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GGD

Amsterdam

A Tale of Two Cities:

**Anal HPV infections and anal dysplasia
in gay and bisexual men
in Amsterdam *and Sydney***

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Public Health Service Amsterdam &
Amsterdam UMC, Amsterdam, the Netherlands

Sydney, 28 September 2018



Conflicts of interest

- Our institution received funding from Sanofi Pasteur MSD for a sub-study on HPV in MSM.
- My institution received in-kind contribution for an HPV study from Stichting Pathologie Onderzoek en Ontwikkeling (SPOO)
- I was a co-investigator in a Merck-funded investigator-initiated study
- I was an investigator on a Sanofi Pasteur MSD sponsored trial
- I served on a vaccine advisory board of GSK
- The presented research was funded by Janssen Infectious Diseases and Vaccines



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MENU**

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Ak 47	€ 6.00
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Research questions

- What is the prevalence, incidence and clearance of anal HPV infections in MSM?
- What is the long-term persistence of newly acquired anal HPV?
- Can we identify risk factors (demographic, behavioral, clinical, or HIV-related) for HGAIN?
- Can we identify biomarkers for HGAIN?



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Overview

- A. H2M study design
- B. Results of H2M: prevalence, incidence and clearance
- C. HRA database Amsterdam: risk factors for HGAIN?
- D. H2M2: the search for biomarkers for HGAIN



Study design H2M

- Prospective cohort study among HIV- and HIV+ MSM (≥ 18 yrs) ^{1,2}
- Enrolment at 3 sites in Amsterdam, the Netherlands
- First enrolment period: July 2010 - July 2011
- Semi-annual follow-up during 24 months per participant
- Interruption of follow-up
- Second enrolment & follow-up period: Nov 2014 – Nov 2015



Research aims

To assess:

1. the incidence rate of anal hrHPV infections
2. the clearance rate of incident anal hrHPV infections
3. the determinants of incidence and clearance of anal hrHPV infections

among MSM

This study provides updated estimates from Mooij S, AIDS 2016



Enrolment & follow-up

	Jul '10	Jul '11	Jul '12	Jul '13		Sep '14	Apr '15	Nov '15
First enrolment								
HIV-	+	+	+			+	+	
HIV-		+	+	+			+	+
HIV+	+	+	+			+	+	
HIV+		+	+	+				
Second enrolment								
HIV-						+	+	
HIV-							+	+
HIV+						+	+	
HIV+							+	+



Data and sample collection

- Anal self-swabs
- Samples were analysed for HPV using the highly sensitive SPF₁₀-PCR-DEIA-LiPA₂₅-system¹
- Regarded as hrHPV types² :
 - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
- Serum was tested by multiplex serology for antibodies to:
 - L1, E6, E7 proteins (tested for HPV 16, 18, 31, 33, 45, 52, 58);
 - E1 and E2 (only for HPV 16 and HPV18)



¹ Molijn J, Clin Vir 2005; 2. Bouvard V, Lancet Oncol 2009; 3 Waterboer 2005



Data and sample collection

- Questionnaire:
 - Demographic characteristics
 - Sexual behaviour
 - Other behavior affecting health (e.g., smoking, drug use)

- Screening for STIs

- Data from HIV treating physicians:
 - HIV RNA VL
 - CD₄ count (baseline and nadir)
 - cART

