



A new explanation for rising rates of anal cancer

A SYNDEMIC INTERACTION

Dr Jenny McCloskey, Sexual Health Physician, Head Sexual Health Services, Royal Perth Hospital.
Dr Michael Phillips, Director MRF Biostatistics Unit, Harry Perkins Institute for Medical Research.

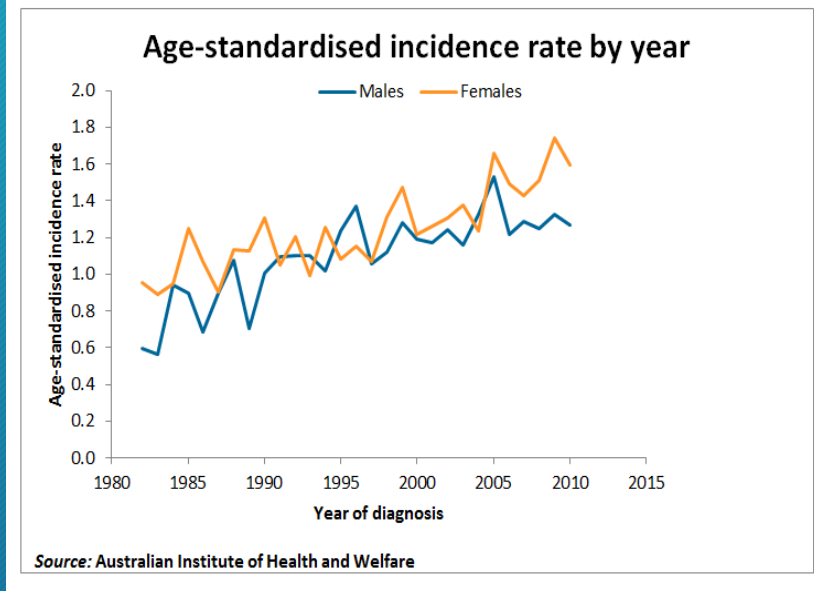


BACKGROUND: ANAL CANCER RATES ARE RISING IN MEN AND WOMEN WORLDWIDE



- AIN associated with HrHPV as a precursor to anal cancer
- anal warts associated with high rates of AIN especially in HIV infection
- cofactors other than HPV are likely to be associated with the development of anal cancer and its precursors

Anal cancer age standardised rates/100,000 in Australia by sex



BACKGROUND: COFACTORS REPORTED WITH DEVELOPMENT OF ANAL CANCER



- Receptive anal SI
- SI before the age of 30
- Lifetime number of sexual partners
- Female sex
- Current cigarette smoking
- Immune suppression post organ transplantation
- HIV infection
- Anal fistulae & epithelial trauma

Genital wart related associations

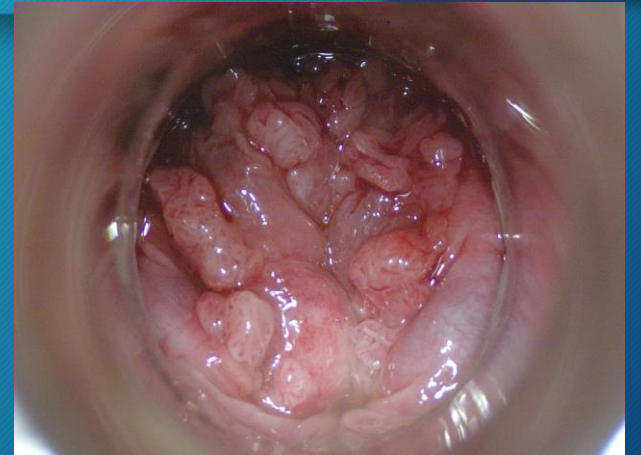
- Patients with GW have significantly increased risk of anal cancer & other cancers e.g. head & neck cancers
- Anal warts- cancer seen to arise out of anal warts
- **Persistence of HrHPV in Danish women with genital warts**

BACKGROUND: THE ROYAL PERTH HOSPITAL SURGICAL DATABASE : HIGH RATES OF HSIL IN WARTS

J McCloskey,* C Metcalf* M French,* V Burke**



- Established 1996
 - a surgical data base of patients treated for anal warts in theatre
 - epidemiological & histological data collected prospectively
 - findings previously reported^{1,2}
 - 52% high-grade in males with HIV
 - 20% high-grade in males without HIV
 - HIV rates of AIN at least double that of HIV negative population



1 McCloskey J, Metcalf C, French M, Flexman J, Burke V, Beilin L. The frequency of high-grade intraepithelial neoplasia in anal/perianal warts is higher than previously recognised. *Int J STD & AIDS* 2007; 18:538-42

2 McCloskey J, Phillips M, French M, Flexman J, McCallum D, Metcalf C. Update on the Royal Perth Hospital Anogenital Wart Database. In: Barros E, editor. *HIV Infection- Impact Awareness and Social Implications of Living with HIV/AIDS: In Tech*; 2011. p. 81-90.

