Effect of Human Papillomavirus Vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA): A Randomized, Placebo-Controlled Trial

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Background

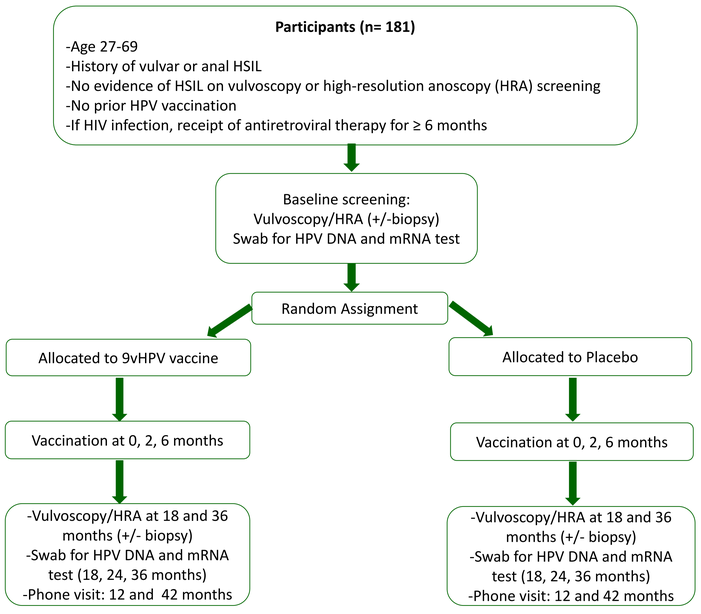
- Approximately 630,000 (5%) new cancers per year are attributable to human papillomavirus (HPV) infection worldwide, and more than 4,000 vulvar and 7,000 anal cancers are diagnosed annually in the U.S.
- Vulvar and anal high-grade squamous intraepithelial lesions (HSIL) are cancer precursors caused by HPV with the potential to progress to invasive cancer.
- ~30-50% of vulvar and anal HSIL recur following initial treatment.
- Recurrent lesions require multiple treatments leading to substantial morbidity, psychosocial trauma, and high medical expenses.
- The 9-valent HPV (9vHPV) vaccine (Gardasil-9) protects against infection when administered to HPV-naïve persons. Data evaluating a therapeutic benefit of the 9vHPV vaccine have been mixed.

Study Aims

- Primary Aim: to test whether the 9vHPV vaccine (Gardasil-9) will lead to a 50% reduction of recurrent HSIL compared with unvaccinated persons previously treated for vulvar or anal HSIL.
- Secondary Aims: to assess vaccine safety.

Study Design

- Study sites: University of Washington/Fred Hutch Cancer Research Center (Seattle, WA) and University of Alabama at Birmingham (Birmingham, AL)



References: Seer.cancer.gov/statfacts/html/anus.html, Seer.cancer.gov/statfacts/html/vulvar.html.; Stankiewicz Karita HC, Hauge K, et al. Effect of HPV vaccine to Interrupt Recurrence of Vulvar and Anal Neoplasia (VIVA): A Trial Protocol. JAMA Netw Open, 2019;2(4):e190819; CDC/Cancers associated with HPV in the United States

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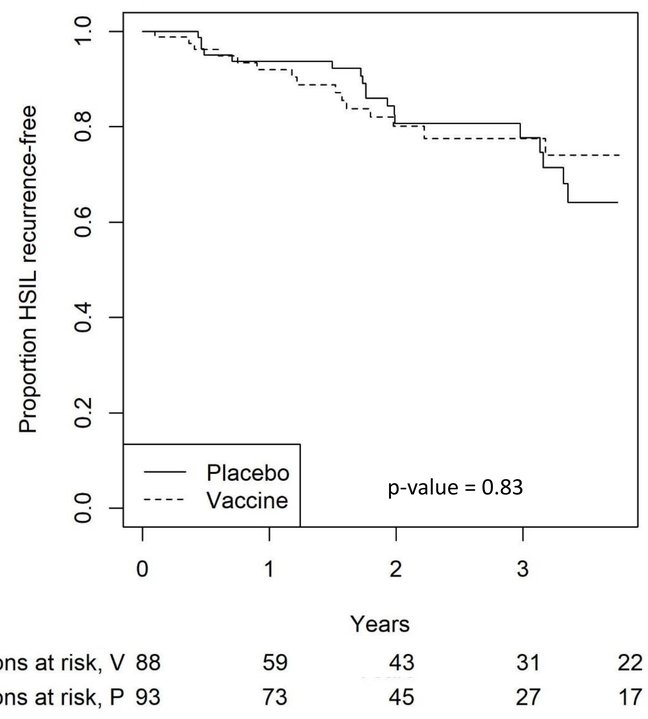
Results

