26TH INTERNATIONAL PAPILLOMAVIRUS CONFERENCE & CLINICAL AND PUBLIC HEALTH WORKSHOPS (CONT.)

PART II - HPV IN MEN

JULY 3-8, 2010 / PALAIS DES CONGRÈS DE MONTRÉAL, CANADA

Abstracts selected by Mauro Romero L Passos, Felipe DL Passos, Marc Steben

APRESENTAÇÃO / *PRESENTATION*

Human papillomavirus (HPV) is the most frequent sexually transmitted infection causing 5% of all cancers in human. HPV is the source of various ano genital genital such as cervical, anal, vulvar, vaginal, penile as well as of oropharyngeal cancers. HPV also causes non neoplastic anogenital and respiratory track papillomatosis. Both high risk and low risk HPV now represent, at least partialy, preventable burden on the health care system and global loss of productivity.

The 26th International Papillomavirus Conference and its two workshops were held under the theme of "Sharing Knowledge for Global Health". Four commitments were made by the local organizing committee and we made sure to keep them to the International Papillomavirus Society: 1) to foster integrative research, 2) to enhance developing countries' capacities, 3) to inspire young researchers and 4) to offer an affordable learning experience.

There were 1978 participants at the conference. Two 2-day Workshops, Public Health Workshop & Clinical Workshop, preceded the main conference. During the conference we had 12 plenary sessions, 29 parallel Oral Communications Sessions, eight Early Morning Workshops (for young researchers and addressing capacity building in emerging countries), 18 Satellite Symposia (12 academic and 6 industries sponsored), 642 regular Posters and 70 e-posters.

The organisers followed very consistently an environment-friendly policy avoiding printed paper documents, increases the distribution of CD-ROM with all conference abstracts, free webcast dissemination of the presentations and the book of abstracts trough www.hpv2010.org. To recognize the strength and the variety of researchers in our society, awards were given for both oral and poster presentation in all of our four group of interest: basic sciences, clinical and laboratory sciences, epidemiology and public health as well as capacity building. Awards for young researchers and from developing countries were also given. The current paper contains short summaries of award recipients. Readers interested in the details of certain sessions or presentations are invited to consultwww.hpv2010.org.

Held under the theme: sharing knowledge for global health, the conference continues the tradition started last year in Malmo where every presentations were made available free to anyone joining the website, after an identification process, anyone can look or download presentations from the conference or the clinical or the public health workshop. This generosity from our speakers makes it possible to access the high quality of science and methods to all and not only to those able to make it to Montréal. This certainly helped us guarantee that in fact we delivered on our theme of sharing knowledge for global health and this unique collaboration with the Brazilian Journal of STD is a vibrant show of the interest our brazilian colleagues have spread the knowledge on HPV to their scientific community of Brazil and the editor has to be applauded for his vision and help in sharing the highest quality of knowledge!

Obrigado,

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ORAL PRESENTATIONS

Viral Oncogene Expression Defines Oropharynx Carcinomas with Active HPV16 Involvement

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Background: A subset of oropharyngeal squamous cell carcinomas (OPSCC) contains HPV16 DNA and appears to have a better prognosis. However, this subset may be heterogeneous. To better define the group of HPV-driven tumors we included HPV RNA analysis in a large OPSCC series and evaluated the association of viral DNA and RNA status with clinical parameters.
Methods: Fresh-frozen tissues from 199 German OPSCC collected between 1990 and 2008 were subjected to semi-quantitative multiplex papillomavirus genotyping (MPG). HPV16 DNA positive tumors were quantitatively analyzed for viral oncogene E6*II RNA expression by NASBA amplification and bead-based hybridization.
Results: HPV16 DNA was present in 97/199 (48.7%) OPSCC, viral load was low (HPV^{+}) in 61 (31.1%) and high (HPV^{++}) in 36 (18.4%) tumors. Prevalence of HPV16 was highest in tonsillar carcinomas (60.7% vs. 41.1% in the other oropharyngeal subsites) and increased by 24.4% from 1990 to 2008. HPV16 E6*II RNA was expressed in 35/37 (94.6%) HPV^{++} tumors but only in 14/60 (23.3%) HPV^{+} tumors. Kaplan Meier analyses showed that viral load and even more viral oncogene RNA were associated with better overall survival (OS) and progression free survival (PFS; OS: $p = 0.015$ vs. $p = 0.035$; PFS: $p = 0.007$ vs. $p = 0.030$, logrank test). Oncogene RNA positive tumors were associated with never smoking and never drinking and with the absence of distant metastasis, but not with younger age.
Conclusion: This study demonstrates a pronounced heterogeneity among HPV16 DNA positive tumors and confirms that DNA genotyping alone is insufficient to define the role of the virus. OPSCC expressing oncogene HPV16 RNA are truly HPV-driven tumors. OPSCC harboring HPV16 DNA but negative for E6*II behave like the HPV negative tumors with regard to clinical parameters.

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HPV Infection Clearance among Men Ages 18-70 Years: The HIM Study

Anna Giuliano[1], Ji-Hyun Lee[1], William Fulp[1], Luisa Villa[2], Eduardo Lazcano[3], Mary Papenfuss[1], Danelle Smith[1], Martha Abrahamsen[1]

Introduction: Little is known regarding the natural history of HPV infections in men. The purpose of this study was to describe the overall, age specific, and country specific duration of genital HPV infections in men.
Methods: 1160 men ages 18-70 years residing in Brazil, Mexico, and the US were examined every six months, with a median follow-up of 27.5 months. Samples obtained from the coronal sulcus, glans penis, shaft, and scrotum were analyzed for presence of HPV DNA. Duration of HPV infection was estimated by the Kaplan-Meier method for any HPV type, oncogenic HPV, non-oncogenic HPV, and HPV 16. Differences in median time to clearance of HPV by age and country were evaluated using the log-rank test.
Results: Median time to HPV clearance was significantly longer for infections positive at enrollment (12.8 months, 95% CI: 12.1, 14.3) vs. newly acquired (7.5 months, 95% CI: 6.8, 8.8). Duration of incident HPV 16 infections was significantly longer at 12.2 months (95% CI: 7.4, 20.2) compared to non-oncogenic HPV types (7.6 months, 95% CI: 6.8, 9.3). Duration of incident HPV 16 infection was also longer among US men (18.2 months) compared with men from Brazil (11.4 months) and Mexico (6.7 months). With increasing age duration of any HPV and non-oncogenic HPV significantly decreased (6.2 months for men 45-70 years compared with 9.5 months for men 18-30 years for any HPV; and 6.5 months for men 45-70 years compared to 9.1 months for men 18-30 for non-oncogenic HPV). In contrast, the duration of HPV 16 was longer for men 45-70 years compared with men 18-30 years (17.3 months vs. 14.7 months).
Conclusion: Overall, HPV 16 had a longer time to clearance than non-oncogenic HPV types, and the duration of HPV 16 was longer for older men, and those residing in the US.

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Circumcision and Acquisition of High-Risk HPV Infection in Young Men

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Background: While previous cross-sectional studies of prevalent HPV infections in men have reported positive associations between lack of circumcision and infection, the role of circumcision in HPV acquisition is not clear.
Objective: To investigate whether high-risk (HR) HPV is acquired differentially based on circumcision status.
Methods: Heterosexual male university students 18-20 years of age were recruited from 2003-2009 and followed tri-annually for up to four years. Samples from the shaft/scrotum and glans, as well as urine, were tested for 37 HPV genotypes by a liquid bead microarray assay (LBMA). Kaplan-Meier methods were used to evaluate the cumulative incidence of HR HPV. To evaluate whether incident detection site (glans and/or urine vs shaft/scrotum only) or number of sites infected at the time of incident detection varied according to circumcision status, all incident type-specific HR HPV infections were included in a multivariate logistic regression model where circumcision status was the outcome and detection site and number of sites were the covariates. Robust variance estimates were used to account for correlation between multiple HPV types within subjects.
Results: Among 464 participants, the 36-month cumulative incidence of HR HPV was 63.1% (95% CI: 57.1,69.2) and did not differ by circumcision status ($p = 0.98$, logrank test). In

multivariate logistic regression, the odds of positivity for HR HPV in the glans and/or urine versus the shaft/scrotum was 2.3 times (95%CI:1.4,3.8) higher in uncircumcised versus circumcised men. Similarly, uncircumcised men had an odds of being positive at all sites (vs only one) 5.6 times higher than uncircumcised men (95%CI:1.6,19.4) at the time of initial detection.
Conclusion: Although the cumulative incidence of HR HPV acquisition did not differ between circumcised and uncircumcised men, incident infections in uncircumcised men were more likely to be detected in the glans and/or urine and to be detected in multiple sites.

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The Effect of Male Circumcision on Incident and Persistent Penile HPV Infections in Men from Kenya

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Background: Male circumcision (MC) may reduce the carriage of penile human papillomavirus (HPV) infection. Proof that MC reduces HPV penile infection acquisition and/or persistence in men can only be obtained through a prospective randomized controlled trial (RCT).
Methods: An HPV-ancillary study was nested within an ongoing RCT of MC in Kisumu, Kenya. The primary aim was to assess the effect of MC on penile HPV incidence and/or persistence. Penile exfoliated cell specimens were collected from the glans/coronal sulcus of sexually active men who were HIV sero-negative, uncircumcised and aged 18-24 years at baseline. Specimens were tested with the GP5+/6+ PCR assay to detect a wide-range of HPV-DNA types. Cross-sectional analyses were conducted to compare HPV-DNA positivity at the baseline and 24-month visits.
Results: A total of 1,809 participating men had HPV-DNA results at both the baseline and 24-month follow-up visits. Of these, 982 (54%) were HPV-negative at baseline in the glans/coronal sulcus specimen. Among the 982 HPV-DNA negative men at baseline, 223 (22.7%) were HPV-DNA positive at the 24-month visit. Incident HPV infections were significantly lower in the circumcised (15.1%) than uncircumcised arm (30.8%) (odds ratio [OR] = 0.4; 95% confidence interval [CI]: 0.3-0.5). Among 827 HPV-DNA positive men at baseline, 292 (35.3%) remained positive at 24-months (23.6% among circumcised compared to 47.4% among uncircumcised men; OR = 0.3; 95% CI: 0.3-0.5). Analyses were similar for incident type-specific HPV 16 infections (2.2% among circumcised, versus 6.5% among uncircumcised men; OR=0.3; 95% CI: 0.2-0.6). Circumcised men were also less likely, albeit non-significantly, to have a persistent HPV type 16 infection (5.6%) compared with uncircumcised men (9.2%) (OR = 0.6; 95% CI: 0.2-2.1). Analyses will be presented on the effect of male circumcision on penile HPV infections, stratified by anatomical site and specific HPV type.
Conclusions: Male circumcision resulted in a decrease in incident and persistent HPV infections 24 months after baseline.

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Association Between HPV-16 L1 VLP Serum Antibodies and Future Risk of Genital HPV Infections in Men

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Background: No study has examined whether anti-HPV-16 serum antibodies elicited by natural infections protect against future genital HPV infections in men.
Objectives: We examined risk of genital infection with HPV 16 and phylogenetically-related types in the alpha-9 genus in an international cohort of men.
Methods: HPV 16 antibodies were detected using an L1-VLP-based ELISA and classified using low and high seroreactivity cut-points. Incidence rates of new infection and 6-month persistent infections with HPV-16 and other alpha-9 genotypes were estimated. Tests based on binomial distribution were applied to compare incidence rates between seropositive and seronegative men.
Results: 2,482 men aged 18-70 years residing in USA, Brazil and Mexico were followed every 6 months for a median duration of 17.9 months. HPV 16 seroprevalence at enrollment was 10.8% and 8.2%, using low and high cut-points respectively. Seroprevalence was significantly higher among men with male sexual partners (MSM and MSMW). Overall the HPV 16 incidence rate was 6.0 and 5.5 per 100-person-years for HPV-16 seropositive and seronegative men (p = 0.796) using the lower cut-point. Incidence of other alpha-9 genotypes was 10.9 and 8.1 per 100-person-years, respectively (p = 0.138). Incidence rates of 6- and 12-month persistent infection with HPV-16 or other alpha-9 genotypes did not differ significantly by enrollment HPV-16 sero-status. No significant differences in incidence rates by sero-status were detected for any age group or subgroups of men with different number of lifetime sexual partners or sexual practice using the lower cut point. When a higher seroreactivity cut-point was applied, a significantly lower incidence rate of genital HPV-16 was observed in seropositive men compared to seronegative men (p = 0.015) among MSM.
Conclusion: The presence of HPV-16 serum antibodies at enrollment does not appear to confer protection against future genital infection with HPV-16 or its phylogenetically-related types. However, a protective effect was observed among MSM with higher seroreactivity at enrollment.

