# Natural history of HPV infection in males

**Dorothy Machalek, PhD**
Global Health Program, Kirby Institute,
University of New South Wales, Sydney

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# Focus of presentation

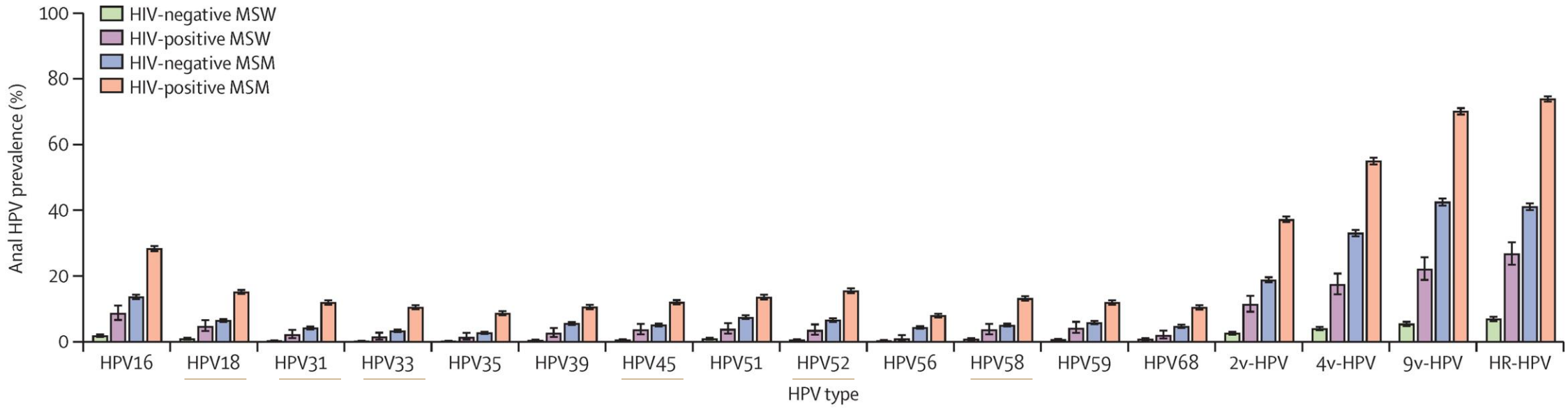
- What do we know about anal HPV natural history in males
- What are the evidence gaps
- What are the implications for prevention strategies

# What do we know about anal HPV natural history in males?

- Anal HPV is common in men, especially MSM and immunocompromised individuals.
- HPV 16 is the most prevalent and oncogenic type.
- Most infections are transient, but persistence, especially of HPV 16 increases risk of developing anal HSIL.
- Anal HSIL is heterogeneous - can clear, persist, or progress to cancer.
- Anal cancer is rare overall, but incidence is markedly elevated in people living with HIV, particularly MSM and older MSM without HIV.
- Vaccination programs reduce anal HPV infections and anal HSIL (trials and real world).
- Screening for anal HSIL followed by treatment can prevent progression to cancer.