METHODS/ RESULTS: PROSPECTIVE CASE SERIES SURGICAL EXCISION OF WARTS

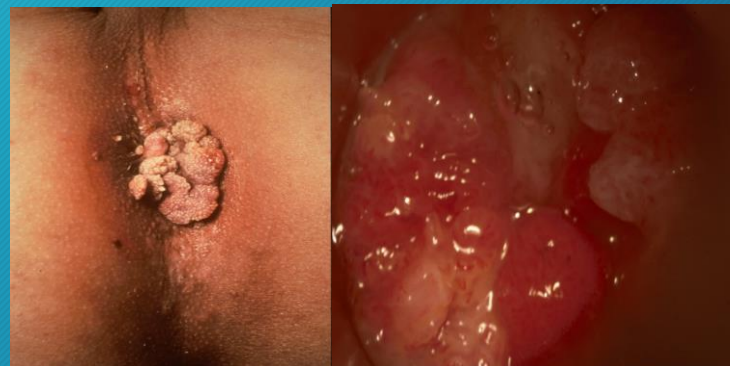


DECEMBER 1995-NOVEMBER 2016**N=463 OPERATIONS=536

- Demographic data collected
 - sex
 - sexual preference
 - lifetime sexual partners
 - history or evidence of gonorrhoea
 - history or evidence of chlamydia
- Anal HPV (HrDigene HCII) June 2005 on

Serology when enrolled for surgery

- syphilis
 - herpes type 2 antibody (HSV2)
 - HAV, HBV, HCV
 - HIV 1 & 2
- All excised samples sent for histopathology



RESEARCH FINDINGS N=314 tested for HrHPV 261 men; 53 women

- The majority of men (75%) were HPV positive compared with 40% of the women
- 80% of the MSM (most of the men) were HPV positive compared with only 47% of heterosexual men
- 40% of the men were HIV positive and HIV was strongly associated with HPV infection
- HPV positivity was associated with 6.5X increased risk of HSIL

WHAT IS A SYNDEMIC¹?- THE WIKEPEDIA DEFINITION²



- ‘A syndemic or synergistic epidemic is the aggregation of two or more concurrent or sequential epidemics or disease clusters in a population with biological interactions, which exacerbate the prognosis and burden of disease.
- The syndemic approach departs from the biomedical approach to diseases to diagnostically isolate, study, and treat diseases as distinct entities separate from other diseases and independent of social contexts.’

The term was developed by [Merrill Singer](#) in the mid-1990s. Syndemics develop under [health disparity](#), caused by [poverty](#), stress, or [structural violence](#) and are studied by [epidemiologists](#) and [medical anthropologists](#) concerned with public health, [community health](#) and the effects of social conditions on health.

1 Tsai AC, Mendenhall E, Trostle JA, Kawachi I. Co-occurring epidemics, syndemics, and population health. The Lancet 2017;389:978-82

2 <https://en.wikipedia.org/wiki/Syndemic> doi 20170905

Structural Equation Models (SEMs)

- SEMs are an alternative to multi-variable models such as logistic regression - the mathematics is the same but these allow other ways to visualise the results.
- They also allow new concepts to be incorporated - particularly path analysis, i.e. what is the route from the predictive variables to the outcome?
- A key element is the concept of a 'Latent' variable - one that cannot be observed directly but can be inferred from other observable variables.