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HPV Transmission in Heterosexually Active Couples over 12 Months

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Background: There are few reports on sexual transmission of HPV types. This study investigated the extent of HPV transmission in couples that were HIV-positive, HIV-discordant (one partner was HIV-positive) and HIV-negative.
Methods: Participants were black, heterosexually active couples, aged 19 to 65 years followed up over a 12 month period. At baseline, 6-month and 12-month visits there were 433, 245 and 159 couples respectively. Cervical and penile HPV types were determined by Roche Reverse Linear Array HPV genotyping assay.
Results: Transmission analysis was restricted to couples in which at least one partner was HPV infected at baseline. In 170 couples observed between baseline and 6 months, there were 44 HPV transmission events in 32 couples. Female-to-male transmission was most common compared to male-to-female transmission (34/44, 77% compared to 10/77, 23%; P < 0.0001). Female-to-male transmission events were mostly HR-HPV types (24/34, 71%) compared to LR-HPV types (10/34, 29%; P = 0.0007), while male-to-female transmission events were mostly LR-HPV types (6/10, 60%) compared to HR-HPV types (4/10, 40%; P = 0.37). In 104 couples observed between baseline and 12 months visit, there were 30 HPV transmissions events in 27 couples. Female-to-male transmission was again most prevalent compared to male-to-female transmission (18/30, 60% compared to 12/30 40%, P = 0.12). Female-to-male HR-HPV transmission events were again more prevalent than LR-HPV types (10/18, 56%) (8/18, 44%); while male-to-female transmission events were more likely to be LR-HPV types (7/12, 58%) compared to HR-HPV types (5/12, 42%) however the difference was not significant. Between baseline and 6-months HPV transmission was higher in couples that were HIV-positive (17/39, 44%) compared to HIV discordant (21/83, 25%; P = 0.04) and compared to couples that were HIV-negative (6/47, 13%; P = 0.001).
Conclusion: HPV transmission is common in sexually active couples especially among HIV-positive and HIV discordant couples compared to HIV-negative couples. The most common type of transmission is female-to-male.

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Incidence Rates of Anogenital Warts in Germany

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Background: HPV types 6 and 11 account for 90 percent of anogenital warts. Assessment of the effectivenessof quadrivalent vaccine on the reduction of anogenital warts requires population-based incidence data to estimate the impact of vaccination on a population level.
Objectives: To estimate the incidence rate of anogenital warts in Germany stratified by age, sex, and region. To determine the specialty of physician who made the initial diagnosis and the type of drug treatment received.
Methods: Historical cohort study in a population aged 18-35 years from a population-based, large healthcare insurance database including more than 14 million insurance members from all over Germany during the years 2004-2006. A case of anogenital warts was considered incident if a disease-free period of twelve months preceded the diagnosis of anogenital warts. Descriptive analyses were conducted as to the physician specialty of the first diagnosing physician and drug treatment received.
Results: 9,553 and 9,642 new cases of anogenital warts were diagnosed in 2005 and 2006, resulting in an overall incidence rate of 406/100,000 person years (py) (95% CI389 to 414/100,000) and 409/100,000 py (95% CI 401-to 417/100,000), respectively. The incidence rate was higher in females (2006: 462/100,000 py) than in males (2006: 345/100,000 py) and showed a peak at earlier ages in females (22 to 23 y vs. 24 y to 29 y). In females, initial diagnosis of anogenital warts was most frequently made by gynecologists (76.8%), whereas in males, anogenital warts were more frequently diagnosed by dermatologists (44.6%) and urologists (31.5%). Women were most frequently treated with imiquimod cream (60.5%), whereas men received more often podophyllotoxin (59.2%).
Conclusions: Incidence of anogenital warts is high in Germany. Ultimately, with longer follow-up extending beyond 2006, our study will allow to analyze the benefit of quadrivalent HPV vaccination on the reduction of the burden of anogenital warts.

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The QOLIGEN Study: Investigation of Quality of Life Loss, Duration of Episode and Treatment Costs Associated with Genital Warts in the UK

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Cost effectiveness analysis (CEA) to inform decisions about vaccine procurement for the UK's national HPV immunisation programme requires data on the cost of treatment and quality of life (QoL) loss associated with genital warts (GW). Initial analyses used data from a study carried out at a single sexual health clinic in England in 2007. To improve on these estimates, we are conducting a larger, multi-site study in eight sexual health clinics in England and Northern Ireland. Recruitment and data collection began in August 2009 and will continue until the end of March 2010, with a projected sample size of 800. Study sites were selected to provide a mix of urban and semi-urban settings, along with clinics of different sizes and case mixes. Patients with GW attending the participating clinics for either a first or follow up visit are asked to complete a standardised QoL questionnaire (the EQ-5D) during their clinic visit and a follow up questionnaire two weeks later. Participants' responses are compared to the UK population reference values to determine QoL-loss associated with GW. Information about the nature and cost of treatment and duration of episodes is being collected by standardised review of the case notes of 320 patients (20 male, 20 female per clinic). In a preliminary analysis of 722 participants

diagnosed with GW, there was no difference in the average EQ-5D index score by participating site. There was a lower average score (indicating a greater QoL loss) in females than males, and the QoL detriment among study participants when compared to the average UK population was greatest amongst younger women. Costs appeared to vary more by site. Results of this multi-site study will also describe the treatment of GW in sexual health clinics and should contribute to CEA informing future vaccine procurement decisions in the UK.

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Male Circumcision Reduces HPV Infection in Female Partners in Rakai, Uganda

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Background: Randomized controlled trials (RCTs) have shown that male circumcision (MC) significantly reduces high-risk human papillomavirus (HR-HPV) prevalence and incidence, and increases clearance (i. e., loss of detection) in males. We assessed the efficacy of male circumcision to prevent HPV infection in female partners.
Methods: An RCT of MC in HIV-negative men was conducted in Rakai, Uganda. Consenting HIV-negative female spouses of male participants were enrolled and followed. 632 spouses of men randomized to immediate circumcision and 576 spouses of men randomized to the control arm (delayed circumcision) were interviewed regarding their sexual risk behaviors and symptoms. Cervical swabs at enrollment, 12 and 24 months were evaluated for HR-HPV by Roche HPV Linear Array. Incident HR-HPV was estimated in women who acquired a new HR-HPV genotype. HR-HPV clearance (loss of detection) was determined in women with prior genotype-specific HR-HPV infections. Rate ratios (RR) and 95% confidence intervals (95% CI) of HR-HPV were estimated by Poisson multiple regression.
Results: Baseline and follow-up characteristics of women in both RCT arms were similar. Female baseline HR-HPV prevalence was 34.4% (208/605) in the intervention and 36.2% (203/561) in the control arm ($p = 0.540$). Year 2 female HR-HPV prevalence was 27.5% (148/538) in the intervention and 38.6% (187/485) in the control arm ($p < 0.001$). HR-HPV incidence was 20.0/100 py (181/904 py) in intervention arm women and 26.1/100 py (203/779 py) in the control arm ($p = 0.010$). Intervention arm women had 542 HR-HPV genotypes detected at enrollment and 357 (65.9%) of these were undetectable at 24 months. Among controls, 552 HR-HPV genotypes were detected at enrollment, of which 326 (59.1%) had cleared at follow up (RR = 1.12, 95% CI: 1.02-1.22).
Conclusions: Male circumcision reduces the prevalence and incidence of HR-HPV infections and increases clearance of HR-HPV infections in female partners.

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Men's Psychosocial Responses to HPV Test Results: Implications for Vaccine Promotion

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Background: There is a rich literature on the psychosocial impact of HPV in women, but limited data on the impact in men due to lack of routine testing.
Purpose: To provide an overview of the full cohort baseline findings from the Cognitive and Emotional Response to HPV in Men (CER) Study, focusing on the major constructs of Levanthal's Parallel Processing Model.
Methods: Men participating in a natural history study of HPV completed a psychosocial survey after receiving their first HPV test results. There were differences between HPV DNA results and what participants reported as test results; thus, self-reported HPV results were used in analyses because they are most closely associated with cognitive and emotional responses.
Results: The majority of the 551 men completing the survey (ages 18-69 years, mean = 30) were white (69%), non-Hispanic (82%), and single (66%); most reported having some college credit (87%) and being insured (74%). Lab results were 41% HPV+ (n = 226), with only 78% (n = 162) self-reporting correctly, and 59% HPV- (n = 325) with 91% (n = 312) self-reporting correctly. HPV knowledge was high in both (self-reported) HPV+ and HPV– groups (mean = 15.1 and 14.6 correct of 20 true/false knowledge questions, respectively, $p = 0.07$). Self-reported HPV+ participants reported more negative emotions in response to test results ($p < .0001$) than HPV– participants; fewer self-reported HPV+ (73%) than HPV– men (89%) reported telling their main sex partner their HPV test result ($p < 0.01$). HPV+ men were significantly more likely than HPV– men to answer 'very likely/likely' when asked if they would get the HPV vaccine if it became available for males (96% vs. 88%; $p = .003$). Participants perceived HPV-related cancers as more of a threat to themselves than to their sexual partners.
Conclusions: Now that the US has approved the HPV vaccine for men, and in other countries, these findings can be used to guide HPV vaccination promotion.

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Model-Based Predictions of the Impact of HPV Immunization Programs for Males and Catch-up Programs for Females

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Background: HPV immunization programs were initiated in 2007 for 9- to 13-year-old females in several Canadian provinces. Catch-up vaccination of older females, and vaccination of males, has also been considered. The long-term impact on HPV prevalence and

disease outcomes can be projected with models, although previous models do model transmission through sexual partnerships.
Objectives: To project the impact of catch-up vaccination of females, and vaccination of males, on prevalence of HPV in females.
Methods: We simulated a dynamic sexual partnership network through which HPV spreads. The population was stratified by age, sex, and sexual activity level. Model outputs included prevalence of types 16, 18, other high-risk, and low-risk HPV by age and time. The model was fitted to survey data on sexual behaviour and epidemiological data on HPV prevalence by age and type. Scenarios of low versus high vaccine coverage were: vaccination of 12-year-old females at 50% or 80% coverage starting in 2007 (baseline); adding vaccination of 12-year-old males at 40% or 70% coverage to baseline starting in 2012; adding catch-up vaccination of 20% or 40% of females aged 17-26 to baseline in 2012.
Results: The average prevalence of types 16/18 in females aged 15-69 drops from 4.4% (± 1.3%) in 2007 to 2.4% (± 1.0%) (resp. 1.9% (± 0.8%)) by 2030 with vaccination of 50% (resp. 80%) of 12-year-old females only. Additionally vaccinating males further reduces this to 2.1% (± 0.8%) (resp. 1.7% (± 0.6%)) by 2030. Catch-up vaccination of females further reduces this to 2.1% (± 0.7%) (resp. 1.4% (± 0.5%)) by 2030, but with a particularly rapid initial decline in 2012. Herd immunity results in moderate declines in prevalence in older, unvaccinated females.
Conclusions: Augmenting existing programs of vaccination of 12-year-old females through either vaccination of 12-year-old males or catch-up vaccination of older females is not predicted to have a large impact on long-term prevalence of types 16/18 in females.

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HPV Burden and Genotype Distribution in Anogenital Cancers Worldwide

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Objective: To describe the HPV prevalence and type distribution in invasive cancers of the cervix, vulva, vagina, anus and penis worldwide.
Methods: Formalin-fixed paraffin embedded invasive cancer cases of the cervix (ICC), vulva, vagina, anus and penis were collected from historical pathology archives from 43 countries. After histological evaluation, HPV detection was done by amplifying HPV/DNA using SPF-10 broad-spectrum primers PCR subsequently followed by DEIA and genotyping by LiPA25 (version 1). Samples were tested by HPV laboratories at ICO (Barcelona, Spain) and at DDL (Voorburg, The Netherlands). HPV type-specific relative contributions were calculated counting single and multiple infections; for the latter, the cases were proportionally distributed taking into account the frequency of each type in the distribution of single infections.
Results: Among 10,575 analyzed ICC cases, 8,977 (84.9%) were HPV positive. The eight most common types identified in ICC were: HPV16 (60.6%), HPV18 (10.2%), HPV45 (5.9%), HPV33 (3.8%), HPV31 (3.7%), HPV52 (2.8%), HPV58 (2.3%) and HPV35 (1.9%). Furthermore, HPV/DNA detection was done in 1,290 vulvar, 356 vaginal, 328 anal and 779 penile cancers. HPV was identified in 25.7%, 67.1%, 78.7% and 32.1% in these cases, respectively. HPV16 was the most frequent type found in all sites, ranging from 60.6% (vagina) to 80.2% (anus); followed by HPV types 18/31/33/35/45/52/58/6 in less than 6% each. Some variability in HPV distributions were observed among different regions and histologies. HPV16,18 or 45 ICC cases were found more often in younger patients than in other HPV types ($p < 0.05$). This age-genotype pattern was not observed in other genital sites.
Conclusions: This study confirms the extraordinary role of HPV 16 in anogenital sites. It identifies that the 8 most common HPV types in cervical cancer are also the most common types in other genital sites. HPV6 is not as rare in penile and anal cancers.

