Natural History of HPV-attributable Anal Dysplasia in HIV-infected Populations

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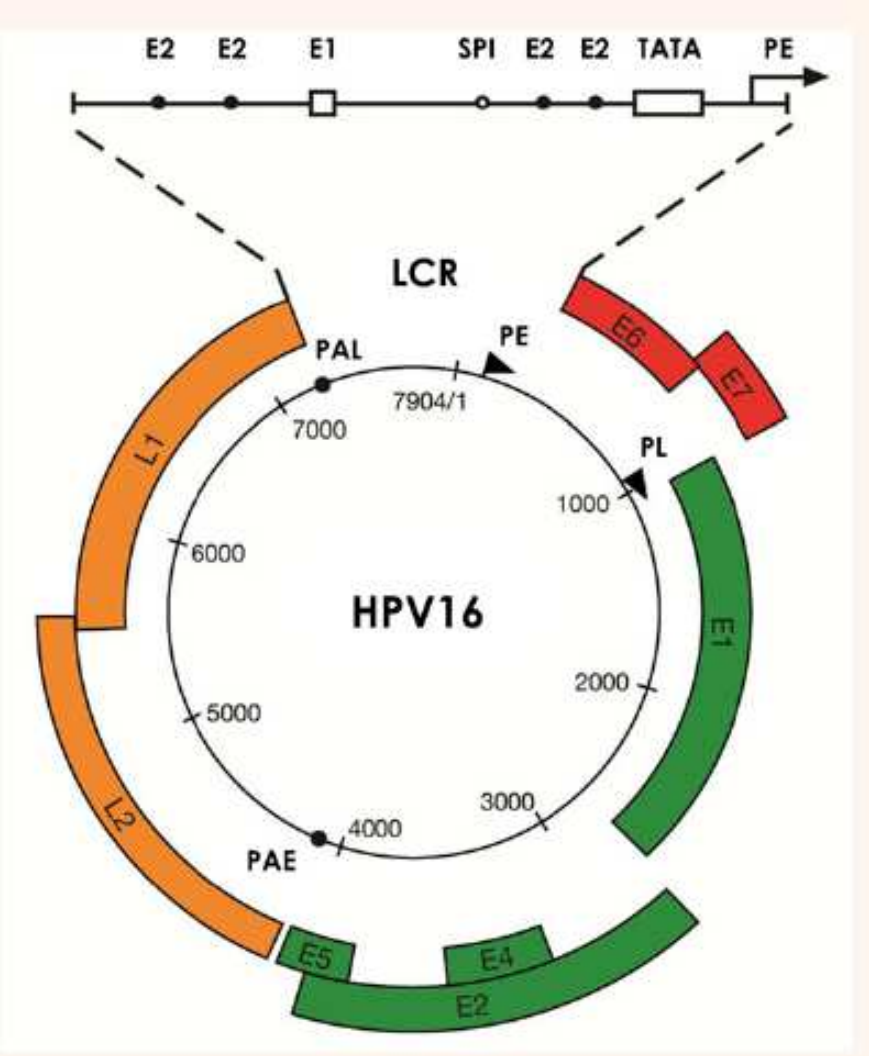
Outline

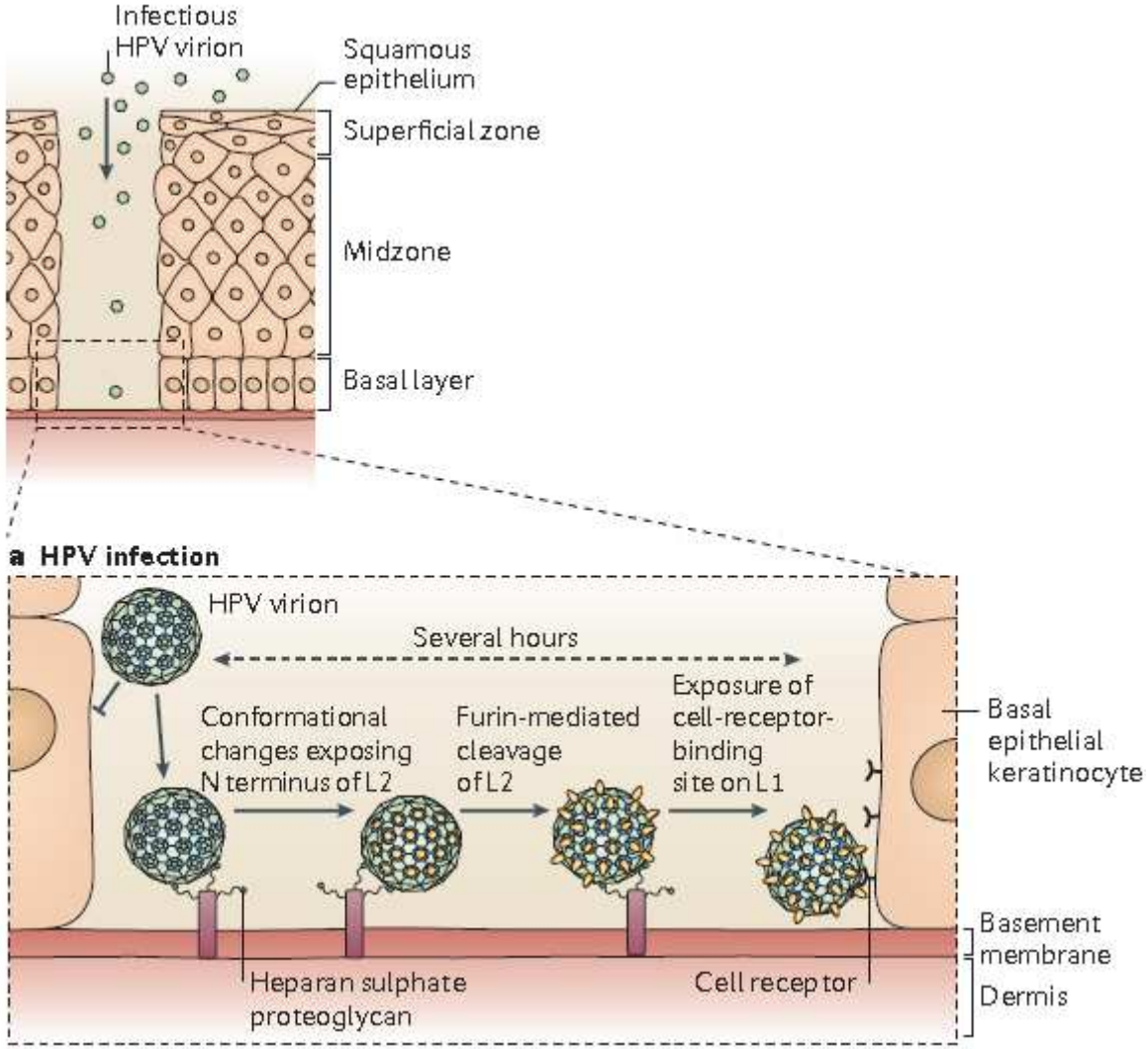
- Virologic and molecular mechanisms of HPV-induced intraepithelial neoplasia
- Natural history of mucosal HPV and HPV-infected tissues (cervix, anus)
- Recent changes in nomenclature of intraepithelial neoplasia: LAST Project
- Risk factors for aHSIL and IAC in HIV-infected populations
- Recent studies of aHSIL progression and regression in HIV-infected populations