Variables included in the structural pathway equation to high-grade intra-epithelial neoplasia

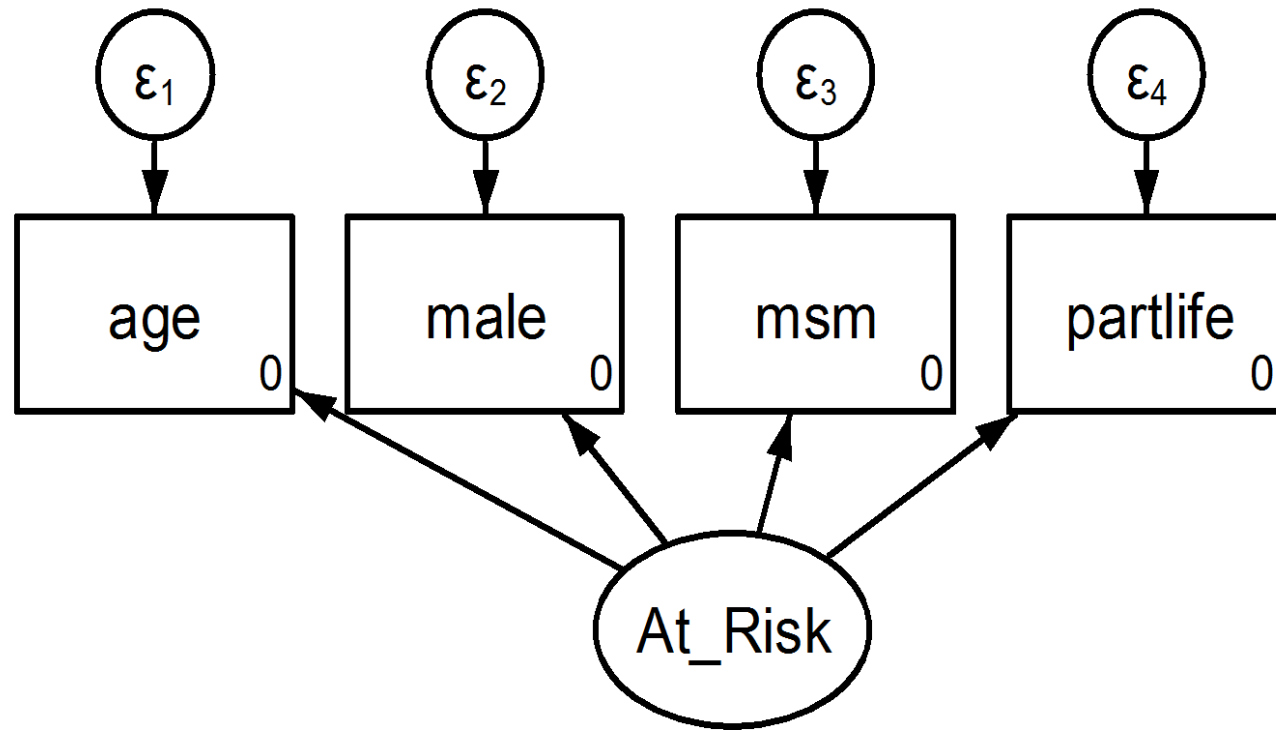
INDEPENDENT variables:

- Warts and high-risk HPV
- HIV
- HSV2
- Gonorrhoea
- Chlamydia
- Hepatitis B infection
- Hepatitis C