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Modeling the Incremental Impact of Vaccinating Boys Against HPV

Marc Brisson[1,2], Nicolas Van de Velde[1], Marie-Claude Boily[2,3]

Objectives: The aim of this study is to examine the potential incremental impact of vaccinating boys, in addition to girls.
Methods: A stochastic individual-based dynamic model of sequential partnership formation and dissolution, and HPV transmission (16, 18, 6, 11 and 14 other high risk HPV types) in a population stratified by age, gender, sexual activity levels and HPV type-specific infection status (susceptible, infected, and immune) was developed. We identified multiple parameter sets that fitted Canadian sexual behaviour and epidemiological data. Strategies investigated included vaccination of: 1) girls and 2) girls+boys. For each strategy, we varied: 1) coverage, 2) duration of vaccine protection and 3) vaccine efficacy.
Results: Under base assumptions (per-act vaccine efficacy = 99%, average duration of protection = 20 yrs, coverage = 70%), the model predicts that vaccinating 12-year-old girls will produce a rapid decrease in vaccine type-specific prevalence in females and males. Furthermore, at equilibrium, HPV-16/18 (HPV-6/11) prevalence in females and males is reduced by 64% [IQR: 51,71] (100% [100,100]) and 62% [54,68] (100% [100,100]), respectively. Assuming 70% coverage, vaccinating 12-year-old boys, in addition to girls, produces a slightly faster decline in vaccine type-specific prevalence as well as a lower prevalence at equilibrium. This results in an incremental reduction in HPV-16/18 (HPV-6/11) incidence over 70 years of 16% [13,19] (3% [2,5]) in females and 23% [20,25] (4% [2,5]) in males. The incremental impact of vaccinating boys decreases significantly with improved vaccination characteristics (i.e. higher vaccine efficacy and coverage, and longer duration of protection).
Conclusions: Given the important direct and herd immunity impact of vaccinating girls under moderate to high vaccine coverage,

the incremental gains of vaccinating boys are limited. These results partly explain why many modeling studies show that male vaccination is not cost-effective when coverage is high in girls.

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Efficacy of the Quadrivalent HPV Vaccine to Prevent Anal Intraepithelial Neoplasia among Young Men Who Have Sex with Men

Joel Palefsky[1]

Introduction: Most anal cancers are associated with HPV, particularly HPV 16. The incidence of anal cancer is increased among men who have sex with men (MSM) compared with the general population. Screening and treatment of anal intraepithelial neoplasia (AIN), the anal cancer precursor, are not yet standard of care, and prevention efforts are needed to reduce the incidence of anal cancer. We tested the quadrivalent HPV vaccine to determine its ability to reduce the incidence of AIN/anal cancer.

Methods: 598 MSM aged 16-26 years with 5 or fewer lifetime sex partners were randomized to receive vaccine or placebo at enrollment, month 2 and month 6. Subjects underwent detailed anogenital exams and HPV sampling from the penis, scrotum, perineal/perianal and anal canal at enrollment, month 7 and at 6-month intervals afterwards. Efficacy analyses were performed in a per-protocol (PPE) population (sero-negative and DNA-negative from day 1 through month 7 to the relevant vaccine HPV type) and in all enrollees in an intent-to treat (ITT) analysis. Median follow-up of the PPE population was 2.5 years (post-dose 3).

Results: Vaccine efficacy against HPV 6/11/16/18-related AIN and anal cancer in the PPE population was 77.5% (95% CI: 39.6, 93.3) (5 vaccine cases versus 24 placebo cases). Efficacy against high-grade AIN (AIN 2+) was 74.9% (95% CI: 8.8, 95.4). In the ITT population the efficacy was 50.3% (95% CI: 25.7, 67.2) and 54.2% (95% CI: 18.0, 75.3), respectively. No anal cancer was seen in either treatment group.

Conclusions: These results demonstrate that the quadrivalent HPV vaccine is efficacious in preventing AIN related to HPV 6/11/16/18 in MSM subjects naïve to vaccine HPV types at enrollment, as well as in an ITT population. The quadrivalent HPV vaccine may be a useful measure to reduce the incidence of anal disease in at-risk populations.

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The Dynamics of HPV Infection are Mainly Driven by Female-to-Male Transmission: Implications for Vaccinating Boys

Johannes Bogaards[1,2], Mirjam Kretzschmar[2,3], Maria Xiridou[2], Chris Meijer[4], Jacco Wallinga[2,3], Johannes Berkhof[1]

Objectives: To estimate the contribution of males and females to the transmission dynamics of HPV and to determine the effectiveness of vaccinating boys relative to girls in reducing the prevalence of HPV infections in men and women and of pre-cancerous lesions in women.

Methods and Results: We developed a type-specific susceptible-infected-resistant-susceptible (SIRS) model, which accounts for the transmission of high-risk HPV types in heterosexual couples and the development of persistent infections and pre-cancerous cervical lesions in women. We assumed that women continue to remain infectious after the development of cervical lesions. Type-specific transmission rates and the duration of infection-induced resistance to re-infection with the same type were jointly estimated with progression and clearance parameters from the pre-vaccine prevalence of type-specific HPV infection. Based on this model, we calculated the male and female components of the basic reproduction number R_0 and assessed the impact of vaccinating 12-year-old girls and/or boys on the post-vaccination dynamics of HPV infection. We found that the dynamics of HPV infection were mainly driven by female-to-male transmission, primarily as a result of the asymmetry in the duration of the infectious period between men and women. As a consequence, vaccinating pre-adolescent girls was estimated to be more effective than vaccinating boys at any given coverage of vaccination, both in reducing the prevalence of HPV infections on a population level and in reducing the incidence of cervical lesions.

Conclusions: To prevent cervical cancer as well as to reduce the HPV prevalence in the whole population, it is more effective to vaccinate one additional girl than it is to vaccinate a boy irrespective of the coverage of vaccination. Therefore, the question whether male vaccination is cost-effective needs to be addressed only when vaccine uptake among girls cannot be further increased.

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POSTERS PRESENTATIONS

P-138: Multiple HPV Serum Antibodies Are More Evident in Women than Men

Zizipho Z. A. Mbulawa[1], Dianne J. Marais[1], Tim Waterboer[4], Michael Pawlita[4], David Cotzee[2], Anna-Lise Williamson[1,3]

Background: This study examined human papillomavirus (HPV) serum antibodies in human immunodeficiency virus seropositive (HIV+) and seronegative (HIV–) women and men.

Methods: Sera from 265 HIV+ women, 171 HIV- women, 158 HIV+ men and 278 HIV– men were analysed for HPV antibodies (combined IgG, IgA and IgM) to the major capsid protein L1 of types 11, 16, 18, 31, 33, 35, 45, 52, 58 by Luminex-based multiplex serology. HPV genotyping in cervical and penile cells was performed by the Roche reverse linear array HPV genotyping assay.

Results: For women, HPV11 (34%) seroprevalence was highest followed by HPV31 (30%), HPV16 (24%), HPV18 (24%), HPV45

(22%), HPV35 (18%), HPV52 (14%), HPV58 (11%) and antibodies to HPV33 (8%) were less prevalent. For men, HPV11 (14%) seroprevalence was highest followed by HPV31 (11%), HPV35 (10%), HPV16 (7%), HPV52 (7%), HPV58 (7%), HPV18 (5%), HPV45 (5%) and antibodies to HPV-33 (3%) were less prevalent. Overall, women had a 2-fold to 4-fold higher seroprevalence compared to men, and similar findings were observed when stratified by age. Women had a 2.7-fold higher seroprevalence of multiple (2-9) types compared to men (33%, 143/435 compared to 14%, 54/435, P < 0.0001). HPV seroprevalence increased with increasing age in both women and men, however in women seroprevalence decreased in older women (41-67 years). More HIV– women and men had HPV antibodies to all types compared to HIV+ women and men respectively; however the difference was not significant. Presence of antibodies as well as antibody reactivity did not correlate with genital HPV DNA or HPV viral load, respectively.

Conclusion: More women had antibody responses than men, even when stratified according to age and HIV status. Multiple seroprevalence was more common in women. Serum antibodies correlated poorly with the presence of genital HPV DNA.

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P-182: Associations Between Race, Oral Sex, Marijuana use and Prevalent Oral HPV Infection in the Ohio S3 Study

Robert Pickard[1], Andrea Inman[1], Weihong Xiao[1], Tatevik Broutian[1], Mike Koluder[1], Xin He[2], Maura Gillison[1]

Background: Oral sexual behavior and marijuana smoking have been associated with HPV-positive oropharynx cancer. Despite dose-response relationships, residual confounding of the marijuana-tumor association by sexual behavior remains plausible.

Methods: A cross-sectional study of the association between sexual behavior, marijuana use, and prevalent oral HPV infection was performed among 1,000 young adults age 18-30 at the Ohio State University, Columbus, Ohio. Behavioral data were collected by computer-assisted self-interview (CASI) and oral samples by Scope oral rinse and gargle (ORG). ORG DNA purified by QiaSymphony was evaluated for 37 HPV types by Roche Linear array. Logistic regression was used to model factors associated with infection.

Results: The study population was 54% female, 69% white, and median age was 21 years (IQR 19-23). Sexual behaviors and substance use were strongly associated with gender and race. Oral HPV infections were detected in 2.4% (95% CI: 1.4–3.4), and half were high-risk infections. Factors associated with oral HPV infection in univariate analysis included black race, increasing age, sexual behavior (kissing, oral and vaginal sex) and frequency of marijuana use. Non-significant associations were observed with male gender, history of genital warts, young age at open-mouth kissing and intercourse, and infrequent alcohol use, but not measures of tobacco smoking or marijuana-joint sharing. In multivariable analysis, odds of infection were independently associated with black race (OR = 6.9; 95% CI: 2.3-21.0), five or more lifetime oral sex partners (OR = 5.7; 95% CI: 2.3-14.0), and frequent recent marijuana use (OR = 5.3; 95% CI: 1.3-20.1), after adjusting for gender and age.

Conclusions: Marijuana use is associated with oral HPV infection after adjustment for oral sexual behavior, consistent with a possible biological effect of cannabinoids on oral HPV natural history. Analysis of associations with incident and persistent infection is ongoing.

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P-402: Topical Cidofovir for Treatment of High-Grade Perianal Intraepithelial Neoplasia in HIV-Infected Men and Women

Elizabeth A. Stier[1], Stephen E. Goldstone[2], Mark H. Einstein[3], Naomi Jay[4], J. Michael Berry[4], Timothy Wilkin[6], Lori Panther[7], Joel Palefsky[4], Jeannette Lee[5], David Aboulafia[8]

Objective: Treatments for high-grade perianal intraepithelial neoplasia (PAIN 2-3) include surgical ablation/excision and have significant morbidity and recurrence rates. Cidofovir, a cytidine nucleotide analogue, has broad-spectrum antiviral activity. This multi-center study prospectively evaluated the efficacy, safety and tolerability of topical cidofovir for treatment of PAIN 2-3 in HIV-positive individuals.

Methods: HIV-positive patients with biopsy-proven PAIN 2-3 >= 3 cm^2 were eligible. Subjects applied 1% topical cidofovir for 6 two-week cycles consisting of 5 consecutive days of treatment and 9 days without treatment. Subjects were evaluated every 2 weeks. High resolution anoscopy and biopsy were performed 6 weeks after the last cycle. Results were scored as stable disease (SD), partial response (PR) (> 50% reduction in size), complete response (CR) or progressive disease (PD) based on size and histology.

Results: Twenty-four men and 9 women were enrolled. Mean age was 33 years, median HIV RNA level was < 75 copies/ml and mean CD4 count was 440/µl. HPV DNA was detected in intra-anal swabs of 31 of 32 (97%) subjects with analyzable specimens. The most common type was HPV16 (44%). 27 (82%) subjects completed treatment per protocol-CR: 4 (15%); PR: 12 (44%), SD: 9 (33%); PD: 2 (7%) (1 with a superficially invasive cancer and 1 with new PAIN 2-3). Six subjects did not complete treatment because of discomfort (1), poor compliance (4), and CR after 4 cycles (1). 26 of 33 subjects (79%) reported adverse events likely related to treatment. Most were mild or moderate, including self-limited, localized, superficial ulcerations in the disease area (2 mild, 19 moderate, 1 severe), discomfort (4 mild, 14 moderate), itching (1 mild, 3 moderate), and bleeding (6 mild). Seven (21%) had mild transient proteinuria.

Conclusions: Topical cidofovir is a well-tolerated and effective treatment for PAIN 2-3 in HIV-positive patients. A larger study is warranted.