HPV-16 Genome Organization

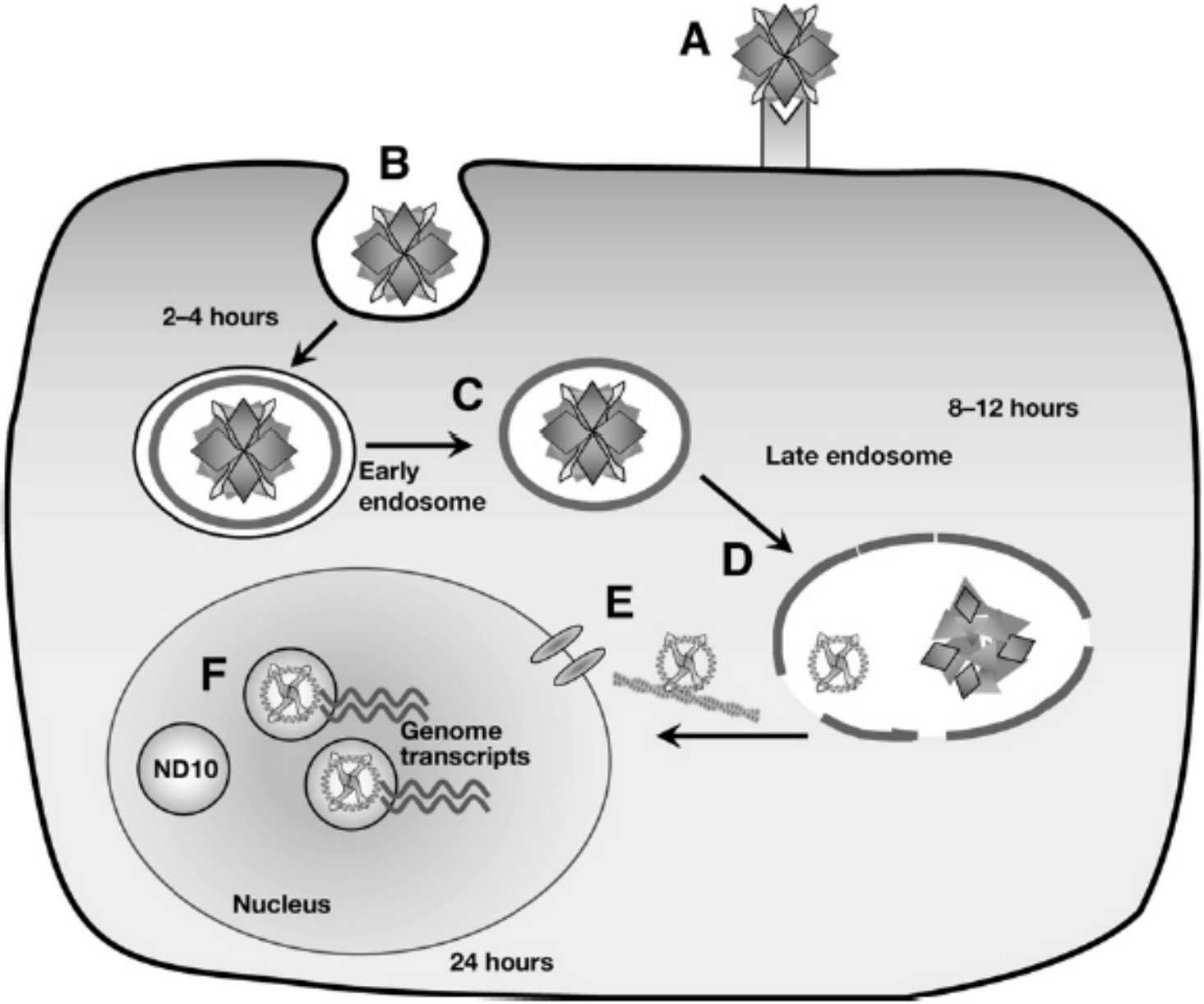


Doorbar et al. Vaccine 30S (2012) F55– F70

Mechanism of HPV Mucosal Infection

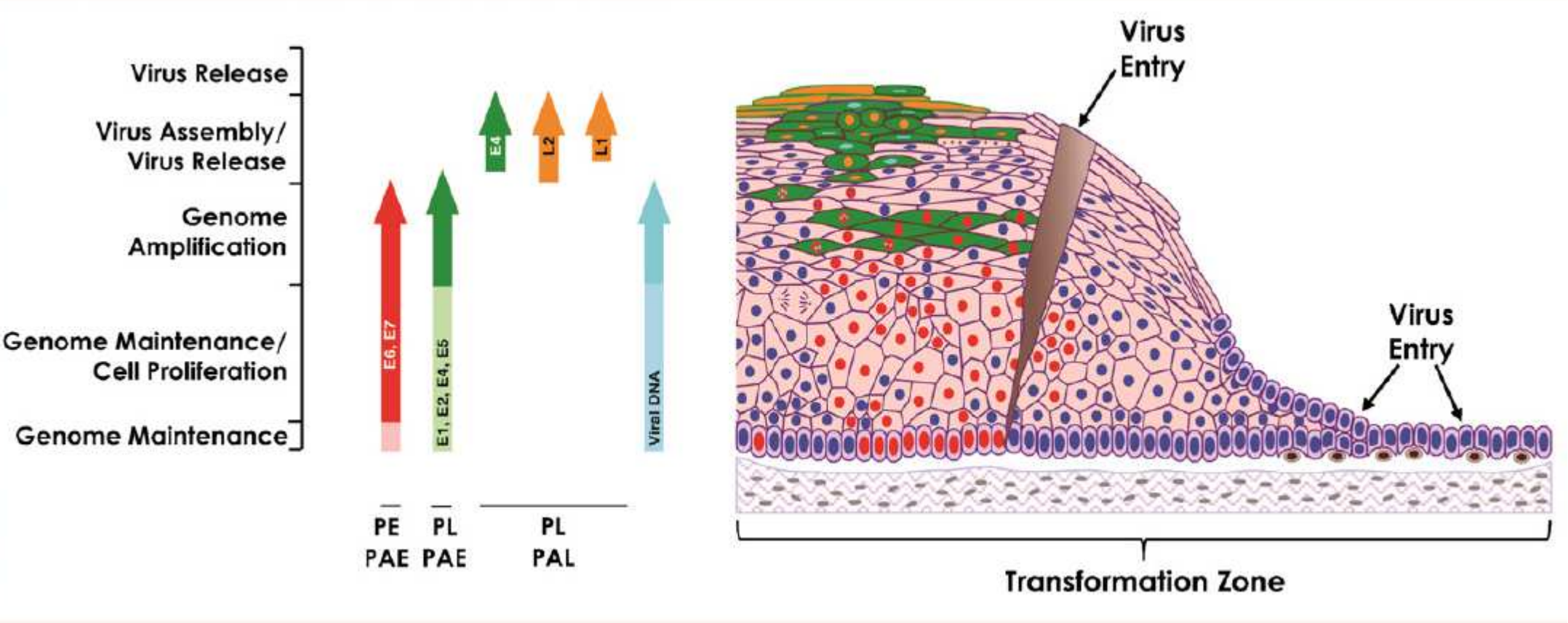


Schiller JT, Lowy DR. Nat Rev Microbiol. 2012 Oct;10(10):681-92



J.T. Schiller et al. Gynecologic Oncology 118 (2010) S12–S17

Mucosal Life Cycle of High Risk HPVs



oorbar et al. Vaccine *30S (2012) F55– F70*

Protein Function and Patterns of Gene Expression in High and Low-Risk HPV Diseases: E6

	High-Risk Alpha	Low-Risk Alpha
E6	encodes E6* products	no E6* products
	binding and degradation of… •p53 •specific PDZ-domain proteins (e.g. Dlg, MAGI-1, Scribble)	weaker binding (no degradation) of… •p53 •no binding of PDZ-domain proteins
	interact with the E6AP ubiquitin ligase inhibition of p53 transactivation and acetylation	
	inhibition of apoptosis	unknown
	bypass of growth arrest following DNA damage	normal growth arrest following DNA damage
	inhibition of keratinocyte differentiation	unknown
	inhibition of interferon response	weaker inhibition of interferon response
	activation of signaling pathways… •Akt •Wnt •Notch •mTORC1	unknown
	telomerase activation	no activation
	c-myc activation	no activation

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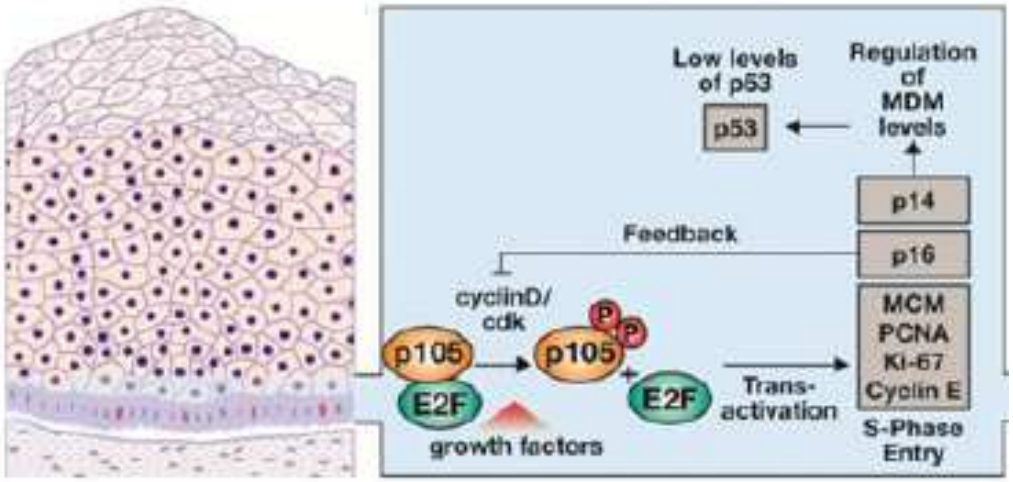
Protein Function and Patterns of Gene Expression in High and Low-Risk HPV Disease: E7

E7	binding and degradation of… •pRb •p107 •p130 binding (no degradation) of… •E2F1 •Cullin2 •HDAC	weaker binding (no degradation) of… •pRb •p107 •E2F1 binding of… •p130
	binding of regulatory proteins including E2F6, p600, HAT, PP2A induction of cell cycle entry and DNA synthesis role in genome amplification	
	induction of genome instability	no stimulation of instability
	suppression of STAT-1 function	no suppression
	immortalization and transformation functions	no such functions
	activation of signaling pathways… •Akt	unknown

oorbar et al. Vaccine *30S (2012) F55– F70*

i) UNINFECTED EPITHELIUM

Cell cycle entry and cell proliferation only in the basal and parabasal cell layers stimulated by growth factors (blue box). No cell cycle entry in the superficial cell layers.



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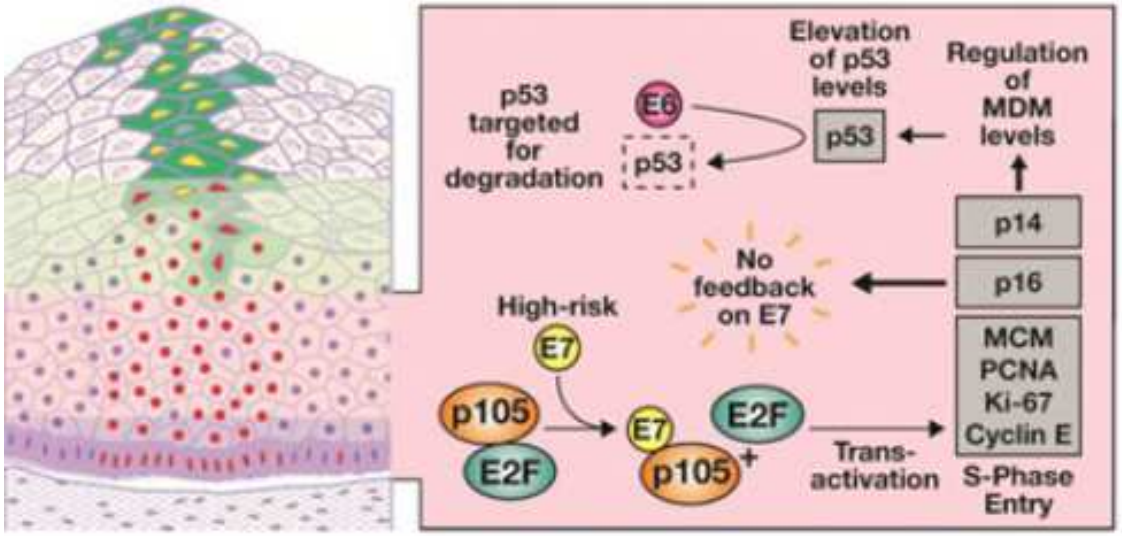
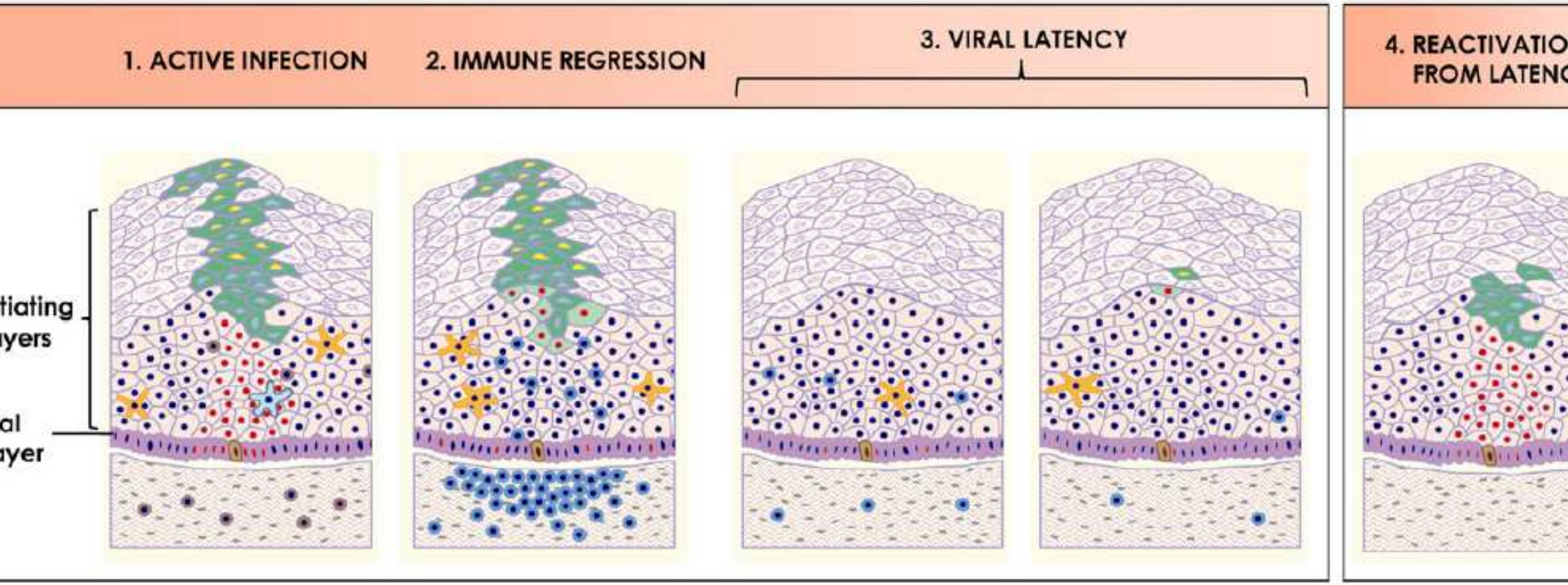
iii) HIGH-RISK HPV INFECTION

In high-risk HPV infections, E6/E7 expression stimulates additional cell cycle entry and cell proliferation in the lower and middle epithelial layers leading to neoplasia (red box). E6/E7 also drive cell cycle entry in the upper epithelial layers to allow genome amplification as shown for low-risk HPV infections (green box).



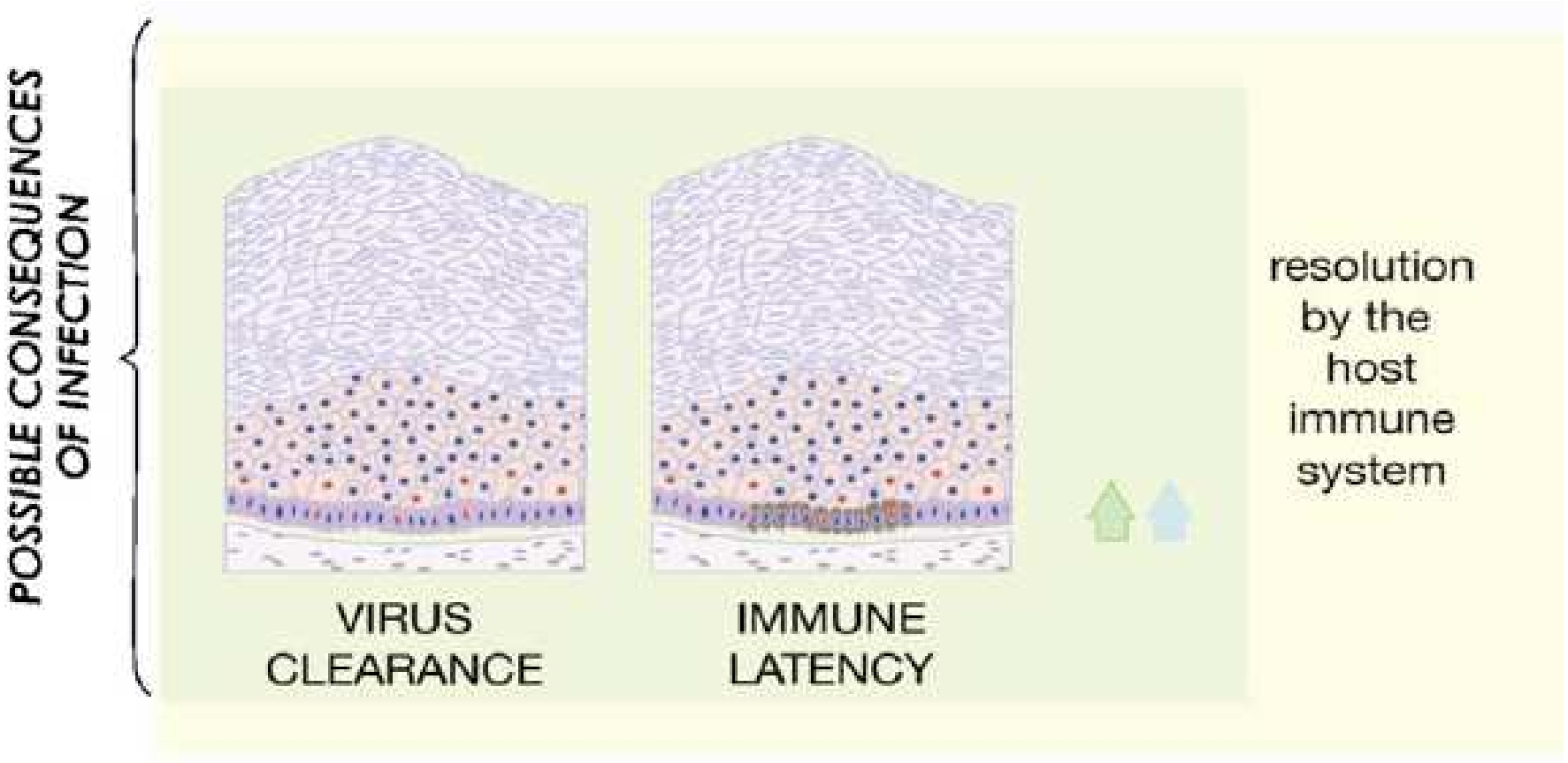
oorbar et al. Vaccine *30S (2012) F55– F70*

Immune Clearance, Latency, & Possible Reactivation



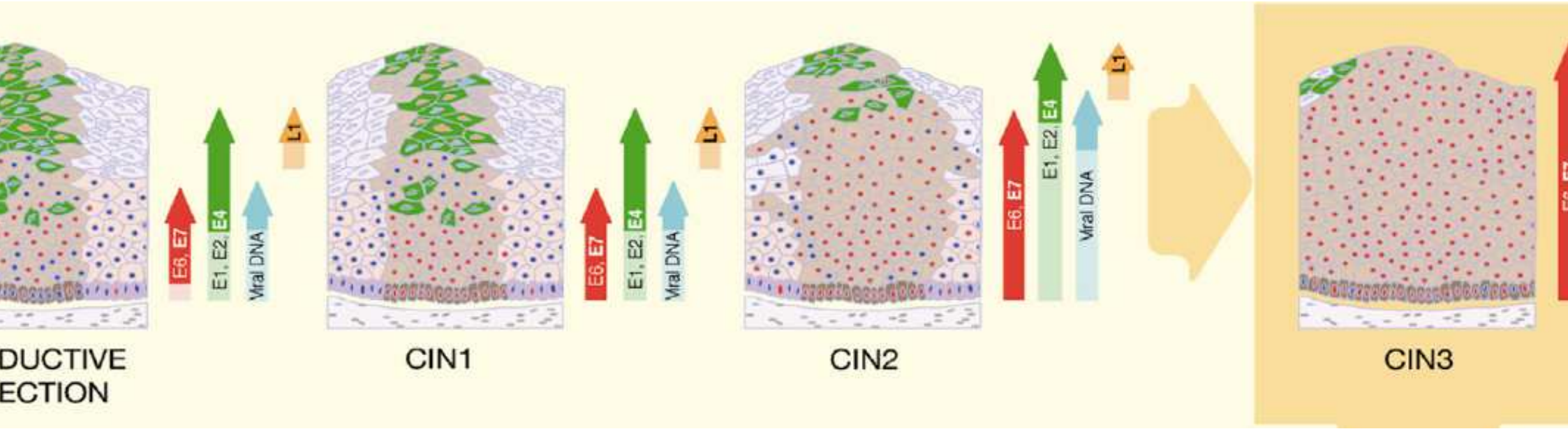
oorbar et al. Vaccine *30S (2012) F55– F70*

Viral Clearance and Immune Latency Pathways:
~ 90% of Immune Competent Hosts



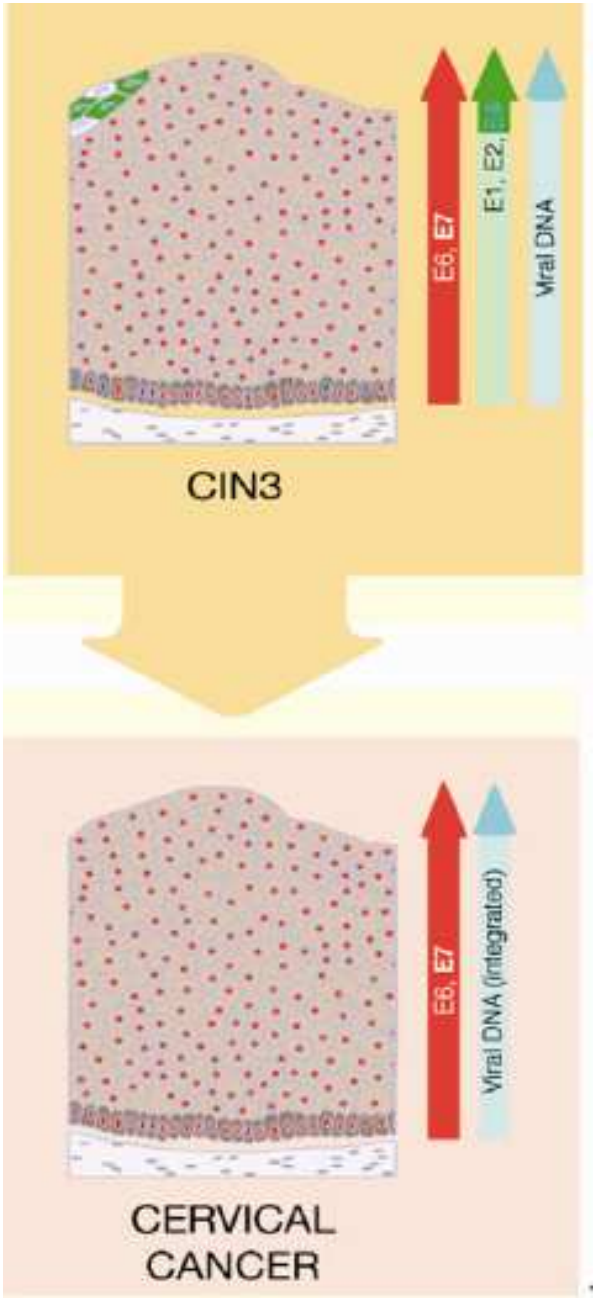
Bosch FX et al. Vaccine. 2013 Nov 22;31 Suppl 8:I1-I31. doi: 10.1016/j.vaccine.2013.07.026.

Intraepithelial Neoplasia Pathway



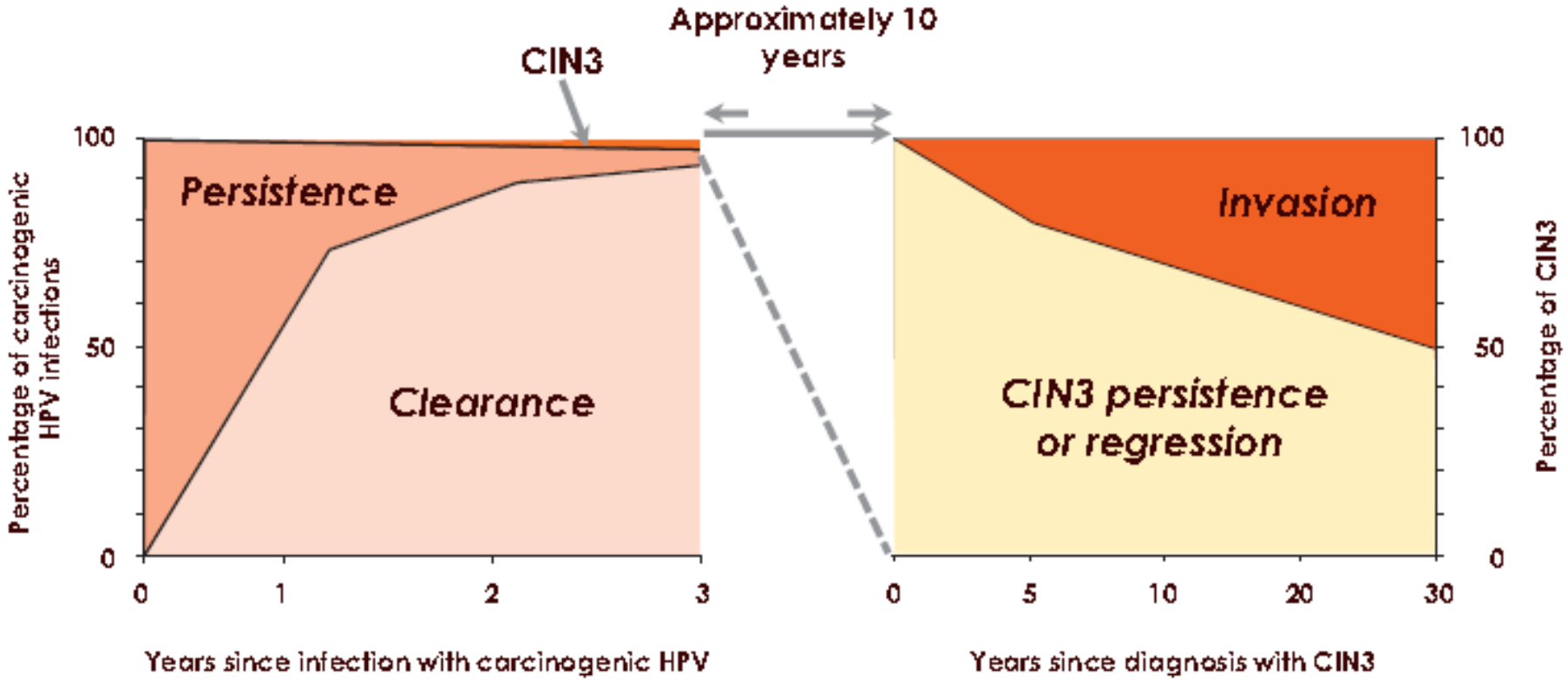
Bosch FX et al. Vaccine. 2013 Nov 22;31 Suppl 8:I1-I31. doi: 10.1016/j.vaccine.2013.07.026.

Persistence & accumulation
of secondary genetic changes



Bosch FX et al. Vaccine. 2013 Nov 22;31 Suppl 8:I1-I31. doi: 10.1016/j.vaccine.2013.07.026.

Natural History of Cervical HPV Infection in Immunocompetent Women



Bosch FX et al. Vaccine. 2013 Nov 22;31 Suppl 8:I1-I31. doi: 10.1016/j.vaccine.2013.07.026.

Natural History of Anal vs Oral HPV Infection in HIV-Infected Men and Women:

ble 4. Persistence of Anal and Oral Human Papillomavirus (HPV) Infections and Prevalence Ratios of Anal Compared to Oral HP tions

e of Infection and Length Persistence	Single Negative Test for HPV Clearance			Two Consecutive Negative Tests Required for HPV Clearance		
	Any Anal HPV	Any Oral HPV	PR (95% CI)[a]	Any Anal HPV	Any Oral HPV	PR (95%
valent—6 mo	63%	46%	**1.4 (1.1–1.7)**	77%	63%	**1.2 (1.1**
valent—12 mo	60%	36%	**1.6 (1.3–2.1)**	73%	53%	**1.4 (1.2**
valent—18 mo	50%	27%	**1.8 (1.3–2.5)**	65%	48%	**1.4 (1.1**
valent—24 mo	39%	25%	**1.5 (1.0–2.3)**	58%	47%	1.2 (.95
dent—6 mo	38%	32%	1.2 (.82–1.7)	64%	54%	1.2 (.91
dent—12 mo	28%	15%	**1.9 (1.1–3.3)**	46%	40%	1.2 (.78
dent—18 mo	24%	10%	2.4 (.94–6.2)	36%	28%	1.3 (.67

achler et al. Journal of Infectious Diseases 2013;208:330–9

Loss of heterozygosity (LOH)	One of the mechanisms of genomic instability involved in the inactivation of tumour suppressor genes. In a specific chromosomal region, the first allele is lost, and the gene present on the second allele is mutated.
Microsatellite instability (MSI)	Another type of genomic instability characterized by widespread mutation of short repetitive DNA sequences known as microsatellites. In many cases, MSI results from inactivation of the DNA mismatch repair gene *MLH1* and secondary mutation of genes with coding microsatellites, such as *transforming growth factor receptor II*.
Oncoprotein	Protein product of an oncogene, a tumour suppressor gene or a virus, associated through various mechanisms with the negative regulation of apoptosis (programmed cell death).

Gervaz et al. *British Journal of Surgery* 2006; 93: 531–538

V negative model
progression

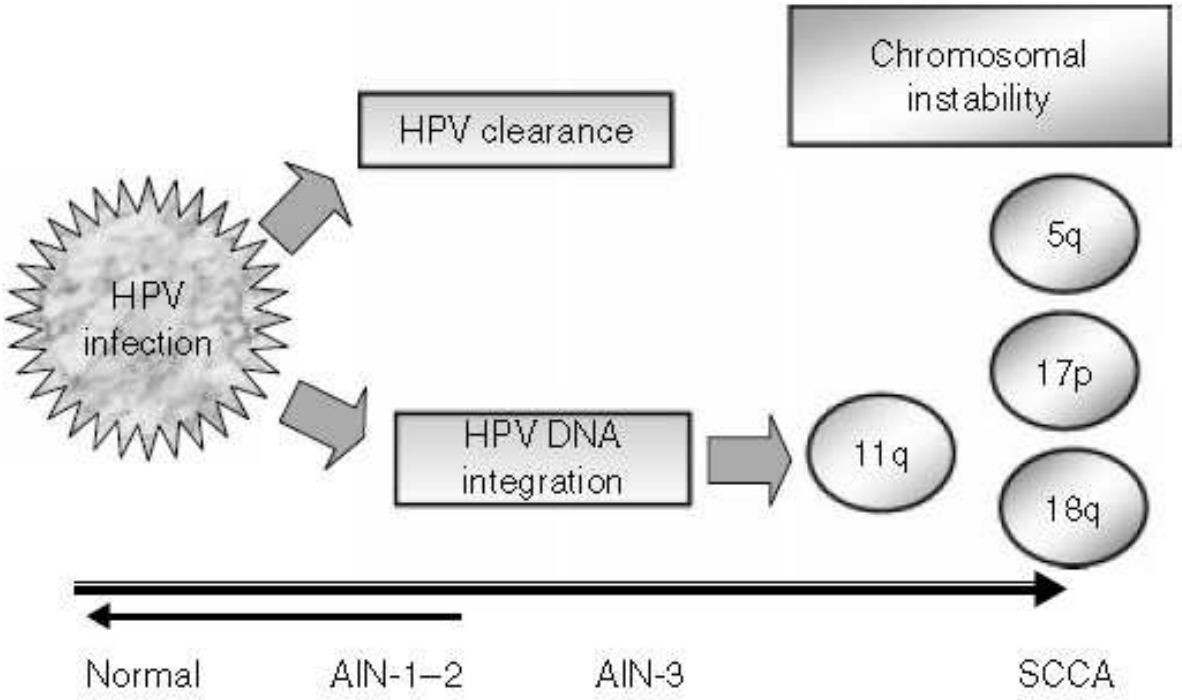


Fig. 1 Model of progression of squamous cell carcinoma of the anal canal (SCCA) in human immunodeficiency virus (HIV)-negative patients. Following integration of human papillomavirus (HPV), progression of anal cancer requires loss of heterozygosity at various loci, including 17p (*p53*), 5q (*APC*) and 18q (*DCC*). The whole process takes an average of 30–40 years to develop, and the median age at diagnosis in this population is 60–70 years. AIN, anal intraepithelial neoplasia

Gervaz et al. *British Journal of Surgery* 2006; 93: 531–538

+ model of progression

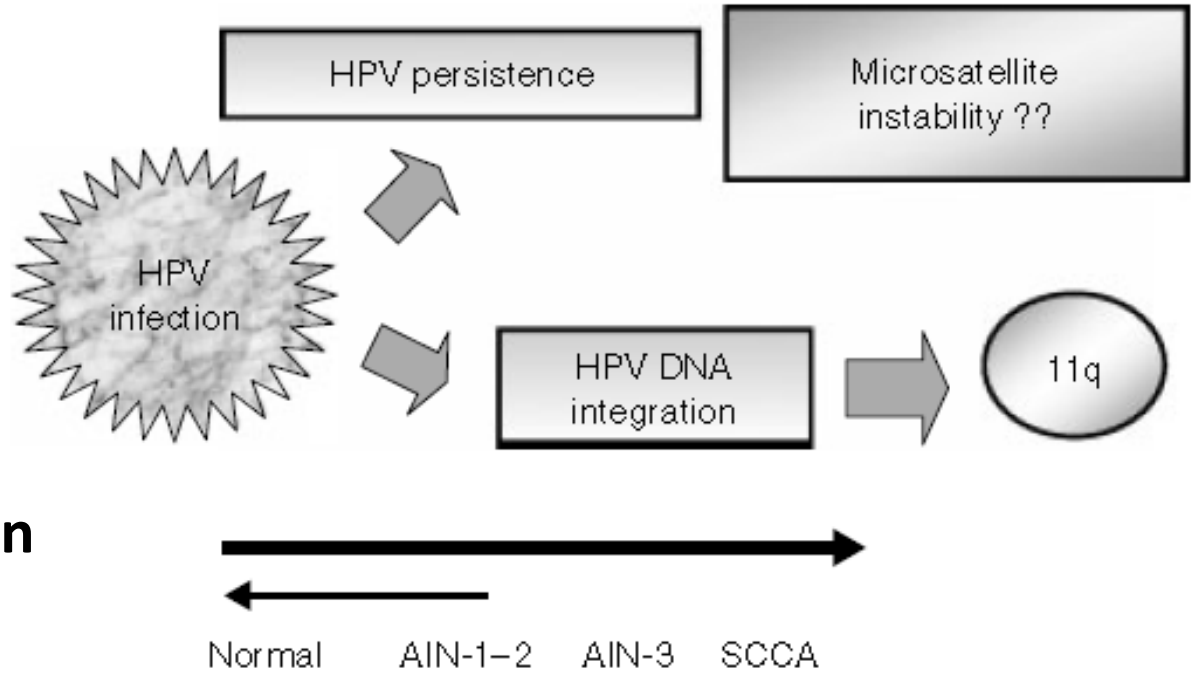


Fig. 2 Model of progression of squamous cell carcinoma of the anal canal (SCCA) in human immunodeficiency virus (HIV)-positive patients. Anal cancer progression is quicker in these individuals, with a median age at diagnosis of 37 years. Persistent human papillomavirus (HPV) infection and the absence of loss of heterozygosity at 17p, 5q and 18q suggest an alternative molecular pathway for SCCA progression in this population. AIN, anal intraepithelial neoplasia

Gervaz et al. *British Journal of Surgery* 2006; 93: 531–538

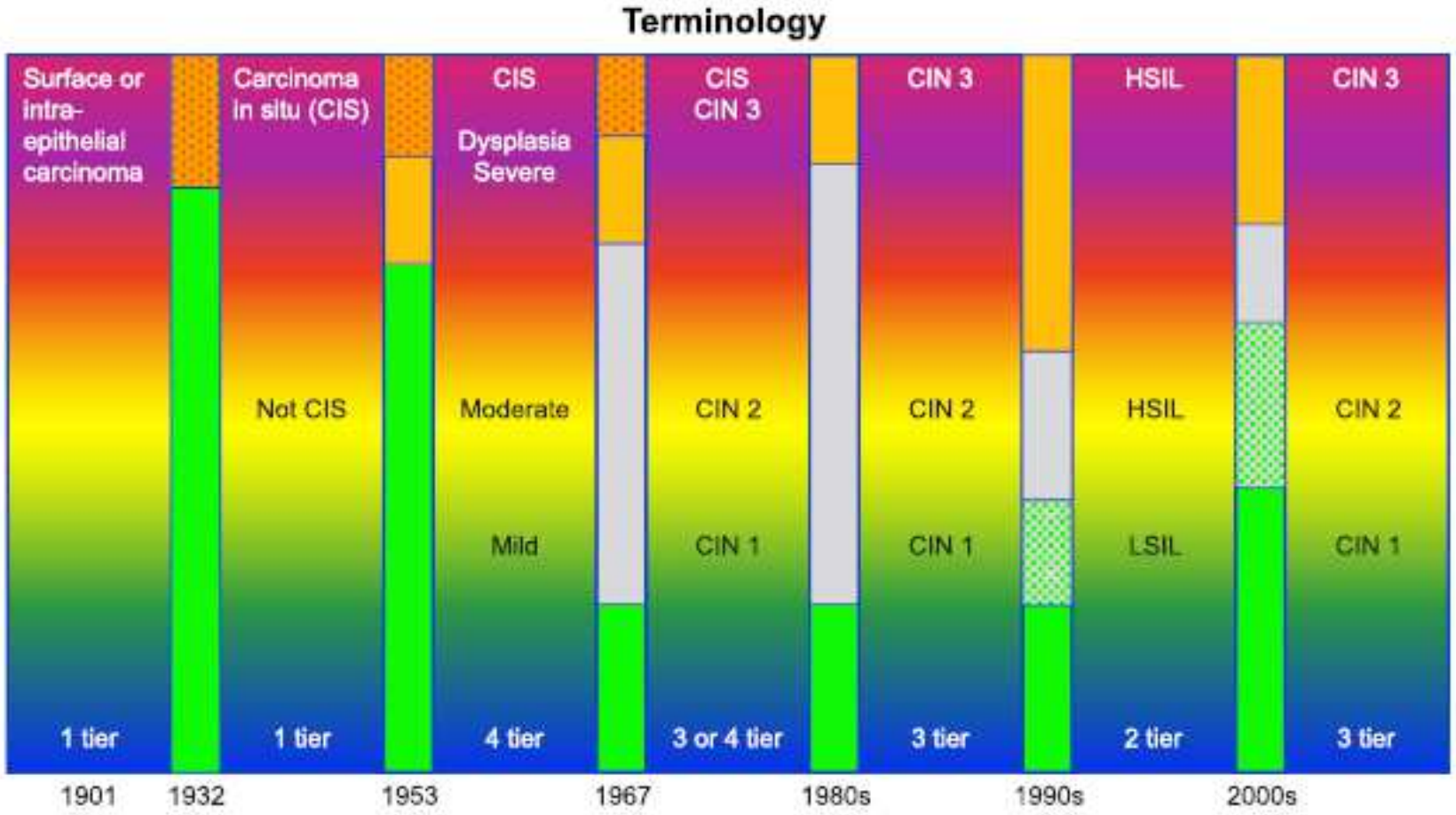
LAST Project Recommendations for Mucosal Terminology for HPV-related Cytology & Histopathology

Table 1. General Principles Underlying the LAST Project

There is unified epithelial biology to HPV-related squamous disease.
Each cytologic or histologic sample is only a statistical representation of the patient's true biology.
The more samples or data points available, the more accurate the assessment of the patient's true biology.
The true biology represents the risk for cancer at the current time and, to a lesser extent, the risk for cancer over time.
Diagnostic variation can be improved by:
Aligning the number of diagnostic terms with the number of biologically relevant categories and
The use of biologic markers.

arragh et al. J Low Genit Tract Dis. 2012 Jul;16(3):205-42

Historical Evolution of Mucosal Terminology for HPV-related Cytology & Histopathology



arragh et al. J Low Genit Tract Dis. 2012 Jul;16(3):205-42

Superficially Invasive Squamous Cell Carcinoma (SISCCA)

6. ANAL CANAL: The *suggested* definition of superficially invasive squamous cell carcinoma (SISCCA) of the anal canal is an invasive squamous carcinoma that:

Has an invasive depth of ≤3 mm from the basement membrane of the point of origin, AND

Has a horizontal spread of ≤7 mm in maximal extent, AND

Has been completely excised.

arragh et al. J Low Genit Tract Dis. 2012 Jul;16(3):205-42

Risk Factors for HGAIN in HIV+ Populations: Smoking

Table 3. Multivariate Logistic Regression of Detailed Smoking Covariates Among Human Immunodeficiency Virus–Infected Men Who Have Sex With Men

	<AIN2, HR-HPV-Positive vs <AIN2, HR-HPV-Negative		AIN2+, HR-HPV-Positive vs <AIN2, HR-HPV-Positive	
Characteristic	OR	95% CI	OR	95% CI
Ever smoker				
No	1.00	Referent	1.00	Referent
Yes	0.89	(0.44–1.78)	**2.71**	**(1.43–5.14)**
Smoked in last 12 mo				
Nonsmoker	1.00	Referent	1.00	Referent
No	0.82	(0.38–1.81)	**2.30**	**(1.11–4.80)**
Yes	1.36	(0.47–3.94)	**3.20**	**(1.45–7.09)**
Number of years smoked[a]				
Nonsmoker	1.00	Referent	1.00	Referent
≤10 y	1.15	(0.35–3.75)	**3.39**	**(1.29–8.93)**
>10 y	1.44	(0.53–3.93)	**3.09**	**(1.33–7.18)**
P-trend		*0.47*		***0.005***
Cigarette packs per day				
Nonsmoker	1.00	Referent	1.00	Referent
≤1/2	1.00	(0.35–2.86)	**2.90**	**(1.27–6.60)**
>1	0.84	(0.21–3.39)	**3.50**	**(1.19–10.28)**
P trend		*0.84*		***0.005***

Adjusted for age at enrollment, ethnicity, CD4 count, number of male partners, and history of chlamydia infection.

hwartz et al. Journal of Infectious Diseases 2013;208:1768–75

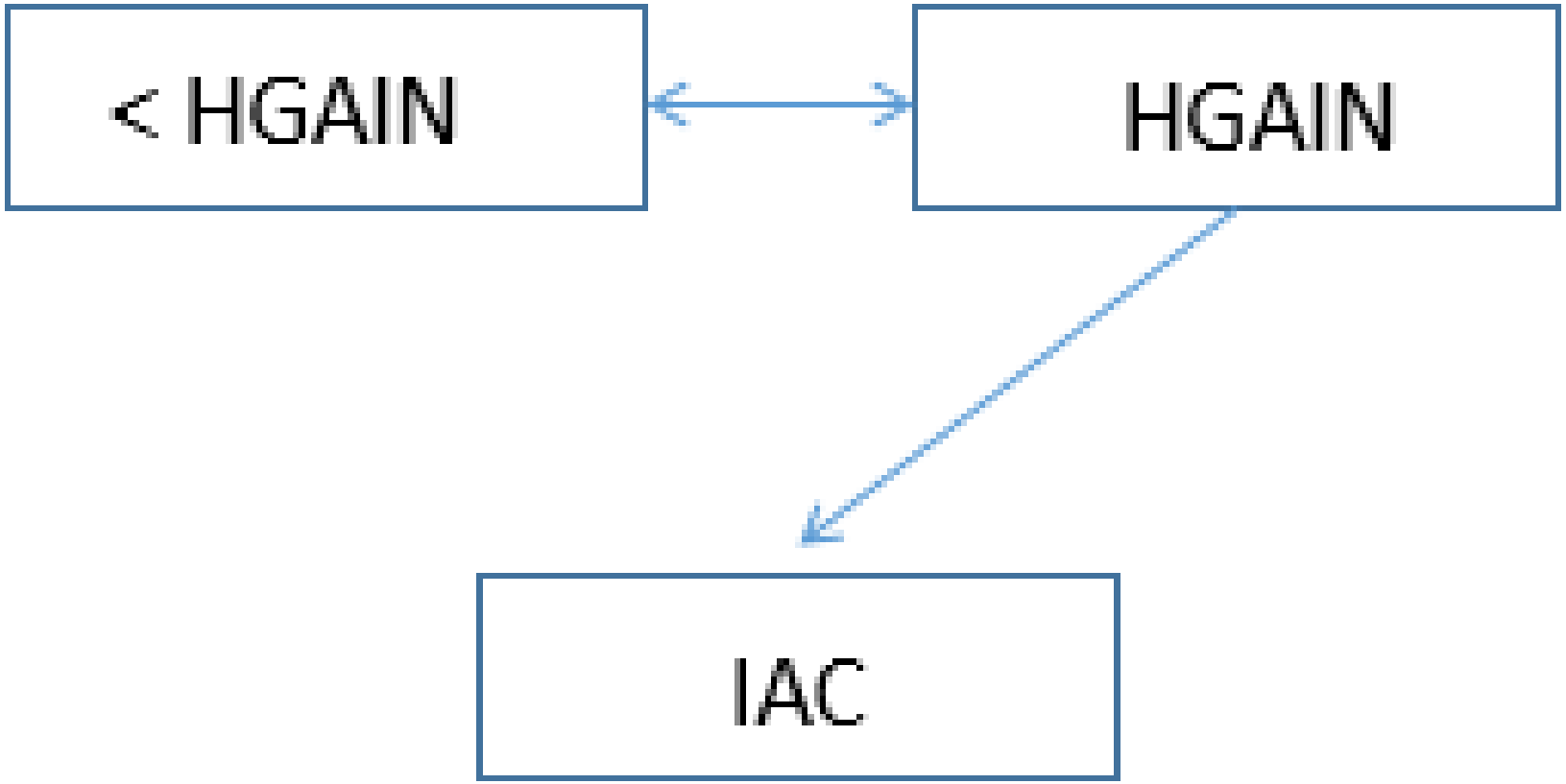
Risk Factors for IAC in HIV-infected Populations

Table 2. Odds Ratios for Anal Cancer by Selected Characteristics at Reference Date,[a] Swiss HIV Cohort Study, 1988–2011

	Cases		Controls		OR[b]	95% CI
	No.	%	No.	%		
Overall	59		295			
Smoking status						
Never	12	22	100	37	1	Referent
Former	5	9	43	16	0.96	0.32, 2.89
Current	37	69	130	48	2.59	1.25, 5.34
Unknown	5		22			
History of cART use						
Never	3	5	39	13	1	Referent
Ever	56	95	256	87	6.85	0.90, 52.40
History of AIDS						
No	34	58	204	69	1	Referent
Yes	25	42	91	31	1.72	0.94, 3.14
Nadir CD4+ cell count, cells/μL						
≥200	15	25	125	42	1	Referent
50–199	20	34	113	38	1.68	0.77, 3.65
<50	24	41	57	19	3.96	1.82, 8.61
Per 100-cell/μL decrease					1.53	1.18, 2.00

rtisch et al. Am J Epidemiol. 2013;178(6):877–884

3-State Model of Progression to IAC



Natural history of CIN: *summary*

	Regress	Persist	Progress to CIS	Progress to invasion
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	< 56%	--	>12%

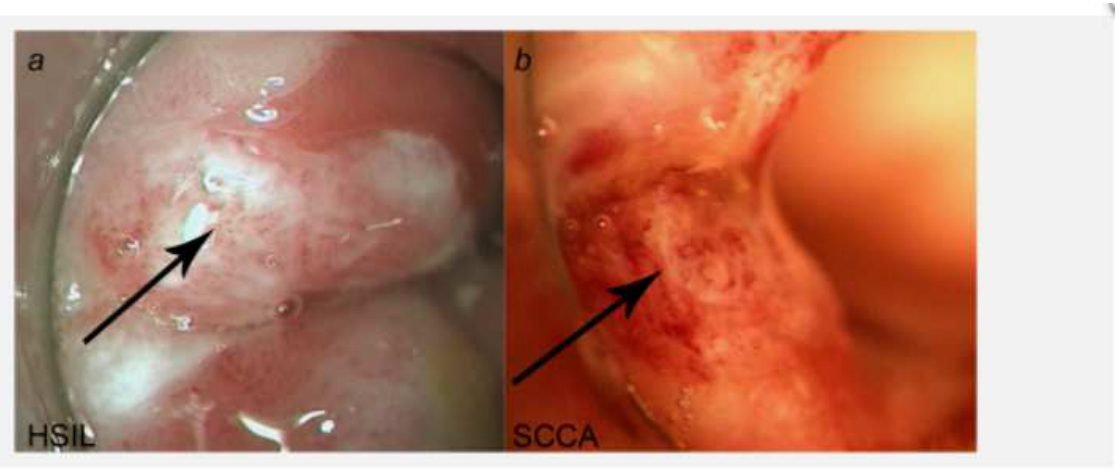
64 studies, 274 carcinomas, 15,473 CIN cases

Followup <1-12 years

Östör A.G, Int J Gyne Path 1993;12:186-192

Progression of Anal HSIL to Invasive Anal Cancer in HIV-infected MSM

- 27 incident cases of IAC developed at same site as previously well documented HSIL histopathology



Case 6. Arrow indicates anal high-grade squamous intraepithelial lesion (HSIL) biopsied in May 2001 at the end of sia Study. Patient lost to follow-up. (*b*) The same man presented with a palpable mass in June 2002 in exactly the s previously biopsied HSIL; arrow indicates invasive squamous cell carcinoma (SCCA). [Color figure can be viewed issue, which is available at wileyonlinelibrary.com.]

Berry et al. Int J Cancer. 2013 Aug 12. doi: 10.1002/ijc.28431

Estimates of HSIL→IAC Progression

- No prior direct estimates of the progression rate from HGAIN to anal cancer in HIV infected inception cohorts.
- From the available data, Machalek[1] calculated a *theoretical progression rate* from HGAIN to anal cancer
  - in HIV+ MSM
    - 1/633 per patient per year (0.00158/yr)
    - **1/377 per patient per year in the HAART era per year (0.00265/yr)**
  - In HIV negative men
    - 1/4196 patients per year in HIV-negative men (0.024%/yr)
- We empirically estimated progression rate in a cytology inception cohort of HIV infected adults during HAART era (2002-2012)
  - **1/263 per year (95% CI: 1/714 - 1/122)**
  - **0.0038 (95% CI: 0.0014 – 0.0082)**

Machalek et al. *Lancet Oncol* 2012; 13: 487–500
Cachay et al 2013 (submitted)

Estimates of HSIL→IAC Progression from a Baseline Cytology Inception Cohort (n=23 IAC cases dx >180d after baseline cytology)

Time in years	Nº patients at risk	Percent developing IAC from baseline [percentage, (95% Confidence interval)]
< HSIL		
1	2182	0.09 (0.02 – 0.36)
2	1827	0.14 (0.05 – 0.45)
3	1516	0.33 (0.15 – 0.73)
4	1223	0.47 (0.23 – 0.95)
5	983	0.47 (0.23 – 0.95)
HSIL		
1	320	0.30 (0.04 – 2.13)
2	266	0.65 (0.16 – 2.60)
3	217	1.03 (0.33 – 3.17)
4	176	1.03 (0.33 – 3.17)
5	141	1.65 (0.59 – 4.52)

Sensitivity analysis includi
10 cases diagnosed d30-d1
HSIL 5-yr incidence
3.24% (95% CI: 1.70 – 6.12

ay et al 2013 (submitted)

Estimates of AIN regression rates (HSIL→<HSIL) in HIV-infected populations

- In the Australian SPANC$_1$ study
  - Among HIV+ men with HSIL at baseline,
    - incidence of change to non-HSIL was **41 per 100 p-yrs**.
    - Applying density method of risk estimation
      - **2 year probability of regression**
        - **1 – exp(- 0.41 * 2) = 0.56**
- In the UCSD Owen Clinic anal neoplasia cohort (2002-2012) using multistate Markov modeling$_2$
  - N=23 IAC cases diagnosed >180 days after baseline cytology result (to avoid prevalence bias)
  - Depending on assumptions regarding sensitivity and specificity of cytology with HRA biopsy as reference standard
  - Regression probabilities at 2 years varied from 0.27 – 0.62

Grulich et al. Sexual Health 2013; 10(6):576
Agmas et al. CROI 2014

Estimated 2-year Transition Probabilities for Progression and Regression from HGAIN Adjusted for Cytology Misclassification Assumptions

Model	SE/SP[1]	2-year Transition Probability [95% C.I.[3]]	
		HGAIN → < HGAIN	HGAIN → IAC[2]
1	0.66 / 0.90	0.27 [0.21 - 0.33]	0.022 [0.014 - 0.033]
2	0.89 / 0.96	0.62 [0.58 - 0.66]	0.015 [0.001 - 0.022]
3	0.74 / 1.0	0.61 [0.58 - 0.65]	0.009 [0.006 - 0.014]
4	0.47 / 1.0	0.32 [0.28 - 0.36]	0.009 [0.006 - 0.013]

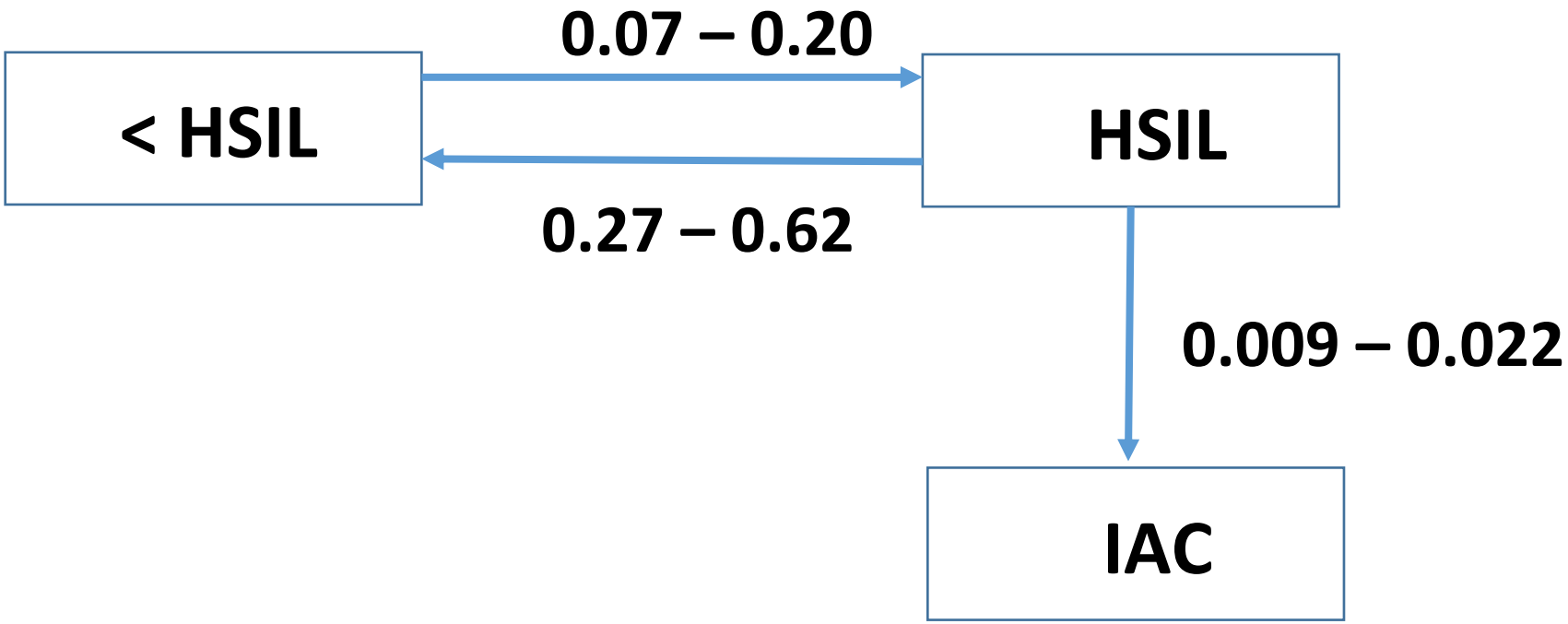
1. SE: sensitivity; SP: specificity [reference standard: HRA-directed biopsy] (from Mathews et al. PLoS One 2010; 5 (8):e12284)

2. HGAIN: high grade anal intraepithelial neoplasia. IAC: invasive anal cancer

3. 95% confidence interval

gmas, Cachay & Mathews. CROI 2014

3-State Model of Progression to IAC: Unadjusted Summary Estimates at 2 years



stimates are 2-year transition unadjusted probabilities from multistate transition models
ange of estimates are based on assumptions regarding sensitivity and specificity of anal cytology

Limitations of the Multistate Model Transition Probability Estimates

- Do not take into account potentially prognostic factors including
  - Extent and location of disease visualized at HRA
  - Smoking status
  - CD4 and viral load
  - Antiretroviral therapy effects

Conclusions

- Given the low short term (2-year) probabilities of progression to IAC AND
- Given the moderate to high probabilities of regression of HSIL to less than HSIL cytology AND
- Given the morbidity of HSIL ablative treatment AND
- Given high recurrence rates among HIV-infected patients
- After careful initial HRA evaluation and biopsy
  - It may be reasonable to defer routine immediate treatment for HSIL provided that close monitoring with HRA and DRE is available

International Anal Neoplasia Society (IANS)

- IANS mission is to provide a forum for exchange of ideas and dissemination of knowledge regarding the pathogenesis, diagnosis, treatment and prevention of anal neoplasia among individuals with a broad spectrum of background, viewpoints and geographic origin.
- http://ians.memberlodge.org/
- IANSociety@gmail.com