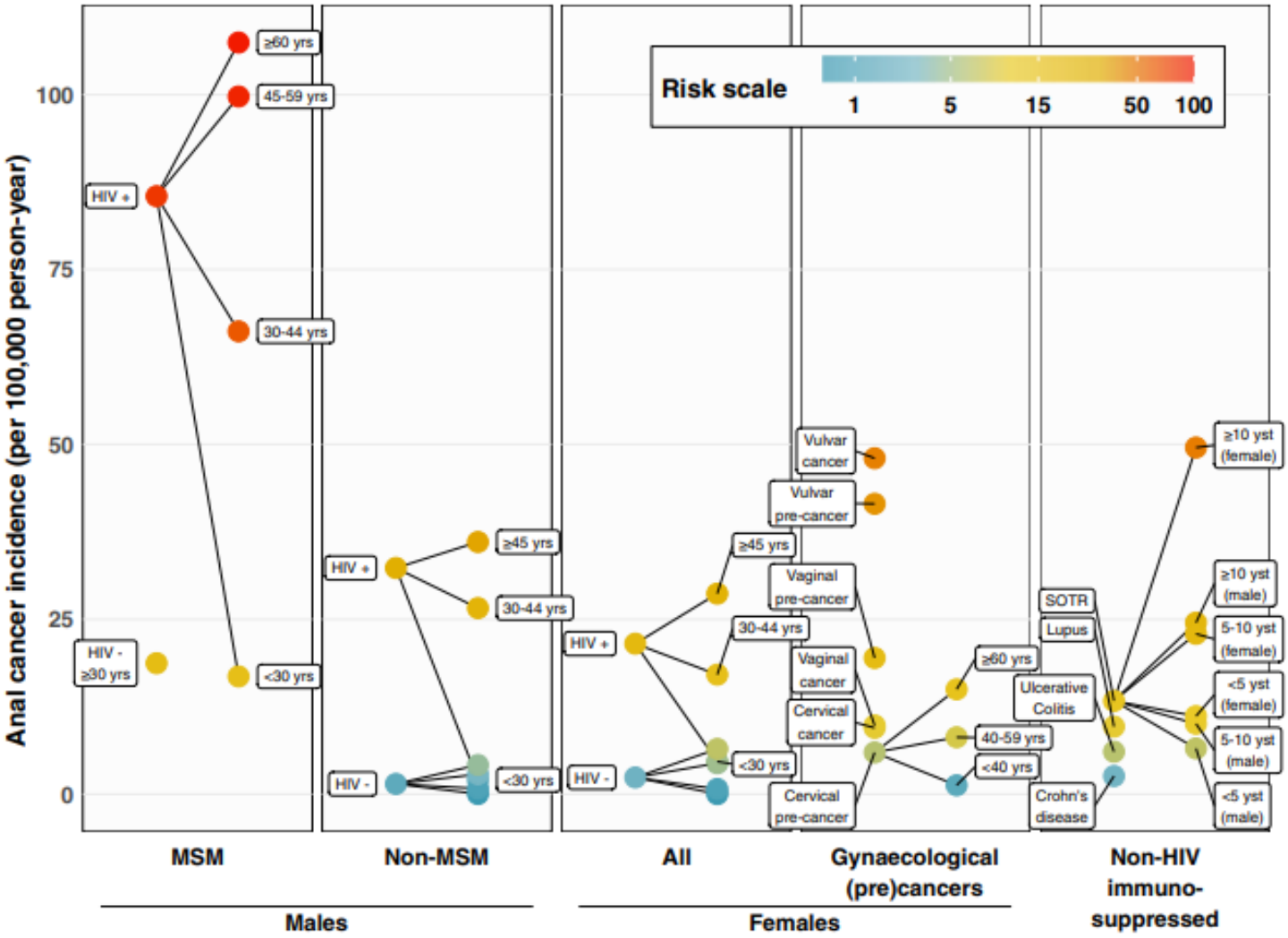
¿Qué nos dicen las guías NO-VIH?

GUIDELINES Organization and year issued	RECOMMENDATIONS	EVIDENCE
ASCRS 2018[13]	Anal cytology may be considered in high-risk population: PLWH, MSM, history of cervical dysplasia.	Weak recommendation. Moderate quality evidence.
	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.	
ASTIDCP 2019[14]	Anal cytology in solid-organ transplant recipients if history of receptive anal intercourse, history of cervical dysplasia.	Weak recommendation. Low quality evidence.
	HRA if abnormal cytology.	
	Normal cytology repeated every 1-3 years.	

GUIDELINES	RECOMMENDATIONS	EVIDENCE
ESMO 2021	No recommendations	---
ESSO 2015	No recommendations	---

https://www.hpvworld.com/articles/current-guidelines-recommendations-for-anal-hpv-related-disease-screening/

Tener en cuenta…



Clifford GM et al. Int J Cancer. 2021 Jan 1;148(1):38-47

ANCHOR Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

J.M. Palefsky, J.Y. Lee, N. Jay, S.E. Goldstone, T.M. Darragh, H.A. Dunlevy, I. Rosa-Cunha, A. Arons, J.C. Pugliese, D. Vena, J.A. Sparano, T.J. Wilkin, G. Bucher, E.A. Stier, M. Tirado Gomez, L. Flowers, L.F. Barroso, R.T. Mitsuyasu, S.Y. Lensing, J. Logan, D.M. Aboulafia, J.T. Schouten, J. de la Ossa, R. Levine, J.D. Korman, M. Hagensee, T.M. Atkinson, M.H. Einstein, B.M. Cracchiolo, D. Wiley, G.B. Ellsworth, C. Brickman, and J.M. Berry-Lawhorn, for the ANCHOR Investigators Group*

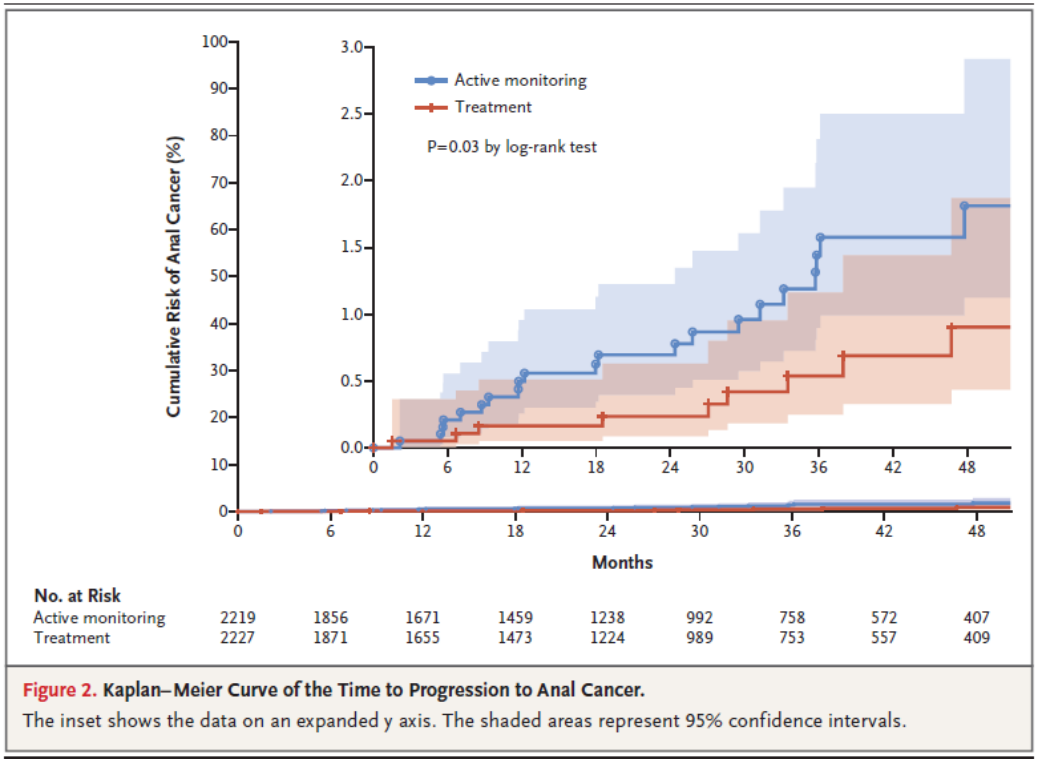


Figure 2. Kaplan–Meier Curve of the Time to Progression to Anal Cancer.
The inset shows the data on an expanded y axis. The shaded areas represent 95% confidence intervals.

