



# HHS Public Access

Author manuscript

*Am J Transplant.* Author manuscript; available in PMC 2015 September 25.

Published in final edited form as:

*Am J Transplant.* 2013 September ; 13(9): 2411–2417. doi:10.1111/ajt.12329.

## Immunogenicity of Quadrivalent Human Papillomavirus Vaccine in Organ Transplant Recipients

D. Kumar<sup>1,\*</sup>, E. R. Unger<sup>2</sup>, G. Panicker<sup>2</sup>, P. Medvedev<sup>1</sup>, L. Wilson<sup>1</sup>, and A. Humar<sup>1</sup>

<sup>1</sup>Alberta Transplant Institute, University of Alberta, Edmonton, Alberta, Canada

<sup>2</sup>Chronic Viral Diseases Branch, Centers for Disease Control and Prevention, Atlanta, GA

### Abstract

Solid organ transplant recipients are at risk of morbidity from human papillomavirus (HPV)-related diseases. Quadrivalent HPV vaccine is recommended for posttransplant patients but there are no data on vaccine immunogenicity. We determined the immunogenicity of HPV vaccine in a cohort of young adult transplant patients. Patients were immunized with three doses of quadrivalent HPV vaccine containing viral types 6, 11, 16 and 18. Immunogenicity was determined by type-specific viral-like protein ELISA. Four weeks after the last dose of vaccine, a vaccine response was seen in 63.2%, 68.4%, 63.2% and 52.6% for HPV 6, 11, 16 and 18, respectively. Factors that led to reduced immunogenicity were vaccination early after transplant ( $p = 0.019$ ), having a lung transplant ( $p = 0.007$ ) and having higher tacrolimus levels ( $p = 0.048$ ). At 12 months, there were significant declines in antibody titer for all HPV types although the number of patients who remained seropositive did not significantly differ. The vaccine was safe and well tolerated. We show suboptimal immunogenicity of HPV vaccine in transplant patients. This is important for counseling patients who choose to receive this vaccine. Further studies are needed to determine an optimal HPV vaccine type and schedule for this population.

### Keywords

Cervical cancer; HPV; immunocompromised; SOT

### Introduction

Human papillomavirus (HPV)-related anogenital diseases are an important cause of morbidity and mortality in the general population. Many types of the virus are sexually transmitted and infect the anogenital region. Low risk types are associated with warts, whereas high risk types are associated with cancer precursors or cancer of anogenital tract (cervix, vulva, vagina, penis and anus). Solid organ transplant recipients are at greater risk of complications from HPV infections due to lifelong immunosuppression. Several studies show increased risk of anogenital malignancy in transplant recipients (1–4). The rate of anogenital disease may be increased up to 14–100-fold in kidney transplant recipients (5–6).

\*Corresponding author: Deepali Kumar, deepali.kumar@ualberta.ca.

### Disclosure

The remaining authors have no conflict of interest as defined by the *American Journal of Transplantation*.

Therefore, careful cervical cancer screening in women is recommended for this population (7). HPV vaccines have been shown to be efficacious in prevention of cervical cancer in the general population (8–10). Quadrivalent HPV vaccine (Gardasil, Merck Vaccines, Whitehouse Station, NJ) is a virus-like particle (VLP) vaccine directed against L1 protein of HPV that contains viral types 6, 11, 16, and 18. Although there are over 120 types of HPV described, HPV 16 and 18 together are responsible for about 70% of invasive cervical cancer (11–13) and HPV 6 and 11 are implicated in up to 90% of anogenital warts. Quadrivalent HPV vaccine is indicated for males and females ages 9–26 years for the prevention of cervical/anal cancer and anogenital warts. The age and gender indications may vary depending on country of licensure. It is a highly effective vaccine and has an overall efficacy of 99–100% for prevention of cervical intraepithelial neoplasia caused by vaccine types in randomized clinical trials. More recently, data have shown that it is also effective in older females up to age 45 years (14). HPV vaccine is not a therapeutic vaccine and has no effect on existing lesions caused by vaccine types. The vaccine is recommended for patients within the indicated age group, who are candidates for transplantation or posttransplant in those who have not previously received vaccine (15). Many transplant centers may choose to prescribe vaccination for persons of any age that are transplant candidates or recipients. However, the immunogenicity of this vaccine in the post-organ transplant population is not known. We conducted a prospective cohort study to determine the immunogenicity of quadrivalent HPV vaccine in a young adult posttransplant population.

## Methods

### Patient population

Adult solid organ transplant recipients, age 18–35 years, were enrolled from outpatient clinics at the University of Alberta Hospital during 2008–2010. Patients were at least 3 months posttransplant and on a stable immunosuppressive regimen that had not changed in the past 1 month. Patients were excluded if they had a history of anogenital warts or cervical lesions such as cervical intraepithelial neoplasia or cervical polyps, were febrile in the past 1 week or had therapy for acute rejection in the month prior to enrollment. Patients were also excluded if they had received intravenous immune globulin therapy in the past 1 month. The study was approved by the institutional research ethics board and all patients provided informed consent. The study was registered on [clinicaltrials.gov](http://clinicaltrials.gov) (NCT00677677).