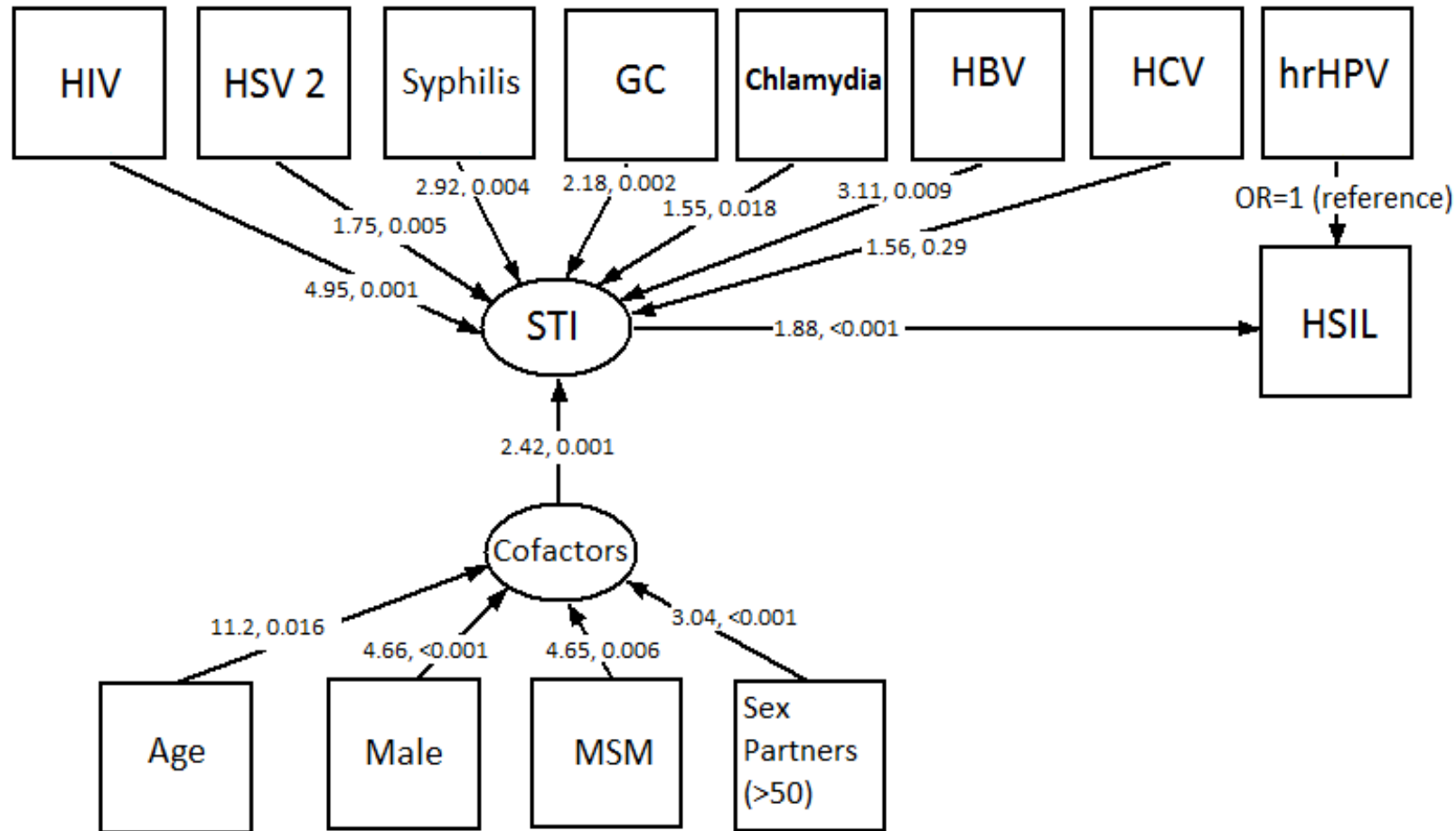
COVARIATES:

- Increasing age
- Males compared to females
- MSM & BSM compared to heterosexual
- Number of sexual partners
(1-10, 11-49, 50 plus)

A simple SEM



HGAIN AS A SYNDEMIC OF STI'S AND OTHER COFACTORS (Structural equation model)



Squares indicate observed variables and ovals indicate unobserved latent variables.

Arrows show hypothetical relationships established by this study.

Values show the odds ratio and p -values for each association indicated by an arrow.

Description of patients

- Men - 261; Women - 53
- Age 33 median; range - 14 to 76
- 80% of men MSM
- 38% of men & 6% of women have more than 50 sexual partners during life
- 75% of men & 40% of women were hrHPV positive
- MEN: 30% HIV +ve, 20% Gonorrhoea +ve, 20% HSV2 +ve, 10% Syphilis +ve
- WOMEN: 0% HIV +ve, 0% Gonorrhoea +ve, 17% HSV2 +ve, 0% Syphilis +ve

Association between high grade dysplasia and high risk HPV

Histology grade		HPV -ve	HPV +ve		Odds ratio (CL _{95%})	p
		n (%)	n (%)			
LSIL	Negative	3 (2.61)	4 (1.17)	306 (67.0)	6.55 (3.39-12.6)	<0.00001
	Atypia, etc.	79 (68.7)	134 (39.2)			
	AIN1	22 (19.1)	64 (18.7)			
HSIL	AIN2	7 (6.09)	68 (19.9)	151 (33.0)	6.55 (3.39-12.6)	<0.00001
	AIN3	4 (3.48)	70 (20.5)			
	Cancer	0	2 (0.58)			
Total		115 (100)	342 (100)	457		

Correlation patterns of STIs

Variable	Component A	Component B	Component C
HPV	0.445		
HIV	0.515		
HSV2	0.437		
HBV	0.518		
HCV		0.702	
Syphilis		0.630	
GC			0.668
CHL			0.723

