Kirby Institute

Using data on pathogenesis and epidemiology to inform anal cancer screening strategies: data from the Study of Prevention of Anal Cancer (SPANC)

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Preventing anal cancer

1. Primary prevention: HPV vaccination

2. Secondary prevention: screening for pre-cancerous anal lesions

3. Tertiary prevention: early detection and treatment of anal cancer

Two main findings from SPANC that impact on prevention strategies 1 and 2

SPANC study

The Study of the Prevention of Anal Cancer (SPANC)

- Natural history study of anal HPV infection and associated anal diseases

Mainly community-based recruitment

- HIV-positive and HIV-negative gay men
- 35 years and above

5 study visits over 3 years

- Baseline, 6-month, and 3 annual follow-up visits
- Participants undergo DRE, anal HPV testing, anal cytology and high resolution anoscopy at all study visits

Cohort characteristics

- 617 men enrolled by August 2015
- Median age 49 years (range: 35-79)
- 35.7% (n=220) HIV+
- 85% were recruitment from the community
- 53% reported more than > 200 lifetime male sexual partners
- 28% reported > 10 partners in the previous 6 months
- Among HIV+ men:
  - 94% on treatment
  - current CD4 count >350 cells/μL in 89%
  - nadir CD4 count <200 in 45%
  - undetectable viral load in 90%

1. Primary prevention: HPV vaccination

Prophylactic HPV vaccination

- Vaccine efficacy and HPV infection (cervical data)
  - **not effective** in those with **current** HPV infection (genotype specific)
  - effective in those with ***past*** HPV infection (ie seropositive, DNA negative)
  - Effective in those with ***treated*** HPV disease
- Efficacious in reducing vaccine-associated anal HSIL in young (<26 years) sexually inexperienced MSM

HPV vaccination will prevent anal cancer in decades to come

Table 2. Vaccine Efficacy against HPV-6, 11, 16, or 18–Related Anal Intraepithelial Neoplasia (AIN) and Anal Cancer in the Per-Protocol Efficacy Population.*

End Point	qHPV Vaccine (N=299)				Placebo (N=299)				Observed Efficacy (95% CI)†
	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	No. Included in Analysis	No. of Affected Participants	Person-Yr at Risk	Events per 100 Person-Yr at Risk	
									percent
By lesion type									
AIN grade 1	194	4	383.1	1.0	208	16	413.8	3.9	73.0 (16.3 to 93.4)
Condyloma acuminatum	194	0	386.8	0.0	208	6	418.2	1.4	100 (8.2 to 100)
Flat lesion	194	4	383.1	1.0	208	11	416.7	2.6	60.4 (−33.5 to 90.8)
AIN grade 2 or 3	194	3	383.9	0.8	208	13	417.2	3.1	74.9 (8.8 to 95.4)

* The per-protocol efficacy population consisted of participants who were seronegative and had HPV DNA–negative swab and biopsy specimens on day 1 for relevant vaccine types, were negative for vaccine-type DNA through month 7, and did not have any protocol violations. To eliminate

Palefsky J *et al*, NEJM 2011

HPV16 seroconversion in gay men

- Based on the Health In Men study of initially HIV- men and positive Health study of HIV+ men in 2000-2007
- HPV serology at the German Cancer Research Centre
- HPV seroconversion common up to age 45

TABLE 1. HPV16 Seroprevalence and Seroincidence by Age-Group

	Seroprevalence				Seroincidence			
Age Group	HIV+ N (%)*	95% CI	HIV− N (%)†	95% CI	HIV+ per 100 PY (95% CI)	Person-Years Follow-Up	HIV− per 100 PY (95% CI)	Person-Years Follow-Up
<35	15 (45)	28–64	124 (19)	16–22	0	14	4.2 (3.2–5.6)	1096
35–44	31 (46)	34–59	129 (28)	24–33	4.7 (1.2–19.0)	43	3.1 (2.2–4.3)	1157
>45	44 (43)	33–53	86 (37)	31–44	0	99	1.4 (0.7–2.5)	739
Total	90 (44)		339 (25)		1.3 (0.3–5.2)		3.1 (2.5–3.8)	

*Number and percentage of HIV-positive men HPV16 seropositive in the age-group.
†Number and percentage of HIV-negative men HPV16 seropositive in the age-group.