Patients were scheduled to receive three doses of HPV4 vaccine (Gardasil, Merck Vaccines, Inc.) at enrollment, 2 and 6 months. Vaccine was purchased for the study from commercially available supply. The vaccine was provided in prefilled syringes and contained 20 µg antigen each of HPV types 6 and 18 and 40 µg antigen of HPV types 11 and 16. Each dose contained 0.5 mL volume and was administered in the deltoid muscle of the nondominant arm. Serum was collected upon enrollment, prior to each vaccination and at month 7 (4 weeks after the third vaccine dose). Sera were also collected at 1-year postimmunization and stored at –80°C for batch testing. Patients were contacted at 48 h and 7 days after each immunization for collection of injection-related adverse events. For other adverse events, we specifically collected infections, biopsy-proven and/or clinically treated rejection up to year 1 after enrollment. At our center, heart transplant patients undergo routine protocol biopsies;

however, other patients undergo allograft biopsy only with clinical suspicion of rejection. Nevertheless, routine monitoring of liver enzymes and creatinine is performed in liver and kidney patients as per clinical protocols. Cervical screening was not part of the study protocol as our intent was to do a vaccine immunogenicity and safety (not efficacy) study. However, at the 3-year timepoint, patient history and routine cervical screening records were reviewed to determine whether any cervical lesions or anogenital warts had developed.

### Laboratory testing using HPV4-plex IgG ELISA

Laboratory testing was performed by the Centers for Disease Control in the United States. All sera underwent testing for type-specific antibodies using a HPV4-plex VLP-IgG ELISA on the Meso Scale Discovery (MSD) platform (manuscript in preparation). HPV VLPs used in this study were produced using the protocol described by Pastrana et al. (16). Assay controls used in this study were pooled adult human sera that were high, low and negative in reactivity to the different HPV types as determined by in-house blocking assay or competitive Luminex Immunoassay (cLIA) (17). For each sample tested for reactivity to HPV VLPs, a blank spot (no VLP only buffer) was also assayed and used for background determination.

MSD 7-plex standard plates were prepared by precoating with HPV 6, 11, 16, and 18 on four-spots in phosphate buffered saline with bovine serum albumin (PBS-BSA). The remaining three spots were coated only with PBS-BSA. The plates were washed four times with PBST (PBS–0.1% Tween 20) using an automated plate washer (ELx405, Biotek, Winooski, VT) after each incubation step. Plates were blocked for 1 h with 5% ECL Blocking Agent (GE Healthcare, Piscataway, NJ) in PBST at room temperature ( $24 \pm 2^\circ\text{C}$ ) on a lab rotator set at 600 rpm. Test sera were 3.16-fold serially diluted for at least three dilutions starting at 1:10 in assay diluent (1% ECL Blocking Agent in PBST [GE Healthcare Biosciences, Piscataway, NJ]). 25  $\mu\text{L}$  of each dilution was added to the plate and incubated at  $37^\circ\text{C}$  for 1 h with shaking at 600 rpm (Millenium 2000, Jencons Scientific Ltd, Bedfordshire, UK). Next, 25  $\mu\text{L}$  of biotin-labeled mouse anti-human IgG (Fc specific) (Biotrend Chemicals LLC, Destin, FL) diluted in assay diluent was added at an optimized concentration. The plates were incubated at  $37^\circ\text{C}$  with shaking at 600 rpm for 1 h. 25  $\mu\text{L}$  of Streptavidin-Sulfo Tag (Meso Scale Discovery (MSD), Rockville, MD) diluted in assay diluent was added to each well. Plates were incubated at  $37^\circ\text{C}$  for 1 h with shaking at 600 rpm. After washing, 150  $\mu\text{L}$  of  $1\times$  Read Buffer T was added to each well. The plate was read on the Sector Imager 6000 (MSD). Data were exported to Microsoft Excel and final relative light units (RLUs) measurement using the parallel line method (PLL) analysis was generated after subtracting the blank spot RLU from each VLP spot RLU. The PLL analysis was performed as described in the WHO HPV Labnet Manual ([whqlibdoc.who.int/hq/2010/WHO\\_IVB\\_10.12\\_eng.pdf](http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.12_eng.pdf)).

The HPV16 International standard (NIBSC, UK) was tested on several plates to enable establishment of a secondary standard and calculate international units (IU)/mL using the PLL. The in-house secondary standard for HPV16 was then used as the reference sample on each test plate. For HPV 6, 11, and 18 a reference sample was tested on each plate to enable PLL calculation, but was assigned arbitrary units as no international standard is currently

available. The cut-off values (COV) used were mean + 5 SD above the PLL units generated from a subset of virginal women and women who were HPV DNA negative and seronegative by the luminex assay. The COV for HPV 6, 11, 16 and 18 were 0.259 arbitrary units (AU), 0.062 AU, 0.448 IU/mL and 0.535 AU, respectively.

### Laboratory testing using competitive luminex assay

In addition to the above testing, a subset of patient samples were also assayed using the type-specific cLIA developed by Merck Research Laboratories and performed at PPD Vaccines and Biologics, Wayne, PA as previously described (17). Since the majority of studies use this assay, these results could be compared to those available in the literature. For cLIA, the lower limit of detection was 7, 8, 11 and 10 mMU/mL (milliMerck Units) for types 6, 11, 16, and 18, respectively. For statistical analysis, samples less than the lower limit of detection were given a value between 0 and the lower limit. Based on studies in immunocompetent persons, a positive value (vaccine response) was defined as  $\geq 20$  mMU/mL for type 6,  $\geq 16$  mMU/mL for type 11,  $\geq 20$  mMU/mL for type 16 and  $\geq 24$  mMU/mL for type 18 (18).

### Statistics

The primary endpoint was immunogenicity at 7 months following the first vaccine dose (i.e. 1 month after the three dose series was completed). Patients who did not receive all three vaccine doses were not included in the primary endpoint analysis but were included in the remainder of the immunogenicity analysis. A positive response to vaccine was defined using the HPV4-plex IgG ELISA.

