IMMUNOGENICITY AND SAFETY OF THE NINE-VALENT HUMAN PAPILLOMAVIRUS VACCINE IN SOLID ORGAN TRANSPLANT RECIPIENTS AND HIV-INFECTED ADULTS.

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Summary: The nine-valent HPV vaccine has not yet been evaluated in HIV-infected persons and transplant recipients. We found that the immunogenicity of the vaccine is excellent in HIV patients but suboptimal in SOT patients. The vaccine is safe in both groups.

Abstract

Background

The burden of human papillomavirus (HPV) in HIV-infected persons and solid organ transplant (SOT) recipients is high. Clinical trials on HPV vaccines in HIV-infected persons and particularly in SOT recipients have been sparse to date, included low numbers of participants and none of them assessed the nine-valent HPV (9vHPV). We investigated the immunogenicity with respect to HPV types 6/11/16/18/31/33/45/52/58 and the safety of the 9vHPV vaccine in HIV-infected persons and recipients of a kidney, lung or heart transplant.

Methods

This is a phase III investigator-initiated study in 100 HIV-infected persons (age: 18-45 years) and 171 SOT recipients (age: 18-55 years). The 9vHPV vaccine was administered at day 1, month 2 and month 6. Primary outcome was seroconversion rates to the 9vHPV types at month 7. Secondary outcomes were geometric mean titers (GMTs) and frequency of adverse events (AEs).

Results

All HIV-infected participants seroconverted for all HPV types, but seroconversion ranged from 46% for HPV45 to 72% for HPV58 in SOT recipients. GMTs ranged from 180 to 2985 mMU/ml in HIV-positive participants and from 17 to 170 mMU/ml in SOT recipients, depending on the HPV type. Injection-site AEs occurred in 62% of participants but were mostly mild or moderate in intensity. None of the reported serious adverse events were deemed vaccine-related. No patients died during the study.

Conclusion

Immunogenicity of the 9vHPV vaccine is high in HIV-infected persons but suboptimal in SOT recipients. The vaccine is safe and well tolerated in both groups.

Key words: Human papillomavirus, nine-valent vaccine, HIV-infected persons, solid organ transplant recipients

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted disease and causes about 5% of all cancers worldwide. HPV causes not only cervical cancer but also anal, vaginal, vulvar, penile and oropharyngeal and mouth cancers [1].

Compared to healthy persons, HPV tends to persist longer among HIV-infected persons and solid organ transplant (SOT) recipients due to decreased CD4+ counts and immunosuppressive treatment, respectively. This leads to more frequent genital warts and HPV-related cancers [2–4]. A meta-analysis reported incidence rates of HPV-cancers that are 6.5 times higher for vaginal cancer and 28.8 times higher for anal cancer in HIV-infected persons; and 15.8 times higher for penile cancer and 22.8 times higher for vaginal cancer in solid organ transplant (SOT) recipients compared to the general population [5].

So far, three preventive HPV vaccines have been authorized: a bivalent vaccine against HPV types 16 and 18, a quadrivalent vaccine (qHPV) against HPV types 6/11/16/18, and a 9vHPV vaccine (9vHPV) against HPV types 6/11/16/18/31/33/45/52/58. Compared to the qHPV vaccine, the 9vHPV vaccine contains five additional Virus-Like-Particles (VLPs) of oncogenic HPV types [6]. The 9vHPV vaccine proved to have more than 95% efficacy in healthy in boys and girls (9 to 15 years of age) and men and women (16 to 26 years of age) [7–10].

Many countries recommend HPV vaccination in young girls and some also in boys. Additionally, some countries like the United States and Belgium recommend HPV vaccination for immunocompromised individuals (including those with HIV infection) [11,12]. However, studies on HPV vaccination in HIV-infected persons and SOT recipients are scarce and none of these studies have evaluated the 9vHPV vaccine yet. The few published studies on the bivalent or qHPV vaccine showed suboptimal immunogenicity in adult SOT recipients but results were better in HIV-infected patients with a reasonable CD4-count (>200 cells/mm²) [13,14]. In the current study, we assessed the immunogenicity and safety of a 9vHPV vaccine in both HIV-infected persons and SOT recipients.

Materials and methods

Study design and population

This is a single center, open-label, investigator-initiated phase III study (protocol V503-044-IC, NCT03525210) in HIV-infected persons and SOT recipients to evaluate the immunogenicity with respect to HPV types 6/11/16/18/31/33/45/52/58 and safety/tolerability of the 9vHPV vaccine (Gardasil®9 (Merck Sharp & Dohme (MSD))). One hundred HIV-infected persons (age: 18-45 years) and 171 SOT (kidney, heart, lung transplant) recipients (age: 18-55 years) were enrolled between April 2018 and January 2019 in the outpatient clinic of the University Hospitals Leuven, Belgium (Figure 1). We allowed older ages in the SOT group to avoid recruitment issues since the SOT recipients followed in the hospital were generally older than the HIV-infected persons and because SOT recipients remain at increased risk for persistent HPV-infection at a later age due to immunosuppressive treatment. The university hospital is a tertiary referral hospital in which approximately 900 HIV-infected persons and 415 heart, 590 lung, and 700 kidney transplant recipients were followed at study onset. All participants had to be in a stable health condition apart from being infected with HIV or having a solid organ transplant. Further requirements for inclusion were no history of previous HPV vaccination, positive HPV test, positive Papanicolaou (pap) test or any HPV-related disease. To facilitate recruitment and since we assess baseline seropositivity, a protocol modification in January 2019 allowed a history of genital warts in HIV-infected persons. In addition, HIV-infected participants were required to have a CD4+ T cell count of at least 200 cells/µl at the latest check-up (< 16 months ago). Organ transplantation had to be performed at least 12 months prior to the first vaccination and the SOT recipients could not have had an acute rejection in the 6 months prior to the first vaccination. Signed informed consent was obtained from all participants. The study was approved by the Ethics Committee Research of UZ/KU Leuven, Belgium (S60879).