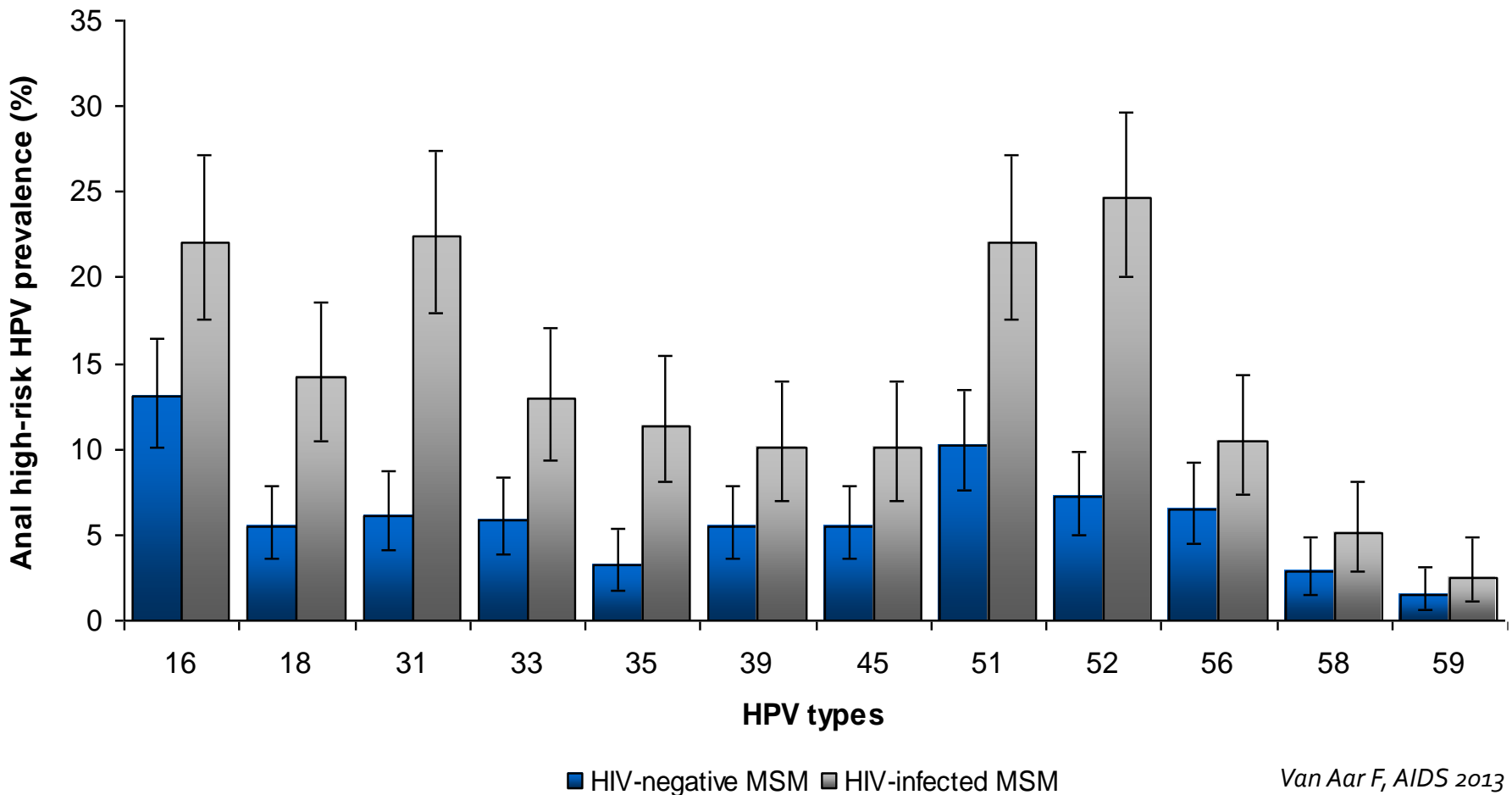


Some key statistics of the study population

N	1044
Median age (IQR) in years	39 (33-47)
Median (IQR) # of lifetime sex partners	150 (50-500)
Median (IQR) # of study visits	5 (2-7)
No. HIV+ (%)	331 (32%)



Anal HPV infection prevalence, by HIV status: 12 hrHPV types



Incidence of anal HPV infections

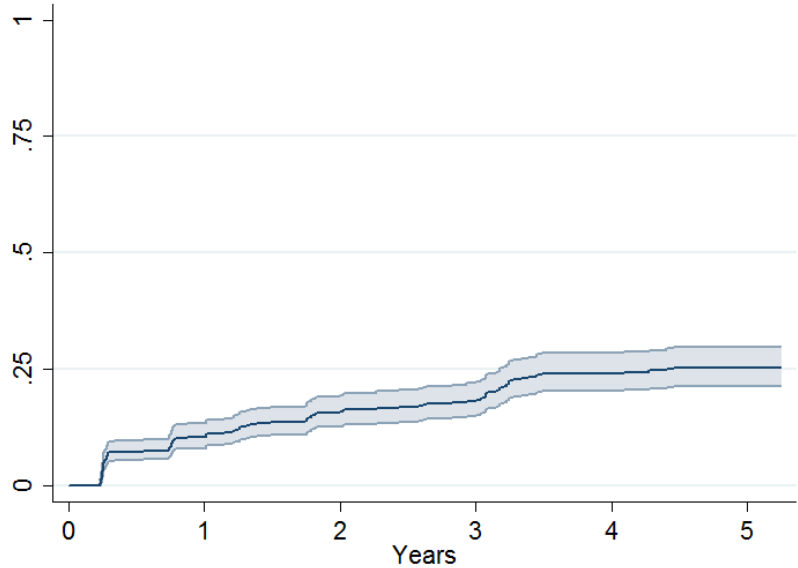
HPV type	n	PYO	IR per 100 pyo	95%CI
HPV-16	134	1704	7.9	6.6-9.3
HPV-18	87	1878	4.6	3.8-5.7
HPV-31	133	1813	7.3	6.2-8.7
HPV-33	82	1881	4.4	3.5-5.4



Clearance of incident anal HPV infections

HPV type	n	PYO	CR per 100 pyo	95%CI
HPV-16	72	141	51.2	40.6-64.4
HPV-18	49	64	77.2	58.3-102.1
HPV-31	84	83	101.6	82.0-125.8
HPV-33	47	67	70.0	52.7-93.1