Descriptive statistics were used for demographics. Chi-square or Fisher's exact test was used to compare categorical variables, and Mann-Whitney U-test was used for continuous variables. Correlations between the two laboratory methods were performed using kappa statistic. All patients who received at least one vaccine dose were included in the safety analysis. Patients who received at least one vaccine dose and had at least one follow-up blood work were included in the immunogenicity analysis. Univariate analysis was performed for factors influencing seroconversion (gender, type of transplant, time from transplant, immunosuppression including each immunosuppressive as a categorical variable and calcineurin-inhibitor levels as continuous variables). All statistical analysis was performed using SPSS version 20 (SPSS, Inc., Chicago, IL).

## Results

### Patient characteristics

We enrolled 50 organ transplant recipients. Of these, two patients did not receive any doses of vaccine and were excluded from further analysis. One additional patient was found to have a prior history of low-grade squamous lesion (LSIL) on cervical Pap test and was excluded. Baseline demographics of the remaining patients (n = 47) are shown in Table 1. Median age was 25.9 years (range 18–35) and patients were a median of 2.7 years from transplant. Most patients had kidney (64%) or lung (23%) transplants. The majority of patients (91.5%) received all three doses of vaccine. Four patients had a history of cutaneous

warts on hands or feet. Immunosuppression consisted of a calcineurin-inhibitors (91.5%) and mycophenolate mofetil (MMF) (87.5%) in the majority of patients. Of those receiving MMF, 52.4% were on high doses (  $\geq 2$  g/day). Three patients had received antilymphocyte globulin at 101, 106 and 135 days prior to commencing immunization and three patients had a history of rejection at 40, 60 and 135 days prior to immunization.

### Immunogenicity: HPV4-plex IgG ELISA

For the immunogenicity analysis using the HPV4-plex IgG ELISA, in the intent-to-treat population (i.e., patients who had received at least one dose of vaccine,  $n = 47$ ), the response rate to at least one vaccine type was 29/47 (61.7%, 95% CI 47.8–75.6%). However, in the per-protocol population (i.e. patients who had received all three doses of vaccine and had completed the pre- and all post-vaccination samples up to month 7), response was evaluable in 38/47 patients. In this group, response to at least one vaccine type was present in 29/38 (76.3%, 95% CI 62.8–89.8%) patients. The positive response to vaccine types ranged from 52.6% (95% CI 36.7–68.5%) for HPV 18–68.4% (95% CI 53.6–83.2%) for HPV type 11 (Figure 1).

Response to all four types in the vaccine was seen in 18/38 (47.4%) of patients. Factors associated with vaccine response are shown in Table 2. Antibody titers were variable depending on vaccine type and type of transplant (Figure 2). Lung transplant patients had a trend to lower vaccine response than kidney transplants (response to at least one HPV type, 54.5% vs. 95.8%;  $p = 0.007$ ). Median titers at month 7 were also significantly lower in lung transplant recipients versus other transplants for some HPV vaccine types (type 16,  $p = 0.025$ ; type 18,  $p = 0.003$ ; Figure 3). Lung transplant patients tended to respond to fewer vaccine types than other transplant types (median 1.0 vs. 4.0;  $p = 0.038$ ). A trend toward lower response was seen in patients who were less than 1 year posttransplant (54.5% vs. 85.2% response in  $>1$  year posttransplant;  $p = 0.088$ ; Figure 4). The median time posttransplant in responders versus nonresponders was 3.24 versus 0.74 years ( $p = 0.019$ ). Median tacrolimus levels were also significantly lower in responders (6.3 vs. 9.4  $\mu\text{g/mL}$ ;  $p = 0.048$ ). A cohort of 29 patients had follow-up sera available for immunogenicity analysis at 1 year postenrolment. At 1 year, titers decreased significantly for all HPV types ( $p < 0.005$  for all vaccine types). However, there were no significant decreases in the percentage of seropositive patients 1 year. A small proportion of patients were seropositive for some HPV types at baseline (Figure 1). These patients generally had a greater antibody titers at month 7 compared to HPV naïve patients (Figure 2).

### Immunogenicity: cLIA

Type-specific antibody determinations using the cLIA method were available for 32/46 patient samples using the cLIA method. At month 7, geometric mean titers for HPV types 6, 11, 16, and 18 were 14.7, 32.6, 36.4, and 11.3 mMU/L, respectively. At month 7 (primary endpoint for patients who had received all three doses), vaccine response (above the defined COVs) was 23.1% (type 6), 66.7% (type 11), 51.9% (type 16) and 14.8% (type 18; Figure 4). Response to one HPV type was seen in 22.2%, two types (29.6%), three types (14.8%) and four types (7.4%). Response to at least one HPV type at month 7 was seen in 74.1% patients. Response rates by organ were kidney 15/18 (83.3%) and lung 4/7 (57.1%). In

patients who had both assays performed ( $n = 27$ ), antibody levels at month 7 tended to be significantly correlated with each other (Spearman's correlation  $>0.9$ ,  $p < 0.001$  for all vaccine types); however, seropositivity was higher with ELISA compared to cLIA. The assay agreement (kappa) at month 7 was 0.27, 0.65, 0.78 and 0.28 for HPV 6, 11, 16 and 18, respectively.