ASSOCIATION BETWEEN HGAIN & HRHPV, HIV & OTHER STI'S

two-way and three way interactions

Other infection	HR-HPV + other	HR-HPV + HIV + other
HSV 2	7.85	9.89
	2.84-21.7	3.85-25.4
	< 0.001	< 0.001
	32	42
Syphilis	5.58	18.6
	1.33-23.4	5.67-61.0
	0.019	< 0.001
	8	21
Gonorrhoea	6.45	9.11
	2.32-17.9	3.40-24.4
	< 0.001	< 0.001
	28	35
Chlamydia	4.80	7.70
	1.78-13.0	2.52-23.5
	0.002	< 0.001
	34	23

HSV 2 in the presence of HrHPV and HIV was Associated with an increased risk of HGAIN OR 9.89 & also in the absence of HIV OR 7.85

Syphilis in presence of HrHPV and HIV was associated with an increased risk of HGAIN OR 18.6 & also the absence of HIV OR 5.58

Gonorrhoea in the presence of HrHPV and HIV was associated with an increased risk of HGAIN OR 9.11 & also in the absence of HIV OR 6.45

Similar pattern for chlamydia and HBV

HOW THIS DATASET COMPARES TO OTHER RESEARCH:

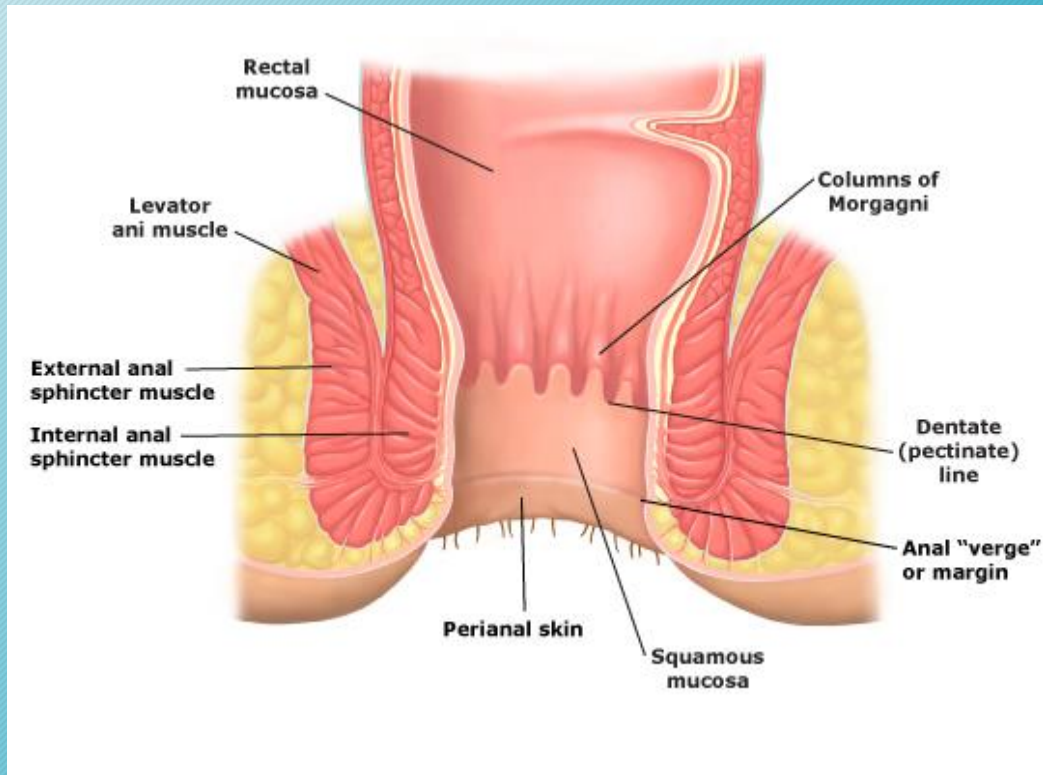
- HrHPV was associated with HSIL OR 4.65 (95%CI 2.28-9.48) $p < 0.001$
- Analysis of HrHPV showed HIV alone was not significantly associated with HSIL OR 1.58 (95%CI 0.17-14.5) $p = 0.68$
- None of the other STI's alone were associated with HSIL

BOOSTED LOGISTIC REGRESSION ANALYSIS ON ODDS RATIO FOR HGAIN

Influence of each variable (%)	
HPV	35.8
HIV	13.9
HSV 2	9.37
Gonorrhoea	9.06
Chlamydia	8.47
Syphilis	8.45
HBV	7.93
HCV	7.00

- Primary importance of HPV demonstrated
- Secondary influence of HIV
- Other STI's very similar and influential in the range of 7-10%

How can STI's act to increase the risk of HSIL?