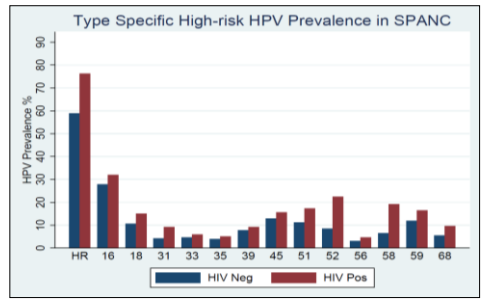
IM Poynten *et al*, STD 2012

Anal HPV Prevalence in SPANC

At baseline

- 86.6% had ≥ one HPV genotype detected
- 65.2% had ≥ one high risk HPV genotype detected
- 64.7% had ≥ one 9v HPV genotype but nil positive for all 9 types
- HPV16 most common (29.4%), followed by HPV6 (18.0%) and HPV52 (13.5%)

Anal high risk HPV Prevalence



Incidence of anal 9v HPV genotypes by age[1]

9V types	Person years	Number positive[2]	Incidence (per 100PY)[3]	95% CI
35-44	78.2	8	10.2	5.1-20.4
45-54	114.0	13	11.4	6.6-19.6
55-64	56.3	9	16.0	8.3-30.7
65+	25.8	4	15.5	5.8-41.3
Total	274.3	34	12.4	8.9-17.3
HPV16	183.8	4	2.2	8.9-17.3

1. Interim incidence, based on data available to August 2015
2. 9v HPV incidence in those participants who are NEGATIVE to ≥ one 9v type at baseline
3. Double positive HPV (at 6 month and 12 month visit)

Anal HPV incidence from first-year follow-up data

- Overall incidence of any 9v HPV types that persisted at 6-month and 12-month study visits was 12.40 per 100 PY (95% CI 8.86-17.35)
- No significant differences by age (p trend=0.143) or HIV status (13.15 per 100 PY in HIV- and 11.10 per 100 PY in HIV+, p=0.785)
- Completely different to the HPV incidence pattern seen in the cervix, of high incidence only in young women

Main SPANC finding no. 1

Continuing high rates of new anal HPV infection across the age range in gay men. Thus, should consider HPV vaccination for all gay men

What we are doing:

1) Anal cancer advocacy group (ACON, Positive Life NSW, AFAO, NAPWHA, Cancer Council NSW, ASHM, Kirby, Hospital reps, affected community) has made a submission to NSW Health and Victorian Health Department - request for funding

"… the quadrivalent HPV vaccine be offered to all MSM aged 26 years or less attending publically funded sexual health clinics … This includes MSM from cohorts too old for the school program and for MSM in the eligible cohorts who miss out."

2) Protocol for RCT of nonavalent HPV vaccination of gay men aged 27-55 years

Nonavalent vaccine RCT study design

Objective: To determine if administration of 9v HPV vaccine reduces the incidence of persistent infection with HPV16, 18, 6, 11, 31, 33, 45, 52, and/or 58 in HIV+ and HIV- gay men aged 27–55 years

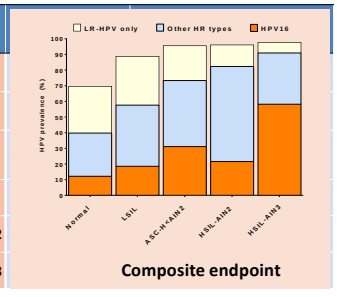
Design: Randomised, placebo-controlled trial. After vaccination, participants followed up 6 monthly for 3 years to measure incidence of 9v-related HPV infection. Powered for 50% reduction in new persistent HPV infection in both HIV+ and HIV- men

308 HIV+ men and 308 HIV- men will be recruited in a 1:1 ratio to receive active vaccine or placebo

2. Secondary prevention: screening for pre-cancerous anal lesions

Anal squamous intraepithelial lesions (ASIL) endpoint definition

Composite endpoint
Negative
Low-grade SIL (LSIL)
ASC-H<AIN2
High-grade SIL (HSIL)
HSIL-AIN2
HSIL-AIN3



Prevalence of ASIL

Lesion grade		Overall (n=616)
Negative		183 (30%)
Low-grade SIL (LSIL)		155 (25%)
ASC-H<AIN2		46 (7%)
High-grade SIL (HSIL)		232 (38%)
	HSIL-AIN2	51 (8%)
	HSIL-AIN3	181 (29%)