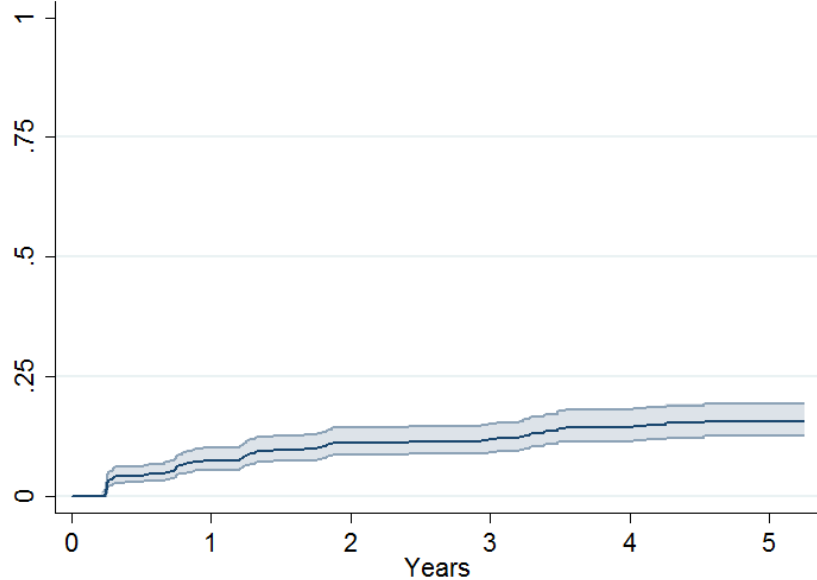
Cumulative incidence of anal HPV16 infection