## Safety

Local and systemic reactions were assessed at 48 h and 7 days after each dose (45/47 patients were successfully contacted at both time points following each vaccine dose). Reactions after the first dose included tenderness at the injection site in 10/45 (22.2%), fatigue in 4/45 (8.9%), subjective fever in one patient (2.2%), dizziness (2.2%) and headache (2.2%). After the second dose, reactions were much lower with only 1/45 (2.2%) with tenderness and 1/45 (2.2%) with fever. No local or systemic reactions occurred after dose 3. Other adverse events that occurred in the 1 year after enrollment included CMV viremia ( $n = 5$ ; all after first dose), CMV enteritis ( $n = 1$ ; after dose 2), acute rejection ( $n = 2$ ), diagnosis of lymphoma in one patient and an unanticipated pregnancy in one patient. This patient had a history of previous spontaneous abortions and went on to have a spontaneous abortion with this pregnancy. Patients that received all three doses of vaccine ( $n = 43$ ) were followed-up with history and medical record review at 3 years postvaccination. Of these, two had died of chronic allograft rejection. In the remaining patients, four (9.8%) had new diagnoses of anal or cervical lesions. New anal intraepithelial neoplasia developed in a male patient after dose 2 but prior to dose 3 of vaccine. Three female patients (two kidney and one lung transplant recipient) were diagnosed with LSIL on cervical smears at 14, 36, and 36 months postimmunization. Vaccine response in this group was variable but none of these four patients developed seropositivity to HPV 18 after vaccination.

## Discussion

We conducted an immunogenicity and safety study of quadrivalent HPV vaccine in solid organ transplant recipients and showed that the vaccine has suboptimal immunogenicity in the posttransplant setting. To our knowledge, this is the first study to provide immunogenicity data on HPV vaccine in the organ transplant population. Using the IgG ELISA, our rate of seropositivity ranged from 52.6% to 68.4% depending on the HPV type. This is significantly lower than that described in randomized controlled trials of young men and women where seropositivity after vaccine ranged from 97% to 99% (14,19). We found that patients who were early posttransplant and lung transplant recipients had especially low vaccine responses. This is similar to findings in studies of other vaccines such as influenza vaccine in organ transplants (20–21). Therefore, vaccinating patients at later timepoints posttransplant may be more beneficial with respect to immunogenicity. We also found that tacrolimus levels tended to be greater in non-responders. Calcineurin inhibitors have also previously shown to diminish vaccine responses (22). Immunogenicity (antibody titers) waned quite rapidly within only 6 months of the last vaccine dose (statistically significant for all HPV types) although the proportion of seropositive patients did not change (Figure 1). This is similar to studies in immunocompetent patients that show an initial decline in titers at approximately 12–24 months postvaccination although patients remain seropositive

(9). Prior studies have shown that HPV vaccine may also benefit those who are positive for some HPV types at baseline by preventing neoplasia by other HPV types in the vaccine (23).

Although there are no previous studies of HPV vaccine in transplant patients, there are several studies of HIV-positive cohorts that show 95–100% seropositivity after vaccination (24–26). However, patients enrolled in these studies have had mean CD4+ T cell counts over 500 cells/ $\mu$ L. Results obtained by cLIA for a subset of patients in our cohort have allowed us to make direct comparison with previously published immunogenicity studies. Titers in studies of immunocompetent individuals are variable and range from approximately 400 to 2,300 mMU/mL for the 24–34-year age group and depend on HPV type (14). With this assay, postvaccination geometric mean titers in our patients were several-fold lower. A variety of assays have been used to determine immunogenicity of vaccines in the population, namely, the cLIA, i.e. VLP-based IgG ELISA and pseudovirion-based neutralization assays (14,19,27–28). However, with either assay there are no clear cutoffs to determine protection from disease. Nevertheless, we show a clear dose–response in our cohort.

We did not find any significant safety concerns with the vaccine. Several patients developed CMV viremia; however, they had other risk factors such as CMV mismatch or were lung transplant recipients. We also found that three patients who had received all doses of the vaccine developed anogenital lesions; however, these were low-grade lesions and we did not confirm whether these were related to HPV-vaccine types.

Our study has some limitations. First, we did not have a nontransplant control group; however, very large immunogenicity studies have been previously reported in the general population using the cLIA assay to assess response rates. We are therefore readily able to compare our cLIA results with those published for the general population. We also did not have a placebo group; however, it was felt to be unethical to withhold vaccine from an age group where it is recommended. Second, our sample size is relatively small due to our conservative inclusion criteria and single center study. Despite this, we are able to show factors significantly affecting vaccine immunogenicity. We also did not do type specific PCR for molecular detection of HPV types. This could potentially be done in a future multicenter study. It is also conceivable that the patients who developed anogenital lesions were infected just prior to the vaccination. Serology may not be directly correlated with efficacy of the vaccine and correlates of protection for HPV vaccine are unknown. However, we are able to compare responses to the prevaccination titer as well as to titers published in the literature. Our study population consisted of a variety of organ transplants and it is possible that some subgroups may derive greater benefit from vaccine. A younger population than in our study may also have better immunogenicity. Other studies have used cell-mediated immunity as a marker for protection which may be useful to further evaluate in this population.

In summary, our study provides much needed data on the immunogenicity of HPV vaccine in immunosuppressed patients. We found suboptimal responses in posttransplant recipients. These results provide an initial look into factors to be considered when making decisions to provide vaccine for transplant recipients and counseling patients on risk. Newer nonavalent

HPV vaccines are under investigation although it is unknown whether these will perform better with regard to immunogenicity. As with other vaccines, pretransplant vaccination may be more beneficial. In addition, vaccination at a younger age may provide greater titers. Further studies are needed to determine ways to enhance immunogenicity such as by giving additional doses or using adjuvanted formulations of HPV vaccine.

## Acknowledgments

The findings and conclusions expressed in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

D. K. has received honoraria from Merck Vaccines and Pfizer; research support from Hoffmann-LaRoche; A. H. has received honoraria from Pfizer; research support from Hoffmann-LaRoche.