Table 1. Baseline characteristics of randomized participants

	9vHPV vaccine (n=88)	Placebo (n=93)	Total (n=181)
Age (years), mean			
at HSIL diagnosis	51	53	52
at study enrollment	53	55	54
HSIL anatomic site			
Vulvar	38 (43%)	40 (43%)	78 (43%)
Anal	50 (56%)	53 (56%)	103 (56%)
HIV status			
Positive	32 (36%)	39 (41%)	71 (39%)
Negative	56 (63%)	54 (58%)	110 (60%)
Time since initial HSIL diagnosis			
< 12 months	22 (25%)	25 (26%)	47 (25%)
>12 months	66 (75%)	68 (73%)	134 (74%)

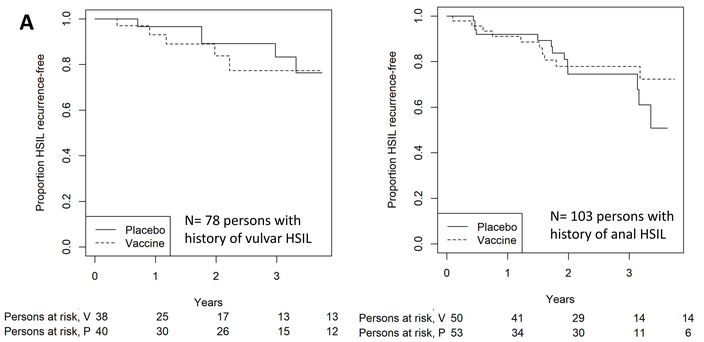
Figure 1. Kaplan-Meier Curve for overall histologically-confirmed HSIL recurrences for 9vHPV vaccine vs. placebo recipients



- HSIL cases: **15/88 (17%)** recurrent cases in 9vHPV vaccine group vs. **18/93 (19%)** cases in placebo group
- HSIL incidence **9.1/100 person-years** in 9vHPV vaccine group vs. **10.0/100 person-year** in placebo group; p= 0.83
- The DSMB recommended stopping the study early because of futility at interim analysis

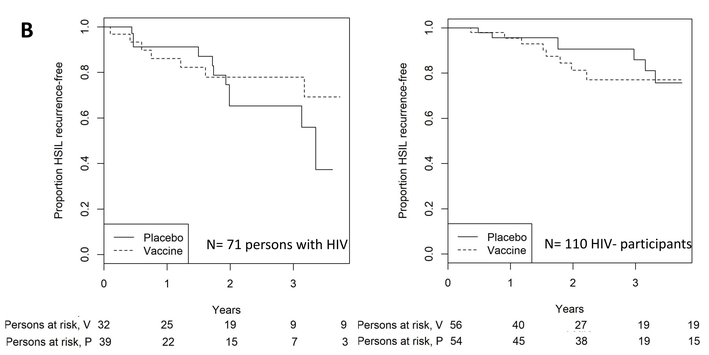
Results

Figure 2. Kaplan-Meier Curve for HSIL recurrences for 9vHPV vaccine vs placebo recipients by anatomical site (A) and by HIV infection status (B)



Vulvar HSIL group: HSIL incidence **5/66 (7.6%)** in 9vHPV vaccine vs. **5/82 (6.1%)** in placebo group

Anal HSIL group: HSIL incidence **10/99 (10.1%)** in 9vHPV vaccine vs. **13/97 (13.3%)** in placebo group



HIV group: HSIL incidence **7/62 (11.3%)** in 9vHPV vaccine group vs. **11/64 (17.2%)** in placebo group

HIV- group: HSIL incidence **8/103 (7.7%)** in 9vHPV vaccine group vs. **7/116 (6.0%)** in placebo group

9vHPV Vaccine Safety

- Overall, there were 36 serious adverse events (SAEs): 20 SAEs in 9vHPV vaccine recipients and 16 SAEs in placebo recipients; none were related or possibly related to the 9vHPV vaccine.
- There were 3 possibly vaccine-related severe adverse events (Grade 3 AEs); all reported among placebo recipients (fatigue in one person and a throbbing big toe and throbbing collar bone in another.

Conclusions

- This study is the first to assess a therapeutic use of the 9vHPV vaccine that included persons without HIV infection and persons with a history of vulvar HSIL.
- We found no benefit of the 9vHPV vaccine for prevention of recurrence in persons with prior vulvar or anal HSIL; no differences were found between anatomical site or HIV status.
- The 9vHPV was safe and well-tolerated.
- Our study underlines the importance of HPV prevention with prophylactic HPV vaccines and the need for novel therapeutic vaccines and antivirals to manage prevalent HSIL that have a high potential to recur.