Vaccine

The 9vHPV vaccine was administered intramuscularly in a 0,1,6 months schedule. A urine pregnancy test was taken before each vaccination in female participants.

Immunogenicity assessment

The primary immunogenicity outcome of this study was seroconversion, which is a change in serostatus of anti-HPV antibodies from seronegative at baseline to seropositive at month 7. The secondary outcome was geometric mean titers (GMTs). Serology testing was performed on serum samples collected at day 1 and month 7 using a competitive Luminex® immunoassay (cLIA), as previously described [15]. Patients were defined as seropositive for anti-HPV 6/11/16/18/31/33/45/52/58 if they had titers above 50/29/41/59/29/22/15/20/15 milli Merck Units (mMU), respectively.

Immunogenicity of the 9vHPV vaccine was assessed using the per-protocol-immunogenicity (PPI) population. This included all patients who received three vaccine doses of 9vHPV vaccine within pre-specified acceptable intervals, were seronegative to a particular HPV type at baseline, had serology results based on serum samples collected within pre-specified acceptable day ranges and had no other protocol deviations that could interfere with the subject's immune response to the 9vHPV vaccine. Data on the all type-specific naïve subjects with serology (ANSS) population are added in supplementary materials. For the ANSS population, protocol deviations that could interfere with the subject's immune response were not taken into account.

Safety assessment

Patients were observed for 15 minutes after each vaccination for immediate reactions. Solicited injection-site adverse events (AEs) and daily evening temperatures were recorded on diary cards from day 1 until day 5 following each vaccination and solicited systemic and other AEs from day 1 to day 15. Serious adverse events (SAEs) were recorded throughout the study (from day 1 until month 7). All patients who received at least one dose and who had safety follow-up data for at least one dose of the vaccine, were included in the safety analysis.

Statistical analysis

A sample size of 100 HIV-infected participants was calculated based on the expectation of having at least 80% seronegative samples for each of the 9 HPV types prior to vaccination. This allowed to estimate an anticipated seroconversion rate of 95-99% for HPV types 6, 11 and 16 with a margin of error of ± 4.8% - 2.2%, and an anticipated seroconversion rate of 90% for HPV type 18 with a margin

of error of ±6.6% [16]. Further, a sample size of 170 SOT patients was calculated based on an expected seroconversion rate of 60% and a desired precision of ±7.5% [14].

Seroconversion rates for HPV types 6/11/16/18/31/33/45/52/58 and GMTs are listed with exact binomial 95% confidence intervals (95%CI). Predictors of seroconversion were assessed with multiple logistic regression in the SOT patients. In the HIV group we analysed predictors of the log transformed titres with multiple linear regression analysis since all subjects were seropositive after vaccination.

The prevalence of AEs and safety measures is given with an exact binomial 95% CI and compared with historical controls using an exact binomial test for proportions. Since the majority of enrolled patients were male (75%) and the safety profile of the 9vHPV vaccine has been shown to be more dependent on gender than on age,[17] historical safety data from males between 16 and 26 were used as comparator [18]. A test probability of 5% was considered statistically significant. All data were analysed with R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria, 2019).

Results

Patient characteristics

In total 287 patients were screened of whom 271 were enrolled in the study, 100 in the HIV group and 171 in the SOT group (56 with a renal transplant (RTX), 57 with a heart transplant (HTX), and 58 with a lung transplant (LTX)) (figure 1). Table 1 shows the baseline characteristics of the patients in each group. The mean age at the first visit was 38.9 years in the HIV group and 46.7 years in the SOT group. In total, 85.0% were male in the HIV group and 69.0% in the SOT group.

In the HIV group 8% had history of genital warts. One person from the SOT group had a history of genital warts which was only revealed at visit 2 and was subsequently excluded from the PPI analysis. Among the HIV-infected subjects, 99% had plasma RNA levels below the detection limit (<1,6 log copies/ml) and 98% used antiretroviral therapy (ART) at time of the first vaccination. In the SOT group, the most frequently used immunosuppressive agents were mycophenolate mofetil (90.1%), tacrolimus (73.1%) and methylprednisolone (48.5%) and most patients (98.2%) used a combination of two or three agents (table 1).

Overall, 75.0% of HIV-infected participants and 27.5% of SOT patients were seropositive at baseline for at least one vaccine HPV type. In the HIV group, the seropositivity rate for each individual HPV type was more than 15%, except for HPV52 (6%), and reached 34.0% for HPV6. In contrast, seropositivity at baseline was below 10% for all HPV types in the SOT group.

Immunogenicity

Table 2 shows GMTs and seroconversion rates of the PPI population. Whereas all HIV-infected participants seroconverted for all HPV types, seroconversion ranged from 46% for HPV45 to 72% for HPV58 in SOT recipients. Seroconversion rates were particularly low in lung transplant patients for HPV types 18 (38%), 31 (43%), and 45 (32%). The GMTs ranged from 180 to 2985 mMU/ml in HIV-infected participants and from 17 to 170 mMU/ml in SOT recipients, depending on the HPV type. GMTs and seroconversion rates of the ANSS population are comparable (supplementary table 1).

Table 3 shows the predictors of seroconversion in SOT recipients of the PPI population. Since this could not be assessed in the HIV group, because all patients seroconverted, predictors of log transformed titers are given. In the HIV group, significant higher log titers were reached in patients with an African origin compared to Caucasians for all HPV type except 6 and 11. There was no clear effect of the CD4 count, except for lower titers with increased CD4-count for HPV45. In the SOT group, seroconversion was higher in women for HPV31 and decreased with higher BMI for HPV6. Moreover, seroconversion was lower for all studied HPV types when the patient received mycophenolate mofetil or tacrolimus, albeit only significant for mycophenolate mofetil.