## Abbreviations

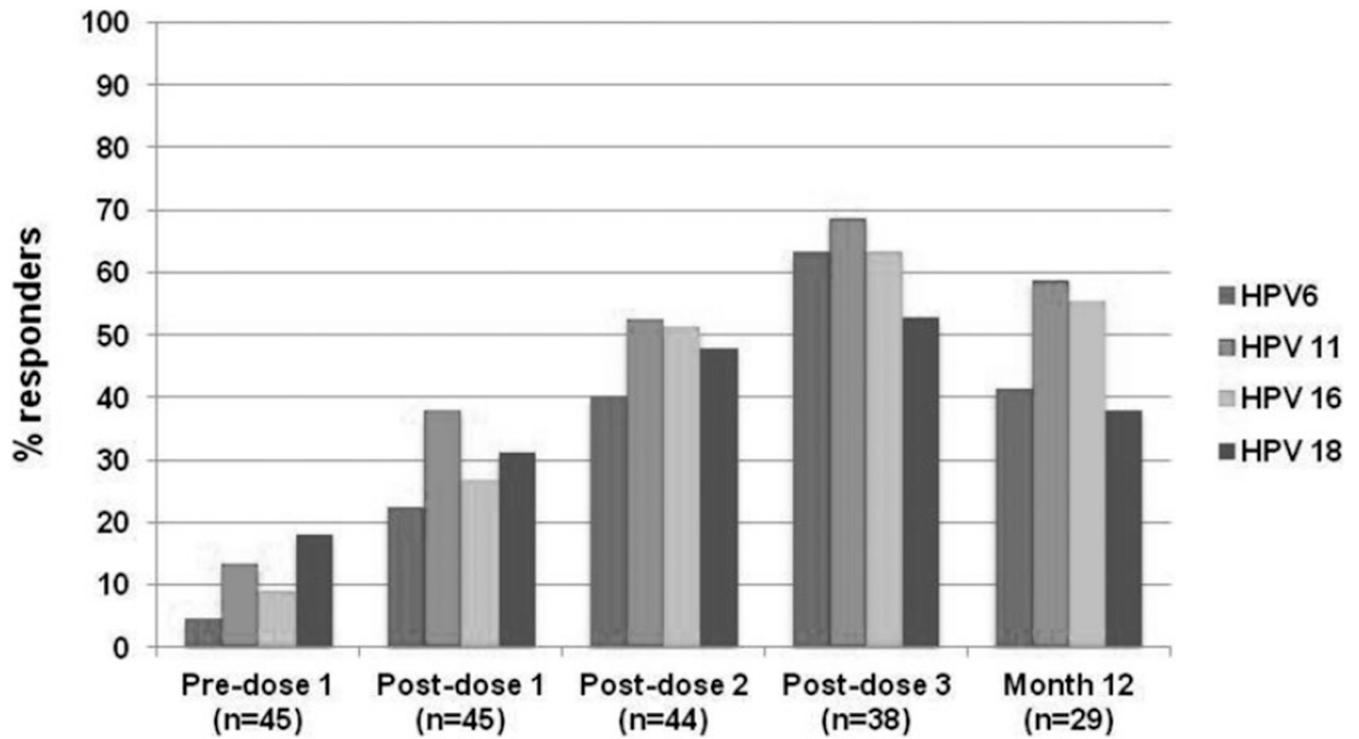
<b>AU</b>	arbitrary units
<b>cLIA</b>	competitive luminex immunoassay
<b>COV</b>	cut-off value
<b>HPV</b>	human papillomavirus
<b>MMF</b>	mycophenolate mofetil
<b>MSD</b>	Meso Scale Discovery
<b>PLL</b>	parallel line analysis
<b>RLU</b>	relative light units
<b>VLP</b>	virus-like particle

