



# HIV&HPV: Partners in Crime

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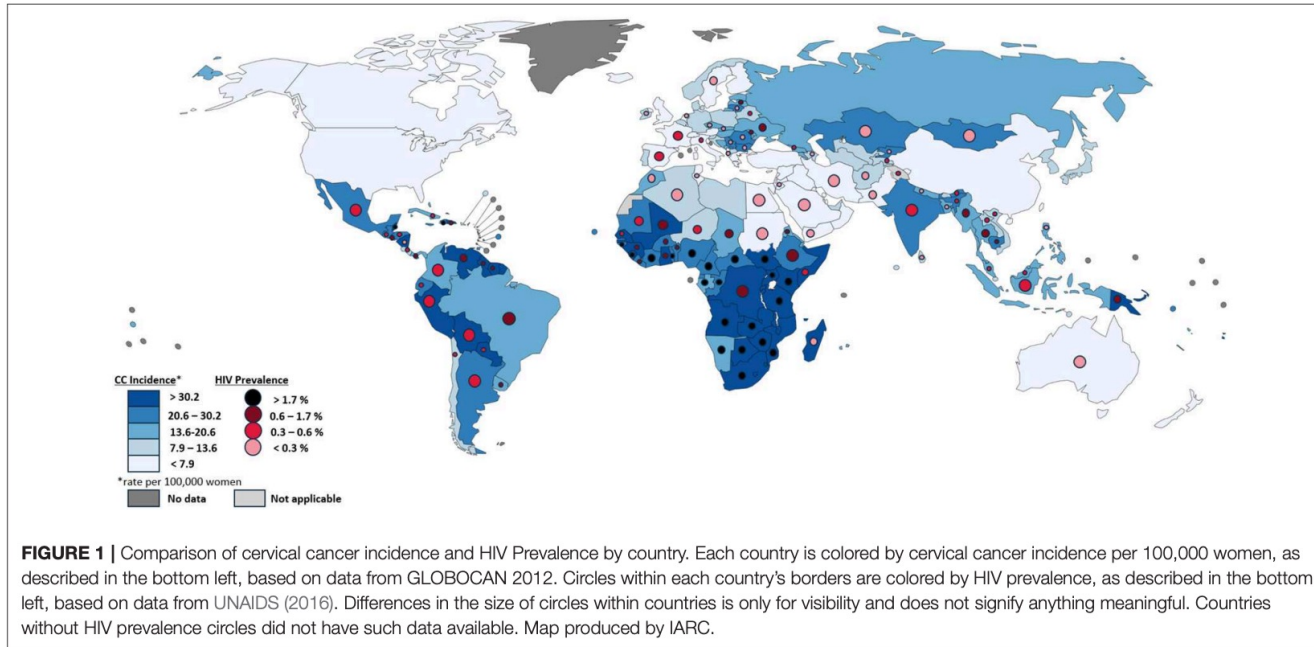
Clinica di Malattie Infettive

Dipartimento di Scienze della Salute

ASST Santi Paolo e Carlo-Presidio San Paolo

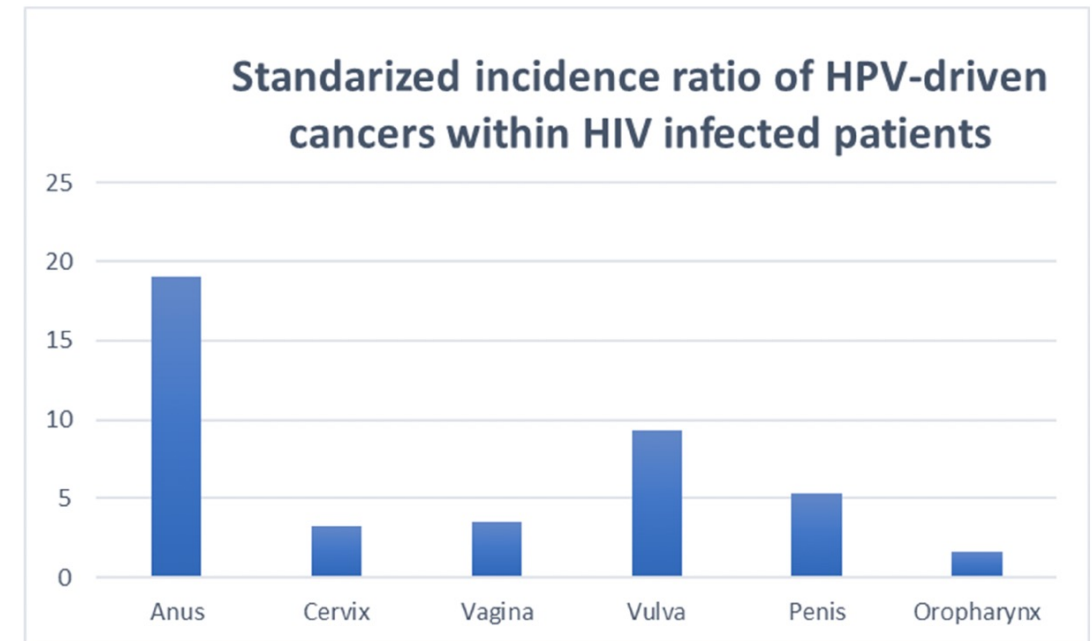
Università degli Studi di Milano

# The Burden of HIV-HPV Co-Infection



Klein, Front Cell Infect Microbiol, 2022

**The overall incidence of HPV-derived invasive cancer in PLWH is higher than in other groups at risk**



Perez-Gonzalez, Microorganisms, 2022

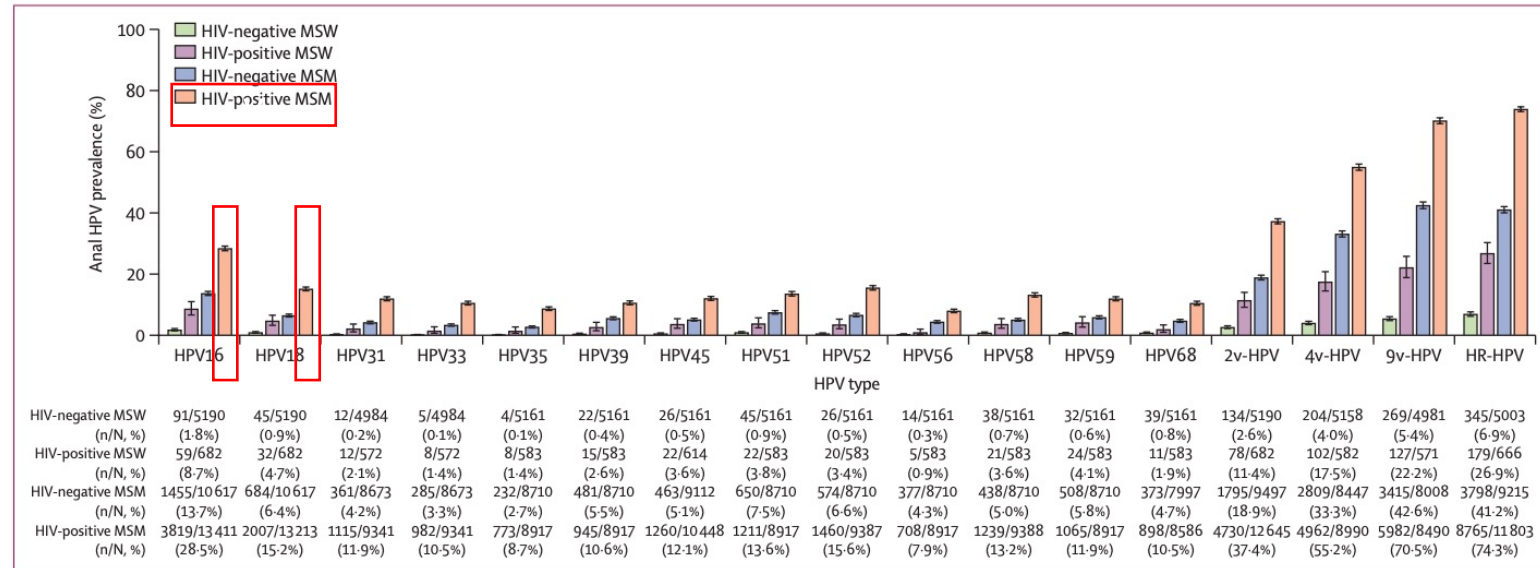
# High Prevalence of HR Genotypes in PLWH

## Women, cervical

## Men, anal

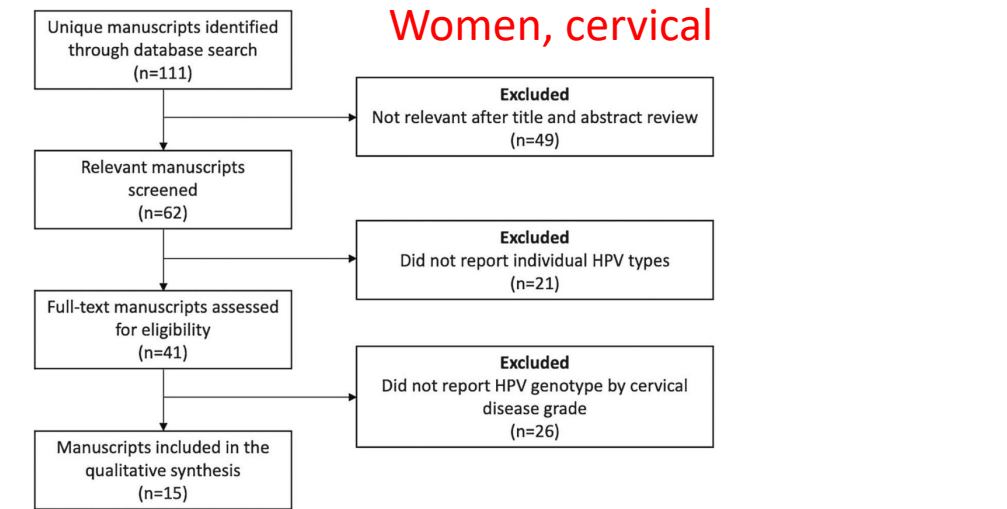
**TABLE 2.** Commonly Detected HPV Types by Cervical Disease Grade and World Region

| Region               | No. Studies* | WHIV, n | HPV+ WHIV, n (%) | HPV+ Cervical Disease Grade (n)                                                | Most Prevalent Types by Cervical Disease Grade   |
|----------------------|--------------|---------|------------------|--------------------------------------------------------------------------------|--------------------------------------------------|
| Africa               | 4            | 3870    | 2542 (65.7%)     | Normal (33)<br>Low grade (1032)<br>High grade (196)<br>ICC (51)                | 52, 18–51–58<br>52, 16<br>16, 33<br>16, 18       |
| Asia                 | 1            | 216     | 58 (26%)         | Normal (139)<br>Low grade (35)<br>High grade <sup>10</sup><br>ICC <sup>3</sup> | 16–18<br>31, 16<br>16, 35–52 <sup>†</sup><br>16* |
| Europe/North America | 4            | 2174    | 862 (39.6%)      | Normal (1590)<br>Low grade (164)<br>High grade (31)<br>ICC (0)                 | 53, 31<br>52, 39<br>31, 16<br>—                  |
| Latin America        | 2            | 668     | 490 (73.4%)      | Normal (207)<br>Low grade <sup>3</sup><br>High grade <sup>2</sup><br>ICC (0)   | 61, 6<br>51–56<br>31, 35 <sup>†</sup><br>—       |



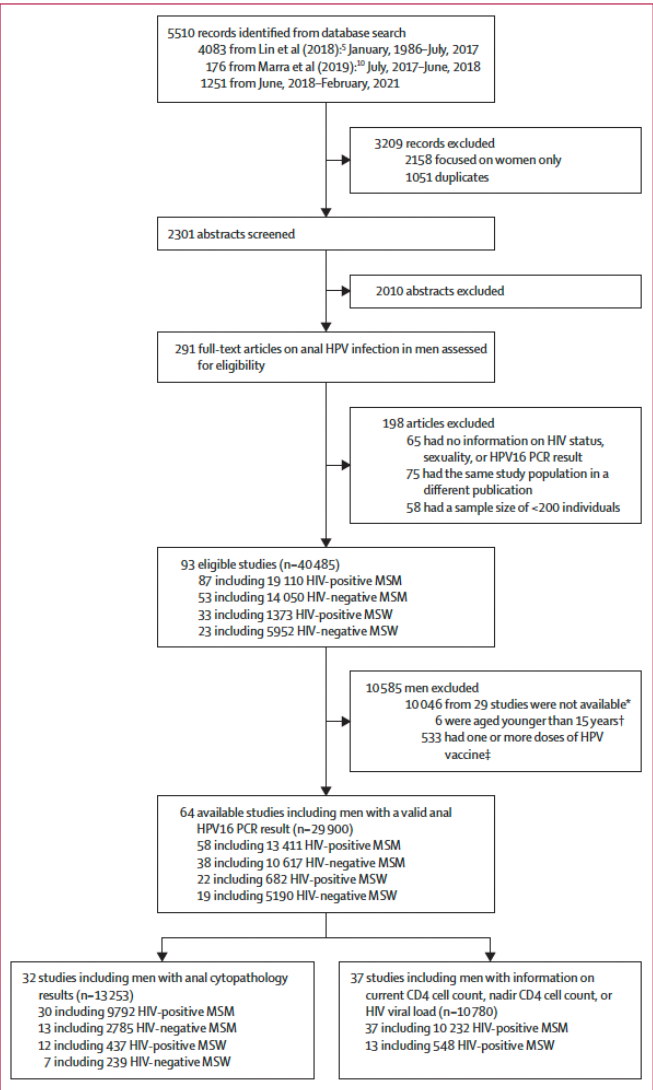
# HR Genotypes Cause High Grade Dysplasia in PLWH

## Women, cervical



| TABLE 2. Commonly Detected HPV Types by Cervical Disease Grade and World Region |              |         |                  |                                 |                                                |
|---------------------------------------------------------------------------------|--------------|---------|------------------|---------------------------------|------------------------------------------------|
| Region                                                                          | No. Studies* | WHIV, n | HPV+ WHIV, n (%) | HPV+ Cervical Disease Grade (n) | Most Prevalent Types by Cervical Disease Grade |
| Africa                                                                          | 4            | 3870    | 2542 (65.7%)     | Normal (33)                     | 52, 18–51–58                                   |
|                                                                                 |              |         |                  | Low grade (1032)                | 52, 16                                         |
|                                                                                 |              |         |                  | High grade (196)                | 16, 33                                         |
|                                                                                 |              |         |                  | ICC (51)                        | 16, 18                                         |
| Asia                                                                            | 1            | 216     | 58 (26%)         | Normal (139)                    | 16–18                                          |
|                                                                                 |              |         |                  | Low grade (35)                  | 31, 16                                         |
|                                                                                 |              |         |                  | High grade <sup>10</sup>        | 16, 35–52 <sup>†</sup>                         |
|                                                                                 |              |         |                  | ICC <sup>3</sup>                | 16*                                            |
| Europe/North America                                                            | 4            | 2174    | 862 (39.6%)      | Normal (1590)                   | 53, 31                                         |
|                                                                                 |              |         |                  | Low grade (164)                 | 52, 39                                         |
|                                                                                 |              |         |                  | High grade (31)                 | 31, 16                                         |
|                                                                                 |              |         |                  | ICC (0)                         | —                                              |
| Latin America                                                                   | 2            | 668     | 490 (73.4%)      | Normal (207)                    | 61, 6                                          |
|                                                                                 |              |         |                  | Low grade <sup>3</sup>          | 51–56                                          |
|                                                                                 |              |         |                  | High grade <sup>2</sup>         | 31, 35 <sup>†</sup>                            |
|                                                                                 |              |         |                  | ICC (0)                         | —                                              |

## Men, anal



|                   | Anal HSIL+ in all MSM (n=12 577) |                               | HPV16-positive anal HSIL+* in all MSM (n=12 577) |                               | Anal HSIL+ in HPV16-positive MSM (n=3409) |                               |
|-------------------|----------------------------------|-------------------------------|--------------------------------------------------|-------------------------------|-------------------------------------------|-------------------------------|
|                   | n/N (%)                          | aPR (95% CI)                  | n/N (%)                                          | aPR (95% CI)                  | n/N (%)                                   | aPR (95% CI)                  |
| Age group, years  |                                  |                               |                                                  |                               |                                           |                               |
| 15–24             | 72/794 (9.1%)                    | 0.98 (0.78–1.22)              | 23/794 (2.9%)                                    | 0.76 (0.50–1.17)              | 23/183 (12.6%)                            | 0.89 (0.62–1.29)              |
| 25–34             | 452/2847 (15.9%)                 | 1 (ref)                       | 200/2847 (7.0%)                                  | 1 (ref)                       | 200/847 (23.6%)                           | 1 (ref)                       |
| 35–44             | 725/3307 (21.9%)                 | 1.00 (0.91–1.10)              | 334/3307 (10.1%)                                 | 0.99 (0.84–1.17)              | 334/965 (34.6%)                           | 1.13 (0.99–1.28)              |
| 45–54             | 778/3278 (23.7%)                 | 0.95 (0.86–1.05)              | 343/3278 (10.5%)                                 | 0.90 (0.76–1.07)              | 343/903 (38.0%)                           | 1.09 (0.95–1.24)              |
| ≥55               | 480/2351 (20.4%)                 | 0.89 (0.79–0.99) <sup>†</sup> | 221/2351 (9.4%)                                  | 0.91 (0.75–1.10)              | 221/511 (43.2%)                           | 1.19 (1.03–1.36) <sup>†</sup> |
| Age, per 10 years | ..                               | 0.96 (0.94–0.99) <sup>†</sup> | ..                                               | 0.97 (0.92–1.02)              | ..                                        | 1.05 (1.01–1.09) <sup>†</sup> |
| HIV status        |                                  |                               |                                                  |                               |                                           |                               |
| Negative          | 314/2785 (11.3%)                 | 1 (ref)                       | 138/2785 (5.0%)                                  | 1 (ref)                       | 138/514 (26.8%)                           | 1 (ref)                       |
| Positive          | 2193/9792 (22.4%)                | 1.54 (1.36–1.73) <sup>†</sup> | 983/9792 (10.0%)                                 | 1.66 (1.36–2.03) <sup>†</sup> | 983/2895 (34.0%)                          | 1.19 (1.04–1.37) <sup>†</sup> |

PRs were adjusted for study, age group, and HIV status, as appropriate. aPR=adjusted prevalence ratio. HPV=human papillomavirus. HSIL+=high-grade squamous intraepithelial lesions or worse. MSM=men who have sex with men. \*Only includes participants with HSIL+ plus HPV16-positive swabs. †Significant aPRs relative to the reference group.