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P-405: Progression and Regression of Anal Squamous Intra-epithelial Lesions (ASIL) in Patients Participating in an Anal Screening Program

Richard Hillman[1], Leon P. Botes[1], Leo H. McHugh[1], Fengyi Jin[1]

Background: Although the pathogenesis of anal cancer shares many similarities with cervical cancer, the natural history of its precursors is still largely unknown. We report the progression and regression of ASIL in a cohort of patients who participated in an anal screening program in Sydney, Australia.

Methods: Case records of patients attending an observational anal dysplasia clinic for high resolution anoscopy between January 2004 and December 2009 were reviewed. Those who had at least two consecutive anal histological assessments were included in the analysis.

Results: Of 75 patients who were followed-up for a total of 182 person-years (PY, median: 2.01), 74 were male and 75% were HIV-positive. At baseline 20.0% had low gradeSIL (LSIL), 40.0% had high grade SIL (HSIL), and 4.0% had cancer. The progression rate was 14.6 per 100 PY from those who had no histological evidence of anal dysplasia to LSIL, and 21.8 per 100 PY for those who were free of dysplasia or LSIL to HSIL. Those who were diagnosed with LSIL at baseline were significantly more likely to progress to HSIL than those who had normal histology (HR = 7.3,95% CI 1.5-35.9). Among those who had HSIL or cancer (n = 46) at previous visit, 15 regressed to LSIL, an incidence of 12.9 per 100PY, and 17 regressed to normal histology at some stage, an incidence of 14.6 per 100 PY. Allowing for multiple events, the overall incidence of disease progression to HSIL was 23.4 per 100 PY and of disease regression from HSIL to LSIL or normal was 22.8 per 100 PY.

Conclusion: ASIL is a dynamic process with surprisingly similar progression and regression rates. Large, carefully designed studies are needed to fully characterise the disease process and investigate possible therapeutic agents.

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P-406: Prospective Study of Topical 5-Fluorouracil Treatment of Anal Intraepithelial Neoplasia in HIV-Positive Men

Olivier Richel[1], Henry de Vries[1], Ulrike Wieland[2], Norbert Brockmeyer[3], Jan Prins[1], Alexander Kreuter[3]

Background: Precancerous anal lesions (Anal Intraepithelial Neoplasia, graded AIN 1 to AIN 3) are present in the majority of HIV+ men who have sex with men (MSM). Unfortunately optimal treatment is insufficiently known. Only a limited number of studies has been performed. We evaluated efficacy and side-effects of topical 5-fluorouracil (Efudix) in the treatment of AIN in HIV+ MSM.

Methods: HIV-positive MSM with histopathological confirmed intra-anal AIN were treated with Efudix 1 g intra-anal twice weekly for a total of 16 weeks after which biopsies were repeated. Anal swabs were obtained before and after treatment for HPV typing and HPV-DNA load determination for the high risk types 16, 18, 31 and 33. In case of complete or partial response patients returned 6 months after treatment for follow-up. Patients with progression, or persisting AIN 3 were referred for routine ablative therapy.

Results: 46 HIV+ MSM were included, of which 12 had AIN 1, 17 AIN 2 and 17 AIN 3. In an intention-to-treat analysis 26 patients (57; 95% CI: 42%-72%%) showed a response, of which 18 (39%; 95% CI: 25%-53%) had histological clearance of AIN and 8 (17 %; CI: 6%-28%) a partial response. During treatment, 19 patients (41%) had moderate to serious side effects consisting of urge, frequent defecation, pain and/or proctitis established by anoscopy. In both responding and non-responding patients there was a significant decrease in cumulative viral load of HPV 16, 18, 31 and 33. Non-responding patients also showed a siginificant decrease in number of HR HPV types. Six months after treatment 8 of 16 complete responding patients had a recurrence.

Conclusion: Topical 5-fluorouracil-treatment of AIN has a reasonable response rate and causes a significant decrease in HPV load in responding and non-responding patients. However, it is associated with considerable side effects and the recurrence rate is high.

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P-409: High Acceptability of Self-Collected Anal Swabs and High Resolution Anoscopy (HRA)

Leon P. Botes[1,2], Sarah Pett[2,3], Debbie Marriott[2], Andrew Carr[2], David A. Cooper[2,3], Richard J. Hillman[1,2]

Background: Anal cancer is the most common cancer among HIV+ men, with rates as high as 137/100 000 in HIV+ Men who have Sex with Men (MSM). Both self-collected anal cytological sampling (using moistened Dacron swabs) and HRA (performed via anoscope, without anaesthetic) are proposed components of screening for early anal cancer detection. We conducted a prospective anal cancer screening study using these methodologies in HIV+ MSM attending a Sydney-based clinic. Participants with cytological gradings of Atypical Squamous Cells of Undetermined Significance, Atypical Squamous Cells - possible High-grade, and High-grade Squamous Intraepithelial Lesions were referred for HRA.

Methods: A four-question anonymous evaluation form regarding self collection was offered to all participants, for completion the following day. We evaluated ease and acceptability of self-collected swabs, degree of pain and amount of post-sampling bleeding. Each response was allocated 0-4 points (4 = highest and 0 = lowest score). The maximum possible score was 16/16 (= highly acceptable). An

eight question anonymous evaluation form regarding HRA was offered to all participants, for completion the following week. We evaluated HRA-acceptability including amount of pain (including duration), bleeding, analgesia requirements and any post-HRA intervention. Each response was allocated 0-4 points (4 = highest and 0 = lowest score). The maximum possible score was 32/32 (= highly acceptable).

Results: Of 291 men who self-collected anal swabs, 263 (90%) returned completed evaluation forms. Of these, 193 (73%) scored 12/16, i. e. 75% acceptable. Of those who underwent HRA (n = 73), 61 (84%) returned completed evaluation forms. Of these, 47 (77%) scored 24/32 i. e. 75% acceptable. There were no serious sequelae post-HRA; 4 participants needed paracetamol analgesia and three reported slight bleeding for up to one week.

Conclusion: Self-collected anal swabs and HRA were rated highly acceptable by those who completed the surveys.

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P-544: Imiquimod 2.5% and 3.75% Applied Daily for up to 8 Weeks to Treat External Genital Warts

Daron Ferris[1], David Baker[2], Stephen Tyring[3], Kenneth Trofatter[4], Gabrielle Barry[5], Tiepu Liu[6], Sharon Levy[6], Jason Wu[6]

Background: Imiquimod 5% to treat external genital warts involves non-intuitive dosing (3x/week) and long duration (up to 16 weeks).

Objectives: Evaluate new imiquimod formulations applied daily for up to 8 weeks.

Methods: In 2 identical phase 3 studies, subjects ≥ 12 years of age with 2-30 external genital warts and a total wart area ≥ 10 mm^2 were randomized to placebo, imiquimod 2.5% or 3.75% (1:2:2). Up to 250 mg of cream per dose was applied once daily to warts for up to 8 weeks or until complete clearance of all (baseline and new) warts, if earlier. Clearance assessment was up to an additional 8 weeks post-treatment. In subjects with complete clearance, 12-week sustained complete clearance was assessed

Results: For the 981 subjects enrolled, mean age was 32.6 years and 54.4% were female. Mean disease duration was 4.9 years, wart count 8.7 and total wart area 158.8 mm^2. For placebo, imiquimod 2.5% and 3.75%, respectively, complete clearance of all warts was achieved in 9.4% (19/202), 22.1% (84/380) and 28.3% (113/399) of subjects by intent-to-treat ($p < 0.001$, 2.5% and 3.75% versus placebo, $p = 0.025$ 3.75% versus 2.5%) and in 11.5% (18/157), 27.0% (75/278) and 33.8% (95/281) by per-protocol. Clearance was greater for females than males (e. g. 36.6% versus 18.6%, imiquimod 3.75%, per-protocol). With respect to safety, 0.5%, 1.6% and 1.5% of subjects discontinued early due to safety-related reasons; 1.0%, 15.0% and 16.3% experienced severe local skin reactions; and 2.0%, 27.4% and 31.5% required rests, for placebo, imiquimod 2.5% and 3.75%, respectively. Of subjects who achieved initial complete clearance and entered the 12-week follow-up, complete clearance was sustained in 92.3% (12/13), 59.5% (44/74) and 69.6% (71/102) of subjects for placebo, imiquimod 2.5% and 3.75%, respectively.

Conclusions: Imiquimod 2.5% and 3.75% daily for up 8 weeks were well tolerated and more efficacious than placebo in treating genital warts.

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P-547: Intratype Variation of Complete HPV 6 Genomes in Laryngeal and Pharyngeal Papillomas

Agustin Enrique Ure[1], Joakim Dillner[1], Ola Forslund[1]

Background: Laryngeal and pharyngeal papillomas are primarily caused by HPV types 6 or 11. These lesions are quite difficult to treat, provoking the question of whether there may be pathogenically relevant genetic changes of the HPV genomes in these lesions. The knowledge concerning intratype sequence variation of HPV 6 and 11 is limited. The aim of the study was to analyse genomic diversity of HPV 6 and to search for nucleotide signatures specific for laryngeal and pharyngeal papillomas.

Methods: From patients aged 24-68 attending otorhinolaryngology clinics in Sweden, nine HPV type 6 positive laryngeal and one pharyngeal papillomas were included. Complete genomes of HPV 6 were obtained by long range PCR and direct sequencing.

Results: Hitherto, two complete HPV 6 genomes were obtained. From a 58 year old male with epipharyngeal papilloma, an HPV 6 genome of 8031 bp showed closest nucleotide identity with HPV 6vc (AF092932) (99.4%). The upper regulatory region (URR) showed insertions of 20 bp and 19 bp segments not present in the HPV 6vc and HPV 6a genomes, respectively. In comparison to HPV 6vc, this genome showed 15 silent, 6 neutral and 6 missense mutations distributed in all ORFs and 3 mutations in the URR. From a 67 year old female with a laryngeal papilloma, an HPV 6 genome of 7996 bp showed 98.8% identity with HPV 6b (X00203). The URR contained an insertion of 94 bp, suggested to be deleted in the original clone of HPV 6b (Heinzel et al., 1995). Only one silent mutation was detected in the E1 ORF and another in the URR.

Conclusion: Complete nucleotide sequences of HPV 6 isolates can be generated by straightforward long range PCR and direct sequencing. Analysis of complete HPV 6 genomes from laryngeal and pharyngeal papillomas will be presented.

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P-548: Understanding the Psychosocial Burden of Genital Warts in Canada: A Prospective 6-Month Study

Melanie Drolet[1,2], Marc Brisson[1,2], Elizabeth Maunsell[1,2], Alex Ferenczy[3,4], Eduardo Franco[3], François Coutlée[6], Joel Palefsky[7], James Mansi[8]

Objectives: The aim of the PISCES study was to assess the psychosocial burden of genital warts (GW), given the scarcity of data on the subject.

Methods: Between 10/2006 and 10/2007, 271 GW cases seeking care for a first (n = 131) or a recurrent (n = 140) episode were recruited across Canada. Health-related quality of life (HRQoL) was assessed at recruitment, and 2 and 6 months later with the following instruments: EuroQol (EQ-5D and VAS), Short Form-12 (SF-12), short Spielberg State-Trait Anxiety Inventory (STAI-6), and HPV Impact Profile (HIP, overall score and 7 scales).
Results: First or recurrent GW had a significant effect on all HRQoL outcomes at recruitment. Compared to age-gender matched population norms, a greater proportion of women with a first GW episode reported problems in their usual activities (6% norms vs. 21% GW), pain/discomfort (30% norms vs. 52% GW) and anxiety/depression (32% norms vs. 67% GW). The same EQ-5D health domains were affected for men with a first GW episode and for men and women with recurrent GW. Results of the HIP indicated that GW had the most severe impact on self-image, sexual activity and partner issues/transmission. Women with either first or recurrent GW consistently reported greater negative impact than men for all HIP scales. Prospective analysis indicated that the negative effect of GW on HRQoL (all outcomes), irrespective of sex, was maintained as long as GW persisted. The median duration of a first GW episode was estimated at 125 days.
Conclusions: These results improve our understanding of the psychosocial burden of GW. Future analyses will identify the characteristics of individuals with a greater negative psychosocial impact of GW.