## References

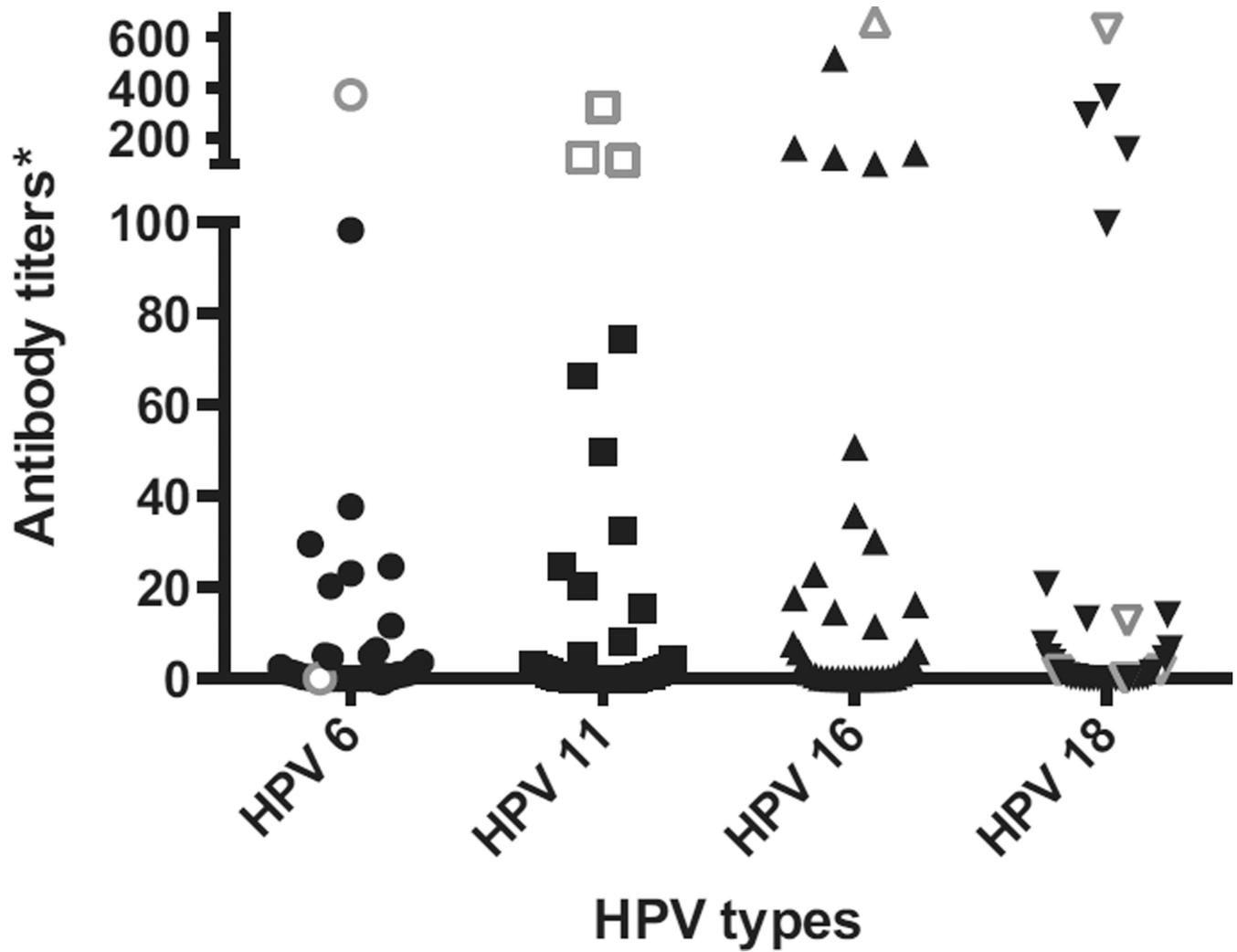
1. Meeuwis KA, Melchers WJ, Bouten H, et al. Anogenital malignancies in women after renal transplantation over 40 years in a single center. *Transplantation*. 2012; 93:914–922. [Comparative Study]. [PubMed: 22377788]
2. Park ST, Song MJ, Park JS, Hur SY, Lee CW. Incidence and clinicopathologic behavior of uterine cervical carcinoma in renal transplant recipients. *World J Surg Oncol*. 2011; 9:72. [Clinical Trial Comparative Study]. [PubMed: 21752252]
3. Paternoster DM, Cester M, Resente C, et al. Human papilloma virus infection and cervical intraepithelial neoplasia in transplanted patients. *Transplant Proc*. 2008; 40:1877–1880. [PubMed: 18675077]
4. Patel HS, Silver AR, Levine T, Williams G, Northover JM. Human papillomavirus infection and anal dysplasia in renal transplant recipients. *Br J Surg*. 2010; 97:1716–1721. [PubMed: 20730855]
5. Meeuwis KA, van Rossum MM, Hoitsma AJ, de Hullu JA. (Pre) malignancies of the female anogenital tract in renal transplant recipients. *Transplantation*. 2011; 91:8–10. [PubMed: 21452406]
6. Mochizuki K, Goda T, Yamauchi K. Gene expression profile in the liver of *Rana catesbeiana* tadpoles exposed to low temperature in the presence of thyroid hormone. *Biochem Biophys Res Commun*. 2012; 420:845–850. [PubMed: 22465015]
7. Kwak EJ, Julian K. Human papillomavirus infection in solid organ transplant recipients. *Am J Transplant*. 2009; 9(Suppl 4):S151–S160. [PubMed: 20070675]

8. Dillner J, Kjaer SK, Wheeler CM, et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, vaginal intraepithelial neoplasia, anogenital warts: Randomised controlled trial. *BMJ*. 2010; 341:c3493. [PubMed: 20647284]
9. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007; 356:1928–1943. [PubMed: 17494926]
10. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 2007; 356:1915–1927. [PubMed: 17494925]
11. Wheeler CM, Hunt WC, Joste NE, Key CR, Quint WG, Castle PE. Human papillomavirus genotype distributions: Implications for vaccination and cancer screening in the United States. *J Natl Cancer Inst*. 2009; 101:475–487. [Research Support, N.I.H., Extramural Research Support, N.I.H., Intramural]. [PubMed: 19318628]
12. Valles X, Murga GB, Hernandez G, et al. High prevalence of human papillomavirus infection in the female population of Guatemala. *Int J Cancer*. 2009; 125:1161–1167. [PubMed: 19415744]
13. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. *Int J Cancer*. 2007; 121:621–632. [PubMed: 17405118]
14. Munoz N, Manalastas R Jr, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11 16, 18) recombinant vaccine in women aged 24–45 years: A randomised, double-blind trial. *Lancet*. 2009; 373:1949–1957. [PubMed: 19493565]
15. Avery RK, Michaels M. Update on immunizations in solid organ transplant recipients: What clinicians need to know. *Am J Transplant*. 2008; 8:9–14. [PubMed: 18093271]
16. Pastrana DV, Buck CB, Pang YY, et al. Reactivity of human sera in a sensitive, high-throughput pseudovirus-based papillomavirus neutralization assay for HPV16 and HPV18. *Virology*. 2004; 321:205–216. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. [PubMed: 15051381]
17. Opalka D, Lachman CE, MacMullen SA, et al. Simultaneous quantitation of antibodies to neutralizing epitopes on virus-like particles for human papillomavirus types 6, 11 16, and 18 by a multiplexed luminex assay. *Clin Diagn Lab Immunol*. 2003; 10:108–115. [PubMed: 12522048]
18. Villa LL, Ault KA, Giuliano AR, et al. Immunologic responses following administration of a vaccine targeting human papillomavirus types 6, 11, 16, and 18. *Vaccine*. 2006; 24:5571–5583. [Clinical Trial, Phase II Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. [PubMed: 16753240]
19. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *N Engl J Med*. 2011; 364:401–411. [PubMed: 21288094]
20. Manuel O, Humar A, Berutto C, et al. Low-dose intradermal versus intramuscular trivalent inactivated seasonal influenza vaccine in lung transplant recipients. *J Heart Lung Transplant*. 2011; 30:679–684. [PubMed: 21377898]
21. Birdwell KA, Ikizler MR, Sannella EC, et al. Decreased antibody response to influenza vaccination in kidney transplant recipients: A prospective cohort study. *Am J Kidney Dis*. 2009; 54:112–121. [PubMed: 19185404]
22. Versluis DJ, Beyer WE, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation*. 1986; 42:376–379. [PubMed: 3532450]
23. FUTURE II Study Group. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. *J Infect Dis*. 2007; 196:1438–1446. [PubMed: 18008221]
24. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. *J Infect Dis*. 2010; 202:1246–1253. [PubMed: 20812850]
25. Levin MJ, Moscicki AB, Song LY, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *J Acquir Immune Defic Syndr*. 2010; 55:197–204. [PubMed: 20574412]