Table: Prevalence of anal HSIL+ in MSM

# Anal Dysplasia and Squamous Cell Carcinoma in PLWH

- PLWH
  - **MSM**: incidence of **85 (95% [CI] 82–89) per 100 000 person-years**, ranging from 16.8 per 100 000 person-years for < 30 years up to 107.5 per 100 000 person-years for **> 60 years**
  - **MSW**: 32 (95% CI 30–35) per 100 000 person-years
  - **Women** have an incidence of aSCC of 22 (95% CI 19–24) per 100 000 person-years
- HIV risk in HIV negative individuals (less studied)
  - cervical cancer survivors: 9 (95% CI 8–12) per 100 000 person-years
  - cervical dysplasia (CIN 2/3): 6 (95% CI 5–7) per 100 000 person-years
  - vulvar cancer survivors: 48 (95% CI 38–61) per 100 000 person-years
  - **MSM**: 19 (95% CI 10–36) per 100 000 person-years per 100 000 person-years
  - **SOT** recipients (renal), > 10 years: women incidence of **50 (95% CI 35.4–67.5) per 100 000 person-years**; men **25 (95% CI 16.3–35.4) per 100 000 person-years**

## **Age is a strong risk factor in the development of aSCC.**

Multiple cohort studies and data from cancer registries show aSCC increasing as a function of age for all risk groups. The median age of anal cancer diagnosis is about **60** years old in the general population, decreasing to about **47** years in men living with HIV.

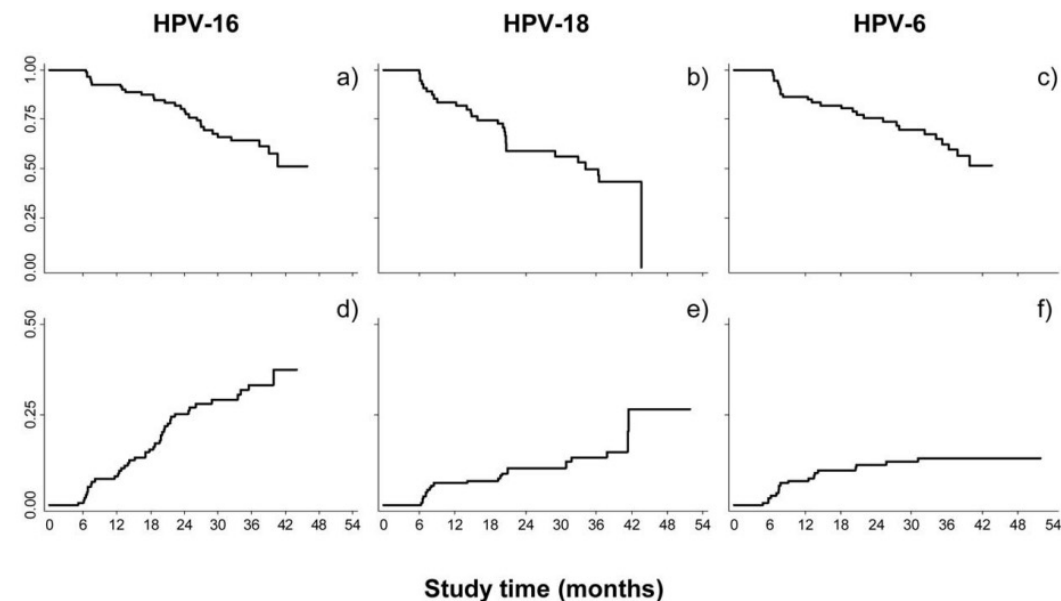
What are the mechanisms underlying HPV-related high-grade dysplasia in PLWH?

# Impaired HPV Clearance in Men LWH

**Table 2. Prevalence at enrollment and clearance of type-specific human papillomavirus (HPV) infection.**

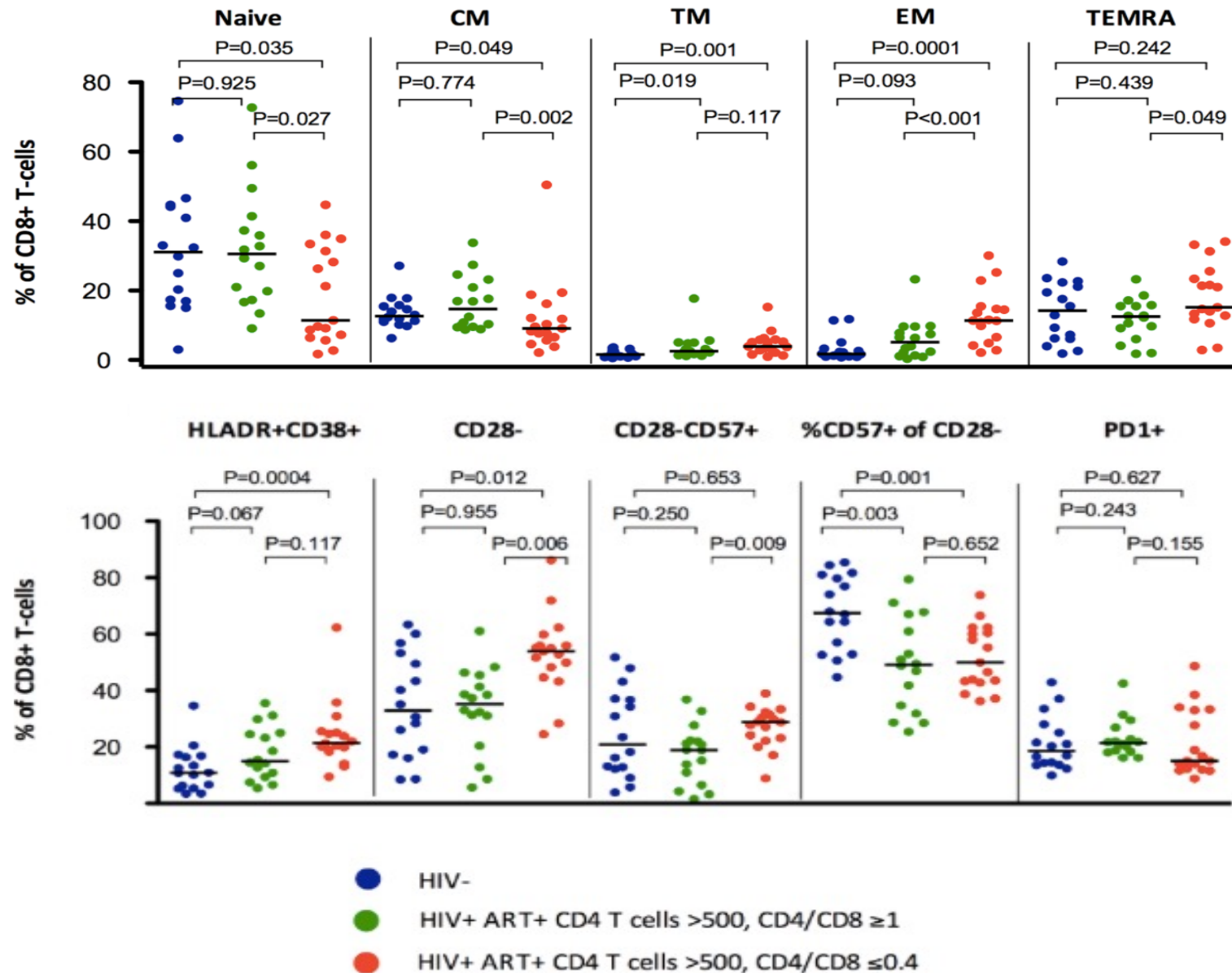
| HPV type          | Prevalence at enrollment, no. (%) of subjects | Clearance (for subjects positive at enrollment) |                                 |                                                              | HPV infection retention time, months |                  |
|-------------------|-----------------------------------------------|-------------------------------------------------|---------------------------------|--------------------------------------------------------------|--------------------------------------|------------------|
|                   |                                               | Cleared episodes, no.                           | Person-months of follow-up, no. | Clearance rate, cleared episodes/1000 person-months (95% CI) | Median (95% CI)                      | Mean (95% CI)    |
| High risk         |                                               |                                                 |                                 |                                                              |                                      |                  |
| 16                | 92 (38.2)                                     | 28                                              | 2286.3                          | 12.2 (8.5–17.7)                                              | ND (37.4–ND)                         | 35.8 (32.7–38.8) |
| 18                | 59 (24.5)                                     | 28                                              | 1375.2                          | 20.4 (14.1–29.5)                                             | 34.2 (20.6–ND)                       | 29.8 (25.9–33.7) |
| 31                | 42 (17.4)                                     | 25                                              | 801.4                           | 31.2 (21.1–46.2)                                             | 22.8 (12.8–36.5)                     | 23.7 (19.2–28.2) |
| 33                | 40 (16.6)                                     | 20                                              | 690.1                           | 29.0 (18.7–44.9)                                             | 23.4 (7.7–ND)                        | 24.6 (18.9–30.4) |
| 35                | 33 (13.7)                                     | 23                                              | 593.9                           | 38.7 (25.7–58.3)                                             | 19.4 (12.5–25.1)                     | 21.7 (17.0–26.4) |
| 39                | 49 (20.3)                                     | 26                                              | 968.1                           | 26.9 (18.3–39.4)                                             | 28.0 (14.8–36.9)                     | 25.8 (21.1–30.4) |
| 45                | 51 (21.2)                                     | 36                                              | 891.4                           | 40.4 (29.1–56.0)                                             | 19.6 (12.9–25.6)                     | 21.3 (17.2–25.3) |
| 51                | 35 (14.5)                                     | 20                                              | 596.1                           | 33.6 (21.6–52.0)                                             | 18.2 (9.4–31.8)                      | 22.1 (16.7–27.6) |
| 52                | 52 (21.6)                                     | 29                                              | 1096.6                          | 26.4 (18.4–38.1)                                             | 25.1 (16.7–37.3)                     | 26.4 (22.2–30.5) |
| 56                | 42 (17.4)                                     | 26                                              | 728.0                           | 35.7 (24.3–52.5)                                             | 14.4 (13.3–32.2)                     | 21.4 (17.1–25.8) |
| 58                | 48 (19.9)                                     | 25                                              | 892.8                           | 28.0 (18.9–41.4)                                             | 21.9 (15.2–ND)                       | 24.6 (20.3–28.9) |
| 59                | 47 (19.5)                                     | 21                                              | 1075.1                          | 19.5 (12.7–30.0)                                             | 32.8 (20.6–ND)                       | 29.4 (25.0–33.9) |
| 66                | 23 (9.5)                                      | 18                                              | 314.5                           | 57.2 (36.1–90.8)                                             | 13.3 (6.9–22.3)                      | 15.5 (11.1–19.9) |
| 68                | 36 (14.9)                                     | 16                                              | 606.7                           | 26.4 (16.2–43.0)                                             | 20.5 (12.5–ND)                       | 24.7 (19.3–30.1) |
| 82                | 14 (5.8)                                      | 10                                              | 254.8                           | 39.3 (21.1–73.0)                                             | 13.5 (6.6–ND)                        | 20.2 (12.5–27.9) |
| Low risk          |                                               |                                                 |                                 |                                                              |                                      |                  |
| 6                 | 85 (35.3)                                     | 26                                              | 1931.4                          | 13.5 (9.2–19.8)                                              | ND (35.2–ND)                         | 33.6 (30.3–36.8) |
| 11                | 56 (23.2)                                     | 18                                              | 1276.0                          | 14.1 (8.9–22.4)                                              | 44.2 (31.1–ND)                       | 33.4 (29.1–37.7) |
| 40                | 19 (7.9)                                      | 11                                              | 199.1                           | 55.2 (30.6–99.7)                                             | 11.1 (6.8–13.5)                      | 15.1 (8.4–21.8)  |
| 42                | 69 (28.6)                                     | 30                                              | 1499.1                          | 20.0 (14.0–28.6)                                             | 36.3 (20.7–ND)                       | 30.4 (26.4–34.4) |
| 44                | 47 (19.5)                                     | 22                                              | 1031.2                          | 21.3 (14.0–32.4)                                             | 33.1 (24.8–41.5)                     | 29.2 (25.0–33.4) |
| 54                | 26 (10.8)                                     | 21                                              | 447.6                           | 46.9 (30.6–72.0)                                             | 14.6 (8.5–21.1)                      | 18.9 (14.1–23.8) |
| 61                | 48 (19.9)                                     | 20                                              | 795.2                           | 25.1 (16.2–39.0)                                             | 25.3 (13.6–ND)                       | 26.8 (21.5–32.0) |
| 70                | 28 (11.6)                                     | 19                                              | 524.9                           | 36.2 (23.1–56.7)                                             | 17.1 (7.8–27.9)                      | 20.8 (15.9–25.8) |
| 72                | 21 (8.7)                                      | 15                                              | 384.6                           | 39.0 (23.5–64.7)                                             | 20.3 (9.1–28.0)                      | 20.8 (15.5–26.2) |
| 81                | 26 (10.8)                                     | 14                                              | 411.0                           | 34.1 (20.2–57.5)                                             | 18.2 (7.6–ND)                        | 21.6 (15.9–27.4) |
| 89                | 40 (16.6)                                     | 25                                              | 660.0                           | 37.9 (25.6–56.0)                                             | 15.5 (9.6–20.8)                      | 22.5 (16.6–28.4) |
| Undetermined risk |                                               |                                                 |                                 |                                                              |                                      |                  |
| 26                | 13 (5.4)                                      | 10                                              | 178.2                           | 56.1 (30.2–104.3)                                            | 12.5 (6.9–25.6)                      | 15.0 (9.5–20.6)  |
| 34                | 3 (1.2)                                       | 3                                               | 26.0                            | 115.3 (37.2–357.5)                                           | 7.4 (5.1–ND)                         | 8.7 (4.6–12.7)   |
| 53                | 44 (18.3)                                     | 26                                              | 858.5                           | 30.3 (20.6–44.5)                                             | 25.6 (8.1–34.7)                      | 23.3 (19.0–27.6) |
| 62                | 21 (8.7)                                      | 12                                              | 440.2                           | 27.3 (15.5–48.0)                                             | 20.2 (14.2–ND)                       | 26.1 (19.3–32.9) |
| 67                | 16 (6.6)                                      | 12                                              | 308.7                           | 38.9 (22.1–68.4)                                             | 19.2 (13.0–27.5)                     | 21.4 (15.5–27.3) |
| 69                | 22 (9.1)                                      | 12                                              | 395.2                           | 30.4 (17.2–53.5)                                             | 26.0 (6.4–39.6)                      | 24.6 (17.7–31.5) |
| 71                | 6 (2.5)                                       | 0                                               | 103.9                           | 0 (ND)                                                       | ND                                   | 42.7 (42.7–42.7) |
| 73                | 40 (16.6)                                     | 22                                              | 801.3                           | 27.5 (18.1–41.7)                                             | 28.9 (12.8–40.5)                     | 25.3 (20.7–30.0) |
| 83                | 16 (6.6)                                      | 9                                               | 220.6                           | 40.8 (21.2–78.4)                                             | 16.9 (7.4–ND)                        | 18.2 (12.5–23.9) |
| 84                | 51 (21.2)                                     | 33                                              | 769.3                           | 42.9 (30.5–60.3)                                             | 14.1 (11.7–20.6)                     | 20.6 (16.2–25.0) |

**NOTE.** HPV types are classified by risk of anogenital cancer according to Munoz et al. [25]. CI, confidence interval; ND, not determined.



Kaplan-Meier estimates of the clearance times for human papillomavirus (HPV)–16 (a), HPV-18 (b), and HPV-6 (c) and of the cumulative incidence of infection with HPV-16 (d), HPV-18 (e), and HPV-6 (f).