Number at risk

585 373 336 302 270 46

Cumulative incidence of anal HPV18 infection

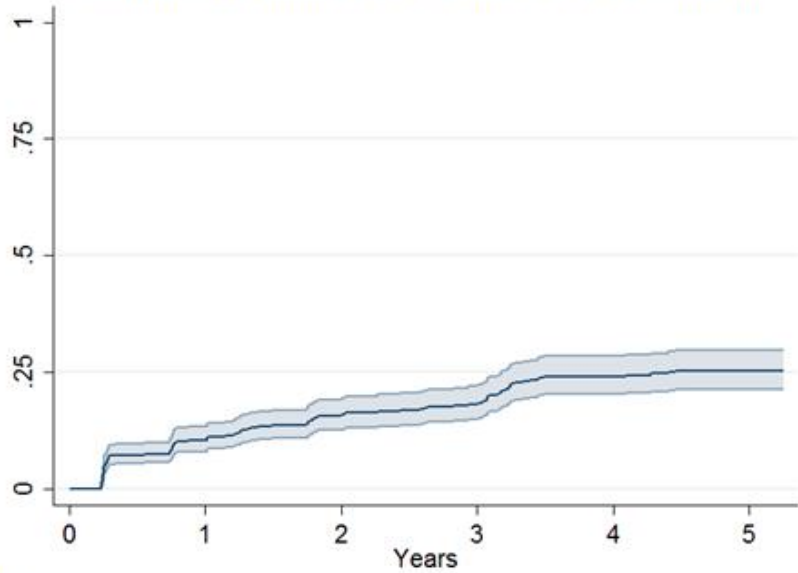


Number at risk

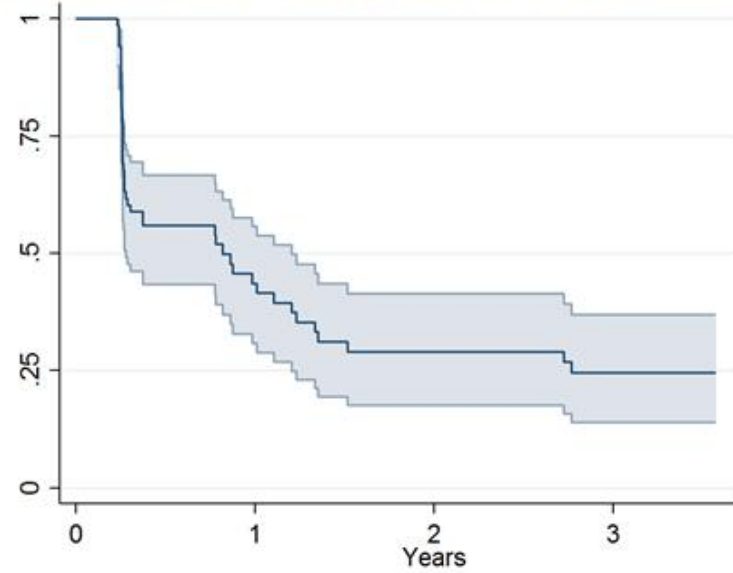
615 395 367 341 321 48

95% CI Survivor function

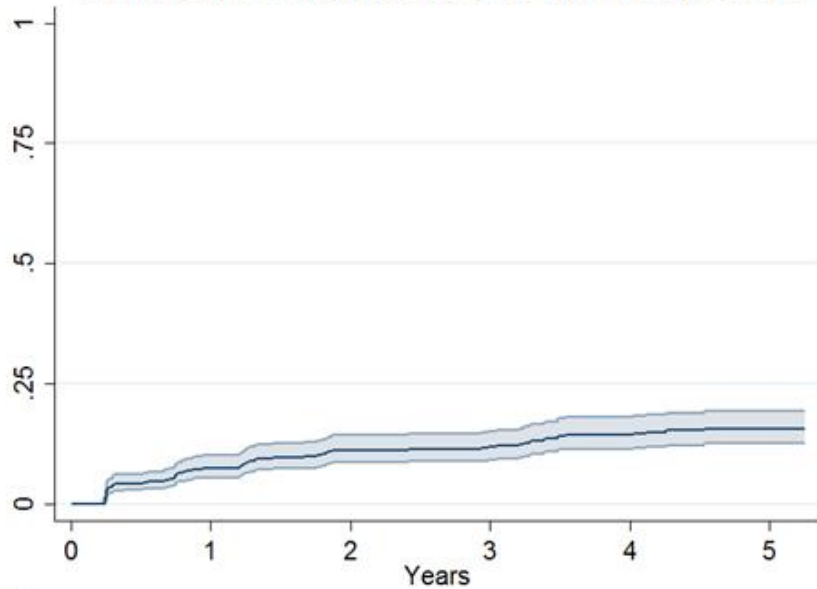
Cumulative incidence of anal HPV16 infection



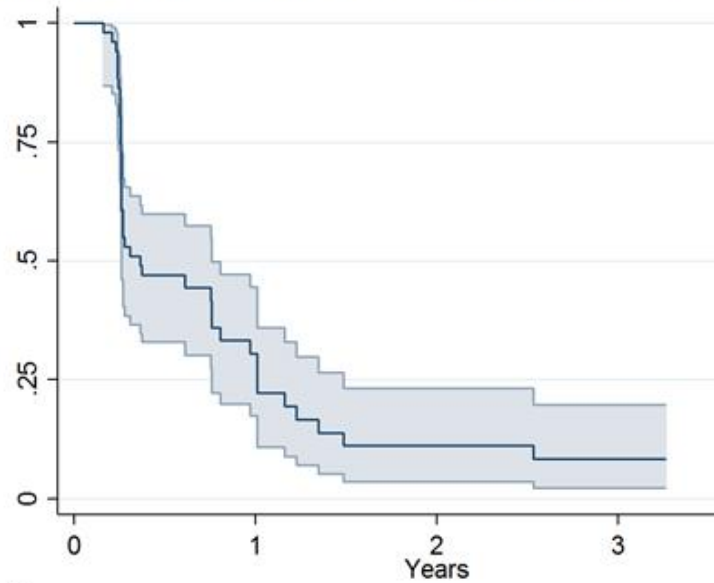
Cumulative clearance of anal HPV16 infection



Cumulative incidence of anal HPV18 infection



Cumulative clearance of anal HPV18 infection



95% CI Survivor function



Discussion - 1

- The incidence rate of anal hrHPV infections among MSM is very high
- Median time to clearance of incident anal HPV16 infection is 12 months
- Even after 36 months, 25% of MSM have not cleared their incident anal HPV 16 infection



Discussion: limitations

- Follow-up was interrupted for a median of 25 months
- HPV DNA detection method very sensitive →
meaning of HPV DNA+?
- Latency versus true incidence / clearance



Discussion

- Higher IR and lower CR of HPV-16 explain its oncogenic potential



HRA database Amsterdam: risk factors for HGAIN?





Research questions

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Introduction



■ Different studies found different risk factors for HGAIN

Variable	Author	Year	N	aOR	(95%CI)	No. Of studies not finding association*
Age (<40 vs ≥40)	De Pokomandy	2011	246	3.1	(1.1-8.5)	11
Current smoking	Alvarez	2010	135	4.8	(1.3-18.6)	8
Current smoking	Schwartz	2013	305	3.0	(1.5-7.1)	8
History of RAI	Gaisa	2014	518	3.0	(1.4-6.3)	1
Anal XTC-use	Richel	2013	311	0.1	(0.0-0.5)	2
H/o AIDS def.illn.	Salit	2009	224	2.4	(1.2-4.8)	3
CD4 nadir <50	De Pokomandy	2011	246	11.6	(1.2-112.3)	6
CD4 at HRA <400	Salit	2009	224	3.0	(1.5-6.0)	11
CD4 at HRA >500	Gaisa	2014	518	0.5	(0.3-0.9)	11
Current ART use	Hidalgo	2014	140	0.2	(0.1-0.8)	7