26. Weinberg A, Song LY, Saah A, et al. Humoral, mucosal, and cell-mediated immunity against vaccine and nonvaccine genotypes after administration of quadrivalent human papillomavirus vaccine to HIV-infected children. *J Infect Dis.* 2012; 206:1309–1318. [PubMed: 22859825]
27. Einstein MH, Baron M, Levin MJ, et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years. *Hum Vaccin.* 2009; 5:705–719. [PubMed: 19684472]
28. Einstein MH, Baron M, Levin MJ, et al. Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18–45 years. *Hum Vaccin.* 2011; 7:1359–1373. [PubMed: 22048172]



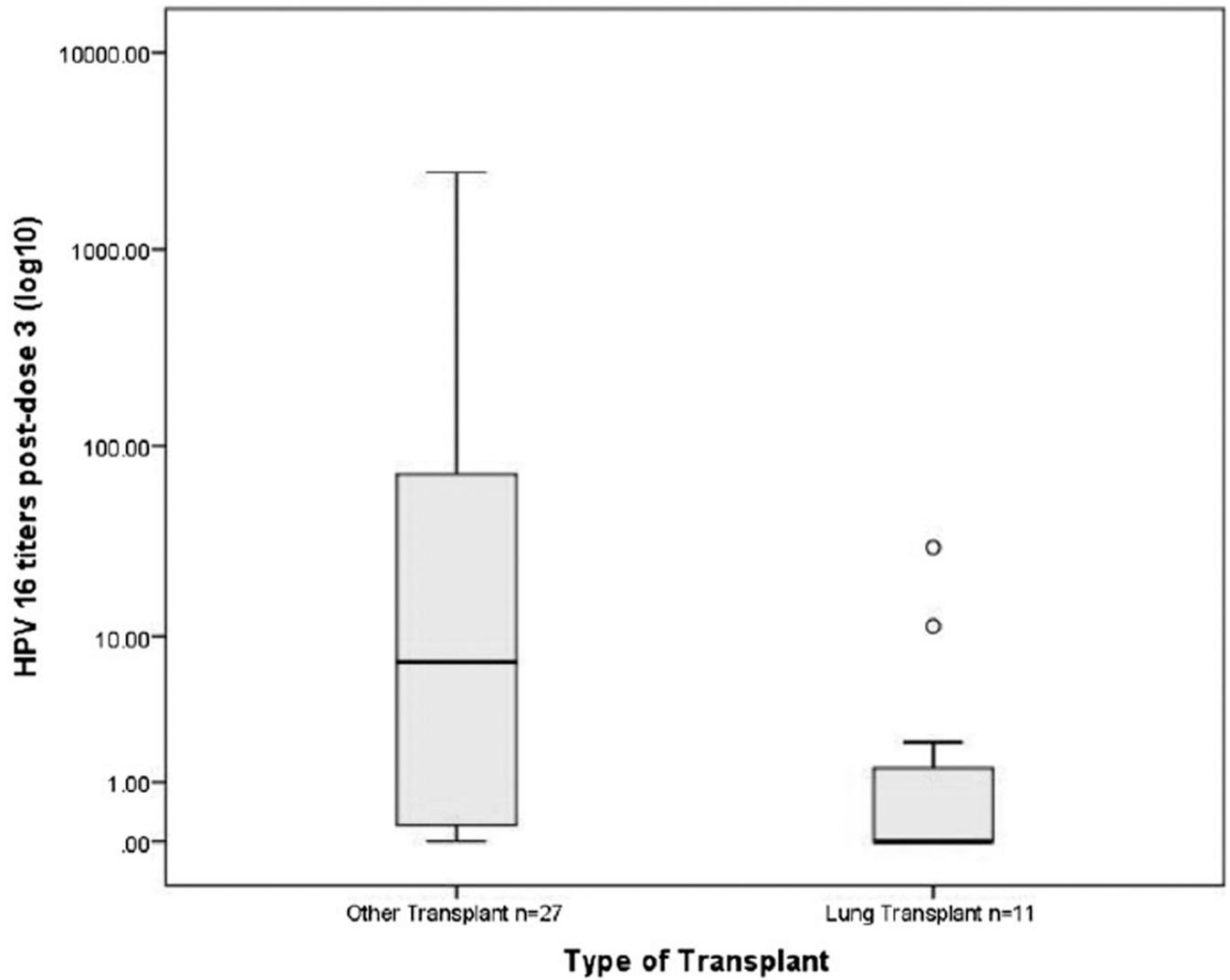
**Figure 1.**  
Vaccine response with Meso Scale Discovery ELISA assay at time points post-vaccine doses.