# Low CD4/CD8 T-cell Ratio Mirrors Peripheral Immune Defects



# Low CD4/CD8 Ratio is Linked to Poor Clinical Outcome in HIV

|                                                                         | Univariable      |         | Model 1 (AIC=3936) |         | Model 2 (AIC=3931) |         |
|-------------------------------------------------------------------------|------------------|---------|--------------------|---------|--------------------|---------|
|                                                                         | RR (95% CI)      | p value | ARR (95% CI)       | p value | ARR (95% CI)       | p value |
| Age (per 10 years older)                                                | 1.56 (1.41-1.73) | <0.0001 | 1.55 (1.38-1.74)   | <0.0001 | 1.54 (1.37-1.74)   | 0.0001  |
| Mode of HIV transmission                                                |                  |         |                    |         |                    |         |
| Heterosexual contacts                                                   | 1.00             | ..      | 1.00               | ..      | 1.00               | ..      |
| Homosexual contacts with men                                            | 1.11 (0.84-1.46) | 0.4589  | 1.15 (0.86-1.54)   | 0.3307  | 1.16 (0.87-1.55)   | 0.3231  |
| Intravenous drug use                                                    | 1.37 (1.07-1.80) | 0.0147  | 1.36 (0.90-2.06)   | 0.1413  | 1.35 (0.89-2.04)   | 0.1546  |
| Other or unknown                                                        | 1.62 (1.07-2.44) | 0.0221  | 1.51 (0.98-2.34)   | 0.0643  | 1.52 (0.98-2.35)   | 0.0612  |
| Years of HIV infection (per 1 year longer)                              | 1.02 (1.00-1.04) | 0.0265  | 1.02 (0.99-1.04)   | 0.1285  | 1.02 (0.99-1.04)   | 0.1216  |
| CD4 count at baseline (cells per $\mu$ L)                               |                  |         |                    |         |                    |         |
| 0-199                                                                   | 1.00             | ..      | 1.00               | ..      | 1.00               | ..      |
| 200-349                                                                 | 0.54 (0.40-0.73) | <0.0001 | 0.76 (0.54-1.06)   | 0.1024  | 0.81 (0.57-1.14)   | 0.2185  |
| $\geq 350$                                                              | 0.56 (0.43-0.72) | <0.0001 | 1.11 (0.79-1.56)   | 0.5645  | 1.18 (0.83-1.67)   | 0.3631  |
| Months since ART start to first viral suppression (per 6 months longer) | 1.03 (1.00-1.06) | 0.0811  | 0.99 (0.96-1.03)   | 0.7333  | 0.99 (0.96-1.03)   | 0.6394  |
| CDC stage category C (vs A and B)                                       | 1.73 (1.37-2.19) | <0.0001 | 1.37 (1.04-1.80)   | 0.0250  | 1.34 (1.02-1.76)   | 0.0365  |
| HCV-Ab status                                                           |                  |         |                    |         |                    |         |
| Negative                                                                | 1.00             | ..      | 1.00               | ..      | 1.00               | ..      |
| Positive                                                                | 1.29 (1.02-1.64) | 0.0362  | 1.05 (0.72-1.53)   | 0.8097  | 1.04 (0.71-1.52)   | 0.8397  |
| Not known                                                               | 1.33 (0.99-1.78) | 0.0557  | 1.17 (0.85-1.60)   | 0.3437  | 1.15 (0.84-1.59)   | 0.3859  |
| Current CD4 count (per 100 cells per $\mu$ L higher)                    | 0.87 (0.85-0.93) | <0.0001 | 0.90 (0.85-0.95)   | <0.0001 | 0.93 (0.87-0.98)   | 0.0107  |
| Current CD4/CD8 ratio                                                   |                  |         |                    |         |                    |         |
| >0.45                                                                   | 1.00             | ..      | ..                 | ..      | 1.00               | ..      |
| 0.30-0.45                                                               | 1.16 (0.86-1.58) | 0.3362  | ..                 | ..      | 0.95 (0.69-1.31)   | 0.7512  |
| <0.30                                                                   | 2.25 (1.73-2.94) | <0.0001 | ..                 | ..      | 1.51 (1.09-2.09)   | 0.0137  |

The model included all the study population (n=3236). Model 1 includes all significant variables in univariable analysis except for the CD4/CD8 ratio; model 2 included also the ratio. AIC=Akaike's information criterion. RR=relative risk. ARR=adjusted relative risk. ART=antiretroviral therapy. CDC=Centers for Disease Control and Prevention. HCV-Ab=HCV antibody.

**Table 3: Two different multivariable Poisson regression models analysing factors associated with clinical progression (defined as non-AIDS-defining event or death)**

|                                                      | Univariable      |         | Model 1 (AIC=1215) |         | Model 2 (AIC=1210) |         |
|------------------------------------------------------|------------------|---------|--------------------|---------|--------------------|---------|
|                                                      | RR (95% CI)      | p value | ARR (95% CI)       | p value | ARR (95% CI)       | p value |
| White                                                | 0.33 (0.19-0.56) | <0.0001 | 0.32 (0.18-0.57)   | <0.001  | 0.66 (0.43-1.00)   | 0.050   |
| Baseline CD4 count (cells per $\mu$ L)               |                  |         |                    |         |                    |         |
| 0-199                                                | 1.00             | ..      | 1.00               | ..      | 1.00               | ..      |
| 200-349                                              | 0.25 (0.14-0.45) | <0.0001 | 0.47 (0.24-0.92)   | 0.0267  | 0.52 (0.27-1.01)   | 0.0548  |
| $\geq 350$                                           | 0.30 (0.19-0.47) | <0.0001 | 1.18 (0.64-2.17)   | 0.5998  | 1.27 (0.63-2.36)   | 0.4495  |
| CDC stage category C (vs A and B)                    | 2.82 (1.88-4.23) | <0.0001 | 2.22 (1.37-3.60)   | 0.0012  | 2.14 (1.32-3.47)   | 0.0020  |
| Current CD4 count (per 100 cells per $\mu$ L higher) | 0.75 (0.68-0.84) | <0.0001 | 0.77 (0.69-0.87)   | 0.0001  | 0.85 (0.75-0.97)   | 0.0187  |
| Current CD4/CD8 ratio                                |                  |         |                    |         |                    |         |
| >0.45                                                | 1.00             | ..      | ..                 | ..      | 1.00               | ..      |
| 0.30-0.45                                            | 1.77 (0.96-3.25) | 0.0655  | ..                 | ..      | 1.30 (0.69-2.46)   | 0.4220  |
| <0.30                                                | 4.96 (3.06-8.04) | <0.0001 | ..                 | ..      | 2.56 (1.38-4.74)   | 0.0029  |

Model 1 includes all significant variables in univariable analysis except for the ratio; model 2 included also the ratio. The model included all the study population (n=3236).

RR=relative risk. ARR=adjusted relative risk. ART=antiretroviral therapy. CDC=Centers for Disease Control and Prevention. AIC=Akaike's information criterion.

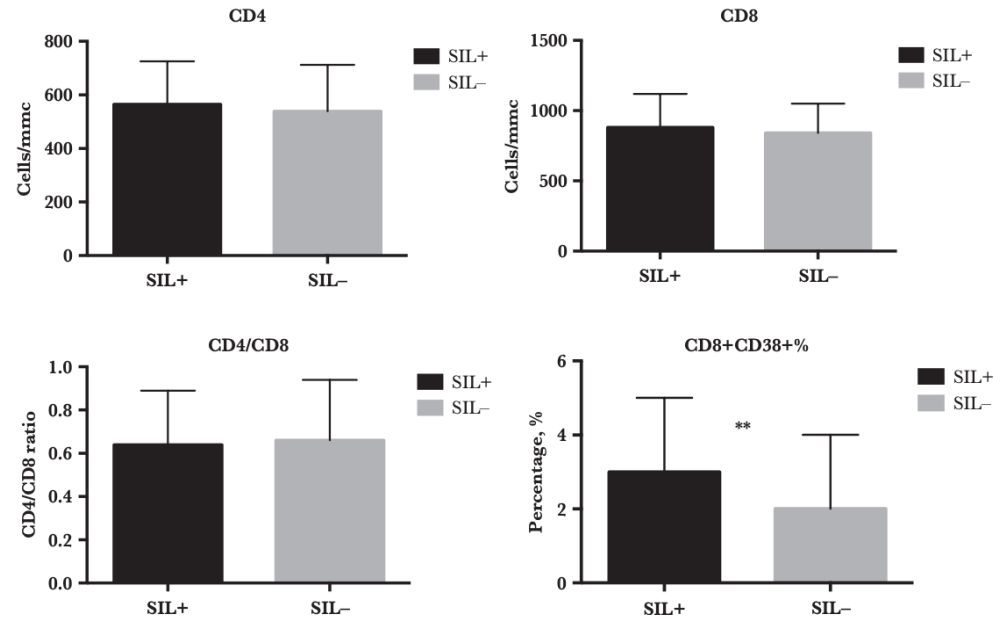
**Table 4: Two different multivariable Poisson regression models analysing factors associated with clinical progression (defined as AIDS event and death due to AIDS event)**

Mussini et al. Lancet HIV 2015

See also: Han et al. AIDS Res Ther., 2018; Lee et al. BMJ Open 2017; Trickey et al. CID 2017; Sauter et al. Medicine 2016;

Hema et al. PlosOne 2016

# T-cell activation as an independent predictor of HPV-related dysplasia in PLWH



**Table 2. Parameters Independently Associated With Cytologic HPV-Related Dysplasia by Fitting 2 Models of Multivariable Logistic Regression Analyses**

A, Model 1 of logistic regression analysis: association between CD8+ CD38+ T-cell percentages and HPV-related anal/cervical dysplasia

| Parameter                                                               | aOR   | 95% CI      | PValue |
|-------------------------------------------------------------------------|-------|-------------|--------|
| Log <sub>10</sub> CD8+ CD38+ T cells, percentages, each additional unit | 3.253 | 1.602–6.605 | .001   |

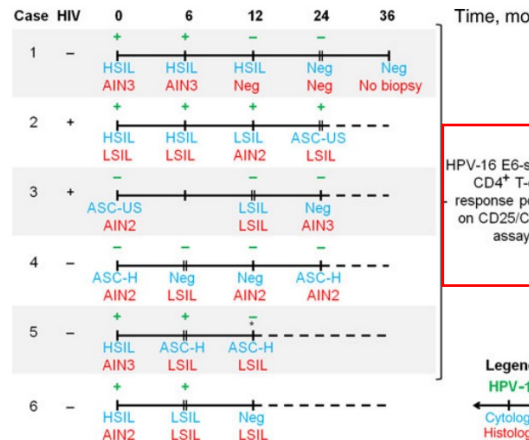
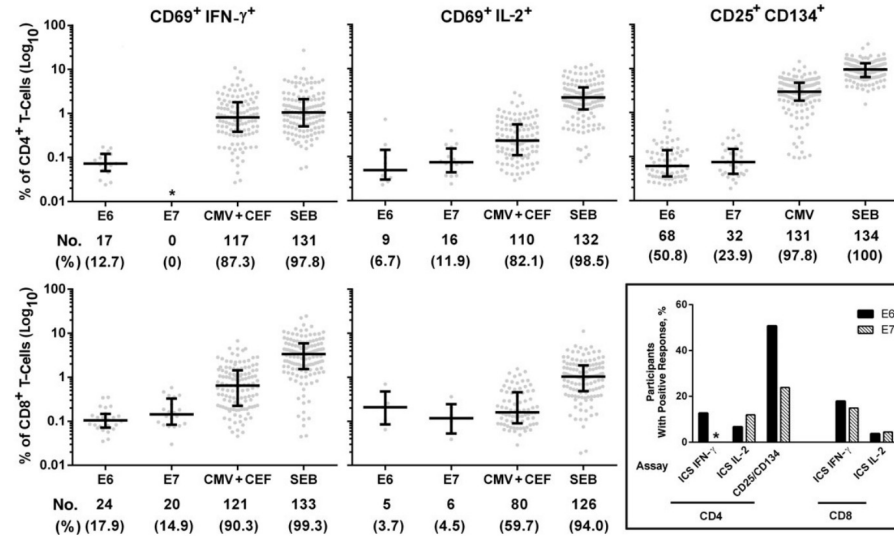
B, Model 2 of logistic regression analysis: association between CD4/CD8 ratio and HPV-related anal/cervical dysplasia

| Parameter                     | aOR   | 95% CI      | PValue |
|-------------------------------|-------|-------------|--------|
| CD4/CD8 ratio, each unit more | 0.998 | 0.242–4.109 | .997   |

# T-cell specific responses in HSIL

**Table 1. Participant Characteristics<sup>a</sup>**

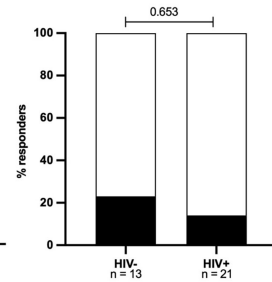
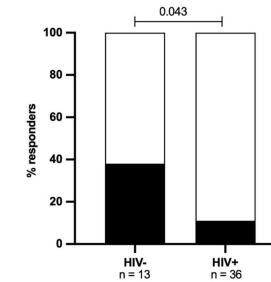
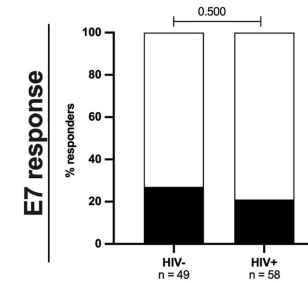
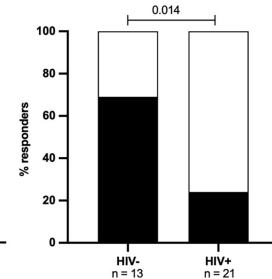
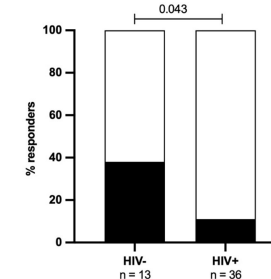
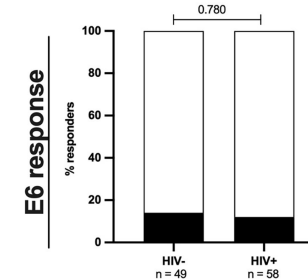
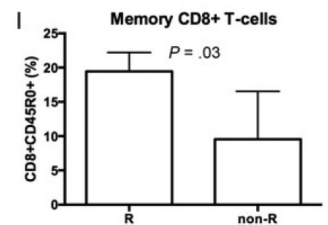
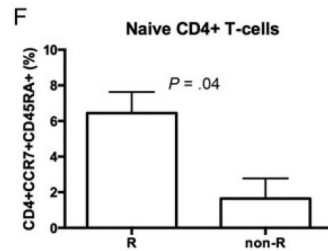
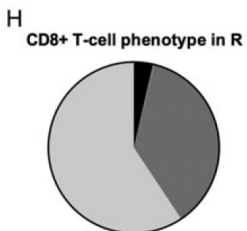
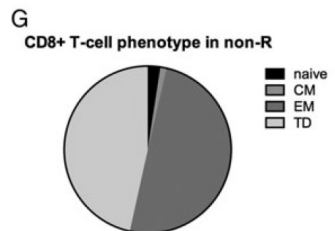
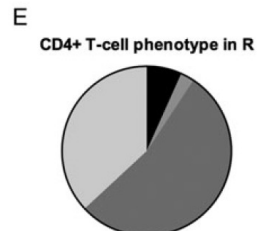
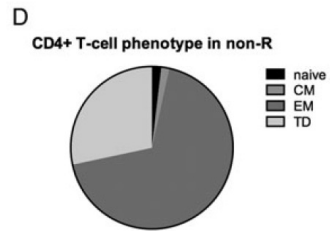
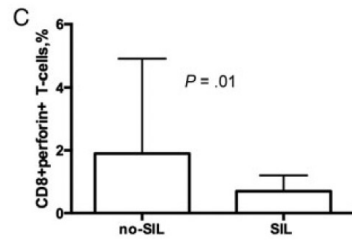
| Characteristic                                                                                 | HIV Uninfected (n = 103) | HIV Infected (n = 31) | All (N = 134)          |
|------------------------------------------------------------------------------------------------|--------------------------|-----------------------|------------------------|
| Age, mean (SD), y                                                                              | 51.2 (9.58)              | 49.5 (8.33)           | 50.8 (9.31)            |
| Interval between baseline and Immunology Substudy blood collection, mean (SD), mo <sup>b</sup> | 13.6 (6.59)              | 12.9 (7.39)           | 13.4 (6.73)            |
| Anal cytological findings                                                                      |                          |                       |                        |
| Unsatisfactory                                                                                 | 6 (5.8)                  | 2 (6.5)               | 8 (6.0)                |
| Negative <sup>c</sup>                                                                          | 41 (39.8)                | 12 (38.7)             | 53 (39.6)              |
| ASC-US                                                                                         | 14 (13.6)                | 4 (12.9)              | 18 (13.4)              |
| LSIL                                                                                           | 8 (7.8)                  | 4 (12.9)              | 12 (9.0)               |
| ASC-H                                                                                          | 18 (17.5)                | 3 (9.68)              | 21 (15.7)              |
| HSIL                                                                                           | 16 (15.5)                | 6 (16.1)              | 22 (16.4)              |
| Total                                                                                          | 103 (100)                | 31 (100)              | 134 (100)              |
| HRA findings                                                                                   |                          |                       |                        |
| Visually normal (no biopsy)                                                                    | 27 (26.2)                | 3 (9.7)               | 30 (22.4)              |
| Visually abnormal (≥1 biopsy)                                                                  | 76 (73.8)                | 28 (90.3)             | 104 (77.6)             |
| Total                                                                                          | 103 (100)                | 31 (100)              | 134 (100)              |
| Anal histological findings <sup>d</sup>                                                        |                          |                       |                        |
| Negative <sup>e</sup>                                                                          | 28 (36.8)                | 7 (25.0)              | 35 (33.7)              |
| LSIL                                                                                           | 16 (21.1)                | 6 (21.4)              | 22 (21.1)              |
| HSIL                                                                                           | 32 (42.1)                | 15 (53.6)             | 47 (45.2)              |
| Total                                                                                          | 76 (100)                 | 28 (100)              | 104 (100)              |
| Anal HPV detected                                                                              |                          |                       |                        |
| HPV-16                                                                                         | 26 (26.3)                | 12 (38.7)             | 38 (29.2)              |
| Any high-risk type                                                                             | 55 (55.6)                | 22 (71.0)             | 77 (59.2)              |
| No. of types, median (IQR)                                                                     | 2 (1–4)                  | 3 (1–6)               | ...                    |
| Total                                                                                          | 99 (100) <sup>f</sup>    | 31 (100)              | 130 (100) <sup>f</sup> |
| Absolute T-cell count, mean (SD), cells/μL                                                     |                          |                       |                        |
| CD4 <sup>+</sup>                                                                               | 822 (253.8) <sup>g</sup> | 584 (249.8)           | 766 (271.5)            |
| CD8 <sup>+</sup>                                                                               | 465 (198.3)              | 859 (496.4)           | 556 (337.1)            |
| CD4 <sup>+</sup> /CD8 <sup>+</sup> T-cell ratio, mean (SD)                                     | 2.0 (0.87)               | 0.8 (0.42)            | ...                    |
| Currently receiving ART <sup>h</sup>                                                           | ...                      | 29 (94)               | ...                    |
| Undetectable HIV load <sup>h</sup>                                                             | ...                      | 28 (90)               | ...                    |
| Ever had AIDS-defining illness <sup>h</sup>                                                    | ...                      | 11 (35)               | ...                    |