Local action- increases hrHPV replication

Gonorrhoea-inflammatory extracellular reaction

Chlamydia-persistence of HrHPV

HSV2- a known mutagen, enables uptake of HPV

Syphilis- other evidence for cancer association

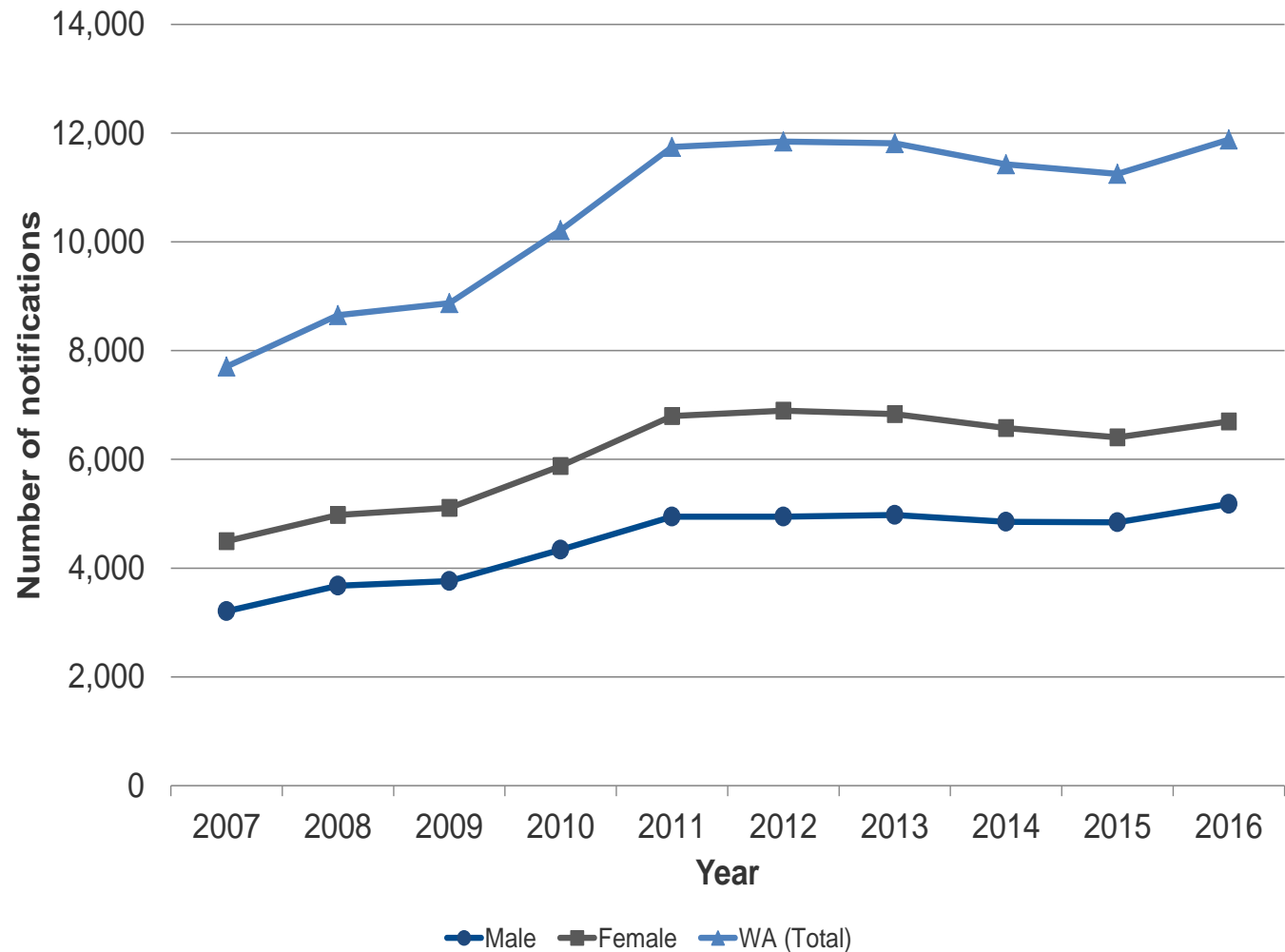
Systemic action

HIV

HBV

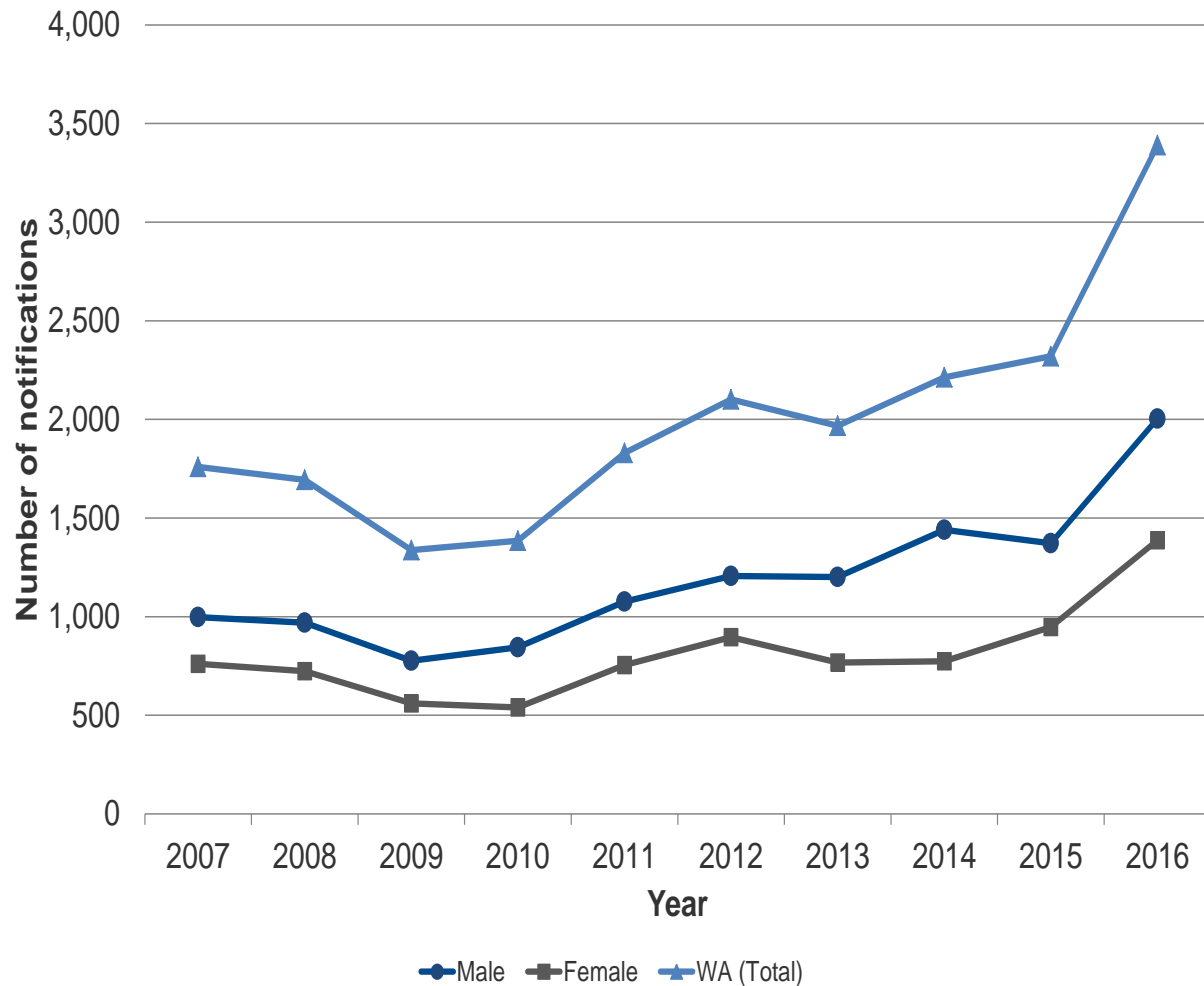
HCV

Number of chlamydia notifications by sex, WA, 2007 to 2016



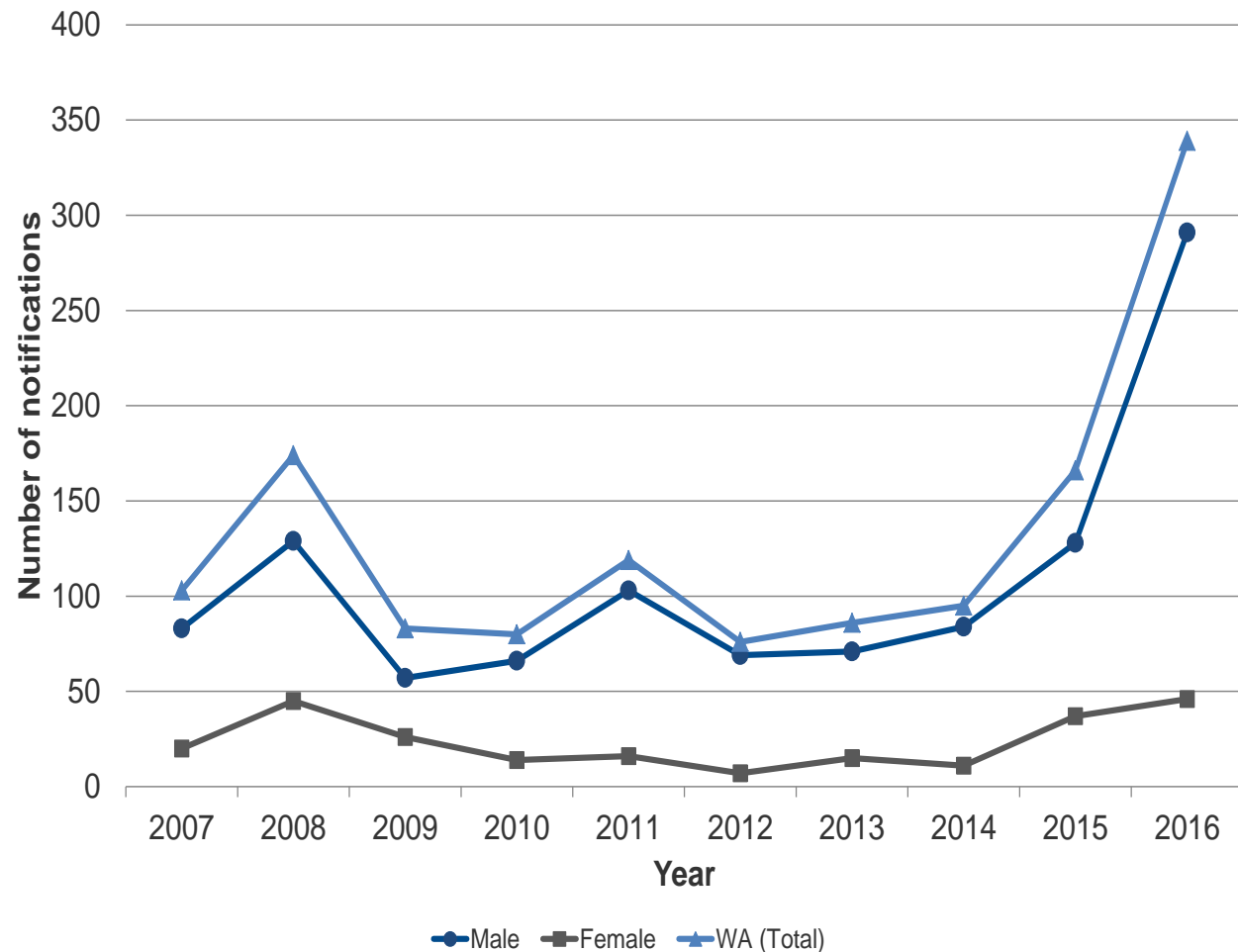
Data courtesy HDWA
Kellie Mitchell and Byron Minas
Source: Epidemiology and Surveillance Program,
Communicable Disease Control Directorate (CDCD)

Number of gonorrhoea notifications by sex, WA, 2007 to 2016



Data courtesy HDWA
Kellie Mitchell and Byron Minas
Source: Epidemiology and Surveillance Program,
Communicable Disease Control Directorate (CDCD)

Number of infectious syphilis notifications by sex, WA, 2007 to 2016



Data courtesy HDWA
Kellie Mitchell and Byron Minas
Source: Epidemiology and Surveillance Program,
Communicable Disease Control Directorate (CDCD)

CONCLUSIONS: increase in anal cancer in MSM predicted

- HGAIN shows syndemic interaction patterns with STIs and behavioural/social factors
- The association of STI's especially gonorrhoea, syphilis chlamydia & genital herpes being linked to the presence of HSIL deserves further study
- Given rates of gonorrhoea are increasing in MSM, they should be counselled to avoid STI acquisition and use condoms
- Detection of HGAIN is problematic with scarce high resolution anoscopy clinics and HSV-2 seropositivity could be used to triage patients at risk of HSIL to these clinics