# Anal HPV prevalence by risk group

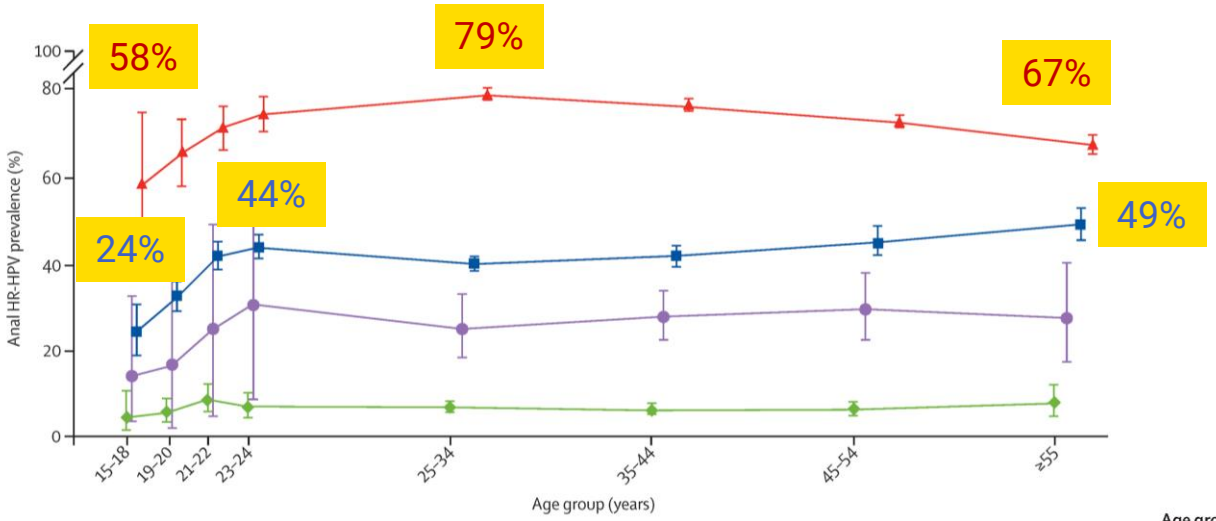
Pooled data from 64 studies including 29,900 men (Wei et al. Lancet HIV 2021): **44·9% MSM with HIV, 35·5% HIV-negative MSM, 2·3% MSW with HIV, 17·4% HIV-negative MSW**