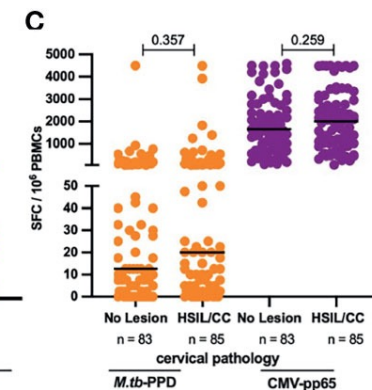
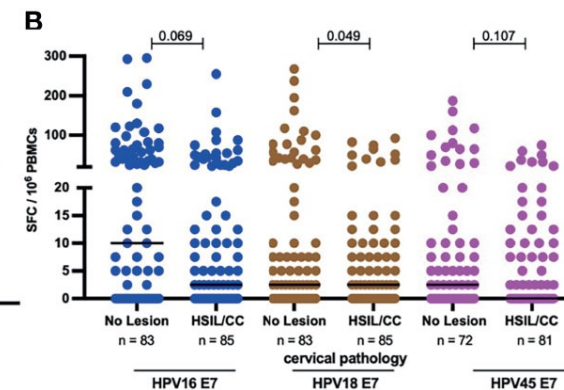
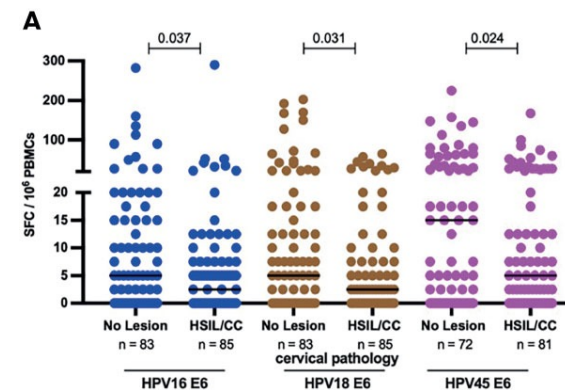
**Table 3. Clinical Associations With Positive HPV-16 E7-Specific T-Cell Responses (Univariable Logistic Regression)**

| T-Cell Subset                                   | CD4 <sup>+</sup>  |                 |                  | CD8 <sup>+</sup>  |                 |                     |
|-------------------------------------------------|-------------------|-----------------|------------------|-------------------|-----------------|---------------------|
| Assay                                           | CD25/CD134        |                 |                  | ICS               |                 |                     |
|                                                 | Prevalence, n (%) | OR (95% CI)     | P Value          | Prevalence, n (%) | OR (95% CI)     | P Value             |
| Age, y                                          |                   |                 | .44 <sup>a</sup> |                   |                 | .61 <sup>a</sup>    |
| 35–44                                           | 12 (37.5)         | 1               |                  | 5 (15.6)          | 1               |                     |
| 45–55                                           | 8 (13.8)          | 0.27 (.09–.75)  |                  | 4 (6.9)           | 0.32 (.08–1.24) |                     |
| ≥55                                             | 12 (27.3)         | 0.63 (.24–1.66) |                  | 8 (18.2)          | 1.20 (.35–4.08) |                     |
| HIV status                                      |                   |                 | .76              |                   |                 | .42                 |
| Uninfected                                      | 25 (24.3)         | 1               |                  | 11 (10.7)         | 1               |                     |
| Infected                                        | 7 (22.6)          | 0.88 (.40–1.98) |                  | 5 (16.1)          | 1.61 (.51–5.05) |                     |
| CD4 <sup>+</sup> /CD8 <sup>+</sup> T-cell ratio | ...               | 0.95 (.62–1.47) | .82              | ...               | 0.80 (.43–1.48) | .47                 |
| Anal HPV status                                 |                   |                 | .17              |                   |                 | .18                 |
| HPV-16                                          |                   |                 |                  |                   |                 | .41                 |
| Not detected                                    | 25 (27.2)         | 1               |                  | 9 (9.8)           | 1               |                     |
| Detected                                        | 6 (15.8)          | 0.50 (.19–1.35) |                  | 7 (18.4)          | 2.08 (.71–6.07) |                     |
| Any high-risk HPV type                          |                   |                 | .49              |                   |                 | .41                 |
| Not detected                                    | 11 (20.8)         | 1               |                  | 5 (9.4)           | 1               |                     |
| Detected                                        | 20 (26.0)         | 1.34 (.58–3.09) |                  | 11 (14.3)         | 1.60 (.52–4.91) |                     |
| No. of HPV types detected                       |                   |                 | .57 <sup>a</sup> |                   |                 | .048 <sup>a,b</sup> |
| 0                                               | 6 (23.1)          | 1               |                  | 0 (0)             | ...             |                     |
| 1–2                                             | 9 (20.0)          | 0.83 (.26–2.68) |                  | 6 (13.3)          | 1               |                     |
| ≥3                                              | 16 (17.2)         | 1.24 (.42–3.64) |                  | 10 (17.0)         | 1.33 (.44–3.97) |                     |
| Anal SIL screening diagnosis                    |                   |                 | .13              |                   |                 | .32                 |
| Cytology                                        |                   |                 |                  |                   |                 | .13                 |
| ≤ASC-H                                          | 22 (21.2)         | 1               |                  | 11 (10.6)         | 1               |                     |
| HSIL                                            | 8 (36.4)          | 2.13 (.79–5.72) |                  | 4 (18.2)          | 1.88 (.54–6.56) |                     |
| Worst histology                                 |                   |                 | .63              |                   |                 | .15                 |
| ≤AIN2                                           | 24 (25.0)         | 1               |                  | 14 (14.6)         | 1               |                     |
| AIN3                                            | 8 (21.1)          | 0.80 (.32–1.98) |                  | 2 (5.3)           | 0.33 (.07–1.51) |                     |
| High-grade disease <sup>c</sup>                 |                   |                 | .73              |                   |                 | .55                 |
| Not detected                                    | 19 (22.9)         | 1               |                  | 11 (13.3)         | 1               |                     |
| Detected                                        | 13 (25.5)         | 1.15 (.51–2.59) |                  | 5 (9.8)           | 0.71 (.23–2.18) |                     |

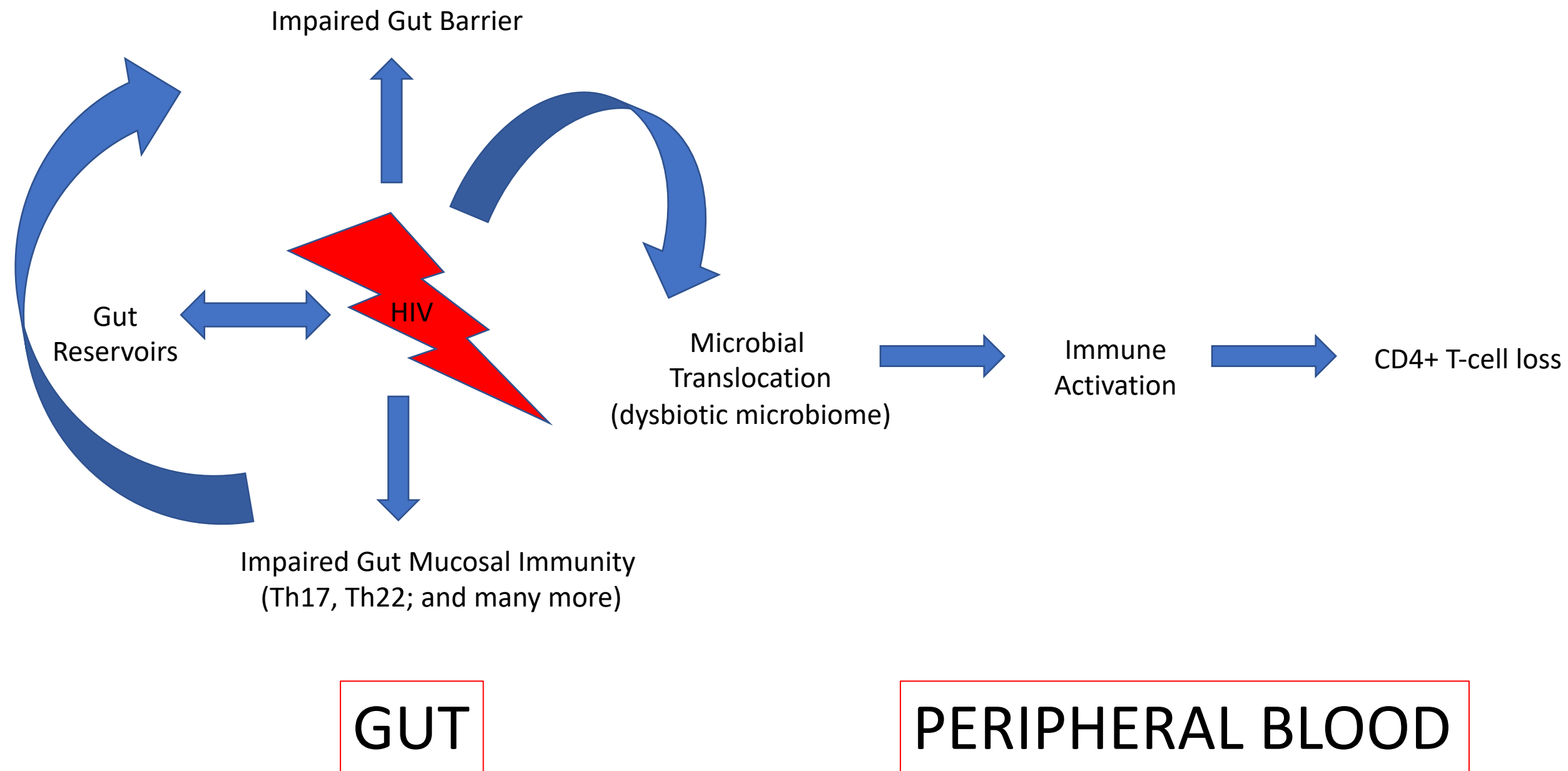
# Role of HPV-specific cells in HR HPV-related dysplasia



■ Responder  
□ Non-responder



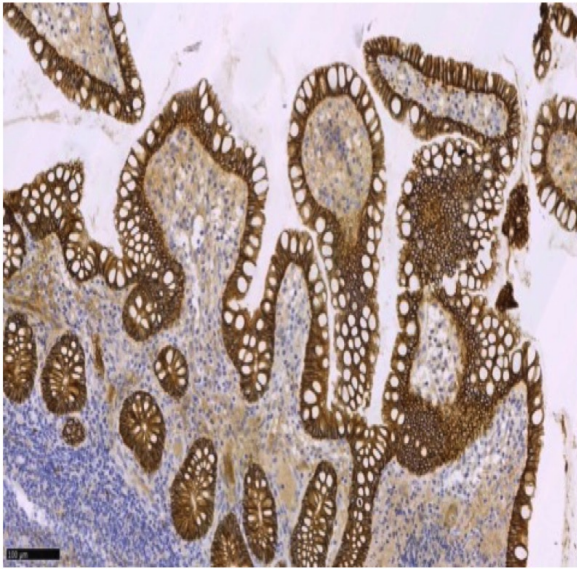
Tincati, CID, 2016



# The Loss of Gut Junctional Protein Expression Occurs in **Early** HIV

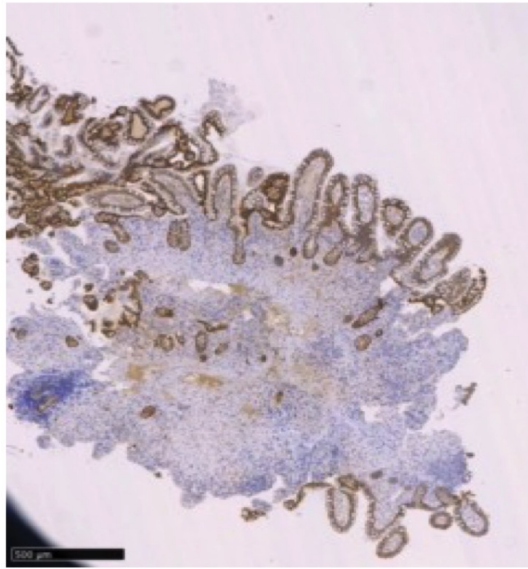
A.

HC



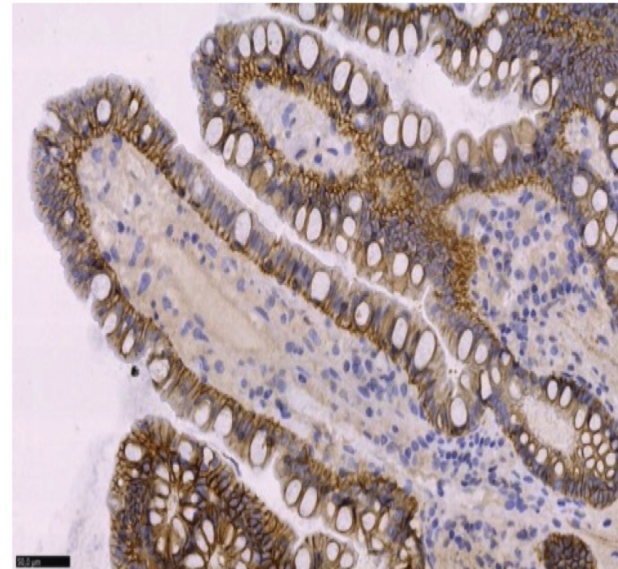
Healthy Control

P-HIV



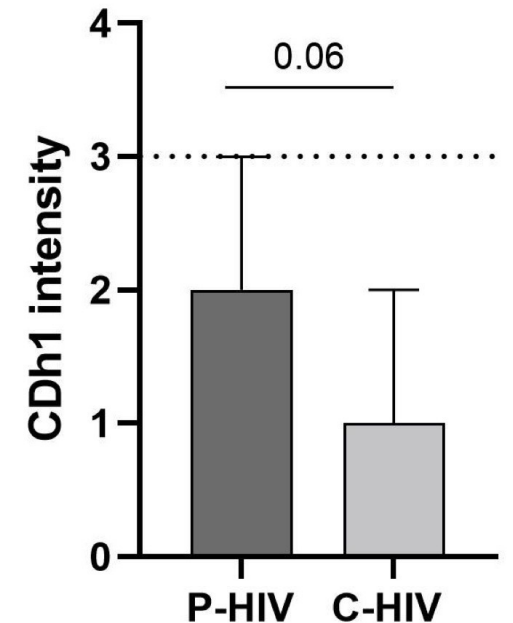
Primary HIV  
(untreated)

C-HIV

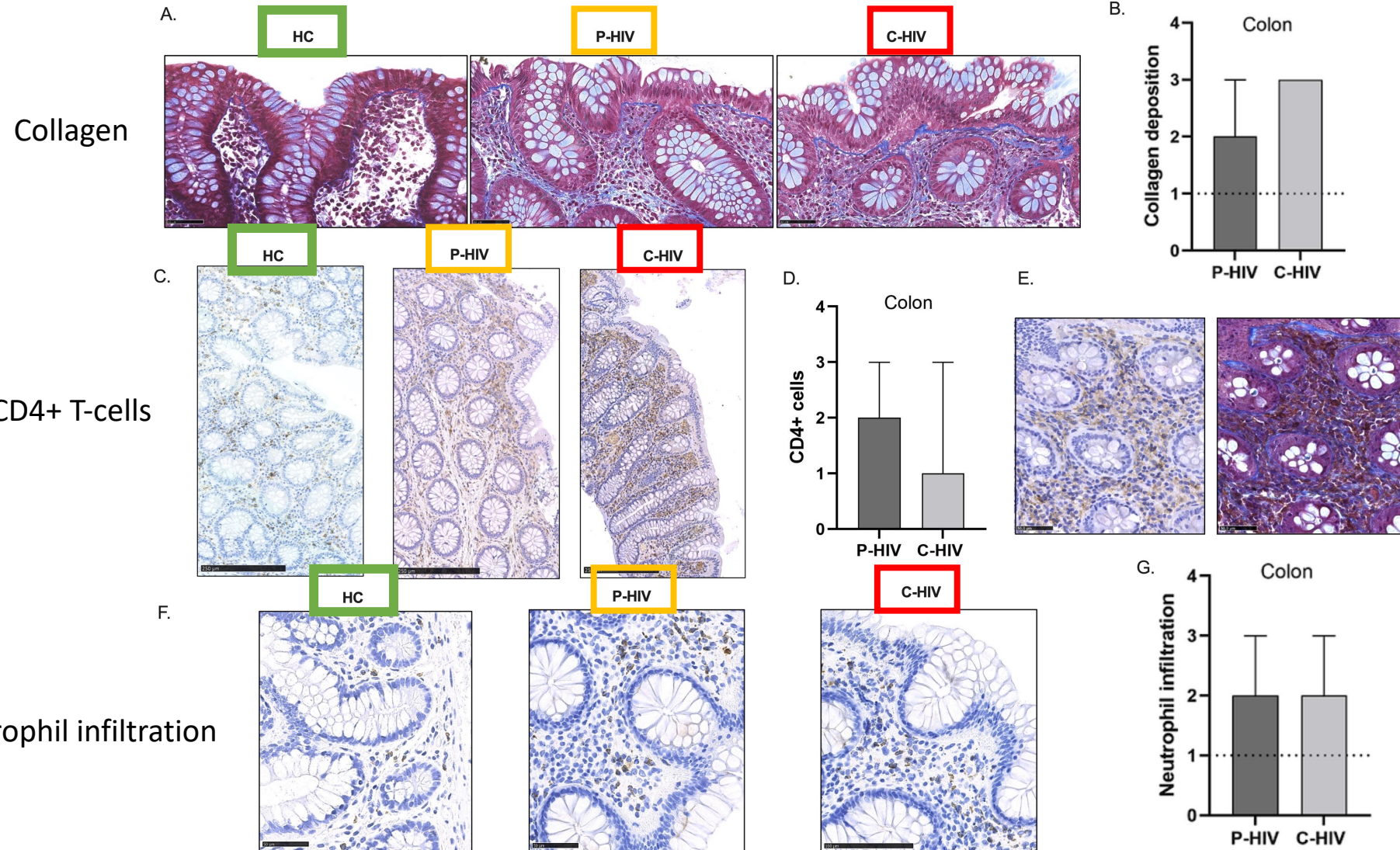


Chronic HIV  
(untreated)