Inclusion of data from patients who were seropositive at baseline in the multiple linear regression models, with an additional dichotomous variable for seropositivity at baseline, showed higher log titers in participants who were seropositive at baseline (supplementary table 3). This was significant for all HPV types, except for HPV52 in the HIV group (p=0.6). Month 7 GMTs were also 1.2 to 2.6-fold higher in HIV-infected participants and 3.0 to 12.5-fold higher in SOT recipients who were seropositive at baseline. The description of Day 1 and Month 7 GMTs in patients who were seropositive at baseline is provided as supplementary data (supplementary table 2).

Safety

A summary of the AEs that occurred within 15 days after vaccination is given in table 4. Over the course of the study, 80.8% of the HIV-infected participants and 74.7% of SOT recipients reported at least one AE within 15 days after vaccination. The most commonly reported AEs were injection-site AEs, which occurred in 69.7% of HIV-infected participants and 57.6% of SOT recipients. It included pain, swelling and erythema and was reported by 67.7%, 7.1%, and 10.1% of HIV-infected participants and 54.7, 8.2%, and 5.9% of SOT recipients, respectively. Injection-site AEs were mostly mild or moderate in intensity. Vaccine-related systemic AEs were reported by 24.4% of HIV-infected participants and 20.6% of SOT recipients. Headache was the most prevalent vaccine-related systemic AE and was reported by 9.1% of HIV-infected participants and 8.2% of SOT recipients.

SAEs are listed by patient group in table 5. Overall, eight SAEs were reported within 15 days after vaccination. All these SAEs occurred in the SOT group. Throughout the study, 58 SAEs were reported, of which 54 occurred in the SOT group. Within the SOT group, hospitalization due to infection was the most frequently reported SAE (10.6%). None of the SAEs were considered vaccine-related.

None of the six study discontinuations were due to adverse events. No patients died during the study. One patient became pregnant during the study and was subsequently excluded by the investigator. The pregnancy resulted in a live birth with no known congenital abnormalities.

The safety profile of Gardasil®9 is generally similar to that of healthy historical controls, but injection-site reactions were reported less frequently compared to historical controls (69.7 % in the HIV group, 57.6% SOT group and 79.0 % in the historical controls, $p<0.05$ for HIV and, $p< 0.001$ for SOT) (Table 4).

Discussion

This is the first study that reports on safety and immunogenicity of a 9vHPV vaccine in HIV-infected persons and SOT recipients. All HIV-infected participants seroconverted after vaccination whereas among SOT recipients, seroconversion ranged from about 45% to 70% depending on the HPV type. The 9vHPV vaccine was safe and well-tolerated in both patient groups.

All participants in the HIV group had a CD4-count of at least 200 cells/µl, and had viral loads below the detection limit. This is known to contribute to better immunogenicity,[19] which is likely why they all seroconverted as reported in healthy women and men between the age of 16 and 26 years [7–10].

Similarly, high seroconversion rates were also found in a study with a qHPV vaccine in HIV-infected women aged 13 to 45 years with CD4+ counts above 200 cells/µl. They found seroconversion rates of 95% to 100% for HPV6, HPV11, and HPV16 and from 85% to 100% for HPV18 [16].

The log titers in our study were generally higher in HIV-infected participants of African origin compared to Caucasian participants. This is in agreement with findings from a study with the qHPV vaccine in men between the 16 and 26 years [20].The absence of a clear effect of CD4-count in one direction for all HPV types in our study might be due to the inclusion of patients with CD4-counts of over 200 cells/µl only.

The observed seroconversion rates and GMTs in SOT patients are noticeably lower compared to data from 16 to 26 year old healthy adults [7–10]. So far, only four studies have reported the immunogenicity of HPV vaccines in SOT patients, and all concerned the qHPV vaccine [14,26–28]. These studies included only 17 to 47 transplant patients and results were inconsistent. One study assessed seroconversion in adult SOT patients and found 63%, 68%, 63.2%, and 52.6% seroconversion for HPV6/11/16/18, respectively, which is similar to the seroconversion rates of 64%, 71%, 69%, and 52%, found with the 9vHPV vaccine in our study [14]. The seroconversion rates were particularly low in lung transplant patients who are usually more immunosuppressed and who took a combination of three immunosuppressive agents more often compared to kidney and heart recipients. Unsurprisingly, the use of mycophenolate mofetil deteriorated seroconversion and log titers and the use of tacrolimus decreased log titers of HPV6/16/18/31/58. Similarly, Kumar et. al found that failure to seroconvert was associated with higher serum levels of tacrolimus [14]. We could not test the effect of use of other immunosuppressive drugs in our statistical models due to the lack of a sufficiently large number of observations. Future research should assess whether a supplemental dose of the 9vHPV vaccine in SOT patients would increase immunogenicity in patients who did not seroconvert. Even though the immunogenicity with the 3-dose regimen is suboptimal, we still believe that vaccination of SOT patients is beneficial given the high burden of HPV disease. More attention should also be paid to pre-transplant vaccination, which we deem highly feasible as a high proportion of patients are carefully evaluated at least a couple of months prior organ transplantation. Although a better immune response in transplant candidates has not yet been studied with the 9VHPV vaccine, this can be supported by a study with the qHPV vaccine in girls and young women which showed a robust

immune response in patients with chronic kidney disease but a suboptimal response kidney transplant recipients [27].

Importantly, HPV vaccination has no therapeutic effect on HPV infections at the time of vaccination. For this reason, it is important to vaccinate at young age, and preferably before sexual onset. However, if vaccination has not yet occurred at later age, it can still prevent infection with not yet acquired HPV-types. This is valuable as for each individual HPV type, 65% to 95% of the HIV-infected participants and more than 90% of SOT recipients were seronegative at baseline. Furthermore, the GMTs in our study were almost 3-fold higher in HIV-infected persons and up to 12-fold higher in SOT patients who were seropositive at baseline, which indicates boosting of pre-existing immunity.