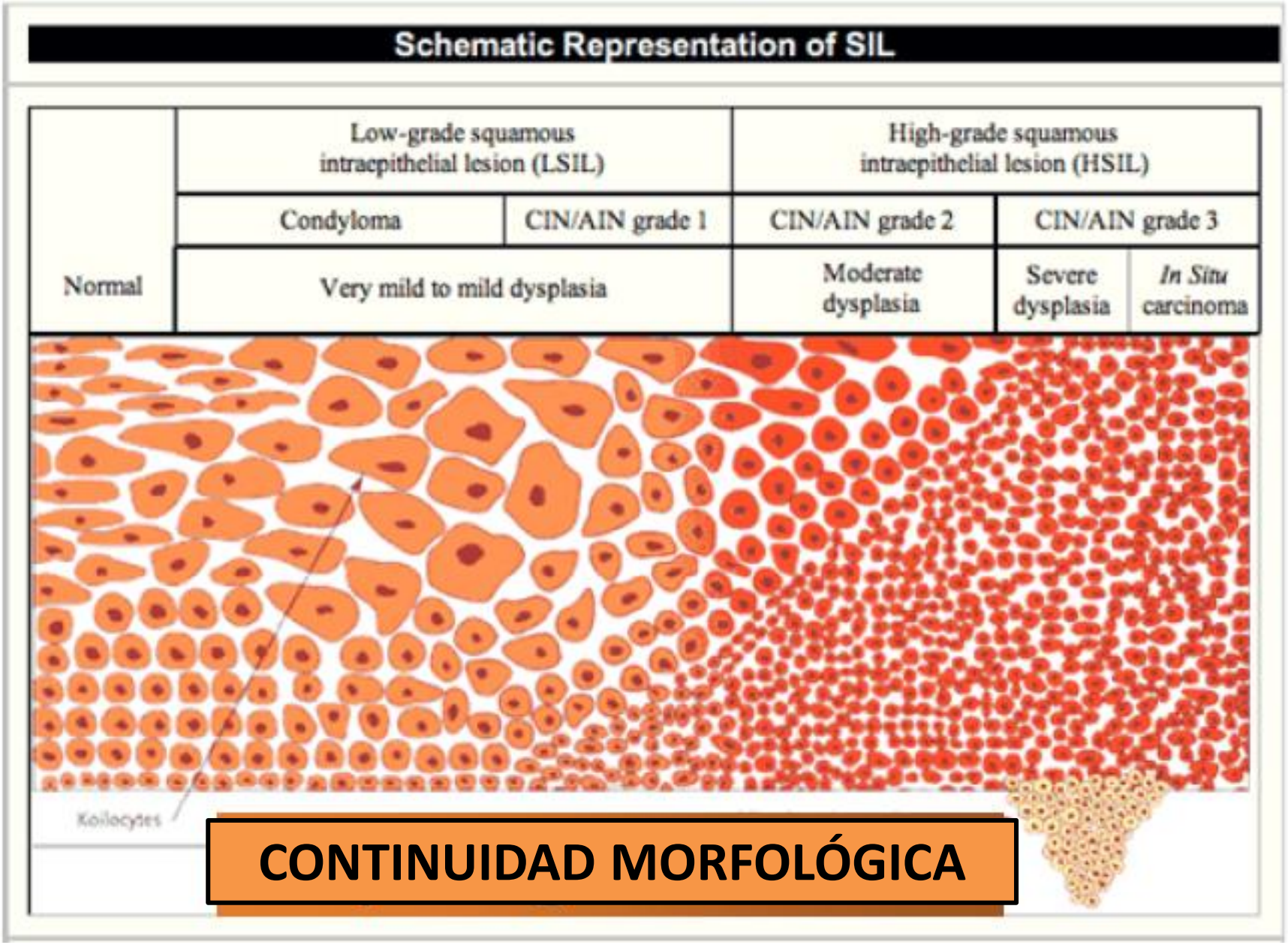
Palefsky JM et al. N Engl J Med 2022;386:2273-82.

Cribado de Displasia y cáncer anal.

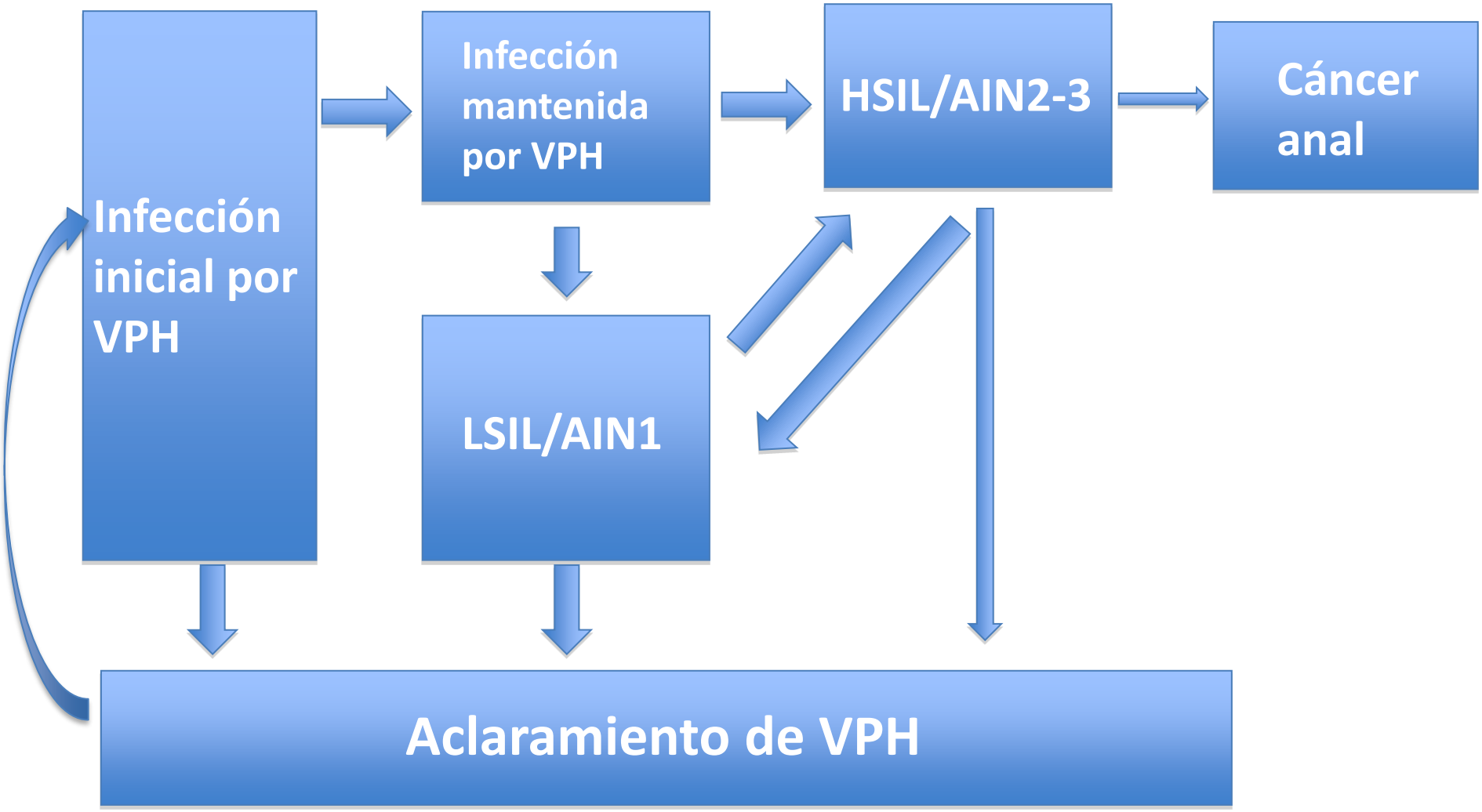
	Sólo Citología (AAR si cito alterada)	Sólo AAR	Cito+AAR (Simultánea)	DARE
Ventajas	Sencilla, Barata No entrenamiento S 90%	S 85% E 40% (Coste efectiva)	Aumenta S y E	Estrategia de mínimos.
Desventajas	E 33% HSIL con cito normal.	Compleja Explorador depend. Citología como control	Mayor coste Entrenamiento Incomodidad paciente	**No es un programa de cribado de displasia.**

Burgos J, Curran A. Enferm Infecc Microbiol Clin. 2016 Aug-Sep;34(7):397-9.