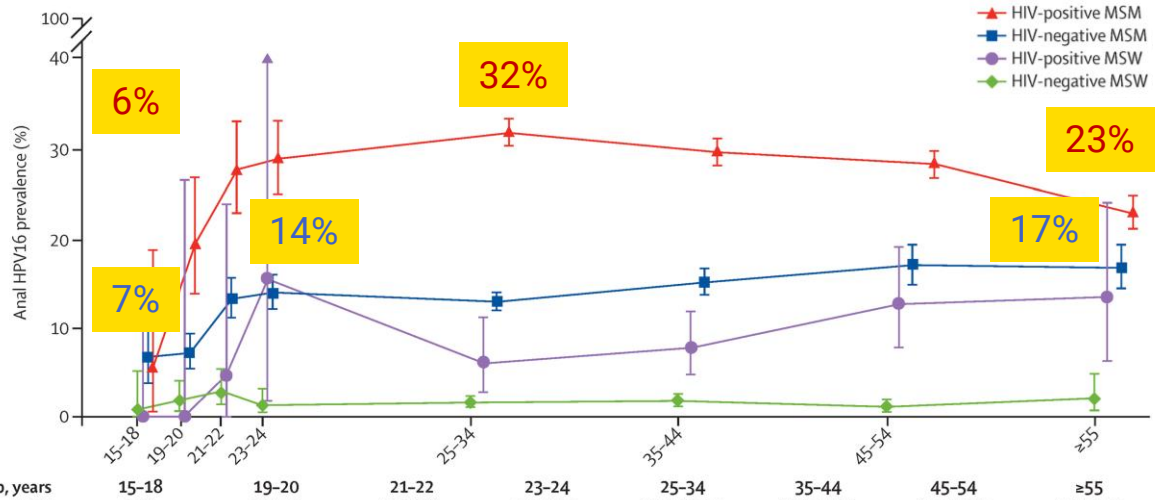

| | HPV16 | HPV18 | HPV31 | HPV33 | HPV35 | HPV39 | HPV45 | HPV51 | HPV52 | HPV56 | HPV58 | HPV59 | HPV68 | 2v-HPV | 4v-HPV | 9v-HPV | HR-HPV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HIV-negative MSW (n/N, %) | 91/5190 (1·8%) | 45/5190 (0·9%) | 12/4984 (0·2%) | 5/4984 (0·1%) | 4/5161 (0·1%) | 22/5161 (0·4%) | 26/5161 (0·5%) | 45/5161 (0·9%) | 26/5161 (0·5%) | 14/5161 (0·3%) | 38/5161 (0·7%) | 32/5161 (0·6%) | 39/5161 (0·8%) | 134/5190 (2·6%) | 204/5158 (4·0%) | 269/4981 (5·4%) | 345/5003 (6·9%) |
| HIV-positive MSW (n/N, %) | 59/682 (8·7%) | 32/682 (4·7%) | 12/572 (2·1%) | 8/572 (1·4%) | 8/583 (1·4%) | 15/583 (2·6%) | 22/614 (3·6%) | 22/583 (3·8%) | 20/583 (3·4%) | 5/583 (0·9%) | 21/583 (3·6%) | 24/583 (4·1%) | 11/583 (1·9%) | 78/682 (11·4%) | 102/582 (17·5%) | 127/571 (22·2%) | 179/666 (26·9%) |
| HIV-negative MSM (n/N, %) | 1455/10 617 (13·7%) | 684/10 617 (6·4%) | 361/8673 (4·2%) | 285/8673 (3·3%) | 232/8710 (2·7%) | 481/8710 (5·5%) | 463/9112 (5·1%) | 650/8710 (7·5%) | 574/8710 (6·6%) | 377/8710 (4·3%) | 438/8710 (5·0%) | 508/8710 (5·8%) | 373/7997 (4·7%) | 1795/9497 (18·9%) | 2809/8447 (33·3%) | 3415/8008 (42·6%) | 3798/9215 (41·2%) |
| HIV-positive MSM (n/N, %) | 3819/13 411 (28·5%) | 2007/13 213 (15·2%) | 1115/9341 (11·9%) | 982/9341 (10·5%) | 773/8917 (8·7%) | 945/8917 (10·6%) | 1260/10 448 (12·1%) | 1211/8917 (13·6%) | 1460/9387 (15·6%) | 708/8917 (7·9%) | 1239/9388 (13·2%) | 1065/8917 (11·9%) | 898/8586 (10·5%) | 4730/12 645 (37·4%) | 4962/8990 (55·2%) | 5982/8490 (70·5%) | 8765/11 803 (74·3%) |

# Age-specific anal HPV prevalence by risk group

Pooled data from 64 studies including 29,900 men (Wei et al. Lancet HIV 2021): **44·9% MSM with HIV, 35·5% HIV-negative MSM, 2·3% MSW with HIV, 17·4% HIV-negative MSW**




| Age group, years | 15–18 | 19–20 | 21–22 | 23–24 | 25–34 | 35–44 | 45–54 | ≥55 |
|---|---|---|---|---|---|---|---|---|
| HIV-positive MSM | 21/36 | 100/152 | 209/293 | 346/465 | 2345/2982 | 2503/3281 | 2111/2915 | 1130/1679 |
| (n/N, %) | (58·3%) | (65·8%) | (71·3%) | (74·4%) | (78·6%) | (76·3%) | (72·4%) | (67·3%) |
| aPR (95% CI) | 0·77 (0·59–1·02) | 0·85 (0·76–0·96)* | 0·94 (0·88–1·00) | 0·96 (0·90–1·01) | 1 (ref) | 0·96 (0·94–0·99)* | 0·91 (0·88–0·94)* | 0·83 (0·80–0·87)* |
| HIV-negative MSM | 54/221 | 216/665 | 373/892 | 501/1142 | 1236/3095 | 673/1611 | 392/867 | 353/722 |
| (n/N, %) | (24·4%) | (32·5%) | (41·8%) | (43·9%) | (39·9%) | (41·8%) | (45·2%) | (48·9%) |
| aPR (95% CI) | 0·74 (0·58–0·94)* | 0·90 (0·80–1·02) | 0·99 (0·90–1·08) | 0·99 (0·92–1·08) | 1 (ref) | 1·04 (0·96–1·11) | 0·99 (0·90–1·09) | 0·99 (0·89–1·11) |
| HIV-positive MSW | 4/28 | 2/12 | 5/20 | 4/13 | 36/143 | 67/240 | 43/145 | 18/65 |
| (n/N, %) | (14·3%) | (16·7%) | (25·0%) | (30·8%) | (25·2%) | (27·9%) | (29·7%) | (27·7%) |
| aPR (95% CI) | 1·83 (0·44–7·67) | 1·15 (0·31–4·20) | 0·87 (0·43–1·78) | 1·41 (0·63–3·16) | 1 (ref) | 0·94 (0·67–1·31) | 0·68 (0·44–1·03) | 0·57 (0·35–0·95)* |
| HIV-negative MSW | 5/103 | 18/303 | 28/317 | 24/333 | 108/1513 | 82/1269 | 62/942 | 18/223 |
| (n/N, %) | (4·9%) | (5·9%) | (8·8%) | (7·2%) | (7·1%) | (6·5%) | (6·6%) | (8·1%) |
| aPR (95% CI) | 0·57 (0·23–1·44) | 0·91 (0·57–1·43) | 1·11 (0·90–1·37) | 0·79 (0·52–1·21) | 1 (ref) | 0·96 (0·74–1·25) | 1·07 (0·86–1·32) | 0·86 (0·53–1·39) |