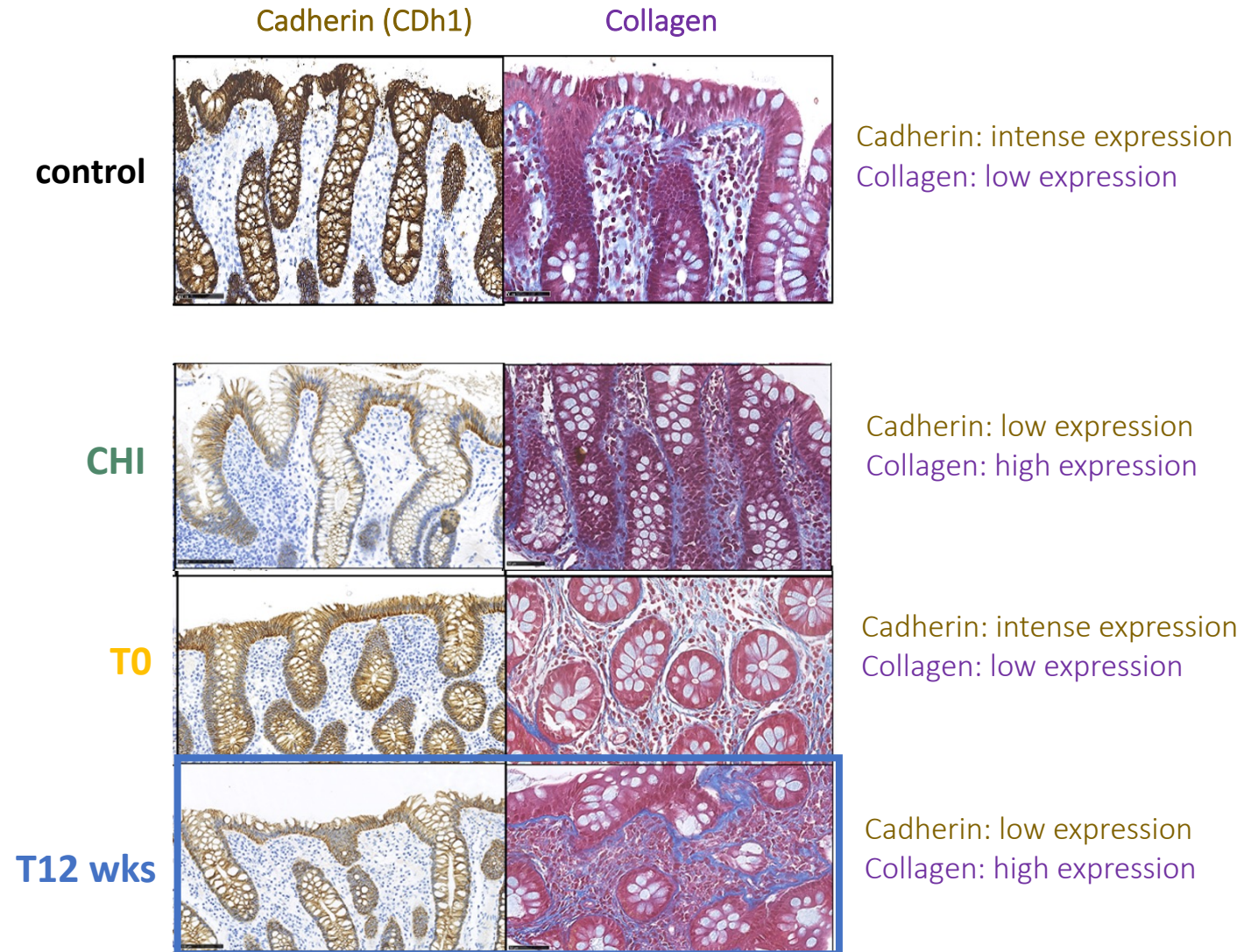
B.



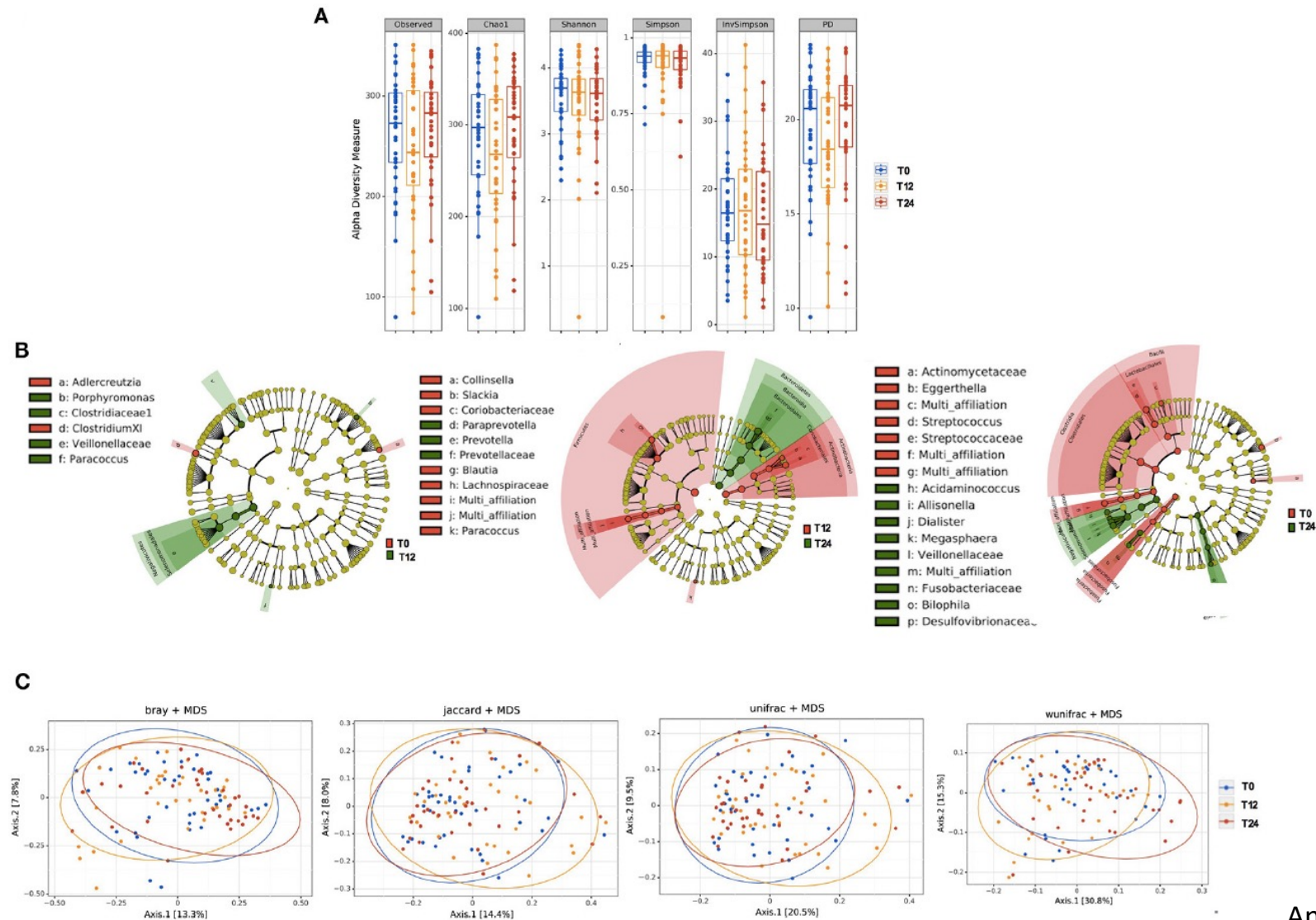
# Gut Fibrosis and Inflammation Occur **Early** in HIV



# And is not reverted by cART (in the short-term)

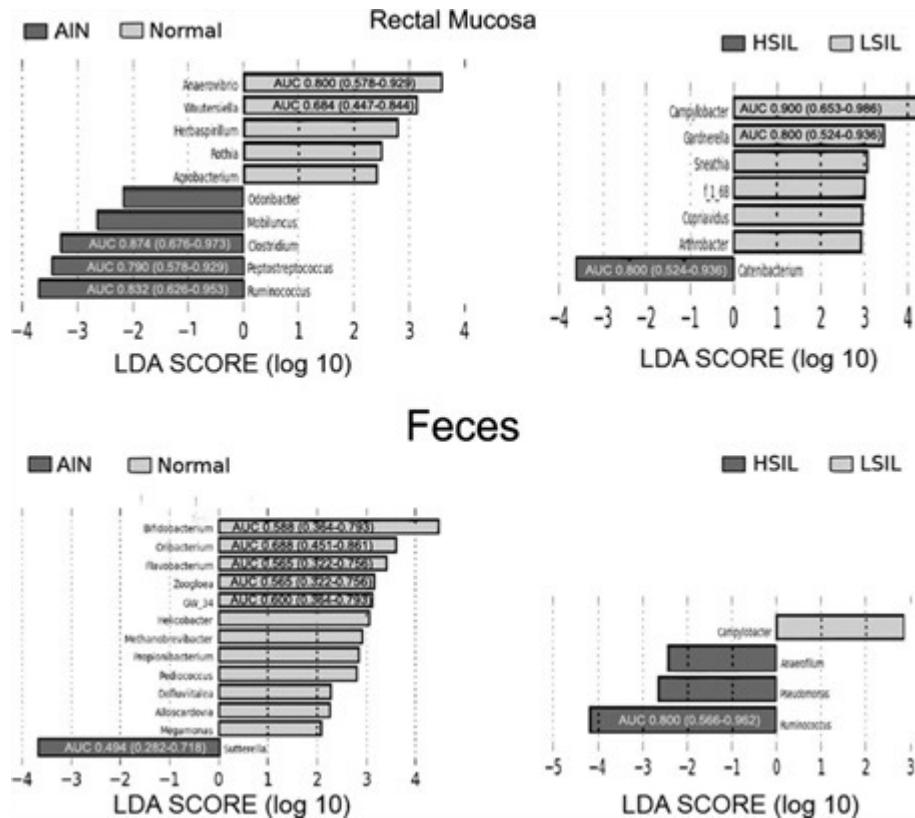


# Gut dysbiosis and cART



# Fecal and rectal microbiota are linked to HPV-related anal dysplasia

N=42 MSM, LWH



frontiers | Frontiers in Immunology

TYPE Mini Review  
PUBLISHED 23 January 2023  
DOI 10.3389/fimmu.2023.1072655

## The microbiota as a modulator of mucosal inflammation and HIV/HPV pathogenesis: From association to causation

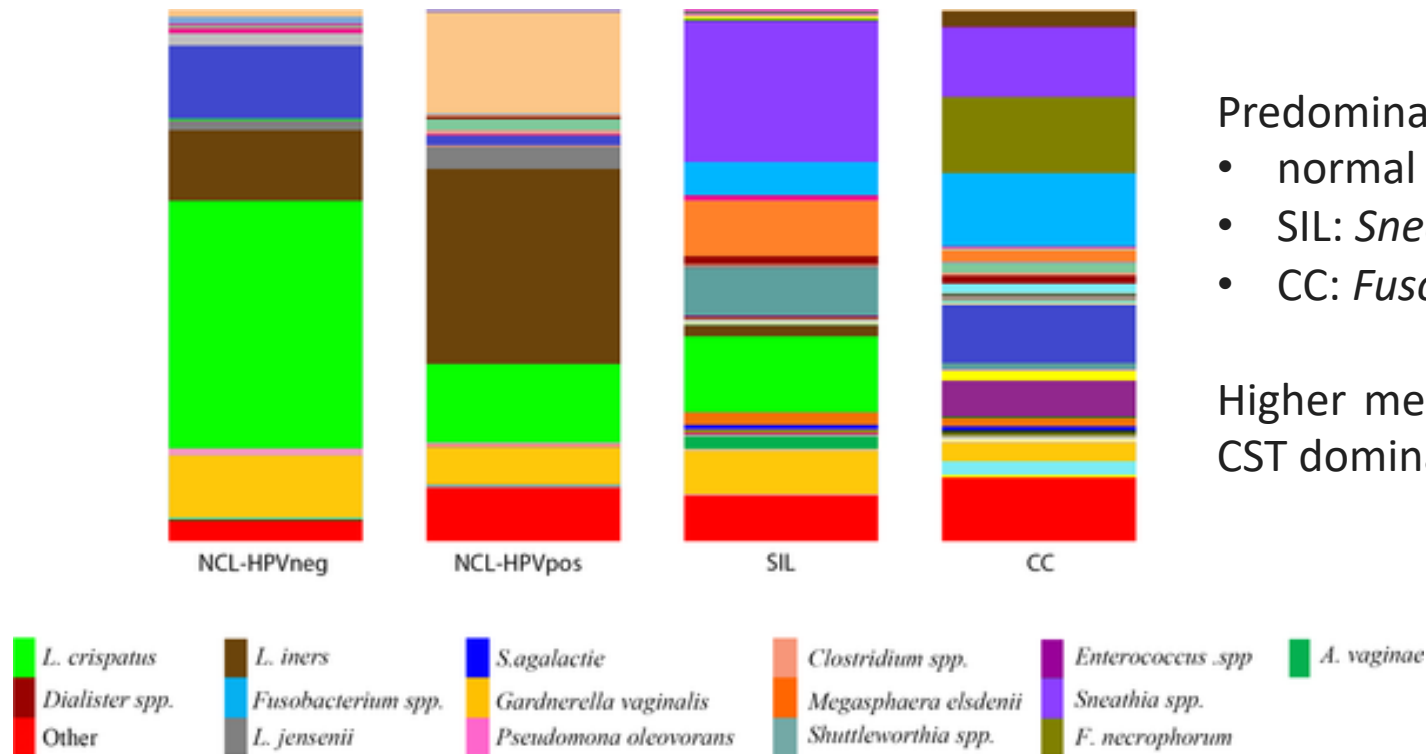
Elena Moreno<sup>1,2\*</sup>, Raquel Ron<sup>1,2</sup> and Sergio Serrano-Villar<sup>1,2\*</sup>

<sup>1</sup>Department of Infectious Diseases, Hospital Universitario Ramón y Cajal, Facultad de Medicina, Universidad de Alcalá, IRYCIS, Madrid, Spain, <sup>2</sup>CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain

Serrano-Villar, AIDS, 2017

See also: Nowak, AIDS Res. Hum. Retrovir. 2019

# The cervical microbiota is implicated in cervical cancer pathology



Predominant bacteria:

- normal cytology: *L. crispatus* and *L. iners*
- SIL: *Sneathia spp.*
- CC: *Fusobacterium spp.*

Higher median cervical levels of IL-4 and TGF- $\beta$ 1 mRNA in the CST dominated by *Fusobacterium spp.*

Can HPV Influence HIV Acquisition?

### Summary of studies of the association of HPV and HIV acquisition

How should HPV infection be managed in PLWH?

# Primary prevention through vaccination (prior to sexual debut)

## GUIDELINES

Version 11.1  
October 2022

English

| Infection                   | Vaccination rationale                                                                  | Comment                                                                                                                                                                                                                                                                                        |
|-----------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Human Papilloma Virus (HPV) | Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer | Vaccinate with 3 doses between ages 9 and 45 (health insurance coverage differs by country according to age, sex, sexual orientation).<br>Use 9-valent vaccine if available.<br>Persons treated for high grade dysplasia could benefit from a full course vaccination for secondary prevention |

| Vaccine                    | Indication                                                                      | Recommendations                                                                                                                                                                                                                                                                                                                                             | Additional Comments                                                                                                                                                                                                                                                                                                                            | ACIP Recommendations             |
|----------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Human papillomavirus (HPV) | Adults and adolescents through age 26                                           | For exposed people who have not received a vaccine or have not received the complete series, administer or complete the HepB vaccine series and administer a dose of HBIG at a separate anatomical site as soon as possible after exposure (ideally within 24 hours, but up to 7 days after percutaneous exposure and up to 14 days after sexual exposure). | If a significant delay occurs between doses, there is no need to restart the series.<br><br>Routine vaccination is <b>not recommended</b> for people ages 27–45 years (AII). Some PWH may benefit from vaccination in this age group, and shared clinical decision-making between the provider and patient is recommended in these situations. | No difference in recommendations |
|                            | Adults and adolescents who previously received bivalent or quadrivalent vaccine | For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, no recommendations exist for additional vaccinations; some experts would give an additional full series of recombinant 9-valent vaccine, but no data currently define who might benefit or how cost effective this approach might be (CIII).    | Vaccination is <b>not recommended</b> during pregnancy (CIII). Delay until after pregnancy.                                                                                                                                                                                                                                                    |                                  |

### Immunizations for Preventable Diseases in Adults and Adolescents with HIV

Updated: April 13, 2023  
Reviewed: April 13, 2023

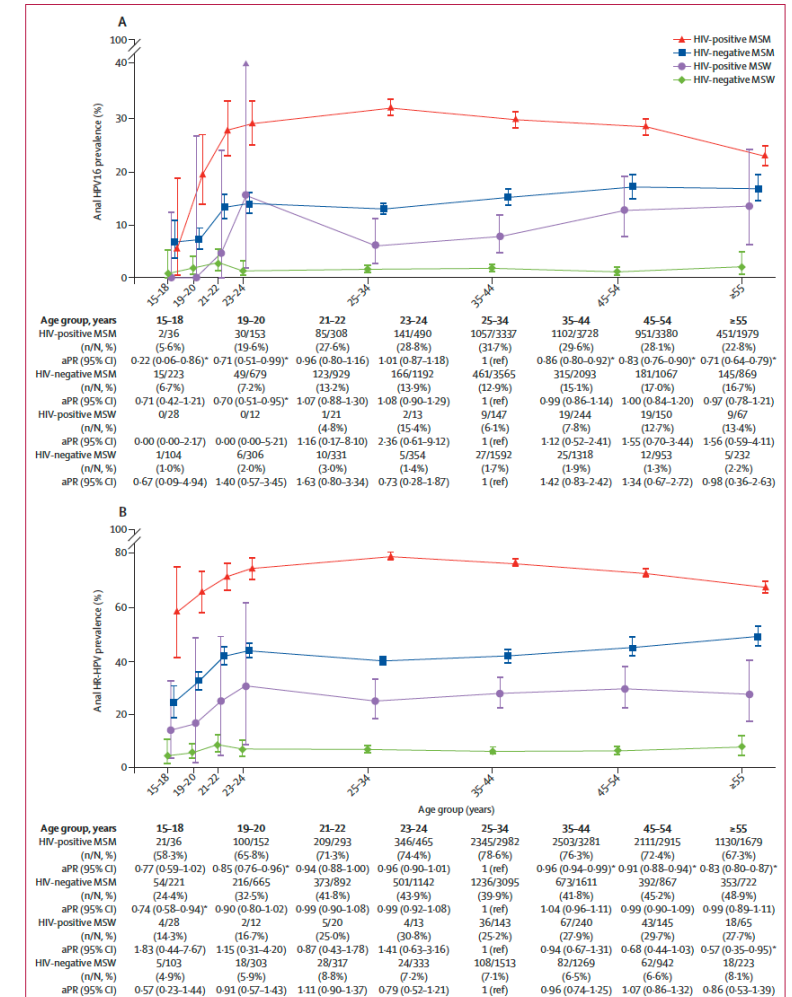
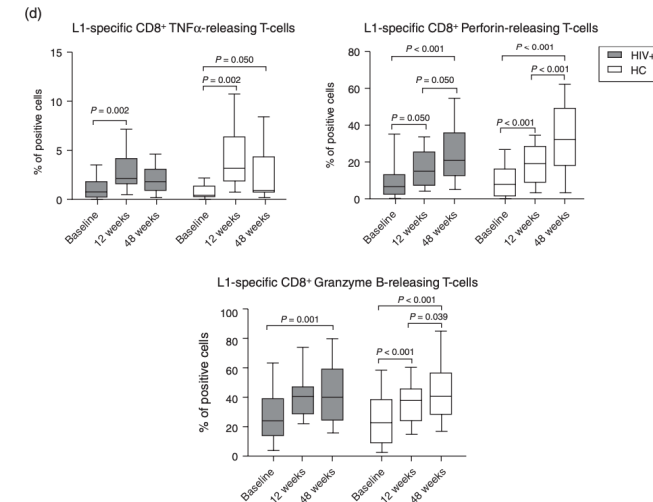
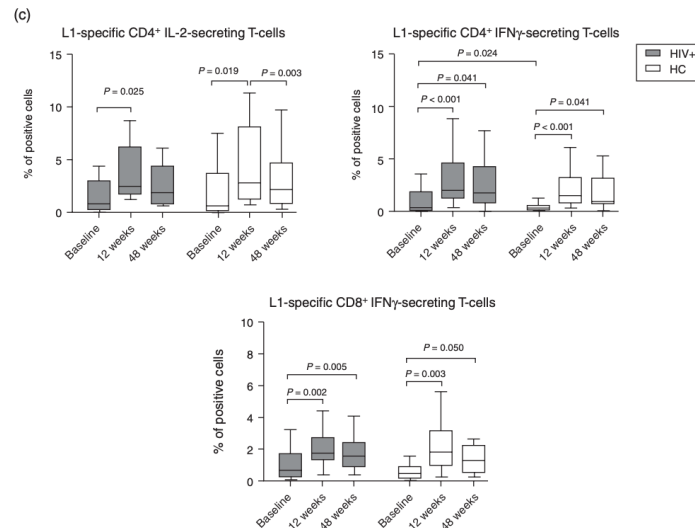
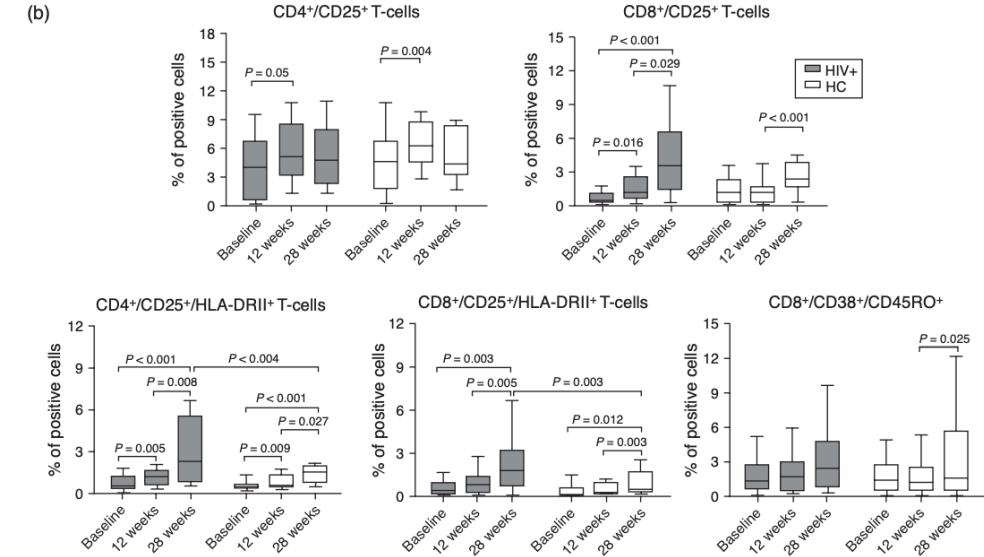
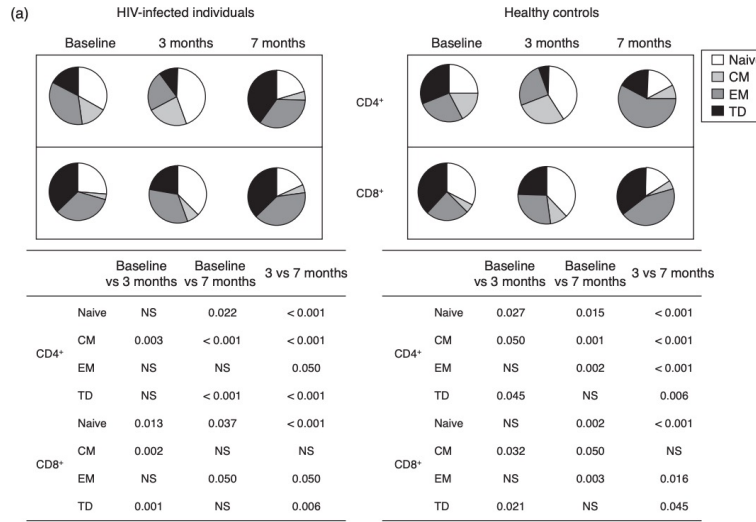


Figure 3: Age-specific prevalence of HPV16 (A) and HR-HPV (B) infection in four male risk groups. Error bars show 95% CIs. PRs were adjusted for study. HR-HPV includes HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. HPV=human papillomavirus. HR-HPV=high-risk HPV. MSM=men who have sex with men. MSW=men who have sex with women. aPR=adjusted prevalence ratio. \* Significant aPRs relative to the reference group.

Wei, Lancet HIV, 2021

# HPV vaccine in PLWH elicits immune responses

- three-dose QHPV vaccination
- N=46 adolescents and young adults



# HPV vaccine effectiveness in Women LWH, yet Low Coverage Globally

**Table 5. Comparison to Unvaccinated Historical Women Living With Human Immunodeficiency Virus**

| Endpoint        | Unvaccinated Historical WLWH (Canadian Women's HIV Study) | Vaccinated WLWH (Present study)    |
|-----------------|-----------------------------------------------------------|------------------------------------|
|                 | Rate per 100 Person-Years (95% CI)                        | Rate per 100 Person-Years (95% CI) |
| Persistent qHPV | 6.0 (4.6–7.7)                                             | 2.3 (1.1–4.1)                      |
| Genital warts   | 2.9 (2.1–3.9)                                             | 2.3 (1.2–4.1)                      |
| CIN2+           | 1.0 (0.5–1.9)                                             | 0 (0.0–0.9)                        |

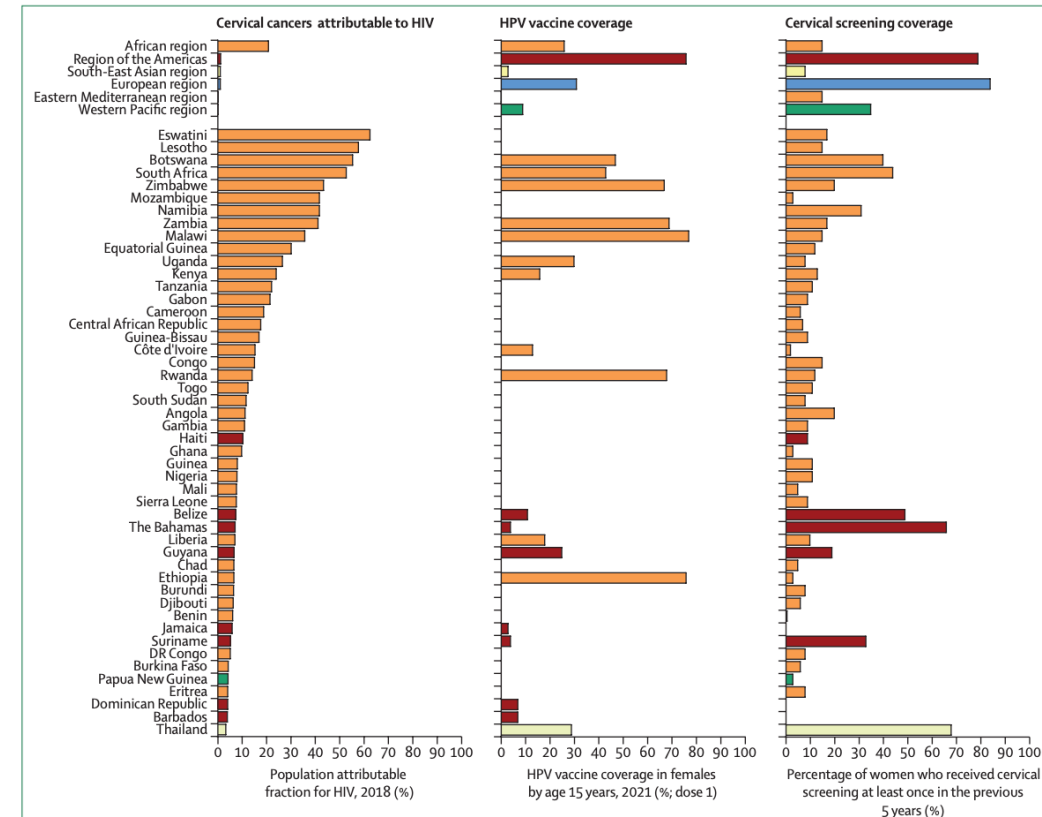
Abbreviations: CI, confidence interval; CIN2+, cervical intraepithelial lesion of grade 2 or higher; HIV, human immunodeficiency virus; qHPV, quadrivalent human papillomavirus (HPV6/11/16/18); WLWH, women living with HIV.

McClymont, CID, 2019

Strong reduction in the risk of persistent cervical HPV infections has also been seen in HPV-vaccinated WLWH

## Key messages

- Ensuring the UNAIDS 95-95-95 targets for HIV testing, treatment, and viral suppression are met will be crucial for WHO's cervical cancer elimination strategy to succeed, given the higher risk of cervical cancer in women with HIV
- Current HPV vaccine coverage is inadequate in low-income and middle-income countries with high HIV burden, with monitoring needed to confirm whether two-dose or single-dose HPV vaccination schedules are protective for people with HIV
- There is an urgent need to determine optimal cervical screening and triage algorithms that are rapidly scalable for populations of women with HIV in low-income and middle-income countries, who have a high prevalence of oncogenic HPV
- Cervical cancer service integration with antiretroviral therapy services can offer crucial opportunities to expand accessible care for women with HIV
- The inclusion of HIV status as a required variable in population-based cancer registries in high HIV burden settings will be essential to monitor progress towards cervical cancer elimination for women with HIV
- Making gender equity a central tenet of cervical cancer interventions will be essential to meeting the ambitions of the WHO cervical cancer elimination strategy



## No woman left behind: achieving cervical cancer elimination among women living with HIV

Kirihano Sharma\*, Dorothy A Machalek\*, Zheng Q Toh, Demisew Amenu, Mazvita Muchengeti, Andrew K Ndlovu, Alex Mremi, Bariki Mchome, Andrew J Vallely, Lynette Denny, Helen Rees, Suzanne M Garland

Cervical cancer is the fourth most common malignancy in women of reproductive age globally. The burden of this disease is highest in low-income and middle-income countries, especially among women living with HIV. In 2018, WHO launched a global strategy to accelerate cervical cancer elimination through rapid scale-up of prophylactic vaccination, cervical screening, and treatment of precancers and cancers. This initiative was key in raising a call for action to address the stark global disparities in cervical cancer burden. However, achieving elimination of cervical cancer among women with HIV requires consideration of biological and social issues affecting this population. This Position Paper shows specific challenges and uncertainties on the way to cervical cancer elimination for women living with HIV and highlights the scarcity of evidence for the effect of interventions in this population. We argue that reaching equity of outcomes for women with HIV will require substantial advances in approaches to HPV vaccination and improved understanding of the long-term effectiveness of HPV vaccines in settings with high HIV burden. Cervical cancer, just as HIV, is affected by social and structural factors such as poverty, stigma, and gender discrimination, that place the elimination strategy at risk. Global efforts must, therefore, be galvanised to ensure women living with HIV have optimised interventions, given their substantial risk of this preventable malignancy.

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Published Online  
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# HPV Vaccine effectiveness in Men LWH

Clinical Infectious Diseases

MAJOR ARTICLE



## A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected Adults Aged 27 Years or Older: AIDS Clinical Trials Group Protocol A5298

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Clinical Infectious Diseases

MAJOR ARTICLE



## High Prevalence of Anal High-Grade Squamous Intraepithelial Lesions, and Prevention Through Human Papillomavirus Vaccination, in Young Men Who Have Sex With Men Living With Human Immunodeficiency Virus

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Table 2. Vaccine Efficacy for Persistent Anal Infection, Persistent Oral Infection, Anal High-Grade Squamous Intraepithelial Lesions on Anal Biopsy, and Abnormal Anal Cytology

| Endpoint                                                                                             | Vaccine Group |           | Control Group |           | Efficacy<br>(95.1% Confidence Interval) |
|------------------------------------------------------------------------------------------------------|---------------|-----------|---------------|-----------|-----------------------------------------|
| Persistent anal infection                                                                            | n             | Endpoint  | n             | Endpoint  |                                         |
| mITT-including single detection at final visit                                                       | 286           | 27        | 283           | 33        | 22% (–31% to 53%)                       |
| mITT-persistent infection only                                                                       | 286           | 14        | 283           | 17        | 21% (–61% to 61%)                       |
| Per protocol analysis                                                                                | 276           | 7         | 277           | 10        | 31% (–82% to 74%)                       |
| Full ITT                                                                                             | 288           | 28        | 286           | 41        | 35% (–5% to 60%)                        |
| Persistent oral infection                                                                            |               |           |               |           |                                         |
| mITT-including single detection at final visit                                                       | 288           | 7         | 286           | 10        | 32% (–80% to 74%)                       |
| mITT-persistent infection only                                                                       | 288           | 1         | 286           | 8         | 88% (2% to 98%)                         |
| Per-protocol analysis                                                                                | 278           | 1         | 280           | 3         | 66% (–70% to 96%)                       |
| Full ITT                                                                                             | 288           | 6         | 286           | 14        | 58% (–9% to 84%)                        |
| Improvement of anal high-grade squamous intraepithelial lesions on anal biopsy outcomes <sup>a</sup> |               |           |               |           |                                         |
| Full ITT                                                                                             | 288           | 46        | 286           | 45        | 0% (–44% to 31%)                        |
| Abnormal anal cytology                                                                               |               |           |               |           |                                         |
| Week 52                                                                                              | 231           | 123 (53%) | 229           | 121 (53%) | 0% (–19% to 16%)                        |
| Week 104                                                                                             | 199           | 98 (49%)  | 198           | 108 (55%) | 9% (–10% to 25%)                        |
| Week 156                                                                                             | 130           | 58 (45%)  | 132           | 72 (55%)  | 17% (–6% to 35%)                        |

Abbreviations: ITT, intention-to-treat analysis; mITT, modified ITT analysis.  
<sup>a</sup>High-grade squamous intraepithelial lesions on anal biopsy specimens were not tested with human papillomavirus (HPV) DNA polymerase chain reaction to determine the causative HPV type.

Table 5. Low-Grade Squamous Intraepithelial Lesions or High-Grade Squamous Intraepithelial Lesions in the Merck 020 Per-Protocol Placebo Group Compared With the AMC-072 Per-Protocol Naive Vaccinated Group

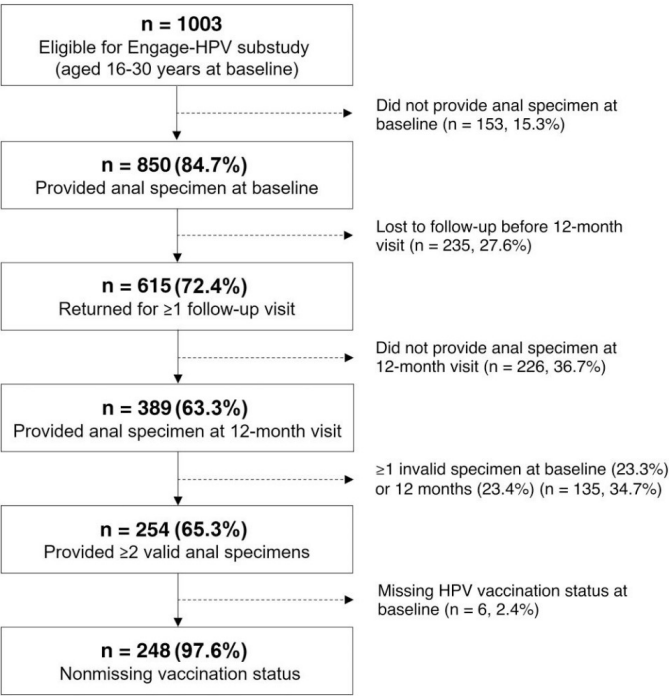
| Endpoint: Anal/<br>Perianal LSIL/HSIL <sup>a</sup><br>Related to | Per-Protocol Merck 020 Placebo Group <sup>b</sup> |                                 |                         |                                           | Per-Protocol AMC-072 Naive Vaccinated Group |                                 |                         |                                           | P <sup>c</sup> |
|------------------------------------------------------------------|---------------------------------------------------|---------------------------------|-------------------------|-------------------------------------------|---------------------------------------------|---------------------------------|-------------------------|-------------------------------------------|----------------|
|                                                                  | No. Included<br>in Analyses                       | No. of Affected<br>Participants | Person-Years<br>at Risk | Events per 100<br>Person-Years<br>at Risk | No. Included<br>in Analyses                 | No. of Affected<br>Participants | Person-Years<br>at Risk | Events per 100<br>Person-Years<br>at Risk |                |
| HPV6                                                             | 144                                               | 10                              | 298.5                   | 3.4                                       | 15                                          | 0                               | 25.0                    | 0.0                                       | .447           |
| HPV11                                                            | 144                                               | 6                               | 298.2                   | 2.0                                       | 35                                          | 0                               | 55.2                    | 0.0                                       | .361           |
| HPV16                                                            | 170                                               | 6                               | 341.9                   | 1.8                                       | 39                                          | 0                               | 65.4                    | 0.0                                       | .350           |
| HPV18                                                            | 193                                               | 4                               | 387.4                   | 1.0                                       | 47                                          | 0                               | 75.6                    | 0.0                                       | .490           |
| HPV6, 11, 16, or 18 <sup>d</sup>                                 | 208                                               | 24                              | 411.6                   | 5.8                                       | 58                                          | 0                               | 93.0                    | 0.0                                       | .008           |

Abbreviations: AMC, AIDS Malignancy Consortium; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; qHPV, quadrivalent human papillomavirus.  
<sup>a</sup>Analyses required having both histology and anal biopsy HPV DNA determination at a given visit. AMC-072 participants with qHPV type-specific AIN1 or perianal condyloma at baseline were removed (HSIL was an exclusion criteria); “baseline” DNA HPV type based on visits 0 and 3. Case counting occurred after month 7 at visits 4, 5, and/or 6.  
<sup>b</sup>The per-protocol Merck 020 placebo group were HIV-negative men who have sex with men, were naive for a given qHPV type, and did not have LSIL or HSIL at baseline.  
<sup>c</sup>Merck placebo and AMC-072 naive group comparison of event rates based on exact Poisson calculation (1-sided test).  
<sup>d</sup>Consistent with the reported Merck V503-020 combined endpoint, analysis of all participants who were eligible for ≥1 of the individual type-specific analyses. A participant would be counted more than once if multiple lesions of different HPV types developed.

See also: Wei, JID, 2023

# HPV vaccine effectiveness (anal HPV) in MSM

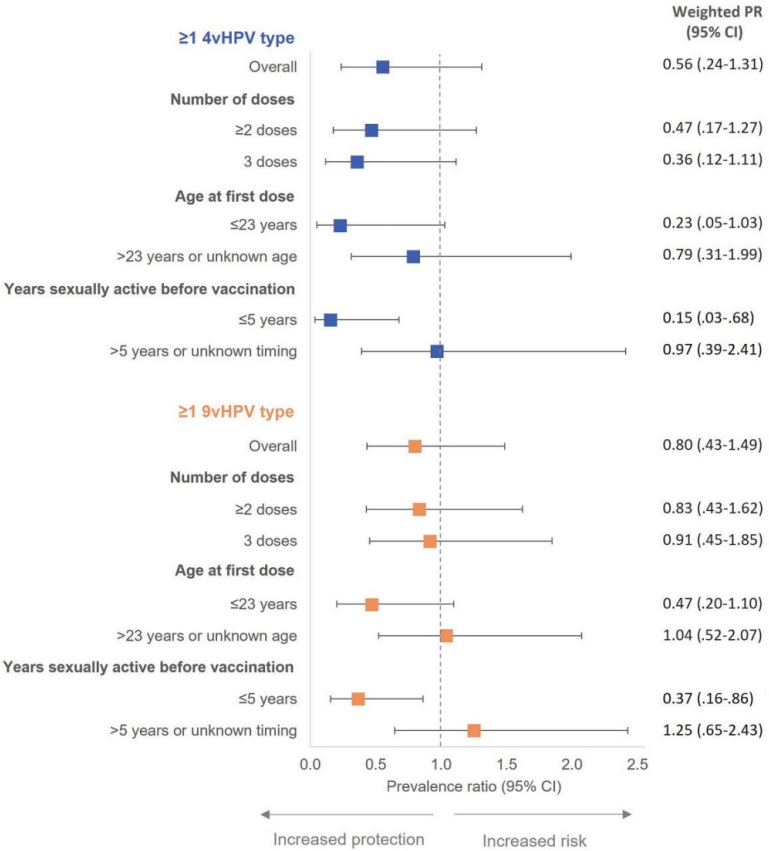
**N=13 HIV+**



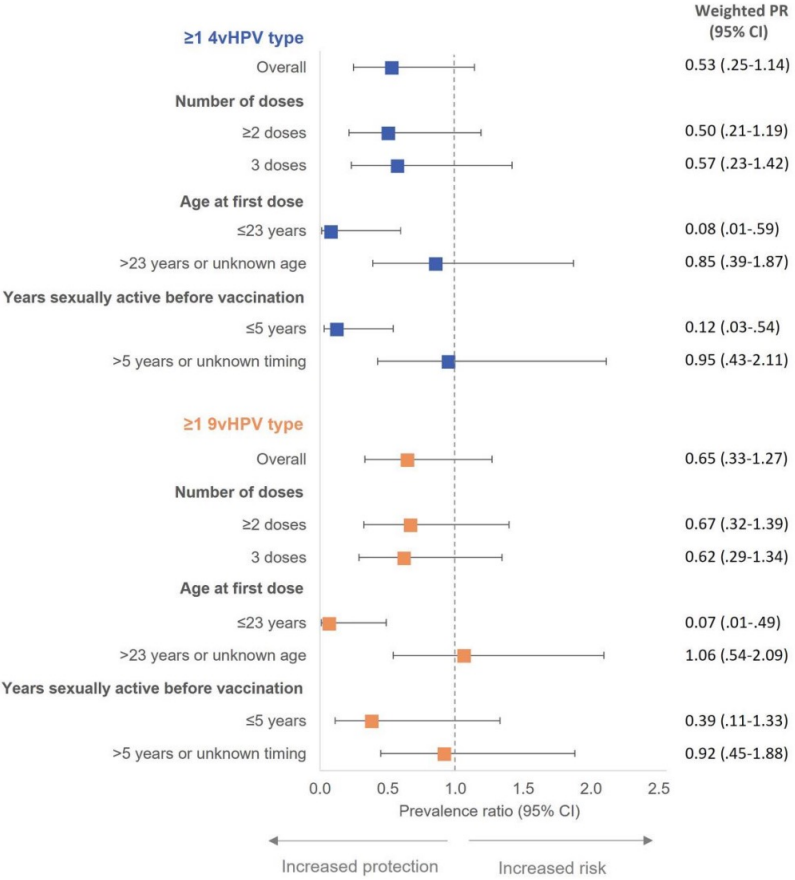
**Age, 16-30**

Chambers, JID, 2023

## IPTW-weighted prevalence ratios for 12-month cumulative incidence of anal HPV infection



## IPTW-weighted prevalence ratios for 12-month persistence of anal HPV infection



# Screening of HPV-related cervical dysplasia in Women LWH

|               | Assessment                            | At HIV diagnosis | Prior to starting ART | Follow-up frequency | Comment                                                                                                       | See page |
|---------------|---------------------------------------|------------------|-----------------------|---------------------|---------------------------------------------------------------------------------------------------------------|----------|
| <b>Cancer</b> | Mammography                           |                  |                       | 1-3 years           | Women 50-74 years                                                                                             | 59       |
|               | Cervical PAP or liquid based cytology |                  |                       | 1-3 years           | women with HIV > 21 years                                                                                     |          |
|               | Rectal exam and anoscopy              |                  |                       | 1-3 years           | MSM and persons with HPV-associated dysplasia. Evidence of benefit not known                                  |          |
|               | Ultrasound and alpha-fetoprotein      |                  |                       | 6 months            | Controversial; persons with cirrhosis and persons with HBV co-infection at high risk of HCC <sup>(xiii)</sup> |          |
|               | Prostate cancer (PSA)                 |                  |                       | 1-2 years           | Men > 50 years with a life expectancy >10 years                                                               |          |
|               | Others                                |                  |                       | As indicated        | Lung cancer and colorectal cancer screening according to local screening programmes                           |          |

# Diagnosis and screening of anal HSIL

Secondary prevention: identification and destruction of precursor lesions (aHSIL) to prevent progression to invasive cancer

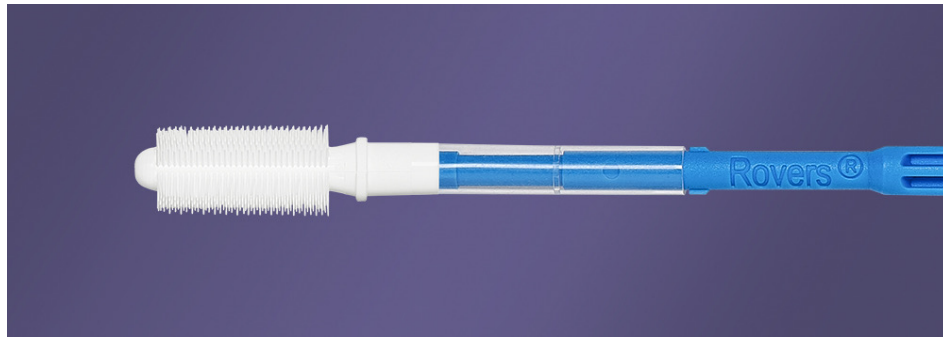
- 1) screening test
- 2) further evaluation of screen positives with a high-resolution anoscopy (HRA) to detect anal HSIL
- 3) treatment of HSIL to prevent progression to anal cancer

Debate regarding the efficacy of anal cancer prevention through aHSIL diagnosis and treatment was directly addressed by the ANal Cancer/HSIL Outcomes Research (ANCHOR) trial

# Anal Cancer Screening Tests

## Anal Pap smear

Liquid-based cytological brushing (ThinPrep<sup>®</sup>) with Anex<sup>®</sup> brush  
(+ HPV genotype testing)



- Anal cytology is collected through insertion of a moistened polyester swab 4–6 cm into the anal canal
- The swab is then withdrawn while applying gentle rotating circumferential pressure and eluted into a liquid transport medium
- Results are reported per the Bethesda nomenclature

# No well-defined evidence-based algorithm for interpretation and triage of abnormal results of anal cancer screening

Local practices based on local expert opinion and available resources

- anal cytology  $\pm$  HPV testing, with HRA triage of abnormal result
- HRA for all MSM living with HIV over a certain age cut-off
- proceeding directly to HRA in all persons living with HIV over age 35
- repeating anal cytology every 6 months, yearly, or every 2 years

# How to treat biopsy-confirmed aHSIL

- Treatment of anal HSIL is not standardized and is guided by available local resources and expertise
- No robust direct comparisons between different treatment options
  - treatments achieve similar results
  - recurrence remains problematic in high-risk populations
- Removal of the entire anal transformation zone would be a prohibitively morbid procedure
- Ablative methods
  - infrared coagulation (IRC), electrocautery treatment (EC), or CO2 laser therapy
- Topical methods
  - Imiquimod
  - 5-fluorouracil (5-FU)

# Does Every aHSIL Lesion Require Treatment?

The NEW ENGLAND JOURNAL of MEDICINE

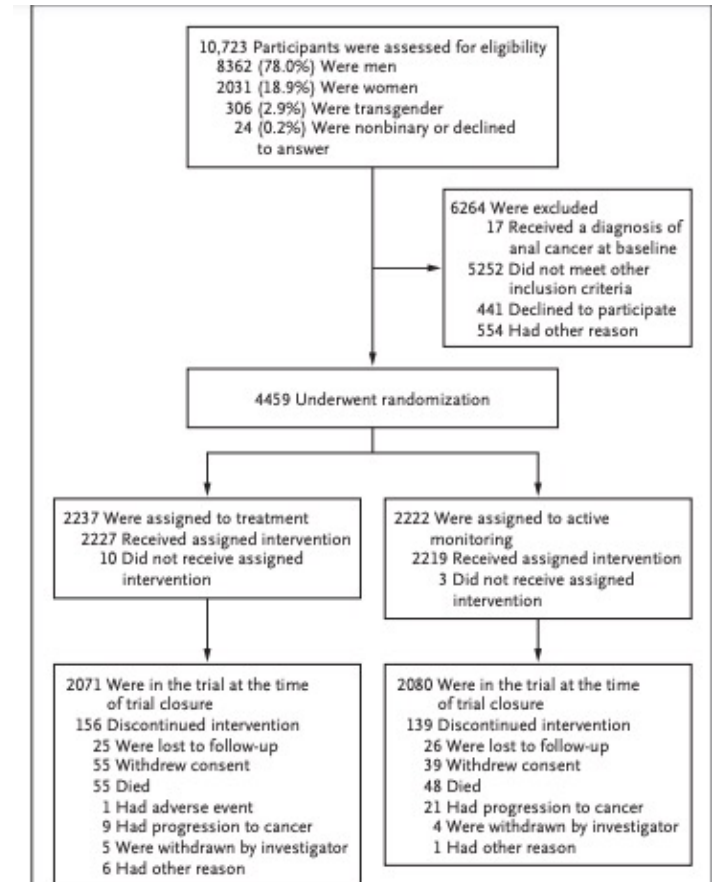
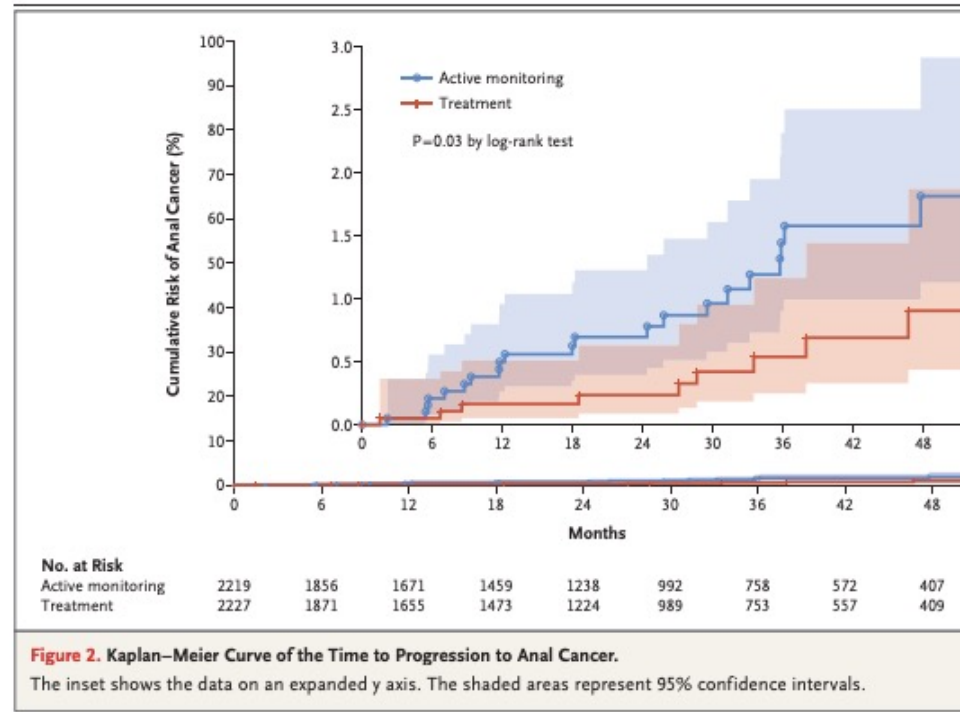
## ORIGINAL ARTICLE

### Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

N Engl J Med 2022;386:2273-82.  
DOI: 10.1056/NEJMoa2201048

- HIV+ > 35 yrs
- biopsy-proven anal HSIL
- randomly assigned, in a 1:1 ratio, to receive either HSIL treatment\* or active monitoring without treatment

\* ablative procedures (infrared coagulation, electrocautery, and laser), ablation or excision under anesthesia, and topical treatments (imiquimod and fluorouracil)

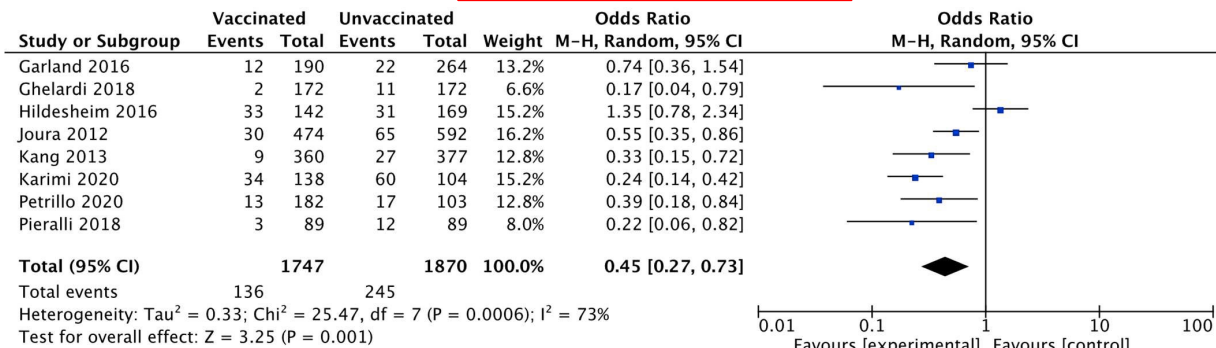


**Figure 1. Screening, Randomization, and Follow-Up.**

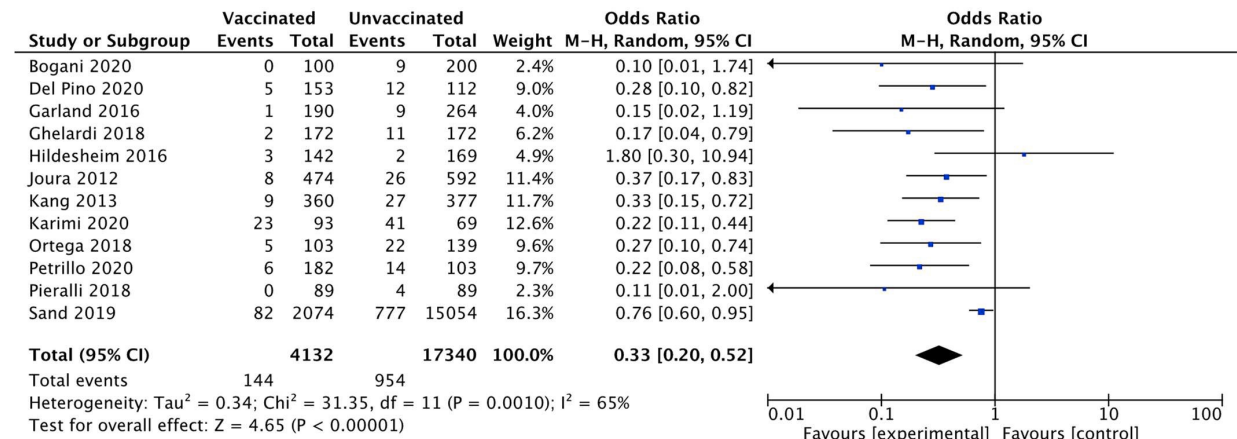
Of the six participants in the treatment group who discontinued the intervention for "other reason," two received a diagnosis of anal cancer but were ineligible for analysis and were discontinued from the trial because they were determined to have had anal cancer before randomization, three relocated to a nontrial site, and one received immunomodulatory agents after a kidney transplantation. Of the two participants in the active-monitoring group who discontinued the intervention for "other reason," both relocated to a nontrial site. A total of 25 of 2219 participants (1.1%) in the active-monitoring group were considered to be nonadherent because they had received treatment for anal high-grade squamous intraepithelial lesions at some time after randomization.

# Effectiveness of adjuvant HPV vaccination in CIN recurrence

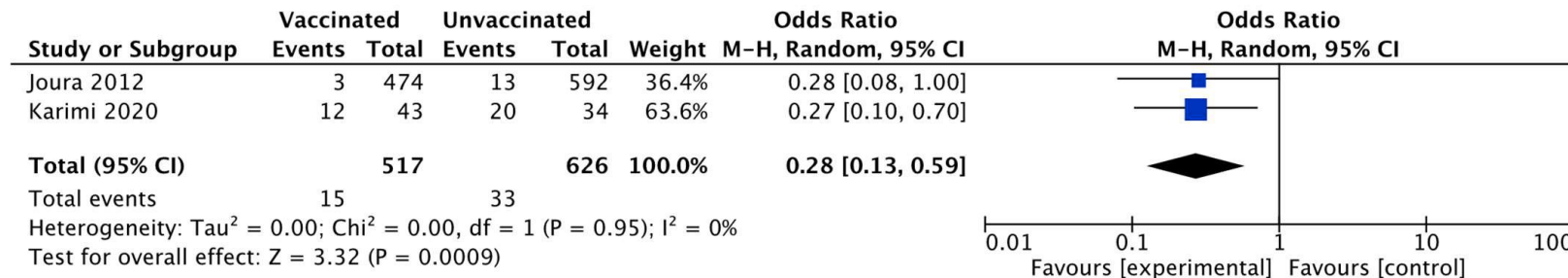
## CIN 1+ recurrence



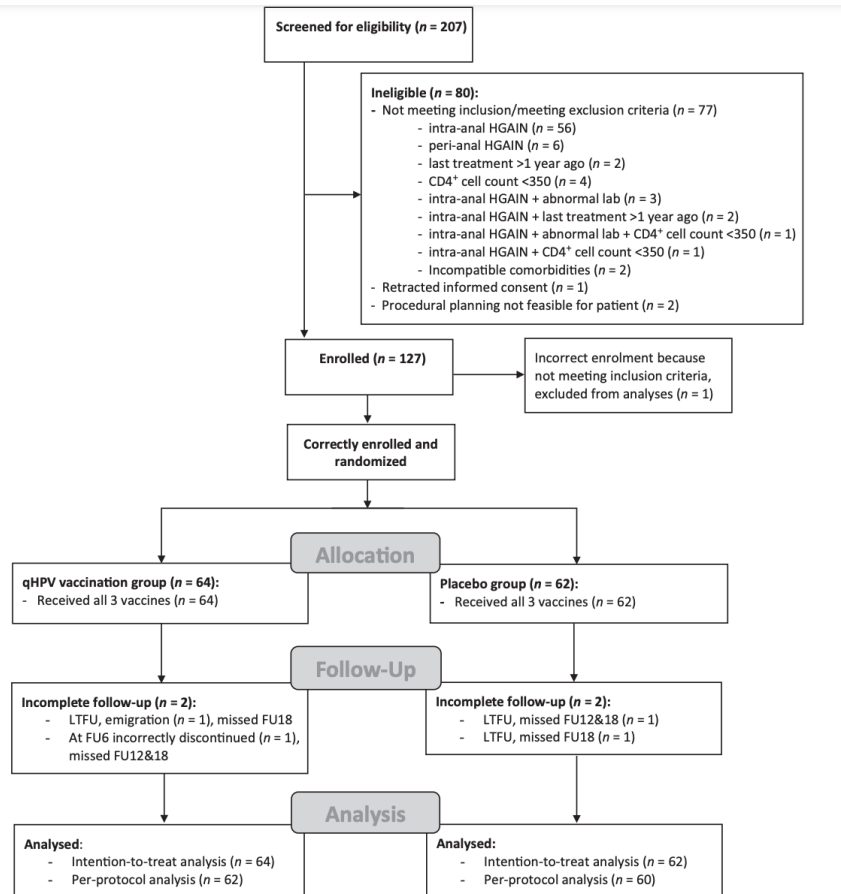
## CIN 2+ recurrence



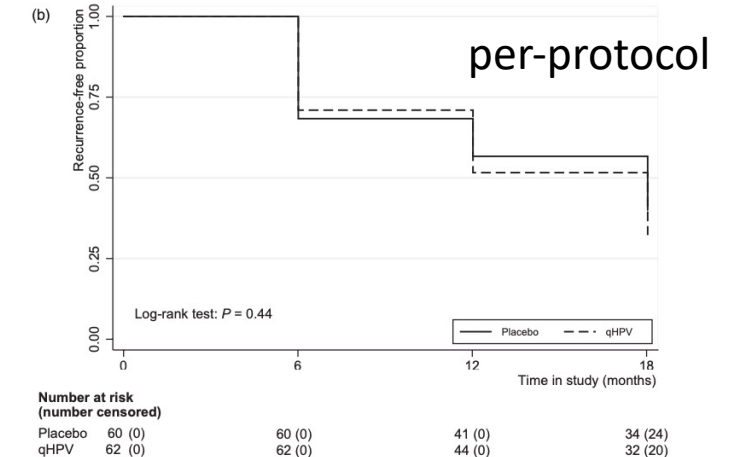
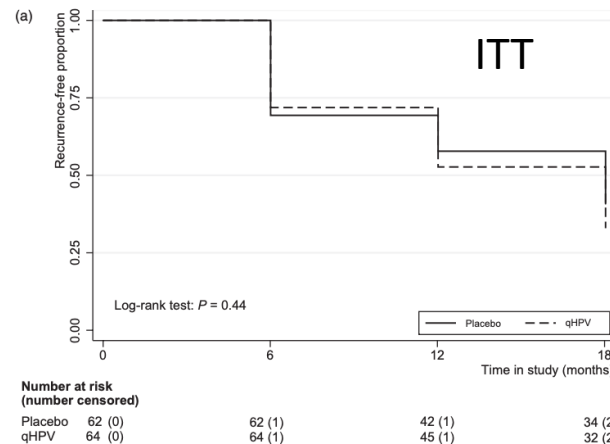
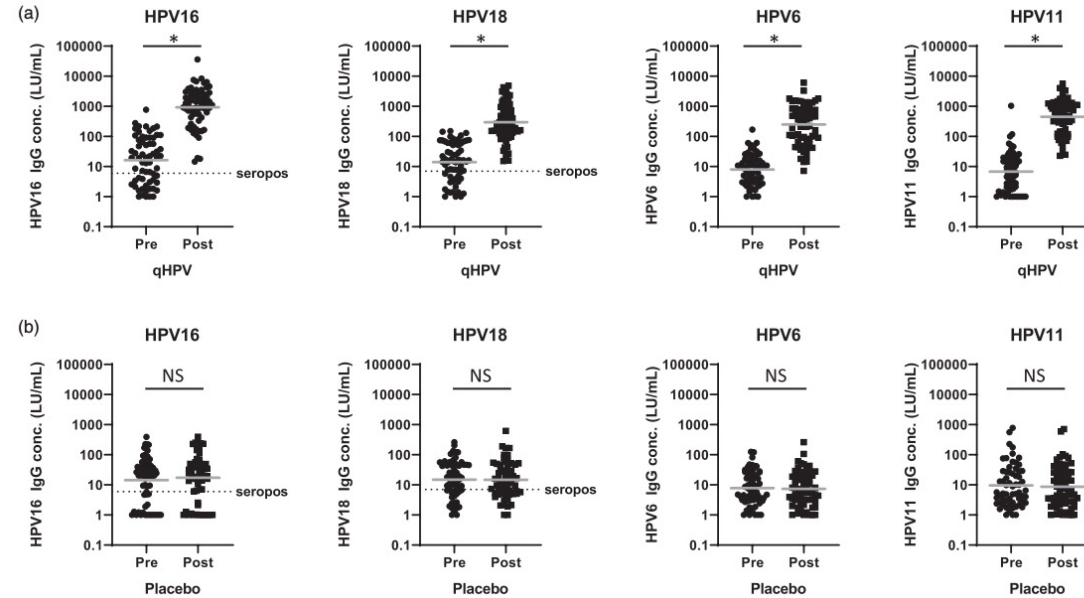
## CIN 3+ recurrence

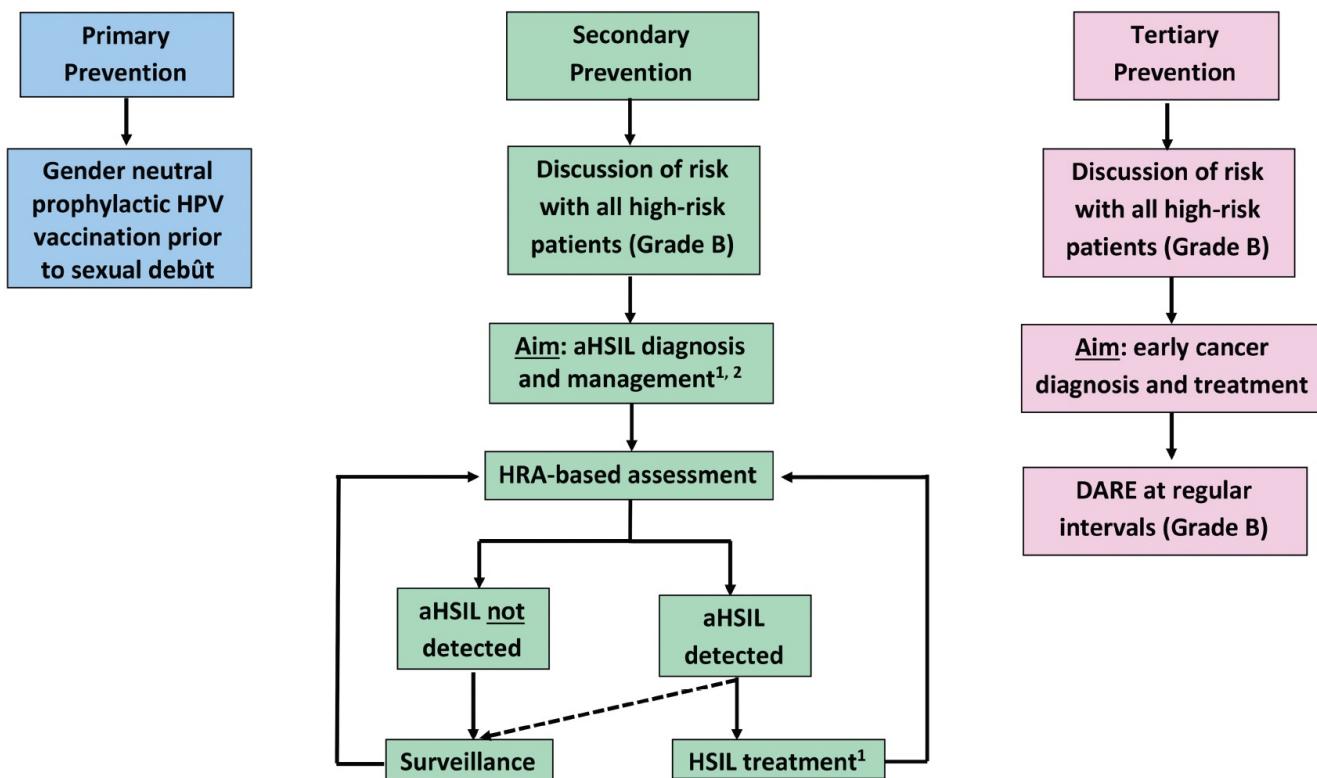


# Effectiveness of adjuvant HPV vaccination in AIN in Men LWH?



**Fig. 1. Trial profile.** FU, follow-up; HGAIN, high-grade anal intraepithelial neoplasia; LTFU, lost to follow-up; qHPV, quadrivalent human papillomavirus vaccine.





<sup>1</sup> Grade A for PLWH ≥ 35 yo

<sup>2</sup> Typically includes screening tests such as anal cytology +/- HPV testing

The DARE is a low cost and readily available exam that should:

- (1) be offered to all patients undergoing anal cancer screening;
- and (2) can be offered as tertiary prevention when HRA is unavailable

It is an integral part of every HRA exam as it supplements the information gained from cytology and biopsy

**Figure 2.** Strategies. Abbreviations: aHSIL, anal high-grade squamous intraepithelial lesions; DARE, digital anal rectal exam; HPV, human papillomavirus; HRA, High Resolution Anoscopy; PLWH, people living with HIV.

# Conclusions

- HPV in PLWH leads to increased cancer risk
  - multifactorial: role of behaviour, reduced HPV clearance, immunity
- Primary prevention through vaccination in early age
- Screening of HPV-related dysplasia (secondary prevention): many open issues:
  - diagnosis
  - treatment

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