Tener en cuenta…



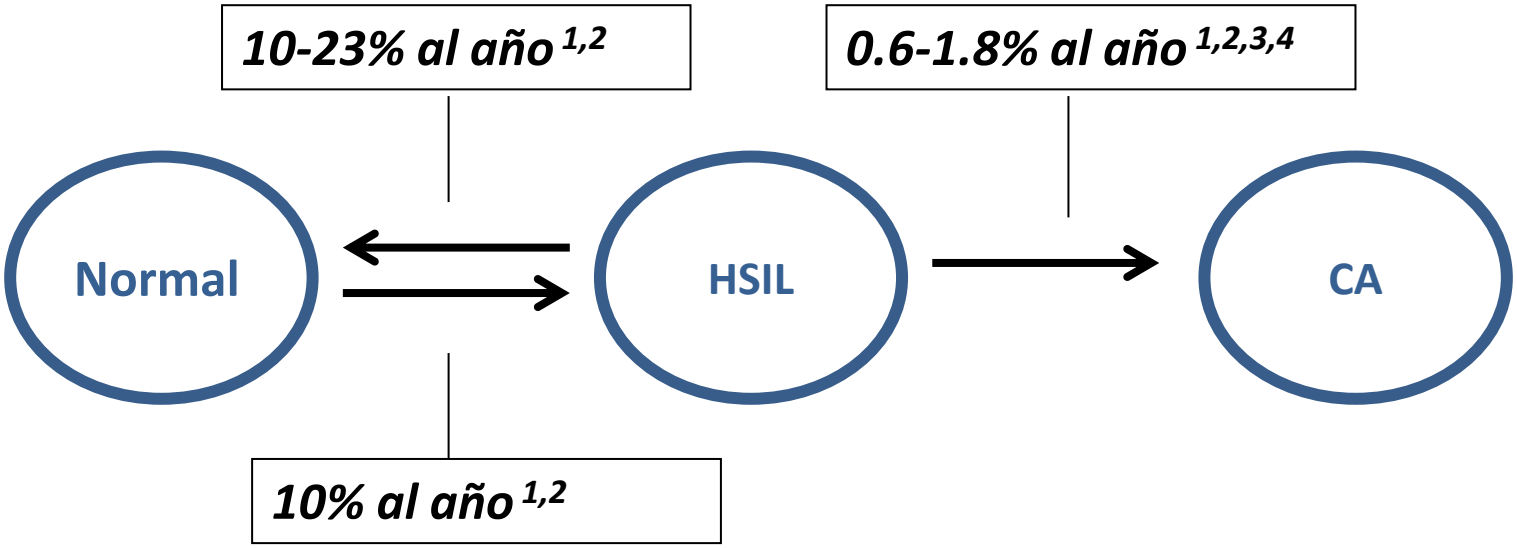
Tener en cuenta…



Diferencias con el cérvix

- **En el cérvix:**
  - Observación “fácil” de toda la zona en riesgo
  - Diferencias anatómicas (cito más fiable)
  - Marcadores predictores de riesgo
  - Tratamiento que permite eliminar TODA la zona de riesgo sin secuelas
  - Años de experiencia/seguimiento
    - Progresión de CIN3 a cáncer demostrada y cuantificable
  - Poblaciones a menudo NO comparables

HISTORIA NATURAL DEL VPH ANAL



1. McCredie M et al. Lancet Oncol 2008; 9:425-34. 2. Tong W et al. AIDS 2013; 27: 2233-43. 3. Dalla Pria et al. AIDS. 2014 ;28:861-7. 4. Palefsky JM et al. N Engl J Med 2022;386:2273-82.

Limitaciones estudios

- **Tong et al.** Progresión a HSIL 7.4/100 personas-año [19/152 casos (12.5%)]. Regresión espontánea a LSIL 24/101 (23.8%) **
  - Estudio retrospectivo. Seguimiento medio de 1.1 años
  - Discusión individual opción tratar o observar si HGAIN: sesgo selección.
  - Sólo 56% pacientes incluidos tienen >1 HRA
  - Mitad pacientes VIH -vo estudio vacuna VPH (edad 16-26 años, menos de 5 parejas)
  - Criterio regresión: AIN3 regresado si biopsia menor grado o citologia normal o HRA visualmente normal

CRIBADO DISPLASIA ANAL

ESTRATEGIA SECUENCIAL

Citología anal

Accuracy of Anal Cytology for Diagnostic of Precursor Lesions of Anal Cancer: Systematic Review and Meta-analysis

TABLE 2. Accuracy of anal cytology for detection of anal intraepithelial neoplasia

Outcomes	*AIN2+ vs normal, % (95% CI)*	*AIN2+ vs AIN1−, % (95% CI)*	*AIN1+ vs normal, % (95% CI)*
All subjects			
Sensitivity	85.5 (83.3–87.6)	85.0 (82.0–87.0)	78.3 (76.7–79.7)
Specificity	51.5 (48.8–54.2)	43.2 (41.4–45.1)	53.3 (50.8–55.8)
DOR	5.499 (4.034–7.496)	3.410 (2.369–4.909)	3.715 (2.756–5.009)
AUC	0.79 (0.74–0.84)	0.72 (0.63–0.81)	0.73 (0.69–0.79)
MSM HIV+			
Sensitivity	86.5 (83.0–89.5)	85.4 (81.8–88.5)	79.9 (77.4–82.3)
Specificity	49.4 (45.2–53.6)	37.7 (34.9–40.6)	49.4 (45.3–53.5)
DOR	6.355 (3.988–10.128)	3.569 (2.585–4.927)	4.397 (2.819–6.857)
AUC	0.87 (0.77–0.97)	0.83 (0.70–0.96)	0.80 (0.70–0.91)
All MSM			
Sensitivity	90.8 (87.7–93.4)	90.8 (87.7–93.4)	85.7 (83.4–87.7)
Specificity	28.6 (24.2–33.4)	35.5 (3.22–38.8)	38.0 (33.8–42.4)
DOR	3.806 (2.264–6.397)	6.788 (2.149–21.434)	3.064 (1.695–5.540)
AUC	0.49 (0.15–0.83)	0.92 (0.80–1.00)	0.81 (0.67–0.94)
All HIV+			
Sensitivity	88.2 (81.3–93.2)	87.4 (80.8–92.4)	78.4 (73.8–82.5)
Specificity	45.3 (39.0–51.8)	35.4 (31.3–39.8)	45.3 (39.0–51.8)
DOR	4.967 (2.400–10.278)	2.360 (1.202–4.633)	2.165 (1.032–4.540)
AUC	0.79 (0.68–0.90)	0.71 (0.58–0.85)	0.65 (0.58–0.85)

Gonçalves J et al. Dis Colon Rectum. 2019 Jan;62(1):112-120.

Peligros de la citología…

TABLE 2. Histology diagnosis as a function of cytology and HIV status in 847 MSM having HRA

	Histology diagnosis				
Cytology	*Benign*	*LGAIN*	*HGAIN*	*SCC*	*Total*
HIV negative					
Benign	56 (50.5)	38 (34.2)	17 (15.3)	0 (0)	111 (25.0)
ASCUS	108 (45.4)	66 (27.7)	64 (26.9)	0 (0)	238 (53.6)
ASC-H	1 (20)	3 (60)	1 (20)	0 (0)	5 (1.1)
LSIL	6 (7.0)	42 (48.8)	38 (44.2)	0 (0)	86 (19.4)
HSIL	0 (0)	0 (0)	4 (100)	0 (0)	4 (0.9)
Total	171 (38.5)	149 (33.5)	124 (28.0)	0 (0)	444
HIV positive					
Benign	32 (54.2)	10 (17.0)	17 (28.8)	0 (0)	59 (14.6)
ASCUS	57 (35.6)	41 (25.6)	62 (38.8)	0 (0)	160 (39.7)
ASC-H	0 (0)	0 (0)	8 (100)	0 (0)	8 (2.0)
LSIL	14 (8.8)	55 (34.3)	89 (55.6)	2 (1.3)	160 (39.7)
HSIL	0 (0)	1 (6.3)	15 (93.7)	0 (0)	16 (4.0)
Total	103 (25.6)	107 (26.5)	191 (47.4)	2 (0.5)	403

Dalla Pria A, et Al:
27% HSIL tenían citologías normales.

Swedish KA et Al. Dis Colon Rectum. 2011 Aug;54(8):1003-7. Dalla Pria A et Al. AIDS. 2014 Mar 27;28(6):861-7.

Citología anal

Aporta algo mirar VPH para decidir si HRA?

-Rationale: enviar para AAR ASC + VPH alto riesgo

-Despistaje VPH alta sensibilidad pero baja especificidad debido a alta prevalencia y múltiples tipos de VPH en canal anal (especialmente en MSM VIH+)