The 9vHPV vaccine was well-tolerated in both patient groups. The most commonly reported AEs were pain, swelling, and erythema at the injection site, usually mild or moderate in intensity, and headache. This is in accordance with data from 9vHPV vaccination studies in healthy individuals [17]. The frequency of injection-site AEs was lower in our study compared to healthy men between the age of 16 and 26 [10]. None of the SAEs were considered vaccine-related. Although an SAE occurred in 16.5% of SOT recipients, the majority of SAEs happened due to infection, which is related to their immunosuppressed state [18].

Some limitations of our study should be addressed. Firstly, this is a monocentric study in which we did not include a healthy control group. We compared our data with historical controls with a different profile with respect to age and gender, both of which might influence immunogenicity and safety. Secondly, we only included HIV-infected persons with a CD4 count above 200 cells/µl and SOT patients were at median of 6 years post-transplant, which is relatively late. This hampers extrapolation of the results to all HIV-infected people and SOT recipients, respectively. Lastly, the study design did not allow for assessment of vaccine efficacy.

We conclude that the immunogenicity of the 9vHPV vaccine is excellent in HIV-infected persons but suboptimal in SOT recipients. The vaccine is safe and well tolerated in both groups. Given the high burden of HPV disease in HIV and SOT patients, the 9vHPV vaccine is beneficial because it covers a broad range of HPV types. With regards to SOT recipients, we propose to vaccinate before transplantation.

NOTES

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Conflicts of interest

CV was the principal investigator for vaccine clinical trials by MSD for which the university received grants. CV also reports institutional grants from GSK and Pfizer, outside the submitted work. All the other authors have nothing to disclose.

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Tables

Table 1: Patient characteristics

	All patients N=271	HIV N=100	Kidney Tx N=56	Heart Tx N=57	Lung TX N=58	All SOT N= 171
Personal data						
Age, median (range)	42 (18-55)	38 (18-45)	47 (22-55)	46 (19-55)	45 (22-55)	46 (19-55)
Male sex, n (%)	203 (74.9)	85 (85.0)	35 (62.5)	46 (80.7)	37 (63.8)	118 (69.0)
Origin, n (%)						
Caucasian	236 (87.1)	68 (68.0)	55 (98.2)	55 (96.5)	58 (100.0)	168 (98.3)
African	25 (9.2)	23 (23.0)	1 (1.8)	1 (1.8)	0 (0.0)	2 (1.2)
Other [a]	10 (3.7)	9 (9.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.6)
Women of child-bearing age, n	49	15	15	6	13	34
Hormonal anticonception, n (%) [b]	26 (48.2)	4 (21.6)	8 (45.7)	4 (61.5)	10 (87.0)	22 (62.0)
BMI, kg/m² median (range)	24.4 (15.2-44.9)	24.4 (15.2-42.2)	25.5 (17.0-44.9)	25.2 (16.0-29.1)	22.6 (17.2-33.6)	24.4 (16.0-44.9)
Disease characteristics						
Number of active comorbid diseases, median (range)	3 (0-22)	2 (0-6)	4 (0-8)	2 (0-7)	4 (1-22)	4 (0-22)
Time since HIV diagnosis or transplantation, years (median (range))	7 (1-31)	8 (1-31)	7 (1-30)	8 (1-27)	4 (1-17)	6 (1-30)
HIV						
CD4+ T-cell count, cells/µl (median(range))		737 (208-1419)				
Nadir CD4, cells/µl (median, range)		274 (0-896)				
SOT						
Immunosuppression at baseline, n (%)						
Type						
methylprednisolone			24 (42.9)	3 (5.3)	56 (96.6)	83 (48.5)
Azathioprine			6 (10.7)	3 (5.3)	17 (29.3)	26 (15.2)
Cyclosporine			4 (7.1)	5 (8.8)	4 (6.9)	13 (7.6)
Tacrolimus			44 (78.6)	45 (79.0)	36 (62.1)	125 (73.1)
Mycophenolate mofetil			51 (91.1)	50 (87.7)	53 (91.4)	154 (90.1)
Sirolimus or everolimus			0 (0.0)	6 (10.5)	1 (1.7)	7 (4.1)
number						
One immunosuppressive agent			0 (0.0)	2 (3.5)	0 (0.0)	2 (1.2)
Two immunosuppressive agents			38 (67.9)	55 (96.5)	7 (12.1)	100 (58.5)
Three immunosuppressive agents			18 (32.1)	0 (0.0)	51 (87.9)	69 (40.4)
HPV-related characteristics						
History of genital warts, n (%)	9 (3.3)	8 (8.0)	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.6)
HPV seropositivity at baseline, n (%) [c]						
All 9vHPV types [d]	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.6)
At least one 9vHPV type [d]	122 (45.0)	75 (75.0)	17 (30.4)	15 (26.3)	15 (25.9)	47 (27.5)
HPV 6	51 (18.8)	34 (34.0)	5 (8.9)	9 (15.8)	3 (5.2)	17 (9.9)
HPV 11	24 (8.9)	17 (17.0)	2 (3.6)	4 (7.0)	1 (1.7)	7 (4.1)
HPV 16	42 (15.5)	32 (32.0)	3 (5.4)	3 (5.3)	4 (6.9)	10 (5.8)

HPV 18	42 (15.5)	28 (28.0)	5 (8.9)	5 (8.8)	4 (6.9)	14 (8.2)
HPV 31	26 (9.6)	21 (21.0)	1 (1.8)	4 (7.0)	0 (0.0)	5 (2.9)
HPV 33	27 (10.0)	21 (21.0)	1 (1.8)	3 (5.3)	2 (3.4)	6 (3.5)
HPV 45	22 (8.1)	15 (15.0)	2 (3.6)	4 (7.0)	1 (1.7)	7 (4.1)
HPV 52	16 (5.9)	6 (6.0)	3 (5.4)	4 (7.0)	3 (5.2)	10 (5.8)
HPV 58	32 (11.8)	25 (25.0)	3 (5.4)	2 (3.5)	2 (3.4)	7 (4.1)

N= number of participants in each patient group that received at least one dose of the vaccine

ART = antiretroviral therapy, SOT = solid organ transplantation, Tx= transplantation

[a] Other origin includes people with Asian and Latin-American origin.