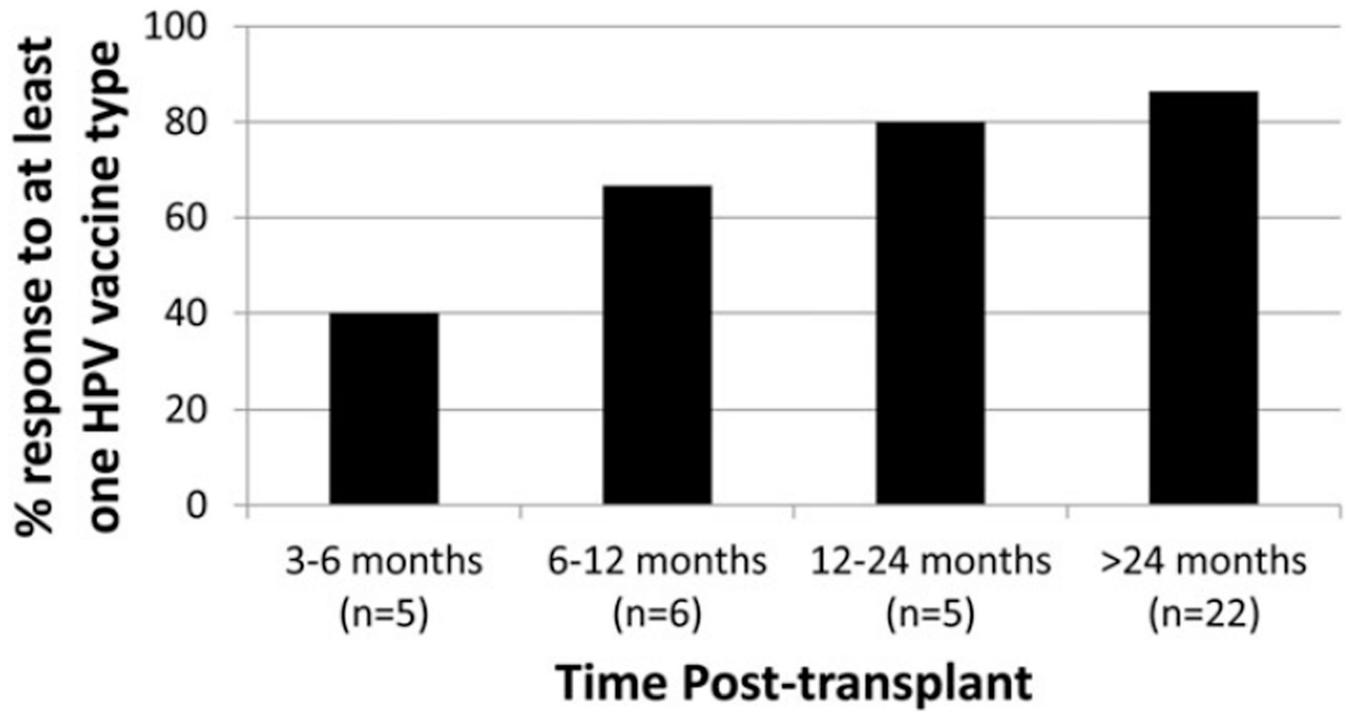
**Figure 2.**

Antibody titers after dose 3 (n = 38) for HPV vaccine types.

\*Titers are expressed as arbitrary units for HPV 6, 11, 18 and IU/mL for HPV 16. Hollow gray symbols indicate patients that were seropositive prior to vaccination. One patient's HPV 16 titer not shown on graph for clarity (2467 IU/mL). This patient was also seropositive prior to vaccine.



**Figure 3.** Antibody titers to HPV 16 using the Meso Scale Discovery ELISA comparing lung transplant recipients to other types of organ transplants at month 7 postvaccination.



**Figure 4.** Effect of time posttransplant on percentage of patients who responded to at least one HPV vaccine type.

**Table 1**

## Demographic characteristics of study population

Characteristic	N = 47
Age, median (range), years	25.9 (18–35)
IQR (years)	22–30
Gender (men/women)	16/31 (34%/66%)
Time from transplant, years (median; range)	2.7 (0.28–13.6)
Type of transplant	
Kidney	30 (63.8%)
Lung	11 (23.4%)
Heart	3 (6.4%)
Liver	1 (2.1%)
Other (heart/lung; multivisceral)	2 (4.3%)
Number of vaccine doses	
1	47 (100%)
2	45 (95.7%)
3	43 (91.5%)
Immunosuppression	
Prednisone	36 (76.6%)
Dose (mg, median, IQR)	5.0 (2.5–8.75)
Calcineurin-inhibitor	43 (91.5%)
Cyclosporin trough level (µg/L; median)	179
Tacrolimus trough level (µg/L; median)	6.7
Mycophenolate mofetil	42 (87.5%)
Dose (mg, median, IQR)	2000 (1470–2000)
Sirolimus	3 (6.4%)
Sirolimus level (µg/L; median)	9.1

**Table 2**

Univariate analysis of factors affecting response to at least one HPV vaccine type

Variable	Odds ratio (95% CI)	p value
Age (18–26 vs. >27 years)	0.71 (0.15–3.41)	0.67
Male gender	0.76 (0.17–3.47)	0.73
Time from transplant (<1 year vs. >1 year)	0.21 (0.04–1.03)	0.05
Type of transplant (lung vs. other)	0.21 (0.04–1.02)	0.05
Immunosuppression		
Prednisone use	0.60 (0.06–5.9)	0.66
MMF use	0.92 (0.08–10.2)	0.95
Tacrolimus level	0.64 (0.43–0.95)	0.03

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript