

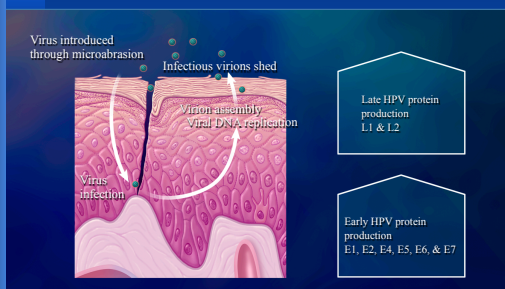
# IMMUNOTHERAPY FOR HPV-RELATED DISEASE IN HIV-POSITIVE AND HIV-NEGATIVE MEN AND WOMEN

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## Outline

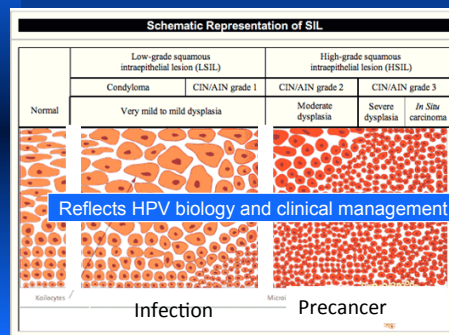
- Epidemiology of HPV-related cancer in the setting of HIV infection
- Pathogenesis of HPV-related cancer in the setting of HIV infection
  - HIV-HPV interactions
  - Immune response to HPV
- Immunotherapy of HPV-related cancer in the setting of HIV infection

## HPV infection and productive life cycle



Adapted from Doorbar J. *J Clin Invest*. 2005;115:87-915.

## 2-tiered system: LSIL & HSIL



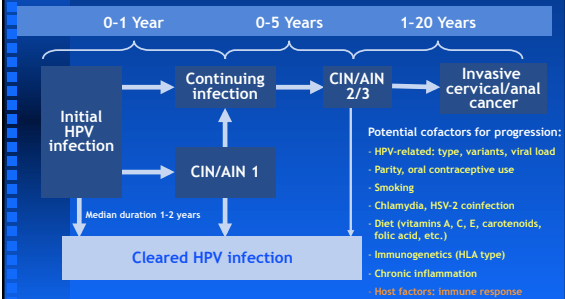
## Incidence of HPV-associated cancers in HIV-cancer registry match

Table 6. Relative risks\* (by human immunodeficiency virus [HIV] exposure group) of human papillomavirus-associated anogenital cancers among 309 365 patients with acquired immunodeficiency syndrome (AIDS) (AIDS-Cancer Match Registry, United States, 1978-1996)

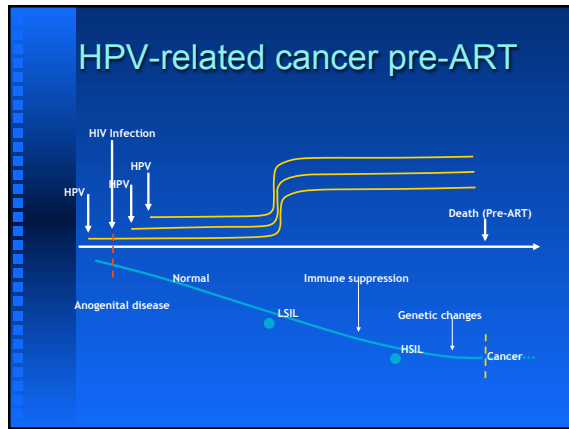
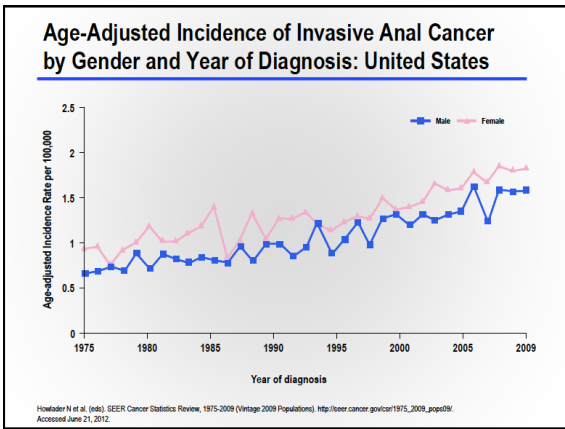
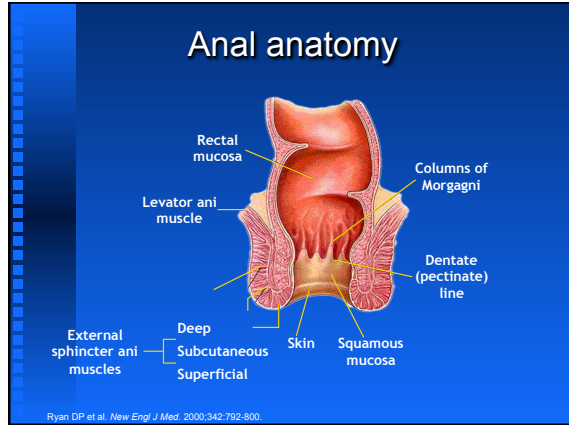
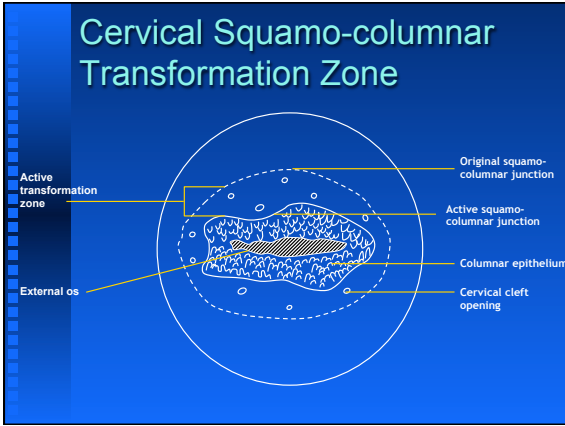
HIV exposure category	Relative risk (95% confidence interval) (No. of observed cancers)			
	Cervix	Vulva/vagina	Anus (women)	Anus (men)
	<b>Invasive cancers</b>			
Homosexual contact†	NA‡	NA‡	NA‡	59.5 (51.5-68.4) [197]
Heterosexual contact	4.9 (2.7-8.2) [14]	7.1 (2.3-16.4) [5]	8.0 (1.7-23.4) [3]	—
Intravenous drug use§	7.0 (4.7-10.0) [20]	5.5 (1.8-12.9) [5]	7.3 (1.5-31.4) [3]	5.9 (2.7-11.2) [9]
Menopausal/transfusion¶	—	—	—	—
Other/unknown	1.4 (0.6-3.2) [1]	7.6 (0.8-23.9) [2]	6.4 (0.3-33.9) [1]	47.1 (7.4-317.9) [8]
All	5.4 (3.9-7.2) [44]	5.8 (3.0-10.2) [12]	6.8 (2.7-14.0) [7]	37.9 (33.0-43.4) [214]
	<b>In situ cancers</b>			
Homosexual contact†	NA‡	NA‡	NA‡	99.8 (81.4-121.2) [102]
Heterosexual contact	4.5 (4.0-5.1) [251]	5.1 (1.7-12.0) [5]	—	—
Intravenous drug use§	4.6 (4.2-5.1) [57]	2.2 (0.5-6.3) [3]	17.2 (0.4-96.0) [1]	5.6 (1.2-16.5) [3]
Menopausal/transfusion¶	3.9 (2.1-6.5) [14]	—	—	—
Other/unknown	5.0 (4.0-6.2) [86]	9.0 (1.9-26.3) [3]	—	7.9 (0.2-43.7) [1]
All	4.6 (4.3-5.0) [722]	3.9 (2.0-7.0) [11]	7.8 (0.3-43.6) [1]	60.1 (49.2-72.7) [106]

Frisch et al; JNCI 2000; 92: 1500-10

## Natural history of cervical and ASIL(AIN)



Adapted from Pinto AP, Crum CP. *Clin Obstet Gynecol*. 2000;43:352-362.



### Anal cancer rates in North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) 1996-2007

Incidence/100,000 (85% CI)

- HIV-infected
  - MSM: 131 (109-157)
  - MSW: 46 (25-77)
  - Women: 30 (17-50)

Silverberg M et al. CID 2012; 54:1026-34

### Cervical cancer incidence

Table 3: Cervical cancer incidence in Latvia (estimations for 2012)

Indicator	Latvia	Northern Europe	World
Annual number of new cancer cases	284	5,382	527,624
Crude incidence rate <sup>a</sup>	23.6	10.6	15.1
Age-standardized incidence rate <sup>a</sup>	17.3	8.7	14.0
Cumulative risk (%) at 75 years old <sup>b</sup>	1.6	0.8	1.4

Table 3: Cervical cancer incidence in Russian Federation (estimations for 2012)

Indicator	Russian Federation	Eastern Europe	World
Annual number of new cancer cases	15,342	33,882	527,624
Crude incidence rate <sup>a</sup>	20.0	21.7	15.1
Age-standardized incidence rate <sup>a</sup>	15.3	16.3	14.0
Cumulative risk (%) at 75 years old <sup>b</sup>	1.4	1.5	1.4

<http://www.hpvcentre.net/statistics/reports/> accessed 22/5/16

## Why is HPV-related cancer increased in the setting of HIV infection?

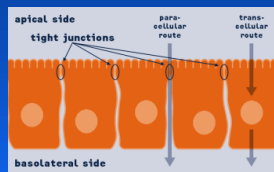
- More exposure to HPV
- Interaction between HIV and HPV at the tissue level
- Attenuated immune response to HPV in the setting of HIV infection

**Table 2. Anal Cytology and Anal Human Papillomavirus (HPV) Test Results by Participant Category for the 621 Participants in the SUN Study, 2004-2006**

Diagnosis	All Participants	MSM	Women	MSW
<b>Anal cytology results</b>				
Negative	336 (54)	165 (44)	97 (65)	74 (80)
ASC-US	79 (13)	52 (14)	20 (13)	7 (8)
ASC-H	17 (3)	12 (3)	3 (2)	2 (2)
LSIL	149 (24)	116 (31)	25 (17)	8 (9)
HSIL	40 (6)	34 (9)	5 (3)	1 (1)
<b>HPV types detected</b>				
Any	552 (89)	363 (96)	135 (90)	54 (59)
High-risk	510 (82)	336 (89)	126 (84)	48 (52)
Low-risk	471 (76)	324 (85)	110 (73)	37 (40)
16 or 18	255 (41)	192 (51)	47 (31)	16 (17)

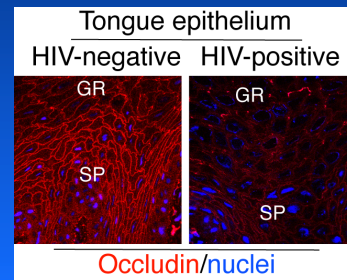
Conley et al. JID 2010; 202:1567-76

## HIV-HPV interaction at the tissue level

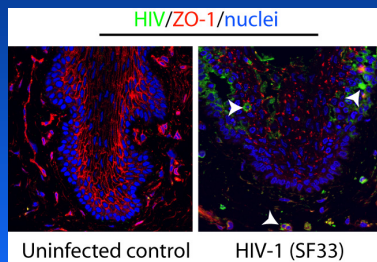


Tat and gp120 reduce integrity of tight junctions?

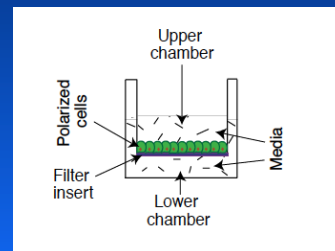
## Disruption of oral epithelial tight junction proteins in HIV-infected individuals



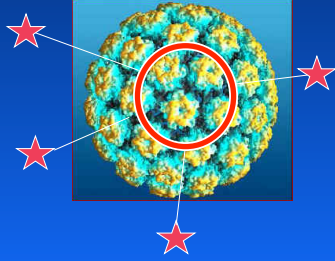
## Dissociation of ZO-1 in HIV-infected tongue tissue



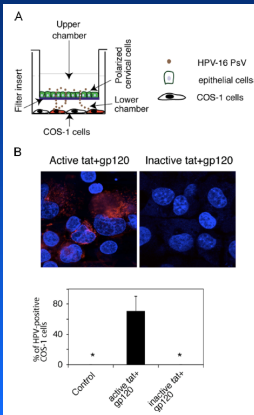
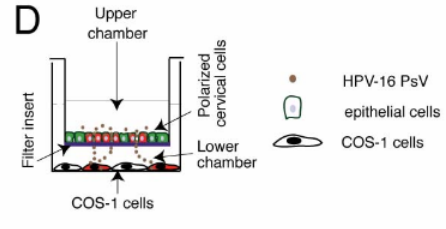
## Polarized tissue culture



### HPV 16 pseudovirions

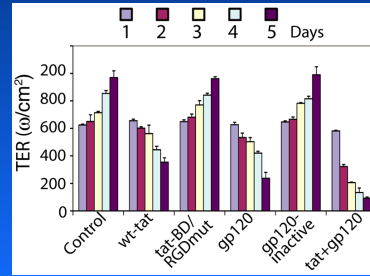


### Polarized tissue culture

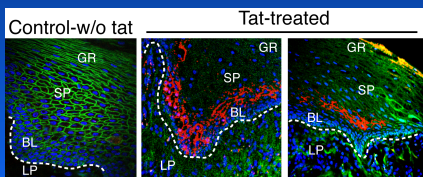


Tugizov S et al  
Virology 2013; 446:  
378-88

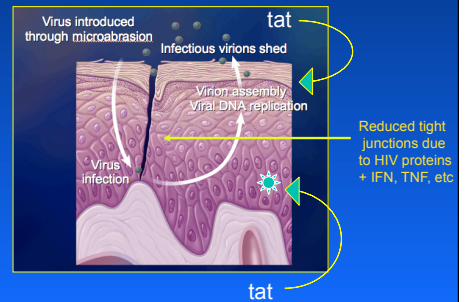
### Effect of tat and gp120 on trans-epithelial resistance



### Tat potentiates HPV entry into epithelium



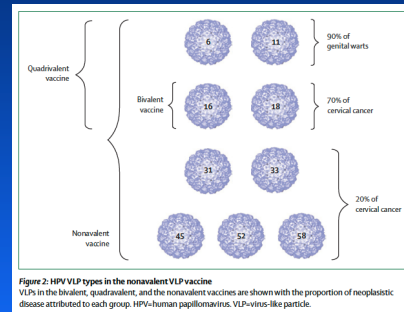
### Model for HPV-HIV interaction in epithelium



## Immune response to HPV

- Cell-mediated immune response
  - Regression of warts preceded by infiltration of T cells
  - Humoral immunity is not therapeutic

## The nonavalent HPV vaccine



Schiller J. Lancet Oncol 2015;16(5):e217-25

## The nonavalent HPV vaccine

TABLE 2. Results of a Phase III efficacy trial comparing 9-valent human papillomavirus (HPV) vaccine (9vHPV) with quadrivalent HPV vaccine (4vHPV), per protocol population\* in females aged 16 through 26 years<sup>†</sup>

Endpoint-related types	Endpoint	9vHPV		4vHPV		Vaccine efficacy	
		No. participants	Cases	No. participants	Cases	%	(95% CI)
HPV 31, 33, 45, 52, 58	≥CIN2, VIN2/3, VIN2/3	6,016	1	6,017	30	96.7	(80.0–99.8)
	≥CIN2	5,948	1	5,943	27	95.3	(79.5–99.8)
	6-month persistent infection	5,939	35	5,953	810	96.0	(94.4–97.2)
HPV 6, 11, 16, 18	≥CIN2 <sup>‡</sup>	5,823	1	5,832	1	—	—
	Anogenital warts	5,876	5	5,893	1	—	—

MMWR / March 27, 2015 / Vol. 64 / No. 11

## Lessons from therapeutic vaccine studies

- Overlapping peptide vaccines
- VGX-3100 E6/E7 DNA vaccine

## Overlapping peptide vaccines

- 20 women with HPV-16–positive, grade 3 vulvar intraepithelial neoplasia were vaccinated three or four times with a mix of long peptides from the HPV-16 viral oncoproteins E6 and E7 in incomplete Freund's adjuvant

Kenter GG et al. New Engl J Med 2009; 61:1838-1847

## Overlapping peptide vaccines

- At 3 months after the last vaccination, 12 of 20 patients (60%) had clinical responses and reported relief of symptoms
  - Five had complete regression, and HPV-16 was no longer detectable in four.
- At 12 months of follow-up, 15 of 19 patients had clinical responses (79%), with a complete response in 9 of 19 patients (47%)

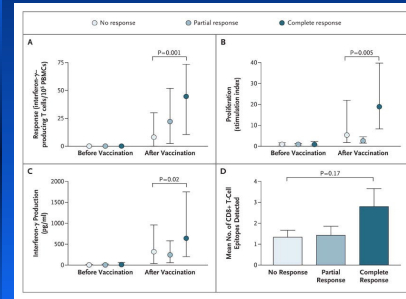
Kenter GG et al. New Engl J Med 2009; 61:1838-1847

## Overlapping peptide vaccines

- Post hoc analyses suggested that patients with a complete response at 3 months had a significantly stronger interferon- $\gamma$ -associated proliferative CD4+ T-cell response and a broad response of CD8+ interferon- $\gamma$  T cells than did patients without a complete response

Kenter GG et al. New Engl J Med 2009; 61:1838-1847

## Immune Response before and after Vaccination



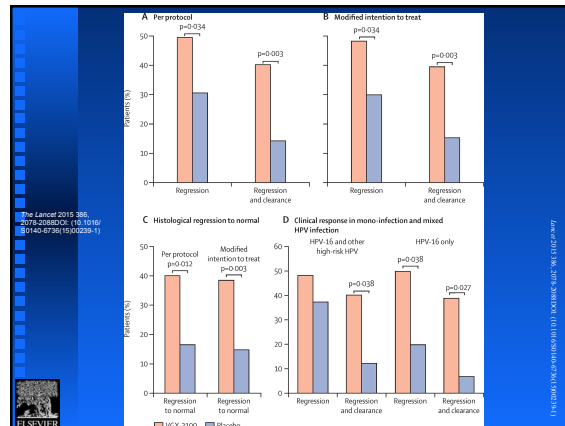
Kenter GG et al. N Engl J Med 2009;361:1838-1847

NEW ENGLAND JOURNAL OF MEDICINE

## VGX-3100 Phase 2b in CIN2/3

- Randomized, double-blind, placebo-controlled study
- 167 immunocompetent women (age 18-55 received) either VGX-3100 (n=125) or placebo (n=42).
- In the per-protocol analysis 53 (49.5%) of 107 VGX-3100 recipients and 11 (30.6%) of 36 placebo recipients had histopathological regression (p=0.034)
- In the modified intention-to-treat analysis 55 (48.2%) of 114 VGX-3100 recipients and 12 (30.0%) of 40 placebo recipients had histopathological regression (percentage point difference 18.2 [95% CI 1.3-34.4]; p=0.034)
- VGX-3100 is the first therapeutic vaccine to show efficacy against CIN2/3 associated with HPV-16/18

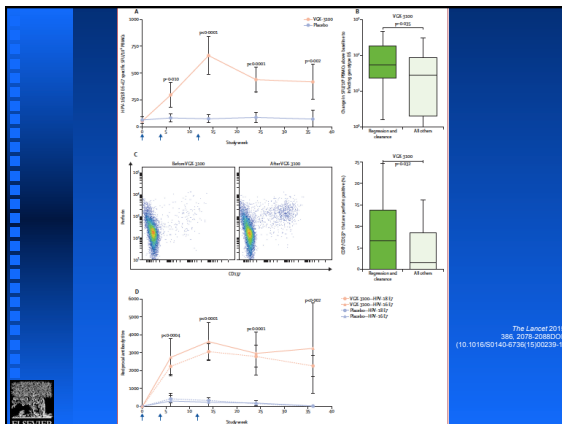
Trimble CL et al. Lancet Oncol 2015; 386: 2078-88



The Lancet 2015; 386: 2078-2088 DOI: 10.1016/S1473-2165(15)00239-1



1473-2165/15/\$30.00 © 2015 Elsevier Ltd. All rights reserved.