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P-570: Human Papillomavirus in Oral Squamous Cell Carcinomas

Daniela Cochicho[1], Luis Martins[1], Mário Cunha[1], Carmo Ornelas[1], Mariluz Martins[2], Carlos Zagalo[2]

Tobacco smoking and alcohol are the main causes of most Head and Neck Cancers Squamous Cell Carcinoma (HNSCC); however a high proportion of these cancers are occurring in patients who never smoked or drank. Human papillomavirus, etiological agent of cervical cancer has been linked to a subset of HNSCC. Up to 60% of oropharyngeal cancers have been associated with oncogenic HPV types, while other head and neck cancers, including oral cavity tumours, have lower HPV prevalence (about 20%). Similar to all other HPV related cancers HPV 16 is the most common type identified in oral cavity cancers followed by HPV 18.
Aim: Detection of HPV in oral squamous cell carcinomas.
Methods: We study a total of 169 samples (smears and biopsies) of 64 patients, 15 females and 49 males with a mean age of 61 years (range 33-89 years) with squamous cell carcinoma of oral cavity. HPV presence was evaluated by real time PCR (SYBR Green) using SPF primers. HPV positive samples were genotyped using Microarrays (PapilloCheck). MRC5, SiHa and B-globin were used as negative, positive and internal controls, respectively.
Results: Most of the samples tested were negative for HPV; however 26.6% (17/64) of patients with oral SCC had at least one positive result for HPV, 5 were females and 12 were males. The most prevalent types detected were HPV16 (2/17) and HPV 51 (2/17); HPV 33 was detected in one sample. Twelve (12) positive samples weren't genotyped.
Conclusions: The rate of HPV detection in oral SCC patients in this study is very similar (26.6% vs. 23.5%) to that found in literature. We also can't conclude anything about type distribution because we were unable to genotype 12 samples using this microarray system. Positive samples that we couldn't genotype are being sequenced. Detection of HPV in HNSCC can be useful regarding the therapeutic approach.

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P-573: Oral and Anal HPV Infection among HIV-Infected Men and Women

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Objectives: Few studies have compared the prevalence and predictors of HPV infection among men and women. We therefore performed such an analysis of HPV infection at two anatomic sites, both oral and anal, among HIV-infected men and women. Additionally, we evaluated the genotype distribution and type-specific concordance at both anatomic sites.
Methods: We included baseline data from 404 HIV-infected individuals enrolled in the Human Oral Papillomavirus Epidemiology (HOPE) cohort study at the Johns Hopkins Hospital. ScopeTM oral rinse samples and anal exfoliated cells were evaluated for HPV DNA using the PGMY09/11 primer system and genotyped for 37 types using Roche linear array. Demographic and behavioral information was collected using an audio computer-assisted, self-interview.
Results: The prevalence of oral HPV infection was similar among men and women (29.7% vs. 23.5%, p = 0.18), whereas anal HPV prevalence was higher among women than men (94.3% vs. 76.0%, p < 0.001). The most prevalent oral genotypes were HPV 55 (4.3%), HPV 83 (3.8%), HPV 72 (3.6%), HPV 61 (2.6%), and HPV 16 (2.6%) and for anal infection were HPV 61 (20.6%), HPV16 (19.8%), HPV 53 (19.5%), HPV 55 (19.5%), and HPV 58 (19.0%). In univariate analysis, measures of same-gender oral-sexual contact were associated with oral HPV infection among men and women, including lifetime number of male oral sex partners among men, and lifetime and recent number of female deep kissing and oral sex partners among women. By contrast, for anal infection, same-gender sex was positively associated with infection among men but negatively associated among women. Nadir CD4 count was more strongly associated with anal infection than current CD4 count among both men and women and no significant associations were observed for oral infection. When infected at one site, individuals were significantly more likely to have concurrent oral and anal HPV infection (OR = 2.55; 95% CI = 1.21-5.84). HPV type-specific concordance of oral and anal infection was greater than expected by chance for HPV types 26, 39, 45, 55, 62, 67, 68, 69, and 81.

Conclusions: Prevalence of oral and anal HPV infections was high among HIV-infected individuals. Among both men and women, sexual orientation was the strongest predictor of HPV prevalence.

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P-591: High Incidence of High-grade Anal Intraepithelial Neoplasia in HIV-Infected Women and Men Dollowing Organ Transplantation

Peter V. Chin-Hong[1], J. Michael Berry[1], Naomi Jay[1], Maria Da Costa[1], Teresa Darragh[1], Michelle E. Roland[1], Peter G. Stock[1], Joel M. Palefsky[1]

Objectives: HIV-infected women and men and transplant recipients are two populations at increased risk of HPV-associated anal cancer and precancer lesions. There is little information on the incidence of HPV-associated anal disease following organ transplantation among HIV-infected individuals. We determined the incidence and determinants of anal intraepithelial neoplasia (AIN) following organ transplantation among HIV-infected individuals.

Methods: We followed 330 HIV-infected women and men who were listed for liver and kidney transplantation in 5 U.S. cities. Of these, 89 received organ transplantation (52% liver, 45% kidney, 3% both). During baseline (pre-transplantation) and follow-up visits post transplantation, we obtained anal cytology, demographics, information on anti-rejection medications, and measured CD4+ T cells and HIV-1 plasma RNA.

Results: At the baseline visit prior to receiving organ transplantation, median age was 49 years (IQR 42-54), median CD4+ T cells = 363 (IQR, 215-527), median HIV-1 plasma RNA < 50 copies/ml, 11% were female and 58% were men who had sex with men. Following organ transplantation, median CD4+ T cells = 216 (IQR, 131-372), median HIV-1 plasma RNA <50 copies/ml, and 24% had received specific T-cell depleting agents. At baseline, 15% were diagnosed with atypia, 27% with low-grade (LSIL) and 2% with high-grade (HSIL) anal cytologic abnormalities. Following transplantation (median = 26 weeks), 13% were diagnosed with atypia, 25% with LSIL and 19% with HSIL. In multivariable analyses, there was evidence for the association of transplantation with HSIL (OR 12.4, 95% CI 1.5-103, P = 0.019), but little evidence for a role for CD4+ T cells, HIV-1 plasma RNA, use of T-cell depleting agents, and type of organ transplanted (P > 0.20).

Conclusions: There is a high prevalence of AIN among HIV-infected women and men pre-transplant. Solid organ transplantation is independently associated with progression to anal HSIL in a prospective cohort of HIV-infected individuals. Further studies will determine the optimal periodicity of anal cancer screening among transplant recipients.

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P-594: Incidence of Genital Warts among Men in the Placebo Arm of a Quadrivalent HPV Vaccine Trial

Stephen Goldstone[1]

Background: Quadrivalent HPV vaccine (GARDASIL®) is 90% (95% CI: 69, 98) efficacious against vaccine HPV type related external genital lesions in men. The purpose of this analysis was to examine the incidence of and HPV types identified in external genital warts (EGW) among heterosexual men (HM) and men having sex with men (MSM) enrolled in an efficacy trial of GARDASIL®.

Methods: Of 4,065 men aged 16-26 years with <5 lifetime sexual partners enrolled in a randomized, double-blind clinical trial, 2,030 received placebo. Subjects underwent genital exams and HPV sampling from the penis, scrotum, and perineal/perianal area at Day 1, month 7 and every 6 months afterwards. All lesions were biopsied for diagnosis and PCR testing. An incident case of EGW was defined as a subject who had no reported history or a diagnosis of EGW at Day 1, but developed a subsequent EGW as determined by the pathology panel. An HPV type-specific endpoint was an incident case of EGW with a specific HPV type (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) found in the lesion via PCR.

Results: Inclusive of 2.9 years of follow-up (median), 83 cases of EGW were identified with an incidence rate (per 100 person years) of 1.83. The incidence rate among HM (1.50) was lower than in MSM (4.70). The incidence rate was 1.12 per 100 person years (0.97-HM, 2.79-MSM) in subjects PCR and seronegative to all 4 vaccine HPV types at enrollment. 71 (86%) of all EGW was related to ≥ 1 of the 4 HPV types in the vaccine. HPV types 6 and 11 were the most common HPV types found in EGW lesions with 48 (58%) and 24 (29%) cases, respectively. Co-infections with other tested HPV types were detected in 20 (24%) of EGW.

Conclusions: These data demonstrate the high incidence of EGW amongst a population of young men with few prior sexual partners. A large proportion of EGW was associated with HPV 6 or11. Considering the high efficacy of GARDASIL® against external genital lesions, these data suggest potential benefit of vaccination with GARDASIL® and prevention of EGW in men.

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P-599: Risk Factors and Age-Specific Prevalence for Anal HPV among Men Having Sex with Women and Men Having Sex with Men

Alan G. Nyitray[1], Roberto J. Carvalho da Silva[2], Dan'elle Smith[1], Martha Abrahamsen[1], Mary Papenfuss[1], Luisa L. Villa[3], Eduardo Lazcano-Ponce[4], Anna R. Giuliano[1]

Introduction: Increasing anal cancer incidence suggests a need to better understand the transmission of HPV to the anal canal. No reports have compared risk factors and age-specific prevalence for anal HPV among men having sex with women (MSW) and men having sex with men (MSM).

Methods: Genotyping for 37 HPV types was conducted for anal samples in 1833 men, ages 18-70, from São Paulo, Brazil; Cuernavaca, Mexico; and Tampa, USA. Eligibility included no history of genital warts and no current STD diagnosis including HIV. Exfoliated cell samples between the anal os and the dentate line of the anal canal were obtained with a saline-wetted Dacron

swab. Potential risk factors for anal HPV were assessed using logistic regression.

Results: Anal canal HPV prevalence was 12.2% among 1305 MSW and 47.2% among 176 MSM. Prevalence of any HPV type was stable across the lifespan in MSW (p trend = 0.81) but declined in MSM (p trend = 0.001). In multivariate analysis with MSW, having ≥ 10 lifetime female sex partners (OR 2.85, 95% CI 1.44-5.67 vs. 0-2 partners), a primary sexual relationship < 1 year old (OR 2.00, 95% CI 1.05-3.80 vs. > 10 years) and a hepatitis B diagnosis (OR 4.64, 95% CI 1.60-13.46) were associated with any HPV and oncogenic HPV. In multivariate analysis with MSM, ≥ 2 recent male anal sex partners (OR 4.99, 95% CI 1.46-16.97 vs. 0 partners) and never using a condom for recent anal sex (OR 6.07, 95% CI 1.47-24.97 vs. always using condoms) were associated with any HPV detection.

Conclusions: These data suggest that number of sex partners is a causal factor for anal HPV in MSW and MSM; however, the mechanism for viral transport to the anal canal, especially in MSW, is not fully understood. Anal HPV infection may be mediated by length of sexual relationship and condom use. Questions: alan.nyitray@moffitt.org.

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P-600: Type-Specific Incidence and Persistence of Anal HPV in Men after Six Months of Follow up: The HIM Study

Alan G. Nyitray[1], Roberto J. Carvalho da Silva[2], Hui-Yi Lin[1], Dan'elle Smith[1], Martha Abrahamsen[1], Mary Papenfuss[1], Luisa L. Villa[3], Eduardo Lazcano-Ponce[4], Anna R. Giuliano[1]

Objectives: While there are a limited number of incidence and persistence estimates for anal HPV in women and men having sex with men (MSM), there are no such reports for men having sex with women (MSW). The purpose of the current study was to estimate anal HPV incidence and persistence in HIV-negative men after six months of follow up.

Methods: Genotyping for 37 HPV types was conducted for anal samples from men, ages 18-70, from São Paulo, Brazil; Cuernavaca, Mexico; and Tampa, USA who provided specimens at a pre-enrolment and 6 month visit of a 4-year prospective study. Eligibility included no history of genital warts or HIV. A total of 1082 men provided evaluable specimens at both visits including 878 MSW and 140 MSM. Incident infection was defined as detection of type-specific infection after a negative result for that type at the pre-enrolment visit. Persistence was defined as type-specific infection at each visit. The Kaplan Meier method was used to estimate cumulative incidence.

Results: After a median follow-up time of 204 days, overall cumulative incidence for any 1 of 37 HPV genotypes was 7.6%. Cumulative incidence was substantially higher among MSM (27.7%) than among MSW (4.7%). Of prevalent infections in MSW and MSM, 3.2% and 27.9%, respectively, were persistent at follow up. A total of 4.3% of MSM had a persistent HPV16 infection at the six month visit. Among 20 MSW with prevalent HPV16 infection, all cleared the infection at follow up.

Conclusions: While anal HPV infection is commonly acquired by both MSW and MSM, the six-month cumulative incidence is several fold higher in MSM. Also, persistence of any HPV genotype was common in MSM and rare in MSW. We observed no HPV16 infections in MSW that were persistent for six months.

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P-601: Cross-National Genital HPV Prevalence among Men Having Sex with Men and Men Having Sex with Women: The HIM Study

Alan G. Nyitray[1], Roberto J. Carvalho[2], Dan'elle Smith[1], Martha Abrahamsen[1], Mary Papenfuss[1], Eduardo Lazcano-Ponce[4], Luisa L. Villa[3]

Introduction: Most investigations of HPV among men having sex with men (MSM) have examined infections in the anal canal with few studies reporting genital HPV prevalence. We estimated genital HPV prevalence in a cross-national sample of MSM and then compared these estimates with genital HPV prevalence among men having sex with women (MSW) recruited from the same population.

Methods: Exfoliated cell specimens from the glans penis, penile shaft and scrotum were obtained with a wetted Dacron swab. Genotyping for 37 HPV types was conducted for specimens from 3718 men, ages 18-70 years, from São Paulo, Brazil; Cuernavaca, Mexico; and Tampa, USA. Evaluable results were available for 3602 men including 335 MSM and 3054 MSW. Recruitment occurred through a sexually transmitted infections (STI) clinic, a health plan, factories, the military, universities, and advertisements to the general public. There was no targeted recruitment for MSM. Eligibility criteria excluded men with a history of genital warts, a current STI, or HIV.

Results: The median age for MSM and MSW was 31.9 and 30.8 years, respectively. A comparable number of MSW were recruited in each city while two-thirds of MSM were recruited in São Paulo. Among MSM, 64.6%, 62.5%, and 39.7% were positive for any one of 37 HPV genotypes in São Paulo, Cuernavaca, and Tampa, respectively. Among MSW, 62.5%, 50.3%, and 47.5% were positive for any one of 37 genotypes in São Paulo, Cuernavaca, and Tampa, respectively. Among MSM and MSW overall, 35.2%, and 31.5% had an oncogenic infection, respectively, and 10.5% and 8.0% had an HPV16 infection, respectively.

Conclusions: We detected genital HPV in a majority of both MSM and MSW with the prevalence being comparable in each group. In contrast, our prior investigations estimated an anal HPV prevalence in MSM that was several fold higher than that observed in MSW.

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P-602: Clinical Characterization and Treatment of Penile Intraepithelial Neoplasia Grade 1, 2 and 3

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Background: Genital HPV infection in men can cause a great variety of lesions. Most of these are benign, but some are categorized as penile intraepithelial neoplasia (PIN) grade 1-3.
Objectives: To describe the clinical presentation and treatment of PIN.
Methods: Male patients attending the STI clinic of Karolinska Hospital for surgical treatment of genital HPV infection were included in the study. Two biopsies were taken from each patient, one for histopathology and one for HPV typing using nested PCR. Patients exhibiting PIN were selected. Lesions were described, treatment and follow-up data were also recorded.
Results: Forty-seven of 293 (16%) male condyloma patients exhibited lesions of PIN. Ninteen men were afflicted with lesions denominated as PIN 1, 13 men had PIN 2 lesions and 15 men exhibited PIN 3 lesions. The lesions were classified in acumiate (n = 6), papular (n = 13), macular (n = 27) and seborrheic keratosis like (n = 1). The foreskin was the most common location, followed by the penile shaft. Low risk HPV types were found in 79%, 23% and 20% of PIN 1, 2 and 3 lesions, respectively. High risk HPV types were correspondingly found in 5%, 54% and 60 % of PIN 1, 2 and 3 lesions, respectively. Five of 47 lesions had a mix of low- and high risk HPV types, and 4/47 lesions were HPV negative. Thirty men had previously received some kind of therapy, while 17 were untreated. The mean duration of genital lesions and/or genital symptoms before inclusion was 16 months. Mean four surgical treatment sessions were performed. Duration of the treatment period from first to last surgical treatment session was mean 27 months.
Discussion: PIN is probably a common disorder, can show different clinical picture and is difficult to treat. Programs for treatment and follow-up do not exist. The condition needs to be further studied.

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P-608: Risk Factors for HPV Related External Genital Lesions in Men: The HIM Study

Gabriella Anic[1,2], Mary Papenfuss[1], Luisa Villa[3], Eduardo Lazcano[4], Martha Abrahamsen[1], Anna Giuliano[1]

Background: Little is known about the natural history of HPV related external genital lesions (EGL) in men.
Objective: Examine the factors associated with the incidence of EGL in men.
Methods: 2,487 men ages 18-70 from the US, Brazil, and Mexico were prospectively examined over a median of 17.9 months. Incident EGL, including 112 genital warts and 29 genital lesions, were identified by visual examination of the external genitalia by a study clinician. EGLs were sampled with a pre-wetted Dacron applicator and tested for HPV DNA by PCR. Sociodemographic and sexual behavior factors were obtained with a questionnaire administered using Computer-Assisted Self-Interviewing.
Results: Sexual behaviors significantly associated with an increased risk of EGL incidence included having 3 or more female sexual partners, compared to no female sexual partners, during the previous 3 months (HR = 2.73; 95% CI: 1.58-4.70), having 20-49 female partners over the lifetime, compared to no female partners (HR = 2.57; 95%CI: 1.06-6.27), and ever having a female sexual partner with an abnormal PAP smear result (HR = 1.82; 95% CI: 1.14-2.91). Increased risk of EGL was also observed among men who tested positive for any HPV type (HR = 2.08; 95% CI: 1.37-3.16) or HPV 6, 11, 16 or 18 (HR = 4.35; 95% CI: 3.06-6.19) on the healthy genital skin at baseline. Risk of EGL was also significantly higher among men residing in the US (HR = 1.57; 95% CI: 1.03, 2.40). There was a reduced risk of EGL among men ages 31-44 (HR = 0.56; 95% CI: 0.38-0.83) and 45-70 (HR = 0.53; 95% CI: 0.20-0.97) compared to men ages 18-30 and among married men compared to single men (HR = 0.50; 95% CI: 0.33-0.77).
Conclusions: Recent sexual behavior and testing HPV positive for HPV 6, 11, 16, or 18 were the factors most strongly associated with EGL incidence.

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P-612: Concordance and Transmission of Human Papillomavirus

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Objective: To describe the rate of HPV concordance over time and the frequency of HPV transmission over six weeks in monogamous couples.
Methods: Twenty-five women who were participating in an ongoing HPV study and had an incident HPV infection were asked if they and their partner, of at least 3 months duration, would participate in this substudy. Couples were tested on the same day for HPV by sampling the anogenital area. After the baseline visit, couples were asked to have sex and return within 24 hours for HPV sampling followed by abstaining from sex and returning 48 hours later (72 hour visit). Couples also returned for sampling 2 weeks and six weeks later. HPV detection used Roche Linear Array HPV Genotyping Test. Transmission was calculated if the couple was discordant at baseline and the type that was not found in one of the partners was found at a subsequent visit.
Results: Type-specific concordance occurred in 73.6% of the 125 visits; 64.8% were positively concordant and 8.8% were negatively concordant. Table 1 shows concordance rates by visit. Concordance was highest at the 24-hours-post-intercourse visit. Out of 70 possible female to male transmission events, 12 transmissions occurred (17% transmission rate). Out of 62 possible male to female transmission events, 2 transmissions occurred (3% transmission rate). The female to male transmission rate was higher than the male to female transmission rate (p = 0.01, Fisher's exact 2-tailed test). Table 2 shows transmission events by visit.
Conclusions: Concordance rates were high in this population of monogamous couples in which the woman had a recent incident HPV detected. The 20% higher rate of concordance 24 hours post intercourse suggests that many DNA detections are contaminant

from the partner. Transmission appears to be more efficient from women to men than vice-versa.

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P-614: Detection of HPV DNA in Urine and Oral Samples of HIV-1 Male in Sao Paulo, Brazil

Fernando Costa[1], Karen Oliveira[1], Roberto Silva[2], Alberto Duarte[1], Jorge Casseb[1]

Background: The relationship between Human Papillomaviruses and several types of cancers is well documented by many studies. However, there are few studies showing the infection in men and there is no consensus on the site of infection. The investigation of oral and genital infection is important due to the high number of cases of cancers described in these regions.
Aim: Evaluate the presence of HPV DNA in genital and oral tract of HIV-1 male patients.
Methods: Adult men HIV-1-infected subjects in the HIV Outpatient clinic were invited to participate to this study. The collection was conducted between December 2009 and February 2010. About 20 ml of urine was collected in a specific room, previously cleaned within the last 3 hours and the samples of the oral tract were obtained by mouthwash with saline solution for 1 minute. The samples were performed to a real time PCR, using Sybr Green® with PGMY09/11 degenerate primers to detect HPV DNA.
Results: Among the twenty samples collected from patients until now, HPV DNA was present in 20% and 5% in urine and oral tract, respectively. No patients presented lesions suggestive of HPV infection in both oral and genital tracts.
Conclusion: HPV infection is very important, especially among patients infected with HIV-1. It is essential to determine the main sites of infection in men. The molecular biology, together with new types of biological samples such as urine and oral wash, which are easy to collect and less invasive, is a very useful tool for the identification of HPV in different sites of possible infection.

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P-622: Evidence for the Protective Effect of Condoms against Male-to-Female Transmission

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Objective: To determine whether condoms offer protection against documented male-to-female HPV transmission.
Methods: We analyzed data from the HITCH Cohort Study (HPV Infection and Transmission among Couples through Heterosexual activity), a study of recently-formed couples (relationships of up to 6 months at enrolment). Women aged 18-24 attending a university or junior college in Montreal, Canada and their male partners were eligible. Self-collected vaginal swabs and clinician-obtained swabs of epithelial cells from the penis and scrotum were tested for DNA of 36 HPV types. We analyzed follow-up data at visit 2 from 99 couples for whom at enrolment the male had an HPV type not found in the female. We defined transmission as the detection of 1+ types in the female at visit 2 that were previously only detected in the male. We report the effect of condom use as a rate ratio (RR) with 95% confidence intervals (CI), as estimated using Poisson regression.
Results: At visit 1, women reported a median of 7 lifetime partners and 78% were infected with 1+ HPV types. Women reported a mean of 73 vaginal sex encounters with their HITCH partner between visits 1 and 2. Rates of condom use were 49% never, 18% rarely, 12% sometimes, 7% most of the time, and 13% always. Among condom users, 74% reported at least one episode of breakage/slippage or partial use. At visit 2, there was evidence of male-to-female transmission in 26% of women with an overall transmission rate of 5.0 per 100 person-months (95% CI 3.4-7.3). Condom use compared to no condom use was associated with decreased rate of transmission (RR = 0.42, 95%CI 0.18-0.95).
Conclusions: Despite imperfect condom use, these data provide evidence that condoms offer protection against male-to-female HPV transmission. HPV prevention strategies should include the promotion of condom use, in addition to vaccination and screening.

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P-642: Genital and Extra-Genital Warts Increase the Risk of Asymptomatic Genital HPV Infection in Men

Brenda Hernandez[1], Yurii Shvetsov[1], Lynne Wilkens[1], Pamela Thompson[1], Xuemei Zhu[1], Marc Goodman[1], Lori Kamemoto[2], Lily Ning[3]

Objectives: Warts can occur at any body site. We sought to examine the relationship of genital and extra-genital warts to the acquisition of genital HPV infection in men.
Methods: A cohort of 357 adult males was followed at 2-month intervals for an average of 431 days. At study entry, the history of warts in genital and extra-genital sites was queried. Genital swab specimens were obtained at each study visit for HPV testing and genotyping. The risk of incident infection was modeled through Cox regression adjusting for age, lifetime number of sexual partners, and sexual orientation.
Results: A history of genital warts was associated with increased risk of acquisition of genital HPV infection (any oncogenic, and non-oncogenic HPV). Genital wart history increased the risk of genital HPV 6 and/or 11 infections (RR: 6.62; 95% CI: 2.35-18.67). Increased risk of genital HPV infection was also associated with a history of non-genital warts (RR: 1.31; 95% CI: 1.07-1.60), specifically finger warts (RR: 1.27, 95% CI: 1.06-1.53) and arm warts (RR: 1.36, 95% CI: 1.05-1.75). These relationships were generally consistent for the glans penis, penile shaft, and scrotum. History of warts at other sites, including the head, mouth, trunk, leg, and foot, was not associated with increased risk of genital HPV infection. A history of genital warts in sexual partner(s) increased the risk of acquisition of genital HPV infection in men by 4%.

Conclusions: The presence of genital warts enhances the risk of new, asymptomatic genital HPV infection, possibly through the spread of virions shed from the wart. Similarly, genital warts in sexual partners augment HPV transmission to men. Warts on fingers and arms also increase the risk of genital HPV, underscoring the role of auto-inoculation from extra-genital sources.

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P-643: Rapid Eluctuation in the Detection of Genital HPV in Male-Female Couples

Brenda Hernandez[1], Yurii Shvetsov[1], Lynne Wilkens[1], Pamela Thompson[1], Xuemei Zhu[1], Marc Goodman[1], Lori Kamemoto[2], Lily Ning[3]

Objectives: Genital HPV infections are highly transmissible yet generally self-limiting. Daily changes in the detection of genital HPV DNA were examined in male-female couples.
Methods: Seventeen couples (17 males and 17 females) self collected genital specimens for 7-14 consecutive days. Each day, men collected 3 external genital swab specimens (penis glans, shaft, and scrotum) and women collected tampon and urine specimens. Couples collected specimens on the same days. Specimens were tested for HPV DNA and genotyped.
Results: At baseline, 8 men and 7 women were HPV-positive. These included 5 couples where both partners were concordant for at least 1 genotype. Overall during the 7-14 days of follow-up, 8 couples were positive for concordant genotypes, 2 couples were positive for different genotypes, 6 couples had only 1 HPV-positive partner (the male partner in 4 of these couples), and 1 couple was HPV-negative on all days. Nineteen individuals (11 males, 8 females) were intermittently HPV-positive. A number of individuals became HPV-positive and/or HPV-negative for one or more genotypes within a 24-hour period. Partners were not the source of most newly detected infections. Viral transmission was observed in three different couples where a genotype present in only 1 partner was subsequently detected in the other partner. In two of these couples, HPV was transmitted to the male partner after being detected in the female partner for a 2-3 day period. In one couple, HPV was transmitted to the female partner after being detected in the male partner for 7 days; only 1 of 3 genotypes present in the male's genitals was transmitted to his partner.
Conclusions: The detection of genital HPV DNA changes rapidly in sexually active couples. While sexual transmission accounts for some of this variability, fluctuation in HPV DNA status is also attributed to cycles of rapid clearance and reactivation of infection within individuals.

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P-665: HPV6/11 Detection and p16-INK4A Expression in Anogenital Carcinomas

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Background: HPV6 and HPV11 are Low Risk types responsible for benign lesions of the anogenital tract. Conversely, relatively few HPV6 and HPV11 positive malignancies have been identified. p16INK4A overexpression is present in cervical lesions related to High Risk types. Laser Capture Microdissection (LCM) is a powerful tool to isolate specific cell populations from tissue sections. HPV6 and HPV11 oncogenic role in anogenital carcinomas remains to be confirmed.
Objectives: To confirm the presence of exclusively HPV6/11, and to evaluate p16INK4A expression in Cervical, Vulvar, Vaginal, Penile and Anal invasive cancers.
Methods: Thirty-two specimens with HPV6 or HPV11 genotypes confirmed by PCR, were selected from a series of approximately 15,000 cases (ICO international survey of anogenital cancers). In addition to HPV 6/11, 53 different HPVs from Alpha, Beta, Gamma, Mu and Nu genus were analysed by SPF10-LiPA25-Aditional strip, HSL-PCR/MPG and E6 PCR/MPG. Tumour cells were isolated by LCM. All whole section HPV6/11 cases were immunostained for p16INK4A. Histology diagnosis was reviewed by a panel of 7 pathologists.
Results: HPV6/11 genotypes were confirmed as single type in 27 cases. Of these, 18 (66.6%) cases displayed verrucopapillary histology. In 15 (83.3%) samples selected tumour cells by LCM/PCR were found to contain HPV6/11 as single infection. Five (55.6%) of non-verrucopapillary carcinomas were HPV positive by LCM/PCR. On verrucopapillary carcinomas p16INK4A staining was negative in 27.8%, patchy in 22.2%, basal diffuse in 16.7% and diffuse in suprabasal layers in 22.2% of the samples. Non-verrucopapillary carcinomas were p16INK4A negative in 55.6%, patchy in 0% and in 33.3% p16INK4A showed a diffuse stain on lower basal layer.
Conclusions: HPV6/11 genotypes are present in some carcinomas, and they display mainly verrucopapillary histology. p16INK4A has an heterogeneous pattern in HPV6/11 related carcinomas. The biological activity of these HPV types will be further investigated by HPV6/11 mRNA analysis.

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P-669: Quadrivalent HPV Vaccine Efficacy Against ana HPV Infection in Men Having Sex with Men

Anna Giuliano[1], Joel Palefsky[2]

Background: We previously demonstrated the efficacy of the quadrivalent HPV vaccine (GARDASIL®) against external genital lesions (perianal/perineal/penile intraepithelial neoplasia and condyloma) and persistent infection in heterosexual men and men who have sex with men (MSM) aged 16 to 26 years with no

more than 5 lifetime sexual partners. In this analysis we examined the efficacy of the vaccine against anal HPV 6/11/16/18 infection in MSM.

Methods: Data are from 598 MSM aged 16-26 years who were randomized to receive vaccine or placebo at enrollment, month 2, and month 6. Subjects underwent detailed anogenital exams as well as sampling from the anal canal at enrollment, month 7 and at 6-month intervals afterwards. Efficacy analyses were performed in a per-protocol population (seronegative at day 1 and DNA-negative from day 1 through month 7 to the relevant vaccine HPV type). Persistent HPV infection was defined as detection of the same HPV type (6/11/16/18) in an anogenital swab or biopsy specimen collected on ≥ 2 consecutive visits ≥ 6 months apart. Individuals with detection of HPV 6/11/16/18 DNA at ≥ 1 visit contributed to the DNA detection endpoint (single-time detection). Median follow-up was 2.5 years (post-dose 3).

Results: Quadrivalent HPV vaccine efficacy against persistent anal infection with HPV 6/11/16/18 was 94.9% (95% CI: 80.4, 99.4) (2 vaccine cases and 39 placebo cases). One vaccine case was related to HPV 6 and one case was related to HPV 16. Resultant efficacy against HPV 6-and 16-related persistent anal infection was 92.1% (95% CI: 47.2, 99.8) and 93.8% (95% CI: 60.0, 99.9) respectively. Quadrivalent vaccine efficacy against single-time anal HPV 6/11/16/18 DNA detection was 84.0% (95% CI: 68.6 92.7).

Conclusions: The quadrivalent HPV vaccine is efficacious in preventing persistent anal HPV 6/11/16/18 infection and single-time anal HPV DNA detection in young MSM.

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P-670: Lower Level of Titers in Response to the HPV Quadrivalent Vaccine among Men who Have Sex with Men Compared with Heterosexual Men

Joel Palefsky[1], Tim Wilkin[2], Anna Giuliano[3]

Introduction: Although the seroconversion rate to the virus-like particles (VLPs) in the quadrivalent vaccine is nearly 100% for all groups studied thus far, titers have varied among groups Little is known about titers in vaccinated HIV-negative men who have sex with men (MSM) compared with HIV-negative heterosexual men (HM) or HIV-positive MSM compared with HIV-negative MSM.

Methods: Merck 020 was an efficacy trial of the quadrivalent HPV vaccine in 3,463 HIV-negative HM and 602 HIV-negative MSM. AIDS Malignancy Consortium (AMC) 052 was a safety and immunogenicity study of the same vaccine in 104 HIV-positive MSM. Merck 020 participants reported 5 or fewer lifetime sex partners; there was no restriction for AMC 052. All were sero- and HPV DNA-negative to the relevant HPV type at baseline. Participants were vaccinated at enrollment, and months 2 and 6. Serum was analyzed at month 7 for antibodies.

Results: The median age of the HM and MSM in Merck 020, and MSM in AMC 052 was 20 (range 16-26), and 44 (range, 22-61) years, respectively. Month 7 titers are shown in Figure 1. Titers to all types were lower for MSM than HM in Merck 020. There were no differences in titers between the Merck 020 HIV-negative MSM in and the AMC 052 HIV-positive MSM.

Conclusions: Titers to all HPV types were lower among Merck 020 MSM than similarly-aged HM. There was no appreciable difference between the titers in the AMC 052 HIV-positive MSM and those of the Merck 020 HIV-negative MSM despite the latter being younger. Being MSM may influence titers; the reasons underlying this observation are not clear but may reflect unmeasured biological confounders that affect immunogenicity. The lower titers among MSM in Merck 020 did not influence vaccine efficacy, which was similar to that of HM.

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P-672: Reactogenicity of Alternative Schedules of Gardasil® Vaccine to Prevent Human Papillomavirus (HPV) Infection

D. Scott LaMontagne[1], Kathleen Neuzil[1], Do Gia Canh[2], Vu Dinh Thiem[2], Vu Minh Huong[3], Diep Ngoc Thi Nguyen[3], Yuxiao Tang[1], Amynah Janmohamed[1]

Background: A new vaccine's effectiveness and safety are primary concerns of recipients and critical to uptake. Human papillomavirus (HPV) vaccine is well tolerated on the licensed 0-, 2-, 6-month schedule. Our study evaluated immunogenicity (in a complementary abstract) and reactogenicity of alternative schedules of HPV vaccination (0-, 3-, 9-months; 0-, 6-, 12-months; and 0-, 12-, 24-months) compared to the standard 0-, 2-, 6-month schedule to determine if alternative dosing schedules would compromise immunogenicity and safety.

Methods: Twenty-one schools in Vietnam were divided into four groups based on size, location, and ethnic mix. Groups were randomized for administration of three doses of Gardasil® to

	HPV 6 titers		HPV 11 titers		HPV 16 titers		HPV 18 titers	
Study group	N	Month 7 (95% CI)	N	Month 7 (95% CI)	N	Month 7 (95% CI)	N	Month 7 (95% CI)
Heterosexual men	978	474 (447, 503)	978	652 (621, 684)	999	2622 (2,485, 2,767)	1032	439 (416, 464)
HIV-negative MSM	114	274 (223, 338)	114	431 (348, 534)	136	1272 (996, 1,623)	142	212 (170, 265)
HIV-positive MSM	60	357 (256, 497)	68	525 (412, 669)	62	1139 (849, 1529)	78	181 (136, 241)

eligible 11-13-year-old girls at 0-, 2-, 6-months; 0-, 3-, 9-months; 0-, 6-, 12-months; or 0-, 12-, 24-months. Informed consents/assents were obtained from guardians/participants. Safety data from three of the four arms (0-, 12-, 24-month group pending) included reactions observed within 30 minutes after injection; solicited and unsolicited reactions reported within seven days post-vaccination; serious adverse events (AE) up to one month following the last dose; and vaccine-related serious AEs at any time.

Results: Of 662 subjects in three groups, seven girls experienced a reaction within 30 minutes of injection: five from the standard group and one each from the 0-, 3-, 9- and 0-, 6-, 12- groups. At least one occurrence of injection site pain (75%-81%), itching (27%-32%), and fever (5%-10%) were the most common solicited seven-day reactions for any dose; the frequency did not vary by vaccination schedule. No participant had a serious vaccine-related AE or died.

Discussion: Gardasil® administered on two of three alternative schedules was well tolerated, and the safety profile did not differ from the standard schedule. These results are encouraging with regard to low-resource settings delivering HPV vaccine at varying time points without compromising vaccine safety.

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P-684: Adjuvant Immunotherapy for Persistent Genital Warts

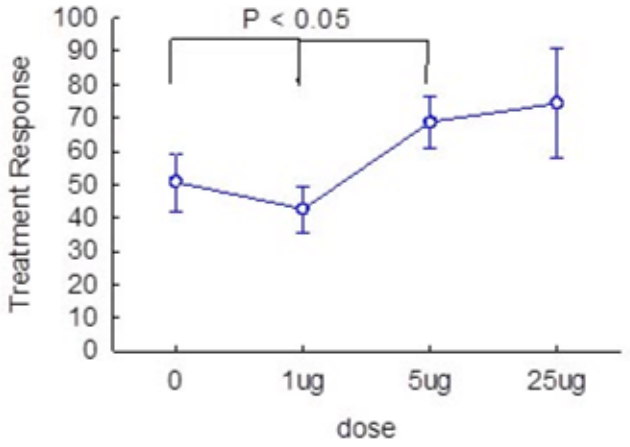
Ian Frazer[1], David Jardine[2], Jieqiang Lu[3], James Pang[1], Cheryn Palmer[2], Quanmei Tu[3], John Chuah[2]

Aim: To determine whether adjunct immunotherapy with HPV6 virus like particles (VLPs) reduces recurrence of genital warts following destructive therapy.

Methods: A randomised placebo controlled blinded study of treatment of recurrent genital warts amenable to destructive therapy, conducted in Australia and China. Patients received conventional destructive therapy of all warts together with intramuscular administration of 1 µg, 5 µg or 25 µg of HPV 6 VLPs without adjuvant, or of placebo, as immunotherapy at week 0 and week 4. Primary outcome, assessed at week 8, was recurrence of visible warts.

Findings: Of 33 protocol compliant recipients of destructive therapy and immunotherapy placebo in Brisbane, 11 were disease free at two months, and a further 9 demonstrated reduction of > 50% in total wart area. Wart area reduction following destructive treatment was related to prior duration of disease. A greater reduction in mean total wart area was observed amongst the 102 protocol compliant recipients of VLP vaccine than amongst the placebo recipients. Reduction was significantly greater ($p < 0.05$) for subjects receiving 5 µg or more of vaccine/dose (71% ± s.e.m.7%) than for subjects receiving placebo (50% ± 7%) or 1 µg/dose (42% ± 7%). Of 52 protocol compliant placebo recipients in Wenzhou, 37 were disease free at two months, and a further 8 had > 50% disease reduction. No significant reduction in mean wart area was observed for the 168 protocol compliant subjects who also received VLP immunotherapy.

Interpretation: This study confirms the findings in a previous open label trial that administration of HPV6 L1 VLPs as immunotherapy assists in clearance of recurrent genital warts where destructive therapy alone is less effective.



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P-724: Physicians' Attitudes and Perceptions of HPV

Thomas Weiss[1], Gregory Zimet[2], Susan Rosenthal[3], Susan Brenneman[4], Jonathan Klein[5]

Objectives: We assessed US physicians' attitudes and perceptions regarding potential human papillomavirus (HPV) vaccination of males.

Methods: We surveyed a random sample of 2,714 pediatricians and family practitioners who had been identified in the administrative claims database of a US health plan as HPV vaccinators of females; 595 pediatricians and 499 family practitioners participated.

Results: Most physicians would recommend HPV vaccination to males ages 11-12 (63.9%), 13-18 (93.4%), and 19-26 (92.7%). Physicians agreed that males should be vaccinated to prevent them from getting genital and anal warts (52.9% strongly and 36.0% somewhat) and to protect females from cervical cancer (75.3% strongly and 20.8% somewhat). Physicians also agreed that a HPV vaccine recommendation for males would increase opportunities to discuss sexual health with their adolescent male patients (58.7% strongly, 35.3% somewhat). Most did not strongly agree (15.4% strongly, 45.4% somewhat) that parents of adolescent male patients would be interested in an HPV vaccination for males, that a gender-neutral HPV vaccine recommendation would increase acceptance by adolescent females and their parents (19.6% strongly, 42.0% somewhat) or that a gender-neutral recommendation would improve current vaccination rates in females (10.4% strongly, 26.0% somewhat).

Conclusions: Physicians who currently vaccinate females against HPV supported the concept of vaccinating males for its benefits for both sexes. They supported a gender-neutral HPV vaccination strategy and believed that it would increase opportunities for

sexual health discussions, but were less sure that such a strategy would change patient or parental attitudes toward HPV vaccination or improve current HPV vaccination efforts.

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P-730: Impact of Genital Warts on Health Related Quality of Life: a Multi-Centre Hospital-Based Study in China

Ju-Fang Shi[1,2], Dian-Ju Kang[1,3], Shu-Zhen Qi[4], Su-Wen Yan[5], Yan-Chun Liu[6], Li-Jun Sun[7], Li Li[8], Karen Canfell[2], You-Lin Qiao[1], on behalf of Chinese genital warts study group[1]

Aim: To measure the health related quality of life (HRQoL) of patients with genital warts (GW).
Methods: A multi-centre hospital-based study was conducted in 18 centres across 7 geographic regions in China, between July 2007 and July 2008, stratified by economic and hospital levels. Male or female patients with GW aged 18+ were enrolled. All subjects were interviewed using the European quality of life (EQ-5D) instrument (Chinese version). Demographic and clinical data were also collected.
Results: A totally of 1,358 GW patients (612 men, 746 women) were included in the analysis (mean age: 32.0 ± 10.6 years). The total EQ-5D visual analogue scale (VAS) score was 65.2 ± 22.0. The dimension of Anxiety/Depression had the highest rate of any self-reported problems (56.4%) (**Figure 1**). The EQ-5D index score of the whole study population was 0.843 using the Japanese Time Trade-Off (TTO) value set. Females with GW have greater psychosocial burden than males ($P < 0.001$). No significant difference was found among different age groups. Other factors such as geography, economic level, and clinical traits could have correlation with HRQoL of GW patients (**Table 1**).
Conclusions: The HRQoL of patients with genital warts is significantly lowered. These results provide utility values associated with genital wart cases which can be utilised for future cost-effectiveness evaluation of prophylactic HPV vaccination.

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Figure 1. Percentages of subjects' reported problems, by dimension and sex.

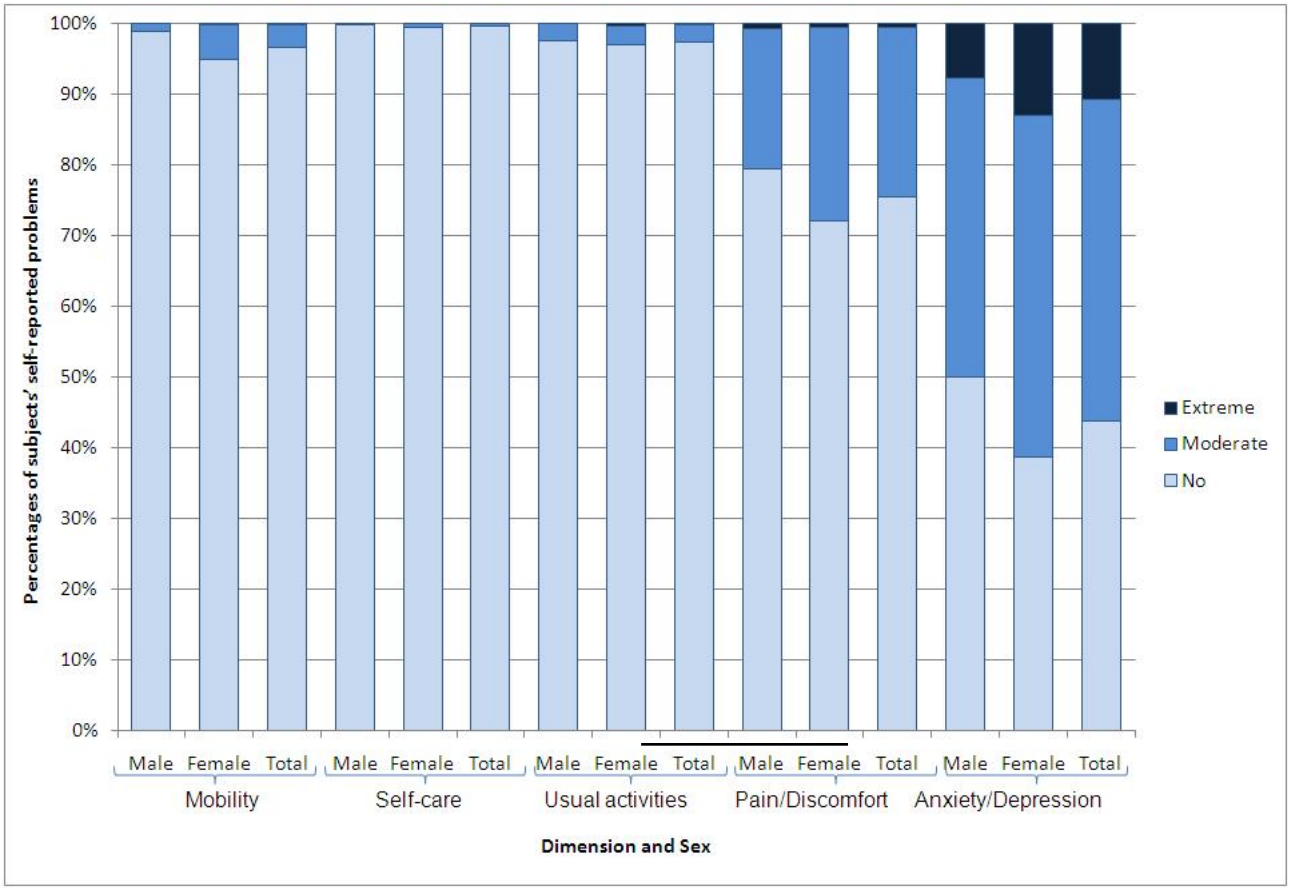

Table 1. Mean of EQ-5D VAS and EQ-5D index score (using Japanese TTO value set), by subjects' characteristics (N=1,358)

	No.	%	EQ-5D VAS			EQ-5D index score		
			Mean	SD	Sig.	Mean	SD	Sig.
Sex								
Male	612	45.1	69.0	21.3	<0.001	0.864	0.130	<0.001
Female	746	54.9	62.1	22.1		0.827	0.126	
Region								
North	372	27.4	66.6	25.0	<0.001	0.866	0.135	<0.001
Northeast	128	9.4	64.0	24.7		0.897	0.125	
Northwest	151	11.1	62.2	20.6		0.790	0.121	
Central	133	9.8	72.3	12.8		0.871	0.120	
Southwest	100	7.4	57.3	22.2		0.790	0.111	
South	135	9.9	66.1	18.6		0.823	0.134	
East	339	25.0	64.5	21.2		0.835	0.120	
Setting								
Urban	1,020	75.1	63.2	22.4	<0.001	0.837	0.126	<0.005
Rural	338	24.9	71.0	19.6		0.862	0.137	
Monthly income (Chinese Yuan) *								
1000 less	364	26.8	63.5	22.4	>0.05	0.827	0.133	<0.005
1000~	422	31.1	66.8	21.3		0.838	0.124	
2000~	223	16.4	65.8	22.8		0.852	0.131	
3000~	347	25.6	64.5	22.0		0.860	0.128	
Frequently smoking								
Yes	301	22.2	68.2	21.2	<0.01	0.860	0.131	<0.05
No	1,057	77.8	64.3	22.2		0.839	0.129	
Number of lifetime sexual partners*								
1	612	45.1	63.8	22.7	>0.05	0.852	0.132	>0.05
2	318	23.4	65.3	21.9		0.839	0.128	
3 or more	421	31.0	67.0	21.0		0.834	0.126	
Clinical situation								
First clinical visit for the first occurred GW	1,032	76.0	65.7	21.8	>0.05	0.853	0.129	<0.001
Follow-up visit for the first occurred GW	146	10.8	64.1	24.4		0.822	0.126	
Recurrency GW	180	13.3	63.9	21.0		0.804	0.124	
Single or multiple genital warts								
Single	356	26.2	68.0	21.2	<0.01	0.869	0.127	<0.001
Multiple	1,002	73.8	64.2	22.2		0.835	0.129	

* Some data missing.

P-746: Cost-Effectiveness of Targeted HPV-16,-18 Vaccination of Men Who Have Sex With Men in the U.S.

Jane Kim[1], Stephen Sy[1], Monisha Sharma[1]

Objectives: Men who have sex with men (MSM), particularly those who are HIV-positive, face the highest risk of anal cancer in the U.S. Targeting HPV vaccination to MSM may be a cost-effective strategy for anal cancer prevention. **Methods:** We adapted a previously-developed Markov model to reflect incidence and mortality of anal cancer among MSM with and without HIV. Using data on incidence of anal cancer, proportion of cases attributable to HPV-16,-18, cancer survival, quality of life, and costs, we estimated lifetime costs and health outcomes associated with anal cancer. We evaluated HPV vaccination of MSM at different ages (12-26 years) and coverage rates (25%-75%), each compared to no vaccination. In our base case, we assumed 25% of the MSM population are HIV-positive and thereby face a higher incidence of anal cancer. We varied HIV prevalence among MSM, prior exposure to HPV-16,-18 infections by vaccination, and duration of vaccine protection.

Results: HPV vaccination of MSM at age 12 (before HPV exposure) had a cost of $90,000 per quality-adjusted life year (QALY) gained, compared to no vaccination. If MSM get vaccinated at later ages, when prior exposure to vaccine-type HPV infections is higher, the cost-effectiveness ratios become less attractive; for example, HPV vaccination of MSM at age 26 exceeds $100,000 and $140,000 per QALY if the probability of prior vaccine-type infections is 10% and 30%, respectively. If protection wanes at 20 years, HPV vaccination of MSM at any age is not cost-effective. Results were also sensitive to HIV prevalence.
Conclusions: Preliminary analyses suggest that HPV vaccination of MSM can be a cost-effective intervention but that there must be strong consideration of age at vaccination and potential for prior vaccine-type infections by the time of vaccination. Future analyses must address other uncertainties, including vaccine benefits in preventing HPV transmission and other HPV-related diseases.

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P-769: Persistence, Acquisition and Clearance of HPV DNA in Penile in HIV Positive Men

Roberto José Carvalho da Silva[1], Jorge Simão Casseb[2], Luisa Lina Villa[3]

Introduction: Co-infection with HPV and HIV modifies its natural history and increases the risk of warts and neoplasia development in the anogenital tract. Cohort studies to address HPV infection in the penis are scarce, mainly in HIV infected individuals.
Methods: At each visit, samples of exfoliated cells were obtained after wetting the penis surface with 5% acetic acid for 5 minutes followed by examination by peniscopy. An endocervical cytobrush with short bristles was used to scrape longitudinally the whole penis skin including the foreskin, glans, shaft, and the sulcus coronarius. Genotyping for 37 HPV types was conducted for penile samples in 72 HIV-positive men, ages 18-70, from São Paulo, Brazil. They were followed for 180 days to determine persistence, acquisition and clearance of HPV DNA in penile compared with plasma HIV viral load, CD4 T-cell count and use of HAART.
Results: HIV-positive men had a higher frequency of multiple HPV infection and the most frequent were oncogenic types. HPV types 16, 6 and 84 were the most frequently found in HIV-positive men. Significantly higher HPV DNA acquisition ($P = 0.002$) and persistence ($P = 0.009$) rates were observed among HIV-positive men not submitted to HAART, with higher HIV loads and lower CD4+ cells count. Among those men using anti-retroviral therapy, lower viral loads and higher T cell counts, higher rates of clearance HPV DNA were observed ($P < 0.000$).
Conclusions: This population is considered to be at high risk of HPV DNA infection, which may change the natural history of HPV infection. More studies are necessary to the understanding of HPV infection in this population.

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