Prevalence of ASIL

Lesion grade		HIV-Negative (n=369)	HIV-Positive (n=220)	p-value
Negative		135 (34%)	48 (22%)	0.001
Low-grade SIL (LSIL)		97 (24%)	58 (26%)	0.603
ASC-H<AIN2		36 (9%)	10 (5%)	0.043
High-grade SIL (HSIL)		128 (32%)	104 (47%)	<0.001
	HSIL-AIN2	30 (8%)	21 (10%)	0.395
	HSIL-AIN3	98 (25%)	83 (38%)	<0.001

Incidence of anal HSIL[1]

Among men HSIL-free at baseline:

Total person-years (PY)	**479**
Incident cases (n)	**66**
Incidence rate	**14/100 PY (95% CI 11-18)**

1. Interim incidence, based on data available to August 2015

Clearance of anal HSIL[1]

Among those with HSIL at baseline:

Total person-years (PY)	**233**
Number cleared	**90**
Clearance rate	**39/100PY (95% CI 32-47)**

1. Interim clearance, based on data available to August 2015

SPANC participant with persistent HSIL

SPANC ID	XXXX		**Age**	46	
			HIV Status	Negative	
Study visit #	**1**	**2**	**3**	**4**	**5**
Date of visit	February 2011	August 2011	March 2012	March 2013	February 2014
Cytology	**HSIL-AIN3**	**HSIL-AIN3**	**PHSIL**	**PHSIL**	**PHSIL**
Histology	Negative	**HSIL-AIN2**	**HSIL-AIN2**	**HSIL-AIN3**	**HSIL-AIN3**
Number of octants with bHSIL	0	**2**	**1**	**1**	**2**
HPV analysis					
HPV 16	**Positive**	**Positive**	**Positive**	**Positive**	**Positive**
HPV 18	Negative	**Positive**	Negative	Negative	Negative
HPV 31	Negative	Negative	Negative	Negative	Negative
HPV 33	Negative	Negative	Negative	Negative	Negative
HPV 35	Negative	Negative	Negative	Negative	Negative
HPV 39	Negative	Negative	Negative	Negative	Negative
HPV 45	Negative	Negative	Negative	Negative	Negative
HPV 51	**Positive**	Negative	**Positive**	Negative	**Positive**
HPV 52	Negative	Negative	Negative	Negative	Negative
HPV 56	Negative	Negative	Negative	Negative	Negative
HPV 58	**Positive**	**Positive**	**Positive**	**Positive**	**Positive**
HPV 59	**Positive**	Negative	**Positive**	Negative	**Positive**

SPANC participant with resolved HSIL

SPANC ID	XXXX		**Age**	60	
			HIV Status	Negative	
Study visit #	**1**	**2**	**3**	**4**	**5**
Date of visit	May 2011	January 2012	June 2012	March 2013	July 2014
Cytology	**HSIL-AIN3**	HSIL-AIN3	LSIL	PLSIL	Negative
Histology	**HSIL-AIN3**	**HSIL-AIN2**	**HSIL-AIN3**	LSIL	Normal
Number of octants with bHSIL	**1**	**1**	**1**	0	N/D
HPV analysis					
HPV 16	Negative	Negative	Negative	Negative	Negative
HPV 18	**Positive**	**Positive**	**Positive**	**Positive**	Negative
HPV 31	Negative	Negative	Negative	Negative	Negative
HPV 33	Negative	Negative	Negative	Negative	Negative
HPV 35	Negative	Negative	Negative	Negative	Negative
HPV 39	Negative	Negative	Negative	Negative	Negative
HPV 45	Negative	Negative	Negative	Negative	Negative
HPV 51	Negative	Negative	Negative	Negative	Negative
HPV 52	Negative	Negative	**Positive**	Negative	Negative
HPV 56	Negative	Negative	Negative	Negative	Negative
HPV 58	Negative	Negative	Negative	Negative	Negative
HPV 59	Negative	Negative	Negative	Negative	Negative

Main SPANC finding no. 2

Anal HSIL is a highly dynamic disease and thus we need to be able to determine which lesions will persist and need treatment

Findings	**Implication**
HSIL prevalence and incidence high, particularly among HIV+ men **HSIL clearance 39/100py with no treatment**	Not all HSIL requires treatment Target treatment at those with persistent HSIL
	Need a screening test to distinguish persistent from transient HSIL - ? Role of biomarkers
	HSIL treatment trials should have a no treatment comparator (ANCHOR trial)

Watch this SPANC-space!

- Baseline papers on prevalence submitted soon
- Papers on incidence and clearance at 6 and 12 months: late 2016
- Incidence at 36 months: late 2018

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