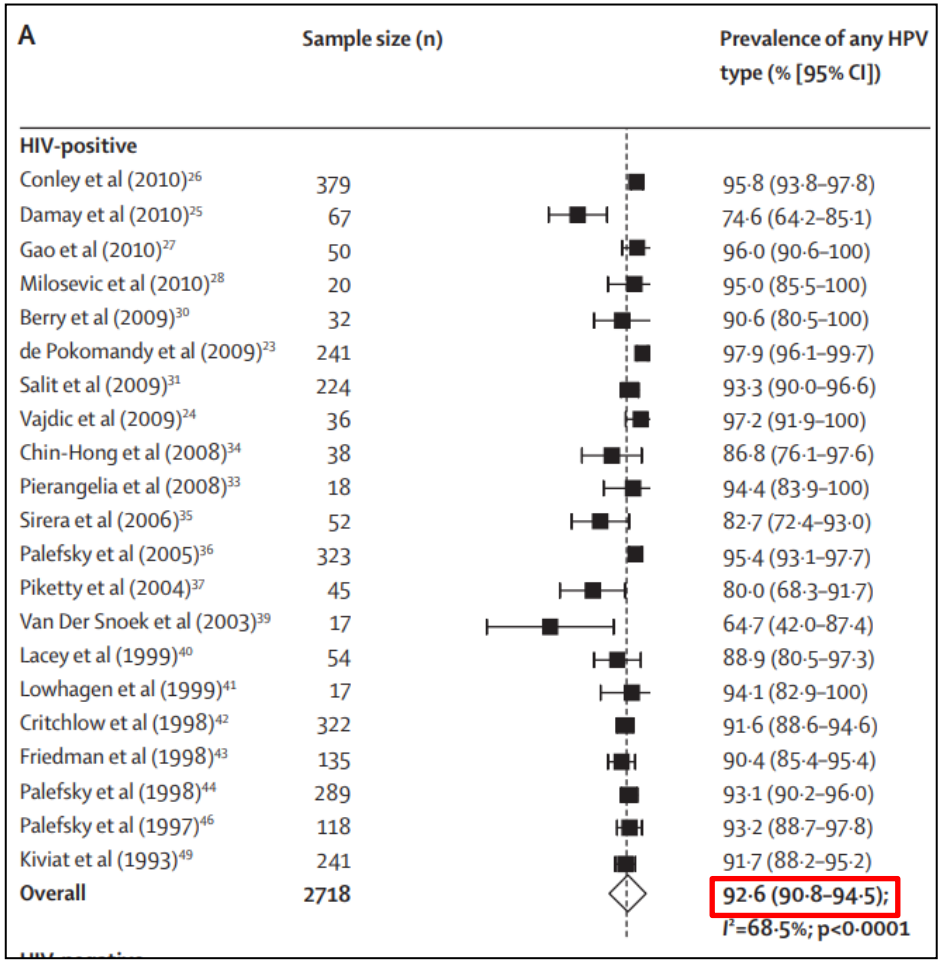
-Por tanto, por el momento probablemente aumenta el coste con baja rentabilidad respecto a citología

-Puede ser útil para estudios epidemiológicos

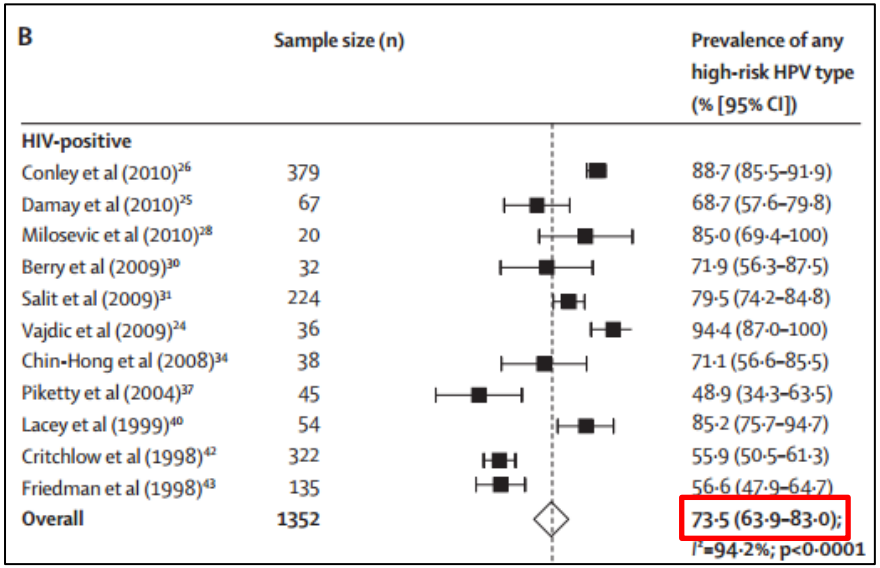
-Pre-vacunación??

Cachay E et al. AIDS Rev 2013; 15: 122-33.

HR-HPV en HSH.



Prevalencia HPV alto riesgo.



Machaleck DA et al. Lancet Oncol 2012; 13: 487-500

High Prevalence of Anal Human Papillomavirus–Associated Cancer Precursors in a Contemporary Cohort of Asymptomatic HIV-Infected Women

Table 3. Anal Cytology, High-Resolution Anoscopy, Anal Histology, and Human Papillomavirus Results in HIV-Infected Women (n = 171)

Characteristic	No.	%
Anal HPV (n = 171)		
HR-HPV infection	99	57.9
HPV-16 alone or with other genotypes	29	17.0
Infection with HR-HPV type other than 16	91	53.2
Multiple HPV infection[a]	81	47.4
Anal cytology (by central review) (n = 150)		
Negative	106	70.7
ASC-US/LSIL	28	18.7
ASC-H/HSIL	15	10.0
ASCC	1	0.6
Unsatisfactory specimen	21	
HRA (n = 169)		
Identification of acetowhite areas	69	40.8
Anal histology (n = 64)		
Benign	35	54.7
Low-grade AIN	18	28.1
High-grade AIN	10	15.6
ASCC	1	1.6

Results. Among the 171 enrolled women, median age was 47.3 years and 98% were receiving combination antiretroviral therapy. Median CD4+ count was 655 cells/µL and HIV load was <50 copies/mL in 89% of subjects. High-grade anal intraepithelial neoplasia or worse (**HG-AIN+**) was diagnosed in **12.9%** (n = 21). In multivariable analysis, a history of cervical squamous intraepithelial lesion (odds ratio [OR], 4.2; 95% confidence interval [CI], 1.1–16.4) and anal HPV-16 infection (OR, 16.1; 95% CI, 5.4–48.3) was associated with increased risk of HG-AIN+. Abnormal anal cytology and HPV-16 infection performed best as a screening strategy for HG-AIN+ histology, with positive likelihood ratios of 3.4 (95% CI, 2.3–5.1) and 4.7 (95% CI, 2.5–8.7) and negative likelihood ratios of 0.2 (95% CI, .07–.8) and 0.4 (95% CI, .2–.9), respectively.

	HGAIN	
	S	E
HR-HPV	91%	44%
HPV 16	64%	86%

Heard I et al. Clin Infect Dis 2015; 60: 1559-68

The role of oncogenic HPV determination for diagnosis of high-grade anal intraepithelial neoplasia in HIV-infected MSM.

TABLE 2. Tests characteristics for the detection of high-grade anal intraepithelial neoplasia (HGAIN) at first screening visits

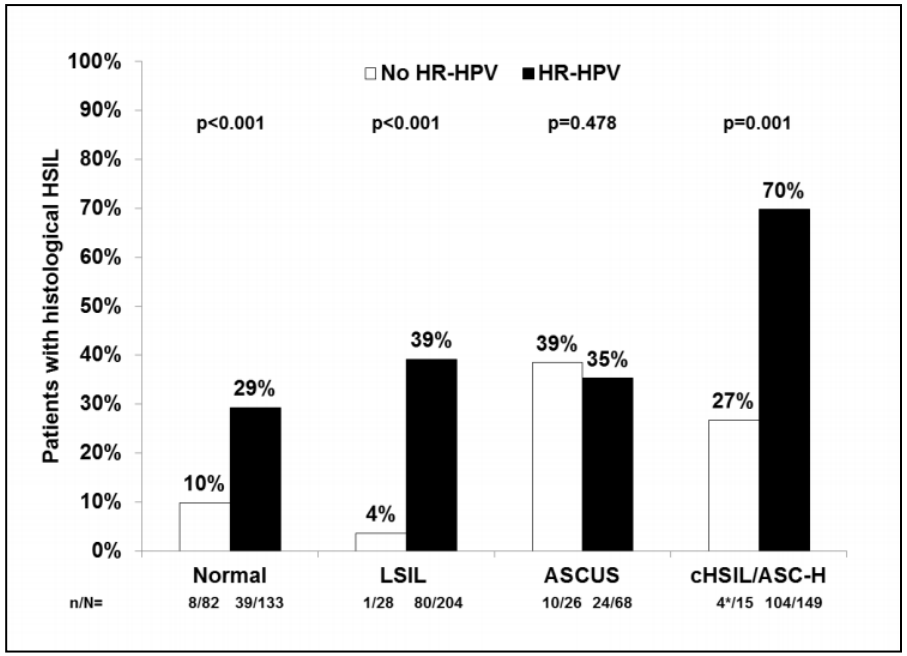
Screening Tests	Sensitivity		Specificity		Positive predictive value		Negative predictive value		LPR	LNR
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)		
Anal cytology	74/ 83	89.2 (80.7-94.2)	252/ 570	44.2 (40.2-48.2)	74/ 392	18.9 (15.3-23)	252/ 261	95.5 (93.6-98.2)	1.598	0.245
Oncogenic HPV detection	70/ 77	90.9 (82-86.8)	121/ 497	24.4 (20.8-28.3)	70/ 446	15.7 (12.6-19.4)	121/ 128	94.5 (89.1-97.3)	1.202	0.373
16 or/and 18 HPV detection	43/ 77	55.8 (44.7-66.4)	185/ 497	62.8 (58.4-66.9)	185/ 228	18.9 (14.3-24.4)	312/ 346	90.2 (86.6-92.9)	1.500	0.703
Anal cytology and/or oncogenic HPV detection	75/ 77	97.4 (91-99.3)	69/ 494	14 (11.2-17.3)	75/ 500	15 (12.1-18.4)	69/ 71	97.2 (90.3-99.2)	1.132	0.186
Oncogenic HPV detection in ASCUS cytology	21/ 23	91.3 (73.2-97.6)	39/ 138	28.3 (21.4-36.3)	21/ 120	17.5 (11.7- 25.3)	39/ 41	95.1 (83.9-98.6)	1.273	0.308
Oncogenic HPV detection in LSIL cytology	30/ 32	93.7 (79.8-98.3)	13/ 138	9.4 (5.6-15.4)	30/ 155	19.3 (13.9-26.2)	13/ 15	86.7 (62,1-96.3)	1,035	0.663