[b] Women of childbearing potential who did not use hormonal contraception, used either a barrier method, were not sexually active or patient or patient's partner were sterilized.

[c] Percentage of patients with antibody titers above 50,29,41,59,29,22,15,20, and 15 mili-Merck Units for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 respectively.

[d] 9vHPV types: HPV type 6,11,16,18,31,33,45,52, and 58

Table 2: Month 7 geometric mean titers and seroconversion in the PPI population

	All patients N=271		HIV N=100		Kidney Tx N=56		Heart Tx N=57		Lung Tx N=58		All transplant N=171	
cLIA assay	n	GMT (95% CI), mMU/ml	n	GMT (95% CI), mMU/ml	n	GMT (95% CI), mMU/ml	n	GMT (95% CI), mMU/ml	n	GMT (95% CI), mMU/ml	n	GMT (95% CI), mMU/ml
Anti-HPV 6	202	181 (146-225)	62	831 (679-1016)	49	91 (62-133)	43	127 (87-185)	48	71 (49-102)	140	92 (74-115)
Anti-HPV 11	226	148 (119-184)	76	693 (566-850)	52	63 (42-95)	48	91 (61-135)	50	54 (37-79)	150	67 (54-85)
Anti-HPV 16	212	382 (287-509)	63	2589 (2096-3197)	51	159 (93-271)	49	334 (193-577)	49	93 (55-158)	149	170 (123-234)
Anti-HPV 18	210	158 (132-189)	67	613 (497-757)	49	79 (60-104)	47	119 (88-161)	47	63 (51-78)	143	84 (72-98)
Anti-HPV 31	222	93 (73-117)	70	441 (349-556)	53	44 (28-69)	48	77 (49-122)	51	28 (20-40)	152	45 (35-58)
Anti-HPV 33	224	88 (73-106)	73	317 (263-382)	53	45 (32-63)	49	65 (44-94)	49	36 (26-51)	151	47 (38-58)
Anti-HPV 45	227	38 (31-47)	77	180 (146-223)	52	15 (11-22)	48	28 (19-40)	50	12 (9-16)	150	17 (14-21)
Anti-HPV 52	235	89 (72-109)	85	326 (261-409)	51	40 (28-56)	49	61 (39-95)	50	32 (23-45)	150	42 (34-53)
Anti-HPV 58	220	78 (63-96)	70	255 (207-314)	51	44 (29-66)	50	69 (43-110)	49	29 (19-46)	150	45 (34-58)
cLIA assay	n	Seroconversion % (95%CI)	n	Seroconversion % (95%CI)	n	Seroconversion % (95%CI)	n	Seroconversion m % (95%CI)	n	Seroconversion % (95%CI)	n	Seroconversion % (95%CI)
Anti-HPV 6	202	75.2 (68.7-81.0)	62	100 (94.2-100)	49	61.2 (46.2-74.8)	43	69.8 (53.9-82.8)	48	62.5 (47.4-76.0)	140	64.3 (55.8-72.2)
Anti-HPV 11	226	80.5 (74.8-85.5)	76	100 (95.3-100)	52	67.3 (52.9-79.7)	48	77.1 (62.7-88.0)	50	68.0 (53.3-80.5)	150	70.7 (62.7-77.8)
Anti-HPV 16	212	78.3 (72.1-83.7)	63	100 (94.3-100)	51	70.6 (56.2-82.5)	49	77.6 (63.4-88.2)	49	59.2 (44.2-73.0)	149	69.1 (61.0-76.4)
Anti-HPV 18	210	67.1 (60.3-73.5)	67	100 (94.6-100)	49	46.9 (32.5-61.7)	47	70.2 (55.1-82.7)	47	38.3 (24.5-53.6)	143	51.7 (43.2-60.2)
Anti-HPV 31	222	69.8 (63.3-75.8)	70	100 (94.9-100)	53	56.6 (42.3-70.2)	48	68.8 (53.7-81.3)	51	43.1 (29.3-57.8)	152	55.9 (47.6-64.0)
Anti-HPV 33	224	77.7 (71.7-83.0)	73	100 (95.1-100)	53	67.9 (53.7-80.1)	49	73.5 (58.9-85.1)	49	59.2 (44.2-73.0)	151	66.9 (58.8-74.3)
Anti-HPV 45	227	64.3 (57.7-70.5)	77	100 (95.3-100)	52	42.3 (28.7-56.8)	48	64.6 (49.5-77.8)	50	32.0 (19.5-46.7)	150	46.0 (37.8-54.3)
Anti-HPV 52	235	77.9 (72.0-83.0)	85	100 (95.8-100)	51	66.7 (52.1-79.2)	49	71.4 (56.7-83.4)	50	58.0 (43.2-71.8)	150	65.3 (57.1-72.9)
Anti-HPV 58	220	80.9 (75.1-85.9)	70	100 (94.9-100)	51	72.5 (58.3-84.1)	50	78.0 (64.0-88.5)	49	65.3 (50.4-78.3)	150	72.0 (64.1-79.0)

The per-protocol immunogenicity population included all participants that received all 3 vaccinations with the 9vHPV vaccine within pre-specified acceptable day ranges, were seronegative to the appropriate HPV type at Day 1, had serology results based on serum samples collected within pre-specified acceptable day ranges and had no protocol deviations that could interfere with the subject's immune response to the 9vHPV vaccine as judged by the principal investigator.