| Age group, years | 15–18 | 19–20 | 21–22 | 23–24 | 25–34 | 35–44 | 45–54 | ≥55 |
|---|---|---|---|---|---|---|---|---|
| HIV-positive MSM | 2/36 | 30/153 | 85/308 | 141/490 | 1057/3337 | 1102/3728 | 951/3380 | 451/1979 |
| (n/N, %) | (5·6%) | (19·6%) | (27·6%) | (28·8%) | (31·7%) | (29·6%) | (28·1%) | (22·8%) |
| aPR (95% CI) | 0·22 (0·06–0·86)* | 0·71 (0·51–0·99)* | 0·96 (0·80–1·16) | 1·01 (0·87–1·18) | 1 (ref) | 0·86 (0·80–0·92)* | 0·83 (0·76–0·90)* | 0·71 (0·64–0·79)* |
| HIV-negative MSM | 15/223 | 49/679 | 123/929 | 166/1192 | 461/3565 | 315/2093 | 181/1067 | 145/869 |
| (n/N, %) | (6·7%) | (7·2%) | (13·2%) | (13·9%) | (12·9%) | (15·1%) | (17·0%) | (16·7%) |
| aPR (95% CI) | 0·71 (0·42–1·21) | 0·70 (0·51–0·95)* | 1·07 (0·88–1·30) | 1·08 (0·90–1·29) | 1 (ref) | 0·99 (0·86–1·14) | 1·00 (0·84–1·20) | 0·97 (0·78–1·21) |
| HIV-positive MSW | 0/28 | 0/12 | 1/21 | 2/13 | 9/147 | 19/244 | 19/150 | 9/67 |
| (n/N, %) | | | (4·8%) | (15·4%) | (6·1%) | (7·8%) | (12·7%) | (13·4%) |
| aPR (95% CI) | 0·00 (0·00–2·17) | 0·00 (0·00–5·21) | 1·16 (0·17–8·10) | 2·36 (0·61–9·12) | 1 (ref) | 1·12 (0·52–2·41) | 1·55 (0·70–3·44) | 1·56 (0·59–4·11) |
| HIV-negative MSW | 1/104 | 6/306 | 10/331 | 5/354 | 27/1592 | 25/1318 | 12/953 | 5/232 |
| (n/N, %) | (1·0%) | (2·0%) | (3·0%) | (1·4%) | (1·7%) | (1·9%) | (1·3%) | (2·2%) |
| aPR (95% CI) | 0·67 (0·09–4·94) | 1·40 (0·57–3·45) | 1·63 (0·80–3·34) | 0·73 (0·28–1·87) | 1 (ref) | 1·42 (0·83–2·42) | 1·34 (0·67–2·72) | 0·98 (0·36–2·63) |