The Lancet 2015; 386: 2078-2088 DOI: 10.1016/S1473-2165(15)00239-1



## Advaxis

- ADXS11-001, a live attenuated *Listeria monocytogenes* listeriolysin O (LLO) immunotherapeutic agent expressing an HPV16-E7 fusion protein
- has been shown to induce HPV-specific T cell responses in animal models, and to have clinical activity in cervical cancer

# Advaxis

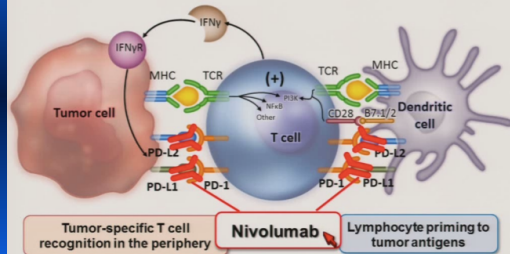
Clinical Pipeline

PRODUCT	INDICATION	PHASE 1	PHASE 2	PHASE 3	Partner
CERVICAL CANCER*	AMDCERN - Adjuvant Randomized vs Placebo			Phase 3	AMGEN
	M Metastatic - COC (DB)		Phase 2		AMGEN
	M Metastatic - Single Arm High Dose		Phase 1/2		
Asialoglycine Receptor	C Metastatic - Combo with durvalumab		Phase 1/2		MedImmune
	HEAD AND NECK CANCER*				
M	Neoadjuvant - Window of Opportunity - Mount Sinai		Phase 2		Mount Sinai
	ANAL CANCER*				
M	RTGG - Adjuvant Randomized vs Control			Phase 3/4	RTGG
	M Adjuvant - Single Arm High Risk - Brown University (BUOG)		Phase 1/2		
	Metastatic (FACETS)		Phase 2		
ADXS-PBA	PROSTATE CANCER				
	C Metastatic - Combo with KEYTRUDA® (pembrolizumab)		Phase 1/2		MSD
ADXS-HER2	HER2-POSITIVE SOLID TUMORS (INCLUDING OSTEOSARCOMA)				
	M Metastatic - Single Arm		Phase 1		
M	Osteosarcoma		Phase 2		

\* Orphan Drug Designation

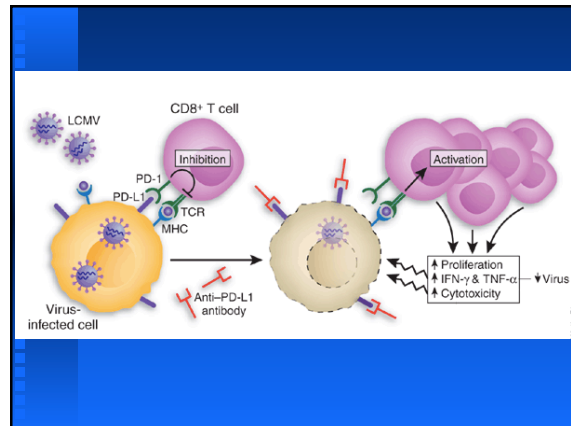
Legend: C Combination, M Monotherapy, Active (orange), Planned (blue)

# Role of the PD-1 pathway in suppressing anti-tumor immunity



# The future

- Need for therapeutic vaccines
- Improvements in antigen delivery
- Checkpoint inhibitors



# The future

- Combination of therapeutic vaccine with checkpoint inhibitors
- Useful in the setting of HIV infection?
  - Nature of immune "lesion" in HIV infection is not clear