* These studies did include this variable



Methods

- Database with clinical data of all HRAs conducted at three Amsterdam clinics in period 2008-2015
- Included: first HRA of each patient
- Patients: HIV+ MSM aged ≥ 18 years
- Outcome: HGAIN
- Exposures of interest:
 - Demographic variables
 - Health and behavioral variables
 - HIV-related variables cohort study
- M-v logistic regression analysis of determinants of HGAIN

Riskfactors for HSIL (vs. no SIL)

	OR	95% CI	aOR	95% CI	P
Age per 10 years increase	0.8	0.7-0.9	0.8	0.7-0.9	0.006
Nadir CD4 count (per 100 cells higher)	1.1	1.0-1.2	1.0	0.9-1.1	0.5
Years with undetectable viral load					
≤1 year	1		1		0.009
1-5 years	0.5	0.3-0.8	0.5	0.3-0.8	
5.01-10 years	0.4	0.3-0.6	0.5	0.3-0.7	
>10 years	0.4	0.3-0.7	0.5	0.3-0.9	



Conclusion

When correcting for all potential confounders,
only **younger age** and
<1 year having an undetectable viral load
were found to be associated with HGAIN
among HIV-positive MSM



H2M2: the search for biomarkers for HGAIN





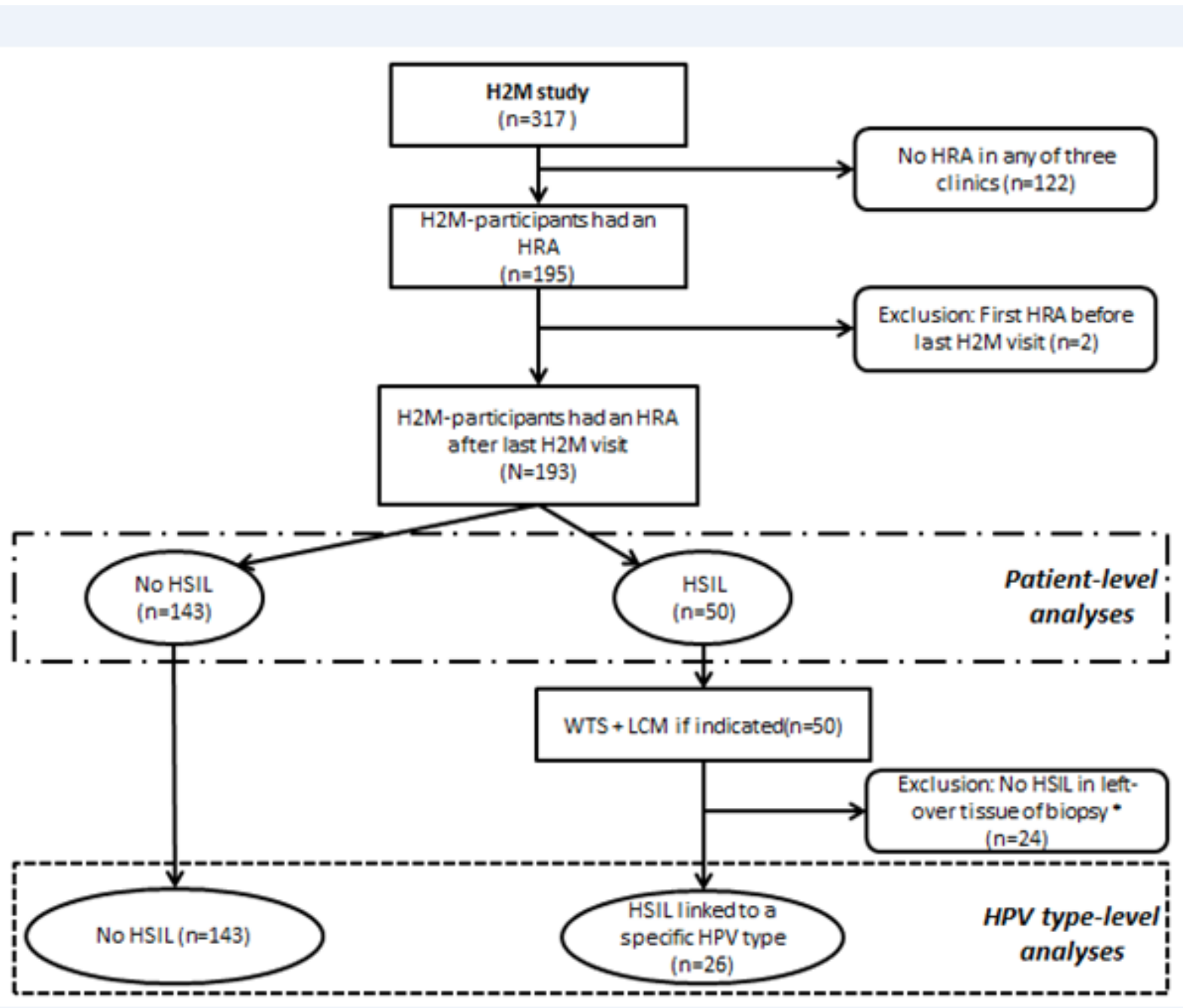
Research questions

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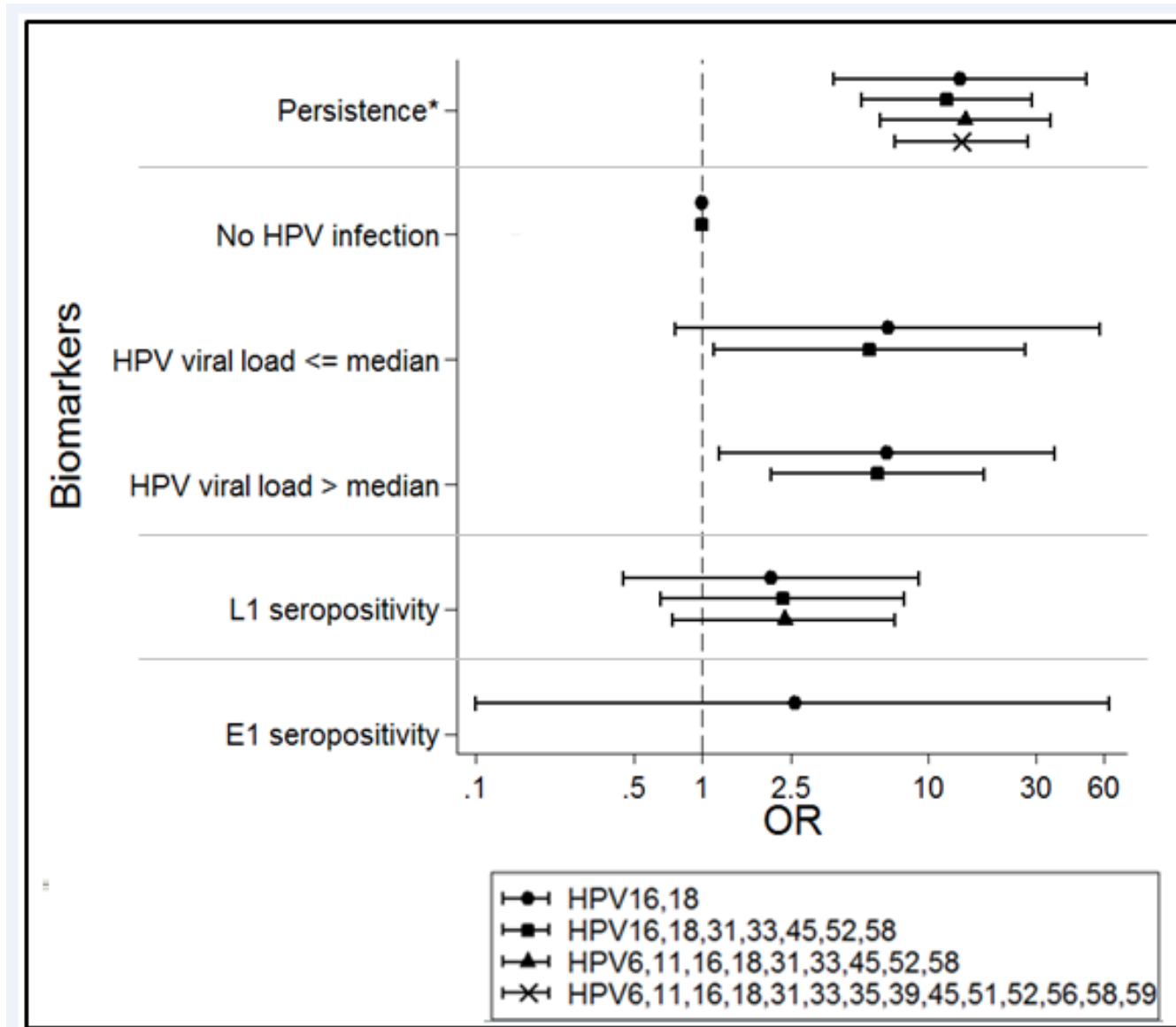
Methods

- Database with clinical data of all HRAs conducted at three Amsterdam clinics in period 2008-2015
- Patients: HIV+ MSM aged ≥ 18 years
- Outcome: HGAIN
- Exposures of interest:
 - L1, E6, E7, E1 and E2 Antibodies
 - HPV anal type-specific persistence
 - HPV anal viral load
- All biopsies of participants with at least one anal HSIL lesion: causative type determined by *laser capture microdissection* and genotyped with SPF₁₀-PCR-DEI-LIPA₂₅-system version 1.0



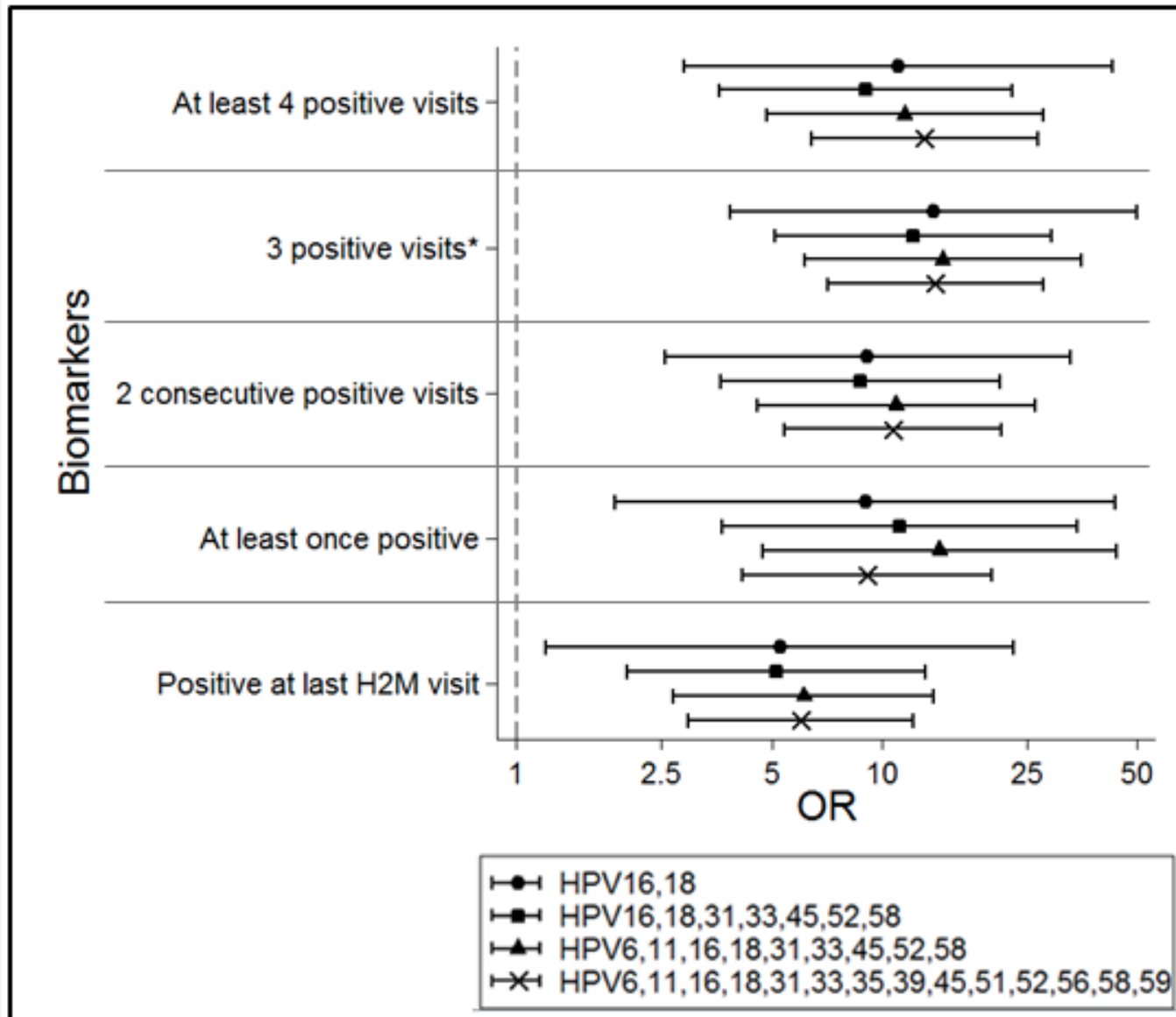


Results: OR for HGAIN for 4 biomarkers





OR for HGAIN for anal HPV detection





Discussion

- Neither anal HPV viral load, nor seropositivity for E1, E2, E6, E7, L1 is associated with HGAIN
- HPV persistence is a very significant determinant of anal HSIL
- These results are in agreement with supposed natural history of HPV infection → anal disease
- Persistence is not a good predictor for anal HSIL diagnosis, and is not useful for triageing HIV-positive MSM for HRA