* Low precision in some groups due to small sample sizes

# Anal HPV incidence and clearance estimates in males

## Pooled longitudinal data from 34 studies, adapted from Wei et al. IJC 2023

| Risk Group | N (with ≥2 valid visits) | HPV-16 Incidence (per 1,000 person months) | HPV-16 Clearance (per 1,000 person months) |
|---|---|---|---|
| MSM with HIV | 4,745 | 14.8 (13.5-16.1) | 61.5 (55.6–67.9) |
| MSM, HIV-neg | 3,459 | 9.1 (8.2-10.1) | 95.5 (86.0–106.0) |
| MSW with HIV | 330 | 3.2 (2.1-5.0) | 170.4 (125.2-231.8) |
| MSW, HIV-neg | 2,691 | 2.0 (1.3-3.1) | 264.6 (193.9- 361.0) |

- Incidence highest in MSM with HIV; lowest in HIV-negative MSW.
- Clearance rates follow inverse pattern: lower clearance in MSM with HIV
- Suggests prolonged infection and higher risk in MSM with HIV.
- Similar patterns for other HR-HPV types

# Predictors of incident anal HPV 16 infection

| Risk Factor | MSM, aHR (95% CI) | MSW, aHR (95% CI) |
|---|---|---|
| Age (per 10 years) | **0.77 (0.72–0.81)** | **0.72 (0.52–0.99)** |
| HIV+ | **1.42 (1.22–1.64)** | **3.33 (1.46–7.64)** |
| High* lifetime sexual partners | **1.22 (1.01–1.47)** | **4.79 (1.38–16.7)** |
| High** recent sexual partners | **1.76 (1.38–2.23)** | 1.90 (0.52–6.91) |
| Ever receptive anal sex | **1.43 (1.11–1.85)** | — |
| >50 lifetime anal sex partners | **1.58 (1.18–2.13)** | — |
| >3 recent anal sex partners | **1.45 (1.17–1.80)** | — |
| Current smoker | **1.21 (1.03–1.43)** | — |
| HSIL at baseline | 1.13 (0.89–1.42) | — |
| **Among individuals with HIV only** | | |
| CD4 350–500 (ref >500) | **1.26 (1.02–1.55)** | — |
| CD4 <350 | 1.12 (0.89–1.42) | — |
| HIV+ VL >10,000 (ref <50) | 1.14 (0.92–1.40) | — |

* >200 for MSM and >3 MSW
** >5 for MSM and >1 for MSW

**Pooled analysis adapted from Wei et al. IJC 2023 (Table 1)**

# Predictors of anal HPV 16 clearance

| Risk Factor | MSM | MSW |
|---|---|---|
| Age (per 10 years) | **0.81 (0.77–0.85)** | 0.91 (0.71–1.17) |
| HIV+ | **0.68 (0.60–0.77)** | **0.37 (0.18–0.75)** |
| High lifetime sexual partners | 0.90 (0.76–1.06) | 0.61 (0.21–1.75) |
| High recent sexual partners | 1.14 (0.91–1.44) | 1.70 (0.44–6.56) |
| Ever receptive anal sex | 1.18 (0.92–1.51) | — |
| High lifetime anal sex partners | 1.24 (0.95–1.61) | — |
| High recent anal sex partners | 1.04 (0.86–1.26) | — |
| Current smoker | 0.94 (0.81–1.09) | — |
| HSIL at baseline | **0.66 (0.54–0.79)** | — |
| Incident infection (vs prevalent) | **2.44 (2.16–2.74)** | — |
| **Among individuals with HIV only** | | |
| HIV+ CD4 350–500 (ref >500) | 1.16 (0.97–1.39) | — |
| HIV+ CD4 <350 | 1.00 (0.82–1.23) | — |
| HIV+ VL >10,000 (ref <50) | **0.76 (0.63–0.92)** | — |

* >200 for MSM and >3 MSW
** >5 for MSM and >1 for MSW

**Pooled analysis adapted from Wei et al. IJC 2023 (Table 1)**

# Cumulative persistence of anal HPV-16

## Pooled longitudinal data from 34 studies, adapted from Wei et al. IJC 2023

| Risk Group | 2-Year Persistence of Prevalent HPV-16 (%) | 2-Year Persistence of Incident HPV-16 (%) | Age Effect on Persistence |
|---|---|---|---|
| MSM with HIV | 58.6 | 30.6 | Increases with age; ≥55 yrs: 69% infections ≥2 years |
| MSM, HIV-neg | 35.7 | 15.4 | Increases with age; ≥55 yrs: 68% infections ≥2 years |
| MSW with HIV | 15.3 | 4.6 | Insufficient data |
| MSW, HIV-neg | 2.7 | 1.2 | Insufficient data |



- Prevalent HPV16 infections persist longer than incident ones.
- Persistence increases with age in MSM (HIV+ and HIV−).
- Older MSM have more long-lasting infections, raising cancer risk.
- Insufficient data to assess patterns in MSW.

# Anal HSIL: A cancer precursor lesion

**HSIL is the precursor to anal cancer (1)**

- The ANCHOR trial showed that treating HSIL in people with HIV reduced anal cancer incidence by 57%, confirming HSIL as a cancer precursor.

**HSIL prevalence in MSM (insufficient data for other groups) (2)**

- **~8-54%** in MSM with HIV
- **~5-43%** in HIV-negative MSM
  *(data from studies using HRA on all participants)*

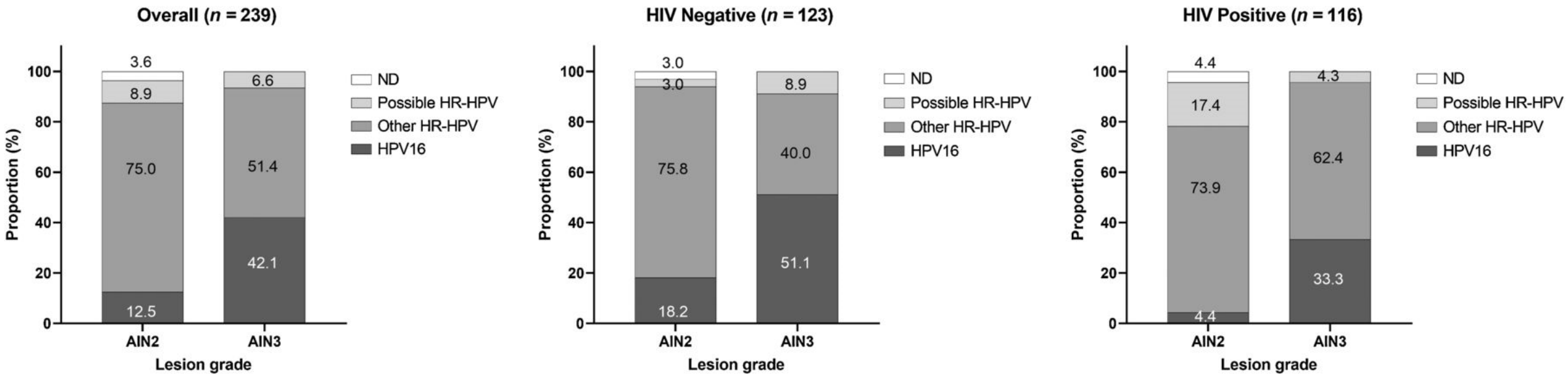
**Risk factors for anal HSIL (2)**

- Strongly associated with HIV and HPV16 infection, but age patterns differ:
- In all MSM: HSIL prevalence decreases with age
- In HPV16-positive MSM: HSIL prevalence increases with age
- Among HPV16+ men, MSM with HIV and low current CD4 counts have highest risk for HSIL

1) Palefsky et al. NEJM 2022; 2) Wei et al. Lancet HIV 2022

# HSIL heterogeneity – HPV types in AIN2 vs AIN3

## HPV types detected in 239 individual HSIL-AIN2 (p16+ve) and AIN3 lesions in the Study of the Prevention of Anal Cancer (SPANC), stratified by HIV status




- In HIV-negative MSM, AIN3 lesions significantly more likely to be caused by HPV16 than AIN2, while AIN2 had more non-16 HR-HPV.
- In MSM with HIV, HPV16 remained more common in AIN3, but non-16 HR-HPV were also more common causes of AIN2 and AIN3.
- Distinction in HSIL (particularly HPV16) may help to further refine those at highest risk

Roberts et al. CEBP 2020

# Predictors of anal HSIL incidence

## Summary of findings from the SPANC Study (Poynten et al. CID 2020)

| | |
|---|---|
| **Overall HSIL incidence:** | 11.3 cases per 100 person-years (PY) |
| **Higher risk groups:** | |
| **Effect of previous lesions:** | |
| **Persistent HPV infection:** | |
| **New HPV16 infections:** | |
| **Incidence after prior HSIL clearance*:** | |
| **Strongest independent predictors:** | |

*New HSIL that develops in someone who had HSIL before, cleared it (it went away), and then got it again during the study.

# Predictors of spontaneous anal HSIL clearance

## Summary of findings from the SPANC Study (Poynten et al. CID 2020)

| | |
|---|---|
| **Overall HSIL clearance:** | 22.0 cases per 100 person-years (PY) |
| **Groups with higher clearance:** | |
| **Persistent HPV infection:** | |
| **Clearance of new HSIL:** | |
| **Clearance of baseline prevalent HSIL:** | |
| **Strongest independent predictors:** | |
| **Durability of clearance:** | |

*New HSIL that developed during the study period.

# Estimates of HSIL progression to cancer

**Untreated populations (1-2):**

- Active monitoring arm of ANCHOR trial (PLHIV): 408 per 100,000 PY (~0.41% per year). Higher rates were found among those with large HSIL lesions.
- SPANC study (Community recruited two-thirds HIV-negative): 0.224 per 100 PY (~0.22% risk per year). The progression rate was 0.324 per 100 PY (95% after HSIL-AIN3 diagnosis.

**People receiving treatment (3-4):**

- Estimates of anal cancer progression of between 0.6% and 1.9% per year in multiple studies.

1) Palefsky et al. NEJM 2022; 2) Poynten et al. CID 2020; 3) Arens et al. DCR 2019; 4) Lee et al. DCR 2018.

# What about latent infections?

**Evidence from SPANC (Poynten et al. CEBP 2022):**

- 58 of 525 men (11%) with follow up reported no sexual partners (in the preceding 6 months) on at least two consecutive annual visits (1225.8 PY of follow-up).
- 29 incident HRHPV detections in 20 men, an average incidence of 2.4 per 100PY (95% CI, 1.64-3.40).
- None tested positive for other STIs – anorectal/pharyngeal gonorrhea, chlamydia or syphilis at the time of incident detection infection.
- **Predictors:** HIV-positive status, older than 55 years. Among men with HIV, longer duration of HIV infection, having a history of AIDS defining illness, and a lower current, and nadir CD4 count.
- No associated cases of HSIL

# Knowledge gaps

- Timing from infection to cancer, especially differences by HIV status and HPV genotype, remains poorly defined.
- Critical host immune factors and the impact of modifiable risks (e.g., smoking) on persistence vs clearance are not fully understood.
- Reliable biomarkers and clinical predictors that accurately distinguish lesions likely to progress from those that regress are lacking.
- Scarce longitudinal/cancer incidence data limit understanding of natural history and progression risk in HIV negative MSM and heterosexual men
- The role of latent infection in cancer risk

# Considerations for prevention strategies

- Early vaccination remains the most effective anal HPV prevention tool in males.
- Catch-up vaccination may have some benefits, but it may not eliminate the need for screening.
- MSM living with HIV—especially those with anal HPV16—are at highest risk for anal cancer and should be prioritises for screening.
- Screening algorithms could incorporate additional risk stratifications (i.e., identifying persistent infection rather than all HPV detection, those with larger lesions, and AIN3).
- First-time screening is likely to detect more persistent infections (higher risk), while re-screening may detect more incident/new infections (lower risk); keeping this in mind may help refine risk stratification.