N= number of participants in each patient group that received at least one dose of the vaccine

n= number of patients contributing to the analysis

9vHPV = nine-valent human papillomavirus, CI = Confidence interval, cLIA = competitive luminex immunoassay, GMT = Geometric mean titer, HPV= Human papillomavirus, mMU = milli-Merck unit, PPI= per protocol immunogencity, Tx = transplant

Table 3: predictors of log-transformed titers in HIV-infected persons and seroconversion in SOT recipients: PPI population

HIV group	**HPV6**	**HPV11**	**HPV16**	**HPV18**	**HPV31**	**HPV33**	**HPV45**	**HPV52**	**HPV58**
Titers	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)
Female sex (vs male)	0.4 (-0.2;1.1)	0.6 (-0.1;1.2)°	-0.2 (-0.9;0.4)	0.0 (-0.6;0.6)	-0.3 (-1.1;0.5)	0.2 (-0.3;0.8)	-0.1 (-0.7;0.5)	0.4 (-0.4;1.1)	-0.1 (-0.8;0.5)
Age (years divided by 10)	-0.1 (-0.4;0.2)	-0.1 (-0.4;0.2)	-0.2 (-0.5;0.1)	-0.2 (-0.5;0.1)	0.1 (-0.2;0.4)	0.1 (-0.2;0.4)	-0.2 (-0.5;0.1)	0.1(-0.3;0.4)	-0.2 (-0.6;0.1)
Origin									
Caucasian	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
African	0.5 (-0.1;1.1)	0.5 (-0.1;1.1)°	**1.0 (0.4;1.5)*** **	**0.9 (0.4;1.5)****	**1.4 (0.8;2.0)*** **	**0.7 (0.2;1.2)****	**0.9 (0.3;1.5)****	**1.3 (0.6;1.9)*** **	**0.8 (0.2;1.4)****
Other [a]	-0.3 (-1.0;0.4)	0.0 (-0.7;0.7)	0.4 (-0.3;1.1)	-0.1 (-0.8;0.6)	0.0 (-0.8;0.7)	0.4 (-0.2;1.0)	0.4 (-0.4;1.1)	0.0 (-0.8;0.8)	0.4 (-0.4;1.2)
BMI	0.0 (-0.1;0.1)	0.0 (-0.1;0.1)	0.0 (0.0;0.1)	0.0 (-0.1;0.0)	0.0 (-0.1;0.0)	0.0 (-0.1;0.0)	0.0 (-0.1;0.0)	**-0.1 (-0.1;0.0)****	0.0 (-0.1;0.0)
CD4+ T-cell count divided by 10	0.0 (-0.1;0.1)	-0.1 (-0.1;0.0)	0.0 (-0.1;0.1)	0.0 (-0.1;0.1)	0.0 (-0.1;0.0)	0.0 (-0.1;0.0)	**-0.1 (-0.2;0.0)***	0.0 (-0.1;0.1)	-0.1 (-0.1;0.0)
SOT group	**HPV6**	**HPV11**	**HPV16**	**HPV18**	**HPV31**	**HPV33**	**HPV45**	**HPV52**	**HPV58**
Seroconversion	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Female sex (vs male)	1.5 (0.6;3.9)	1.1 (0.5;2.6)	1.9 (0.8;5.0)	1.0 (0.4;2.5)	**2.8 (1.2;7.0)***	1.4 (0.6;3.6)	1.0 (0.4;2.3)	1.9 (0.8;4.7)	2.2 (0.9;6.0)
Age (years divided by 10)	0.8 (0.5;1.2)	0.7 (0.5;1.2)	0.8 (0.5;1.2)	0.7 (0.5;1.1)	0.8 (0.5;1.2)	0.9 (0.6;1.4)	0.9 (0.6;1.3)	0.7 (0.4;1.0)°	0.8 (0.5;1.3)
Transplant group									
Kidney Tx	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Heart TX	1.2 (0.4;3.6)	1.4 (0.5;4.1)	1.1 (0.4;3.4)	2.3 (0.8;6.5)	1.7 (0.6;4.5)	0.8 (0.3;2.4)	1.9 (0.7;4.9)	1.0 (0.4;2.9)	1.1 (0.3;3.2)
Lung TX	0.9 (0.2;3.0)	0.8 (0.2;2.6)	0.6 (0.2;1.8)	0.6 (0.2;2.1)	0.5 (0.1;1.5)	0.7 (0.2;2.3)	0.8 (0.2;2.6)	0.6 (0.2;1.8)	1.0 (0.3;3.3)
BMI	**0.9 (0.8;1.0)***	1.0 (0.9;1.0)	1.0 (0.9;1.0)	1.0 (0.9;1.1)	1.0 (0.9;1.1)	0.9 (0.9;1.0)	0.9 (0.9;1.0)	1.0 (0.9;1.1)	1.0 (0.9;1.1)
Years since transplantation	1.1 (1.0;1.1)	1.0 (1.0;1.1)	1.0 (1.0;1.1)	1.1 (1.0;1.1)°	1.0 (1.0;1.1)	1.0 (0.9;1.1)	1.1 (1.0;1.1)	1.0 (1.0;1.1)	1.0 (1.0;1.1)
Immunosuppression at baseline, n [b]	0.5 (0.1;1.6)	0.8 (0.2;2.4)	0.5 (0.2;1.5)	0.6 (0.2;1.7)	0.6 (0.2;1.8)	0.3 (0.1;1.0)°	0.4 (0.1;1.0)°	0.6 (0.2;1.9)	0.4 (0.1;1.3)
Mycophenolate mofetil	**0.1 (0.0;0.4)****	**0.2 (0.0;0.5)****	**0.3 (0.1;0.7)***	**0.1 (0.0;0.4)*** **	**0.2 (0.1;0.5)****	**0.1 (0.0;0.4)*** **	**0.3 (0.1;0.8)***	**0.3 (0.1;0.7)****	**0.2 (0.1;0.6)***
Tacrolimus	0.7 (0.2;2.7)	0.6 (0.1;2.6)	0.3 (0.0;1.3)	0.6 (0.1;2.4)	0.3 (0.1;1.1)°	0.6 (0.1;2.3)	0.6 (0.2;2.6)	0.6 (0.1;2.2)	0.8 (0.2;3.3)

The per-protocol immunogenicity (PPI) population included all participants that received all 3 vaccinations with the 9vHPV vaccine within pre-specified acceptable day ranges, were seronegative to the appropriate HPV type at Day 1, had serology results based on serum samples collected within pre-specified acceptable day ranges and had no protocol deviations that could interfere with the subject's immune response to the 9vHPV vaccine as judged by the principal investigator.