Acknowledgements



GGD Amsterdam

- Sofie Mooij
- Elske Marra
- Sasha Kovaleva
- Sylvia Bruisten
- Anders Boyd
- Ronald Geskus
- Ineke Stolte
- Arjen Speksnijder
- Henry de Vries
- Martijn van Rooijen
- Linda May
- Wilma Vermeulen
- Marc van Wijk
- Marjolein Martens
- Titia Heijman
- Daniëla van Santen
- Olivia Landen

DDL

- Wim Quint
- Anco Molijn
- Annemiek Leeman

AMC Amsterdam

- Jan Prins
- Olivier Richel
- Thijs Siegenbeek
- Karien Gosens

DKFZ

- Tim Waterboer

Janssen

- Gert Scheper
- Martin Struijs

VUmc

- Peter Snijders †
- Chris Meijer
- Daniëlle Heideman

OLVG

- Irina Cairo

RIVM-Cib

- Marianne van der Sande
- Roel Coutinho
- Hein Boot †
- Hester de Melker
- Audrey King
- Jan Sonsma
- Marina Burger
- Fiona van der Klis
- Pascale van der Weele
- Elkse van Logchem
- Fleur van Aar
- Vera van Rijn

MC Jan van Goyen

- Dominique Verhagen

DC Klinieken Zuid

- Arne van Eeden
- Margo Groot
- Wilma Brokking

Stichting HIV Monitoring

All participants





Publications H2M, H2M2 and H2M3 studies-1

- 1: Mooij SH, van Santen DK, Geskus RB, et al. The effect of HIV infection on anal and penile human papillomavirus incidence and clearance: a cohort study among MSM. *AIDS*. 2016 Jan 2;30(1):121-32.
- 2: Welling CA, Mooij SH, van der Sande MA, et al. Association of HIV Infection With Anal and Penile Low-Risk Human Papillomavirus Infections Among Men Who Have Sex With Men in Amsterdam: The HIV & HPV in MSM Study. *Sex Transm Dis*. 2015 Jun;42(6):297-304.
- 3: van Aar F, Mooij SH, van der Sande MA, et al. Twelve-month incidence and clearance of oral HPV infection in HIV-negative and HIV-infected men who have sex with men: the H2M cohort study. *BMC Infect Dis*. 2014 Dec 31;14:668.
- 4: Mooij SH, Landén O, van der Klis FR, et al. HPV seroconversion following anal and penile HPV infection in HIV-negative and HIV-infected MSM. *Cancer Epidemiol Biomarkers Prev*. 2014 Nov;23(11):2455-61.
- 5: Mooij SH, Landén O, van der Klis FR, et al. No evidence for a protective effect of naturally induced HPV antibodies on subsequent anogenital HPV infection in HIV-negative and HIV-infected MSM. *J Infect*. 2014 Oct;69(4):375-86.
- 6: Mooij SH, Boot HJ, Speksnijder AG, et al. Six-month incidence and persistence of oral HPV infection in HIV-negative and HIV-infected men who have sex with men. *PLoS One*. 2014 Jun 4;9(6):e98955.
- 7: van Rijn VM, Mooij SH, Mollers M, et al. Anal, penile, and oral high-risk HPV infections and HPV seropositivity in HIV-positive and HIV-negative men who have sex with men. *PLoS One*. 2014 Mar 20;9(3):e92208.
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- 9: van Aar F, Mooij SH, van der Sande MA, et al. Anal and penile high-risk human papillomavirus prevalence in HIV-negative and HIV-infected MSM. *AIDS*. 2013 Nov 28;27(18):2921-31.
- 10: Mooij SH, Boot HJ, Speksnijder AG, et al. Oral human papillomavirus infection in HIV-negative and HIV-infected MSM. *AIDS*. 2013 Aug 24;27(13):2117-28.

Publications H2M, H2M2 and H2M3 studies-2

- 11: Marra E, Kovaleva A, Bruisten SM, et al. Incidence and clearance of anal high-risk HPV infection and their determinants among HIV-negative men who have sex with men over a period up to five-years. Clin Infect Dis. 2018 Aug 30. doi: 10.1093/cid/ciy738. [Epub ahead of print].
- 12: Marra E, Siegenbeek van Heukelom ML, Leeman A, et al. Virological and serological predictors of anal high-grade squamous intraepithelial lesions among HIV-positive men who have sex with men. Clin Infect Dis. 2018 Aug 28. doi: 10.1093/cid/ciy719. [Epub ahead of print]
- 13: Marra E, King A, van Logchem E, et al. Anal HPV 16 and 18 viral load: A comparison between HIV-negative and -positive MSM and association with persistence. J Med Virol. 2018 Jan;90(1):76-83.
- 14: Twisk DE, van der Sande MAB, van Eeden A, et al. Detection of Incident Anal High-Risk Human Papillomavirus DNA in Men Who Have Sex With Men: Incidence or Reactivation? J Infect Dis. 2018 Aug 24;218(7):1018-1026.