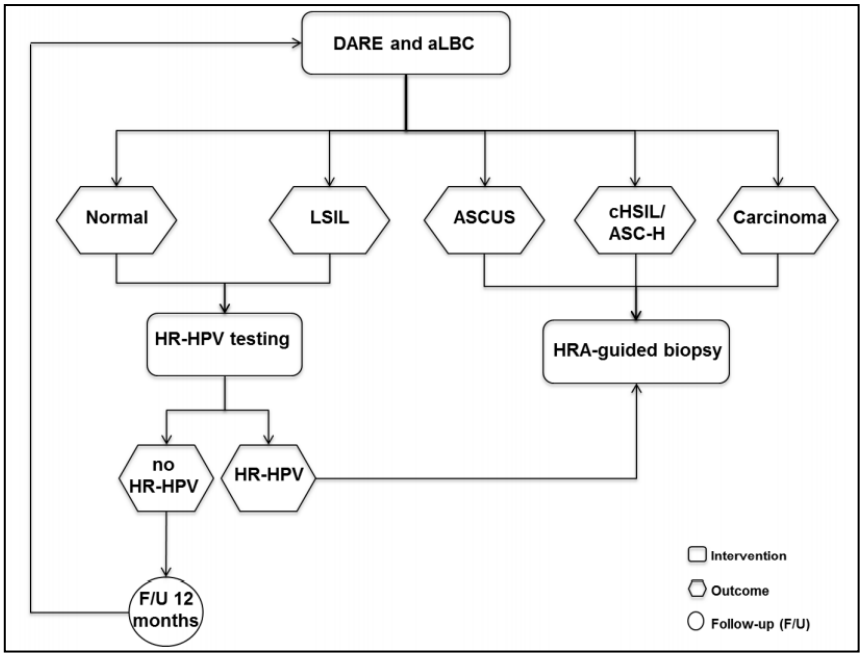
CI, Confidence interval; HPV, Human-papillomavirus; HRA, High-resolution anoscopy; LPR, Likelihood positive ratio; LNR, Likelihood negative ratio

HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82.

Burgos J, et Al. AIDS. 2017 Oct 23;31(16):2227-2233.

High-risk human papilloma virus testing improves diagnostic performance to predict moderate-to-high grade anal intraepithelial neoplasia in HIV-infected men who have sex with men in low-to-absent cytological abnormalities.





Cito + HR-HPV	S	E	VPP	VPN
Normal	83%	44,1%	29,3%	90,2%
LSIL	98,8%	17,9%	39,2%	96,4%

HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59.

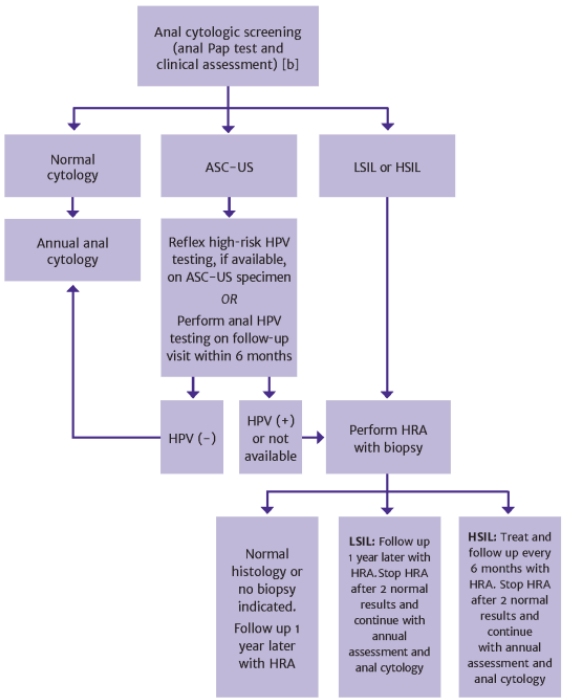
Viciana P, et Al. Clin Infect Dis. 2019 Feb 16.

NYSDOH

For patients with anal cytology results indicating ASC-US, clinicians should perform HPV testing (A2):

- If HPV testing is available and results are negative, repeat anal cytology in 1 year. (A3)
- If HPV testing is available but reflex testing is not available, perform HPV test at follow-up within 6 months. (B2)
- If positive for high-risk HPV or if HPV testing is not available, refer for HRA. (B2)

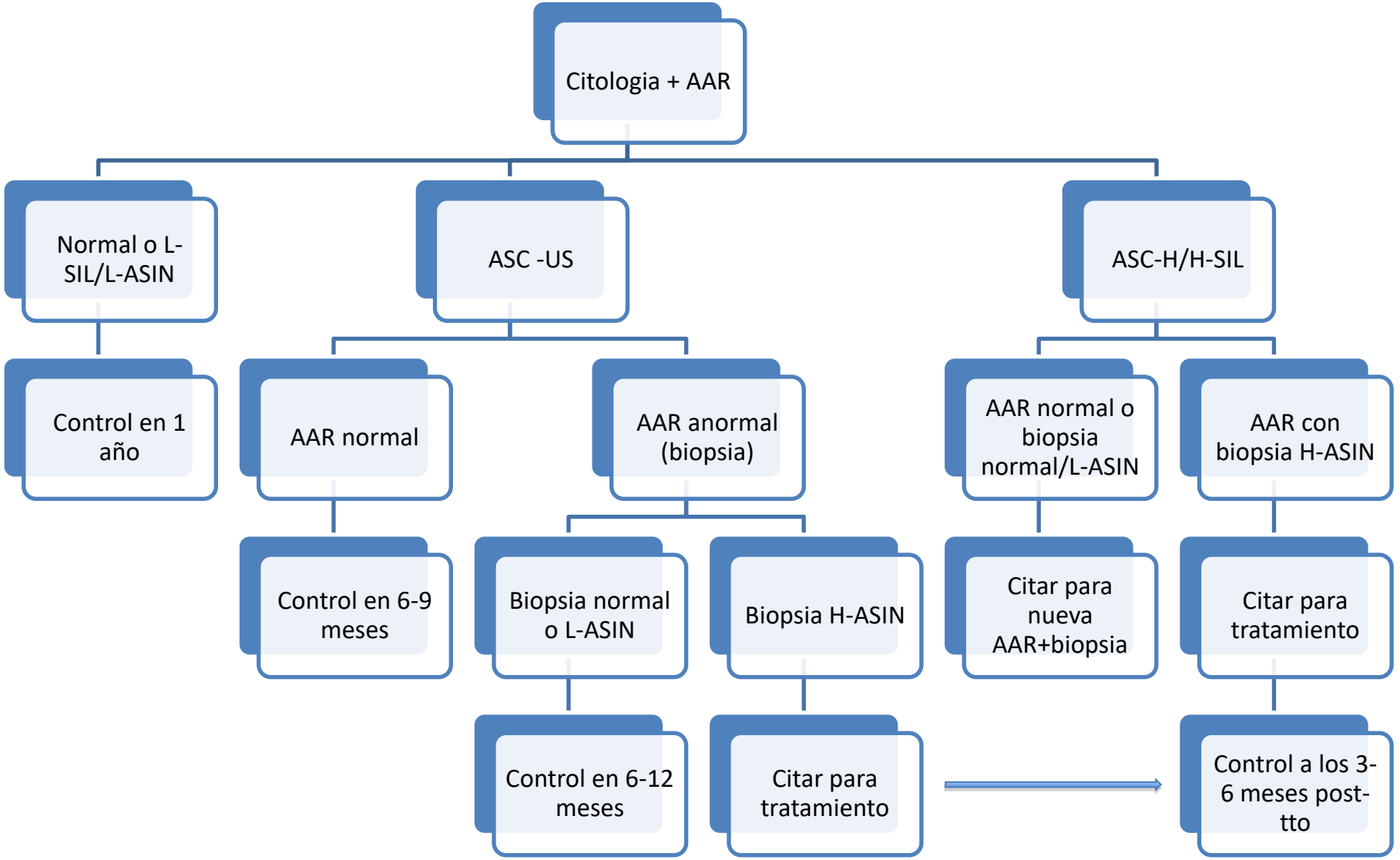
Figure: Follow-Up of Anal Cytologic Screening Results [a]



CRIBADO DISPLASIA ANAL

ESTRATEGIA SIMULTÁNEA

UCDA HVH


Citologia + AAR
Normal o L-SIL/L-ASIN
ASC -US
ASC-H/H-SIL
Control en 1 año
AAR normal
AAR anormal (biopsia)
AAR normal o biopsia normal/L-ASIN
AAR con biopsia H-ASIN
Control en 6-9 meses
Biopsia normal o L-ASIN
Biopsia H-ASIN
Citar para nueva AAR+biopsia
Citar para tratamiento
Control en 6-12 meses
Citar para tratamiento
Control a los 3-6 meses post-tto

Risk of progression to high-grade anal intraepithelial neoplasia in HIV-Infected MSM.

Table 3. Progression to high-grade anal intraepithelial neoplasia according to different factors.

	Progression to HGAIN[a]							
Risk factors	Percentage of population (*n*)	Number HGAIN	Person-years	Incidence (100 person-years)	95% CI of incidence	1-year cumulative risk % (95% CI)	2 years cumulative risk % (95% CI)	3 years cumulative risk % (95% CI)
On HAART, stable sexual partner, normal [b] cytology, normal HRA and no HPV 16 and 18 types infection	8.6% (48)	2	70	2.86	0.35–10.32	0%	3.7 (3.3–10.8)	10.6 (3.9–25.1)
Stable sexual partner, normal [b] cytology and normal HRA	14.4% (80)	4	131	3.06	0.83–7.82	0%	2.2 (2.1–6.5)	9 (1–19)
On HAART, stable sexual partner, normal [b] cytology and normal HRA	12.8% (71)	4	116	3.4	0.91–8.83	0%	2.4 (2.3–7.1)	9.9 (2.8–17)
On HAART, normal [b] cytology, normal HRA and no HPV 16 and 18 types infection	19.4% (108)	8	165	4.8	2.1–9.5	0%	5.3 (0.6–11.2)	16.9 (9.4–24.3)
Normal [b] cytology and normal HRA	33.2% (184)	17	325	5.23	3–8.4	0.7 (0–2)	6.2 (1.7–10.7)	14.2 (6.7–21.6)
On HAART, normal [b] cytology and normal HRA	28.3% (157)	15	277	5.4	3–8.9	0.8 (0.8–2.4)	6.4 (1.5–11.3)	13.9 (6.1–21.7)

Burgos J et al. AIDS. 2015 Mar 27;29(6):695-702.

Risk of progression to high-grade anal intraepithelial neoplasia in HIV-Infected MSM.

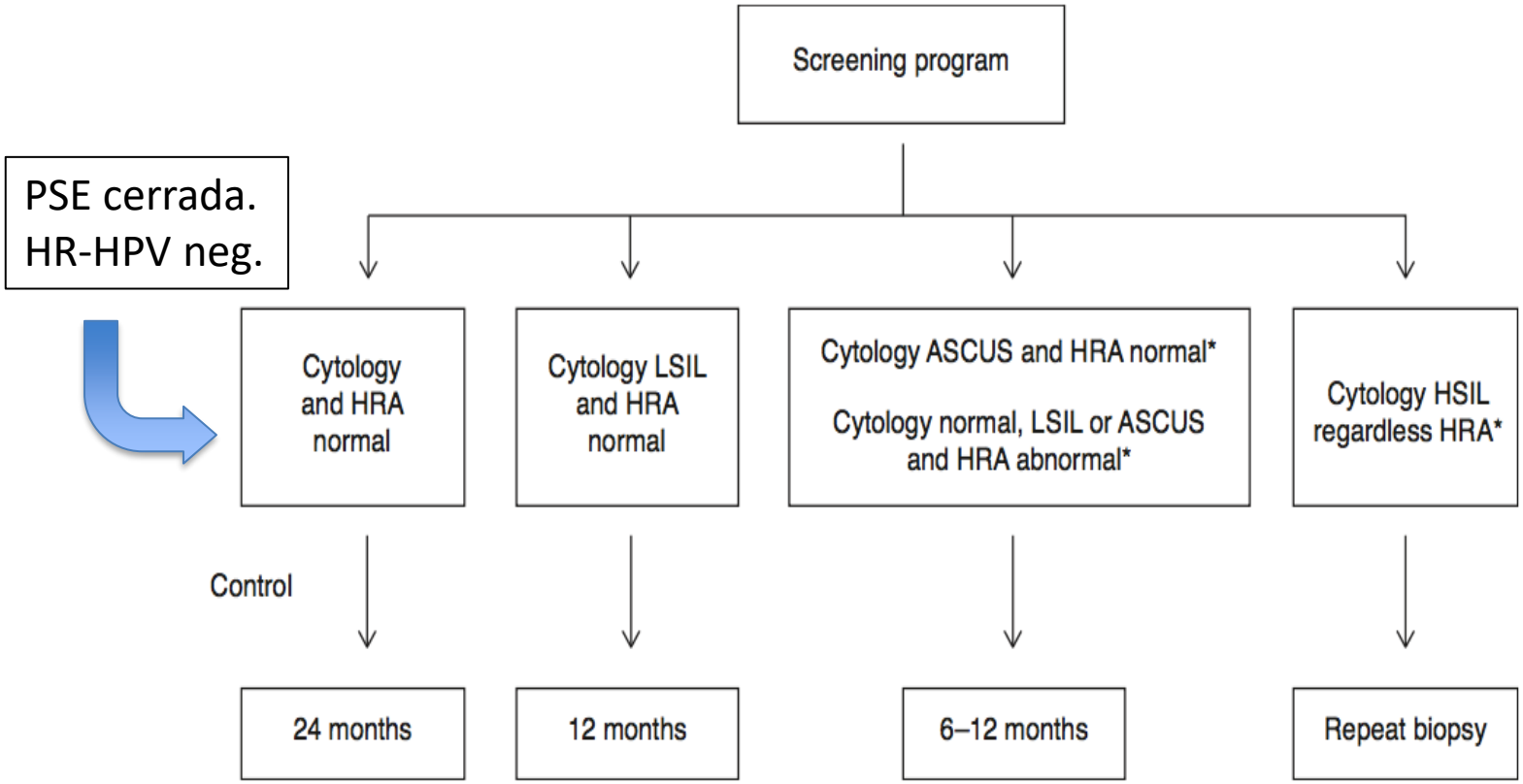


Fig. 2. Periodicity of the screening programme. ASCUS, atypical squamous cells of undetermined significance; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion. *With normal histological result in the biopsy.

Burgos J et al. AIDS. 2015 Mar 27;29(6):695-702.

CRIBADO DISPLASIA ANAL

ESTRATEGIA “SÓLO AAR”

Estrategia más barata.

Estudio coste-eficacia dx AIN 2/3 Canadá

Strategy no.	Strategy	Estimated cost per patient (based on 401 Patients)	Total cost[a]	Total cases detected	Cost	Case detected	Cost/ Case detected	Total cost/Total cases detected
1	No screening	$0.00	$0.00	0	n/a	n/a	n/a	n/a
18	HPV+: ≥ HSIL(HRA), ≤ LSIL(nothing)	$197	$80 948	18	$80 948	18	$4497	$4497
13	Pap: ≥ HSIL(HRA),≤ LSIL(nothing)	$113	$47 099	21	($33 849)	3	($11 283)	$2243
10	Pap: ≥ HSIL(HPV),≤ LSIL(nothing)	$124	$51 582	21	$4484	0	n/a	$2456
12	Pap: ≥ HSIL(HRA),LSIL(HPV),Normal-ASCUS(nothing)	$233	$95 317	72	$48 219	51	$945	$1324
7	Pap: ≥ LSIL(HRA),≤ ASCUS(nothing)	$195	$80 255	73	($15 062)	1	($15 062)	$1099
8	Pap: ≥ LSIL(HPV),≤ ASCUS(nothing)	$244	$99 801	73	$19 546	0	n/a	$1367
17	HPV+: ≥ LSIL(HRA),≤ ASCUS(nothing)	$276	$112 757	73	$12 956	0	n/a	$1545
3	Pap: ≥ ASCUS(HRA),Normal(nothing)	$219	$89 703	82	$9448	9	$1049	$1094
11	Pap: ≥ HSIL(HRA),ASCUS-LSIL(HPV),Normal(nothing)	$265	$108 087	82	$18 384	0	n/a	$1318
5	Pap: ≥ ASCUS(HPV),Normal(nothing)	$276	$112 571	82	$4484	0	n/a	$1373
16	HPV+: ≥ ASCUS(HRA),Normal(nothing)	$296	$120 854	82	$8283	0	n/a	$1474
2	HRA only	$193	$79 283	98	($10 421)	16	($651)	$809
15	HPV+: HRA	$265	$108 093	98	$28 810	0	n/a	$1103
4	Pap: ≥ ASCUS(HRA),Normal(HPV)	$298	$121 427	98	$13 334	0	n/a	$1239
8	Pap: ≥ LSIL(HRA),≤ ASCUS(HPV)	$306	$124 757	98	$3331	0	n/a	$1273
14	Pap: ≥ HSIL(HRA),≤ LSIL(HPV)	$344	$139 836	98	$15 079	0	n/a	$1427
6	Pap: ≥ ASCUS(HPV),Normal(HPV)	$355	$144 297	98	$4461	0	n/a	$1472

All costs reported in 2003 United States dollars.
*Total costs = (estimated cost per patient x 401) + capital costs; where capital cost = $1976.

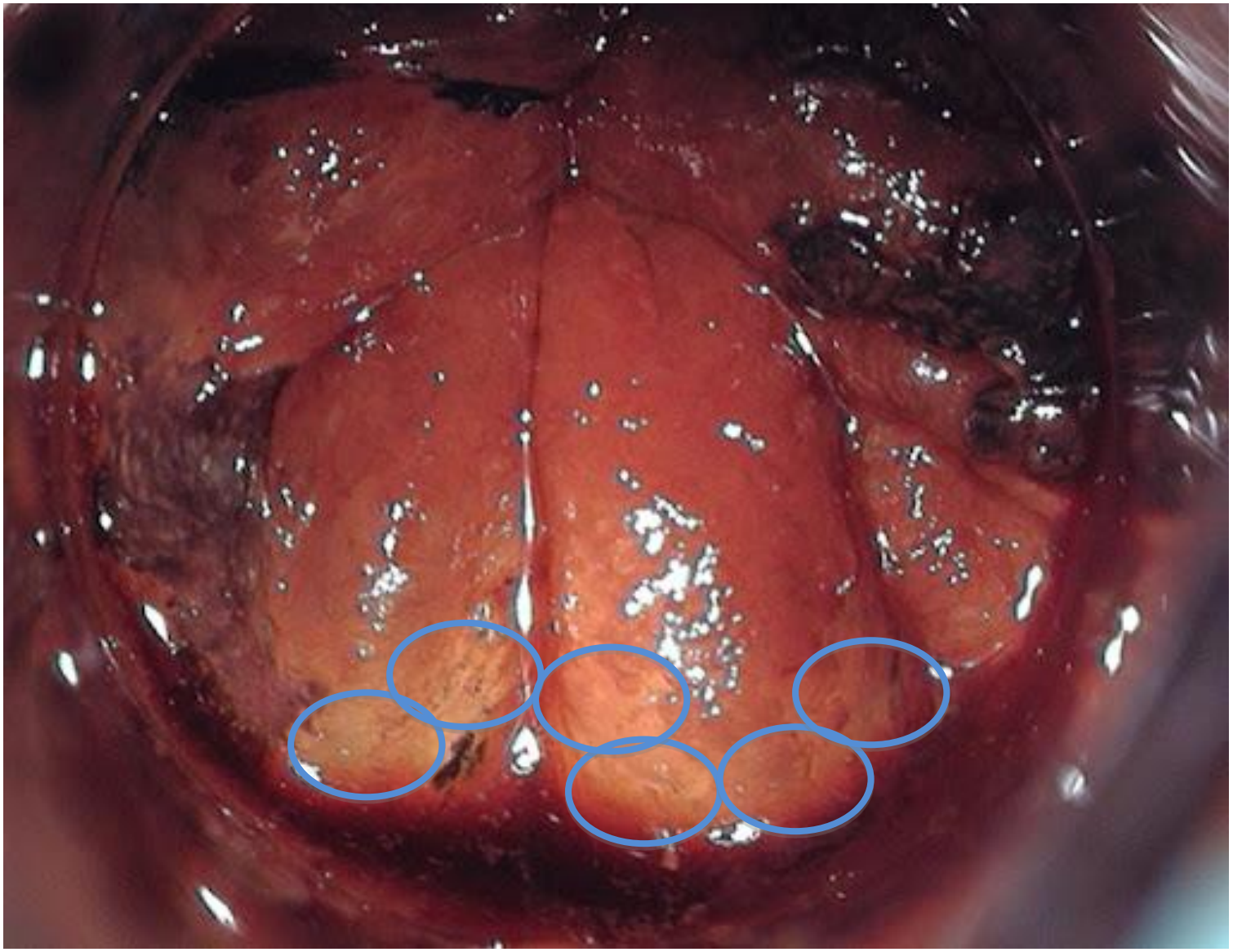
Lam JC et al. AIDS 2011; 25: 635–642

La citología es útil.

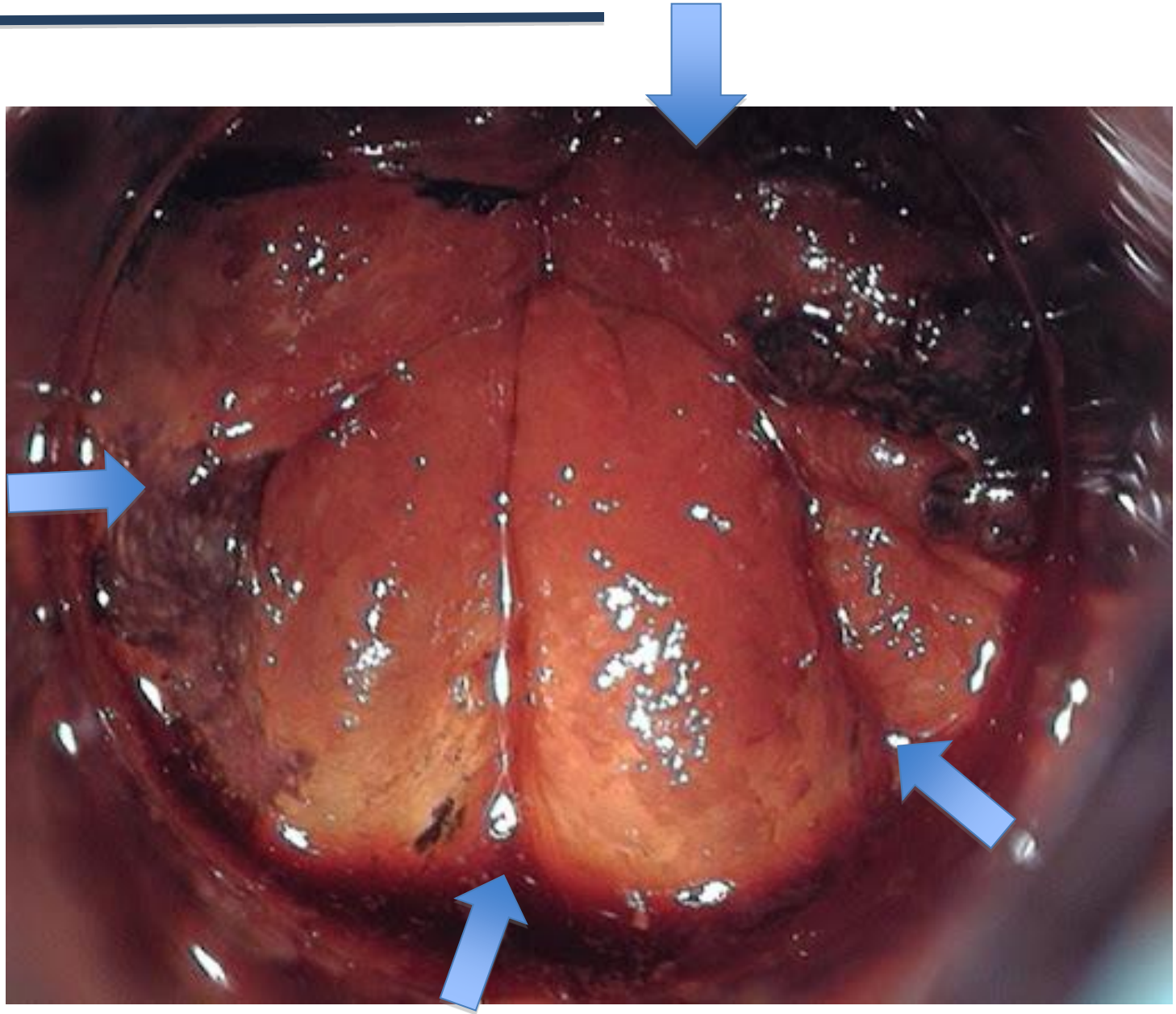
"Control de calidad" Sobre todo en la curva de aprendizaje

Una citología alterada con una AAR normal significa una lesión no diagnosticada. (Especialmente HSIL).

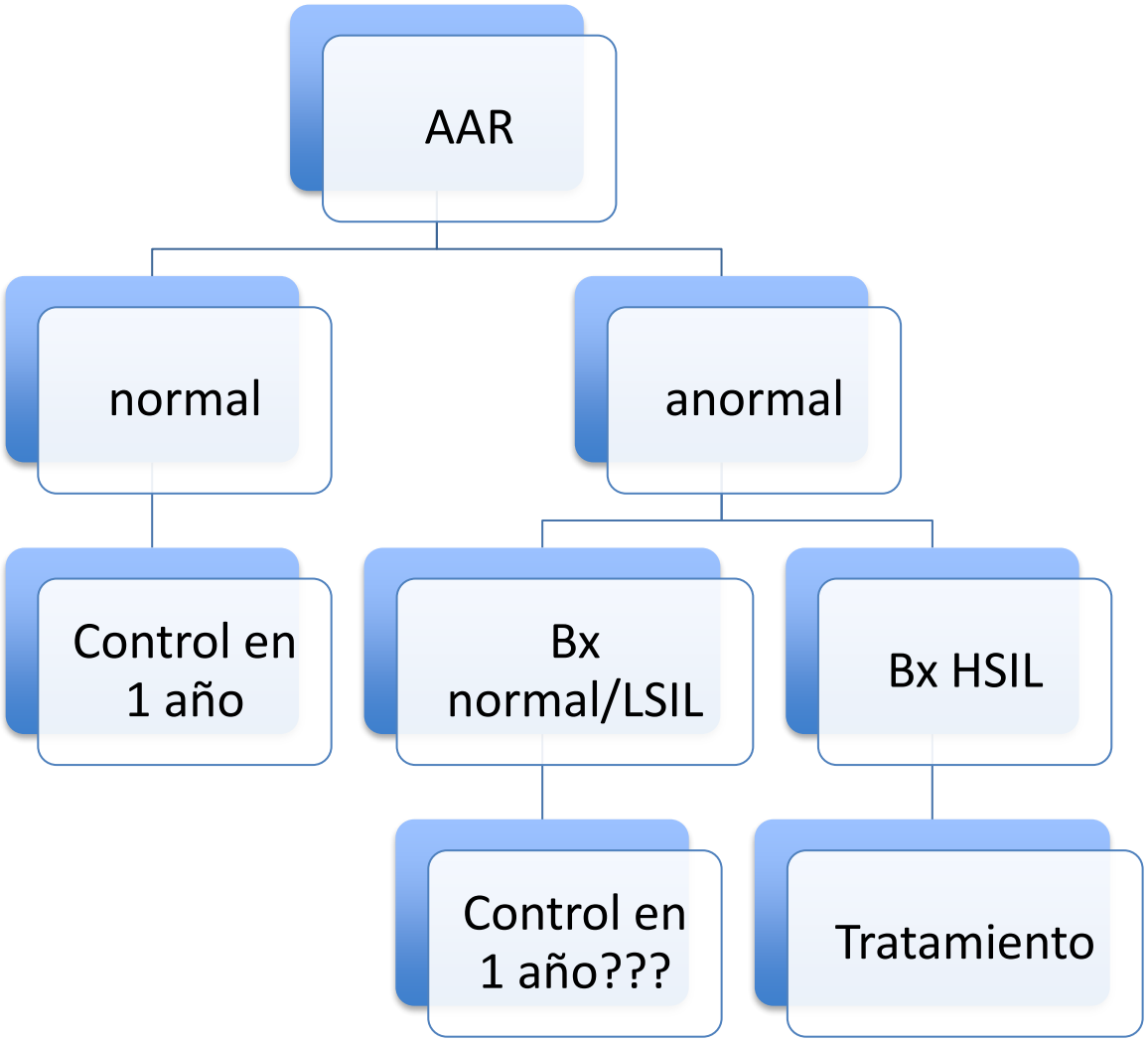
Tener en cuenta… Extensión de la lesión



Técnica observador-dependiente



Estrategia sólo AAR...



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CRIBADO CÁNCER ANAL

TABLE 1. Groups Who May Potentially Benefit From DARE, With Proposed Frequencies

Group	Minimum[a] proposed DARE frequency
Those with symptoms suggesting anal cancer such as: bleeding, anal/perianal mass, tenesmus, pain, altered bowel habit (read, Read et al., 2013)[38]	Immediately, with referral for anoscopy, HRA, or to a colorectal specialist if the initial DARE is negative
HIV-positive MSM	At least annually in men ≥35 y
Those with demonstrated cytologic or histologic anal HSIL	At least annually
Those with a history of treated anal squamous cell carcinoma	Every 4 mo after completion of radiation for first 2 y, then every 6 mo for the next 3 y, then at least annually (Wright et al., 2010)[39]
Other immunosuppressed populations, such as other groups with HIV infection and recipients of solid organ transplants	At least annually in those ≥50 y
HIV-negative MSM	Every 2 to 5 y in those ≥50 y
Women with a history of cervical, vulvar or vaginal neoplasia or cancer	Every 2 to 5 y, depending on further risk assessment (Moscicki et al.,[15] 2015)

- DARE
  - DARE: exploración digital ANO-rectal ≠ tacto rectal!
  - Útil para detección de cáncer anal pero no para displasia anal
- Periodicidad ANUAL

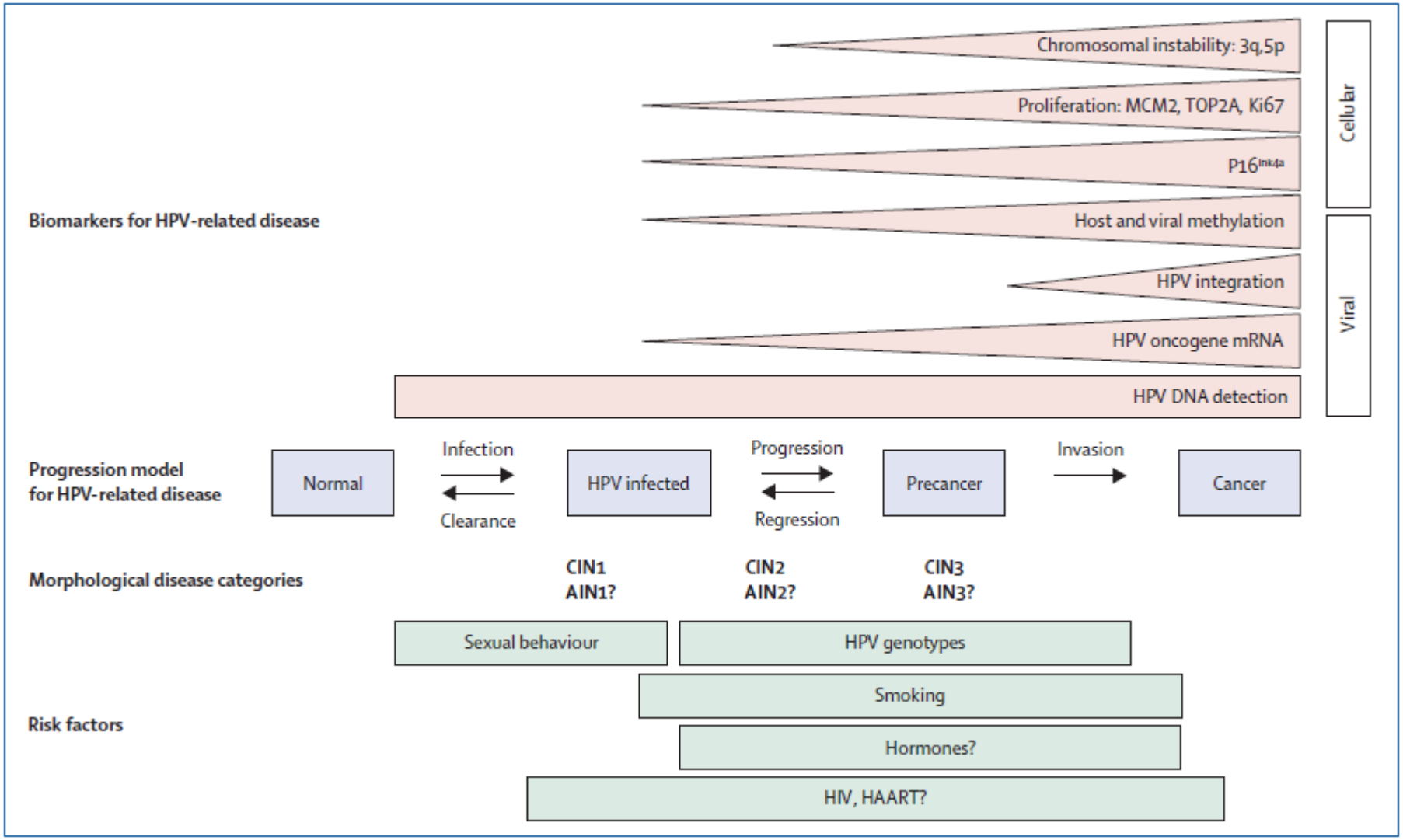
En el futuro…

- Uso de marcadores de “malignidad” en la citología para determinar pacientes con:
  - Riesgo de progresión de HSIL a cáncer: tto vs. actitud expectante
    - Ejemplos: p16/Ki67, HPVE6/E7 mRNA, HR-HPV, metilación
    - En fase de estudio!

- Algoritmos de manejo basados en factores pronósticos de riesgo

Phanuphak N et al. PLOS One 2013; 8: e78291. Wentzensen N et al. AIDS 2012; 26: 2185-92.

Infección por el VPH



Wentzensen N. Lancet Oncol 2012; 13 (5): 438-40.