[a] Other included Asian and Latin-American origin.

[b] Number of immunosuppressive drugs taken by patient.

*b= regression coefficient, TX = transplant, BMI= Body Mass Index, °p< 0.1, *p<0.05, **p<0.01, ***p<0.001.*

Table 4: Summary of safety and tolerability of nine-valent human papillomavirus vaccine in HIV and solid organ transplant patients

	All patients		HIV		Kidney transplant		Heart transplant		Lung transplant		All Transplant	
	%	95% CI	%	95% CI	%	95% CI	%	95%	%	95%CI	%	95%CI
Subjects with follow-up, n	269		99		56		56		58		170	
With ≥1 AE[a]+	**77.0**	**(71.5-81.8)***	80.8	(71.7-88.0)93	73.2	(59.7-84.2)°	**64.3**	**(50.4-76.6)****	86.2	(74.6-93.9)	**74.7**	**(67.5-81.0)***
With vaccine-related[b] AEs[a]+	**71.0**	**(65.2-76.4)*****	74.7	(65.0-82.9)°	**64.3**	**(50.4-76.6)****	**60.7**	**(46.8-73.5)*****	81.0	(68.6-90.1)	**68.8**	**(61.3-75.7)*****
Injection-site event[c]+	**62.1**	**(56.0-67.9)*****	**69.7**	**(59.6-78.5)***	**46.4**	**(33-60.0.3)*****	**51.8**	**(38.0-65.3)*****	74.1	(61.0-84.7)	**57.6**	**(49.8-65.2)*****
Pain[d]+	**59.5**	**(53.3-65.4)*****	**67.7**	**(57.5-76.7)***	**42.9**	**(29.7-56.8)*****	**50.0**	**(36.3-63.7)*****	70.7	(57.3-81.9)	**54.7**	**(46.9-62.3)*****
Mild	58.4	(52.2-64.3)	64.6	(54.4-74.0)	42.9	(29.7-56.8)	50.0	(36.3-63.7)	70.7	(57.3-81.9)	54.7	(46.9-62.3)
Moderate	10.4	(7.0-14.7)	13.1	(7.2-21.4)	3.6	(0.4-12.3)	8.9	(3.0-19.6)	13.8	(6.1-25.4)	8.8	(5.0-14.1)
Severe	0.0	(0.0-1.4)	0.0	(0.0-3.7)	0.0	(0.0-6.4)	0.0	(0.0-6.4)	0.0	(0.0-6.2)	0.0	(0.0-2.1)
Swelling+	**7.8**	**(4.9-11.7)****	**7.1**	**(2.9-14.0)***	10.7	(4.0-21.9)	7.1	(2.0-17.3)	6.9	(1.9-16.7)	**8.2**	**(4.6-13.4)***
Mild (0 to ≤2.5 cm)	7.1	(4.3-10.8)	6.1	(2.3-12.7)	8.9	(3-19.6)	7.1	(2.0-17.3)	6.9	(1.9-16.7)	7.6	(4.1-12.7)
Moderate (>2.5 to ≤5.0 cm)	1.1	(0.2-3.2)	1.0	(0.0-5.5)	1.8	(0.0-9.6)	0.0	(0.0-6.4)	1.7	(0.0-9.2)	1.2	(0.1-4.2)
Severe (<5.0 cm)	0.4	(0.0-2.1)	0.0	(0.0-3.7)	0.0	(0.0-6.4)	0.0	(0.0-6.4)	1.7	(0.0-9.2)	0.6	(0.0-3.2)
Erythema+	**7.4**	**(4.6-11.2)*****	10.1	(5.0-17.8)	8.9	(3.0-19.6)	**1.8**	**(0.0-9.6)****	6.9	(1.9-16.7)°	**5.9**	**(2.9-10.6)*****
Mild (0 to ≤2.5 cm)	7.1	(4.3-10.8)	10.1	(5.0-17.8)	7.1	(2.0-17.3)	1.8	(0.0-9.6)	6.9	(1.9-16.7)	5.3	(2.4-9.8)
Moderate (>2.5 to ≤5.0 cm)	0.7	(0.1-2.7)	1.0	(0.0-5.5)	1.8	(0.0-9.6)	0.0	(0.0-6.4)	0.0	(0.0-6.2)	0.6	(0.0-3.2)
Severe (<5.0 cm)	0.0	(0.0-1.4)	0.0	(0.0-3.7)	0.0	(0.0-6.4)	0.0	(0.0-6.4)	0.0	(0.0-6.2)	0.0	(0.0-2.1)
Pruritus+	1.5	(0.4-3.8)	1.0	(0.0-5.5)	1.8	(0.0-9.6)	1.8	(0.0-9.6)	1.7	(0.0-9.2)	1.8	(0.4-5.1)
Ecchymosis	0.0	(0.0-1.4)	0.0	(0.0-3.7)	0.0	(0.0-6.4)	0.0	(0.0-6.4)	0.0	(0.0-6.2)	0.0	(0.0-2.1)
Induration	0.0	(0.0-1.4)	0.0	(0.0-3.7)	0.0	(0.0-6.4)	0.0	(0.0-6.4)	0.0	(0.0-6.2)	0.0	(0.0-2.1)
Other local events	7.4	(4.6-11.2)	6.1	(2.3-12.7)	5.4	(1.1-14.9)	8.9	(3.0-19.6)	10.3	(3.9-21.2)	8.2	(4.6-13.4)
All systemic events[a]	**46.5**	**(40.4-52.6)°**	**51.5**	**(41.3-61.7)***	50.0	(36.3-63.7)	28.6	(17.3-42.2)°	51.7	(38.2-65.0)	43.5	(36.0-51.3)
Vaccine-related[b] systemic event+	21.9	(17.1-27.4)	24.2	(16.2-33.9)	17.9	(8.9-30.4)	**10.7**	**(4.0-21.9)***	32.8	(21.0-46.3)°	20.6	(14.8-27.5)
Headache+	8.6	(5.5-12.6)	9.1	(4.2-16.6)	7.1	(2.0-17.3)	5.4	(1.1-14.9)	12.1	(5.0-23.3)	8.2 14	(4.6-13.4)
Pyrexia (≥ 37.8°C)+	1.9	(0.6-4.3)	3.0	(0.6-8.6)	0.0	(0.0-6.4)	0.0	(0.0-6.4)	3.4	(0.4-11.9)	1.2	(0.1-4.2)

Nausea+	1.9	(0.6-4.3)	1.0	(0.0-5.5)	0.0	(0.0-6.4)	0.0	(0.0-6.4)	**6.9**	**(1.9-16.7)***	2.4	(0.6-5.9)
Dizziness	1.1	(0.2-3.2)	3.0	(0.6-8.6)	0.0	(0.0-6.4)	0.0	(0.0-6.4)	0.0	(0.0-6.2)	0.0	(0.0-2.1)
Fatigue+	3.3	(1.5-6.3)	4.0	(1.1-10.0)	1.8	(0.0-9.6)	0.0	(0.0-6.4)	**6.9**	**(1.9-16.7)***	2.9	(1.0-6.7)
Other vaccine-related systemic events[a]	13.8	(9.9-18.5)	14.1	(8.0-22.6)	14.3	(6.4-26.2)	8.9	(3.0-19.6)	17.2	(8.6-29.4)	13.5	(8.8-19.6)

n, number of subjects as treated who received at least 1 dose of Gardasil®9 and had at least 1 follow-up visit for AEs

[a] Day 1-15 following any vaccination visit

[b] As reported by the investigator

[c] Days 1-5 following any vaccination visit

[d] Intensities of pain are defined as follows: mild is an awareness of sign or symptom that can be easily tolerated; moderate is discomfort that causes interference with usual activity; severe is inability to work or do daily activities.

+ tested against reference data of historical controls [18]

° p < 0.1; * p < 0.05; ** p < 0.01; *** p < 0.001

Table 5: Serious adverse events by system organ classes

	All patients n=269		HIV n=99		Kidney Tx n=56		Heart Tx n=56		Lung Tx n=58		All Tx N=170	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Days 1-15 after any vaccination												
Subjects with ≥ 1 SAE	8	(3.0)	-	-	1	(1.8)	2	(3.6)	5	(8.6)	8	(4.7)
Infections and infestations	3	(1.1)	-	-	1	(1.8)	-	-	2	(3.4)	3	(1.8)
Nervous system disorders	1	(0.4)	-	-	-	-	-	-	1	(1.7)	1	(0.6)
Respiratory, thoracic and mediastinal disorders	2	(0.7)	-	-	-	-	-	-	2	(3.4)	2	(1.2)
Cardiac disorders	1	(0.4)	-	-	-	-	1	(1.8)	-	-	1	(0.6)
Vascular disorders	1	(0.4)	-	-	-	-	1	(1.8)	-	-	1	(0.6)
Any time during the study												
Subjects with ≥ 1 SAE	31	(11.5)	3	(3.0)	11	(19.6)	5	(8.9)	12	(20.7)	28	(16.5)
Blood and lymphatic system disorders	-	-	-	-	1	(1.8)	-	-	-	-	1	(0.6)
Cardiac disorders	2	(0.7)	-	-	-	-	2	(3.6)	-	-	2	(1.2)
Gastrointestinal disorders	4	(1.5)	-	-	-	-	-	-	4	(6.9)	4	(2.4)
General disorders and administration site conditions	1	(0.4)	-	-	-	-	-	-	1	(1.7)	1	(0.6)
Immune system disorders	1	(0.4)	-	-	-	-	-	-	1	(1.7)	1	(0.6)
Infections and infestations	18	(6.7)	-	-	8	(14.2)	2	(3.6)	8	(13.8)	18	(10.6)
Injury, poisoning and procedural complications	2	(0.7)	1	(1.0)	-	-	-	-	1	(1.7)	1	(0.6)
Metabolism and nutrition disorders	2	(0.7)	-	-	-	-	-	-	2	(3.4)	2	(1.2)
Musculoskeletal and connective tissue disorders	1	(0.4)	-	-	-	-	-	-	1	(1.7)	1	(0.6)
Neoplasms benign, malignant and unspecified	3	(1.1)	-	-	2	(3.6)	-	-	1	(1.7)	3	(1.8)
Nervous system disorders	1	(0.4)	-	-	-	-	-	-	1	(1.7)	1	(0.6)
Psychiatric disorders	1	(0.4)	1	(1.0)	-	-	-	-	-	-	-	-
Renal and urinary disorders	2	(0.7)	-	-	2	(3.6)	-	-	-	-	2	(1.2)
Respiratory, thoracic and mediastinal disorders	4	(1.5)	-	-	1	(1.8)	-	-	3	(5.3)	4	(2.4)
Social circumstances	1	(0.4)	1	(1.0)	-	-	-	-	-	-	-	-
Surgical and medical procedures	2	(0.7)	-	-	1	(1.8)	1	(1.8)	-	-	2	(1.2)
Vascular disorders	1	(0.4)	-	-	-	-	1	(1.5)	-	-	1	(0.6)

n: number of subjects who received at least 1 dose of Gardasil®9 and had at least 1 follow-up visit for AEs

A subject is counted once within a category and may be counted in more than one category

Figure legend

Figure 1: **Study flow for all patients who provided informed consent**

[a] Serum samples were centrifuged at 365 g instead of 1942 g

[b] Received an inactivated vaccine within ±14 days of study vaccination

[c] Received an inactivated influenza vaccine within ±7 days of study vaccination

HIV: human immunodeficiency virus, RTX: renal transplantation, HTX: heart transplantation, LTX: lung transplantation

Figure 1