VIRAL INFECTIONS IN TRANSPLANT RECIPIENTS

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OUTLINES

- Introduction
- HPV
- VZV
- CMV

In-Depth Review

Common Infections in Kidney Transplant Recipients

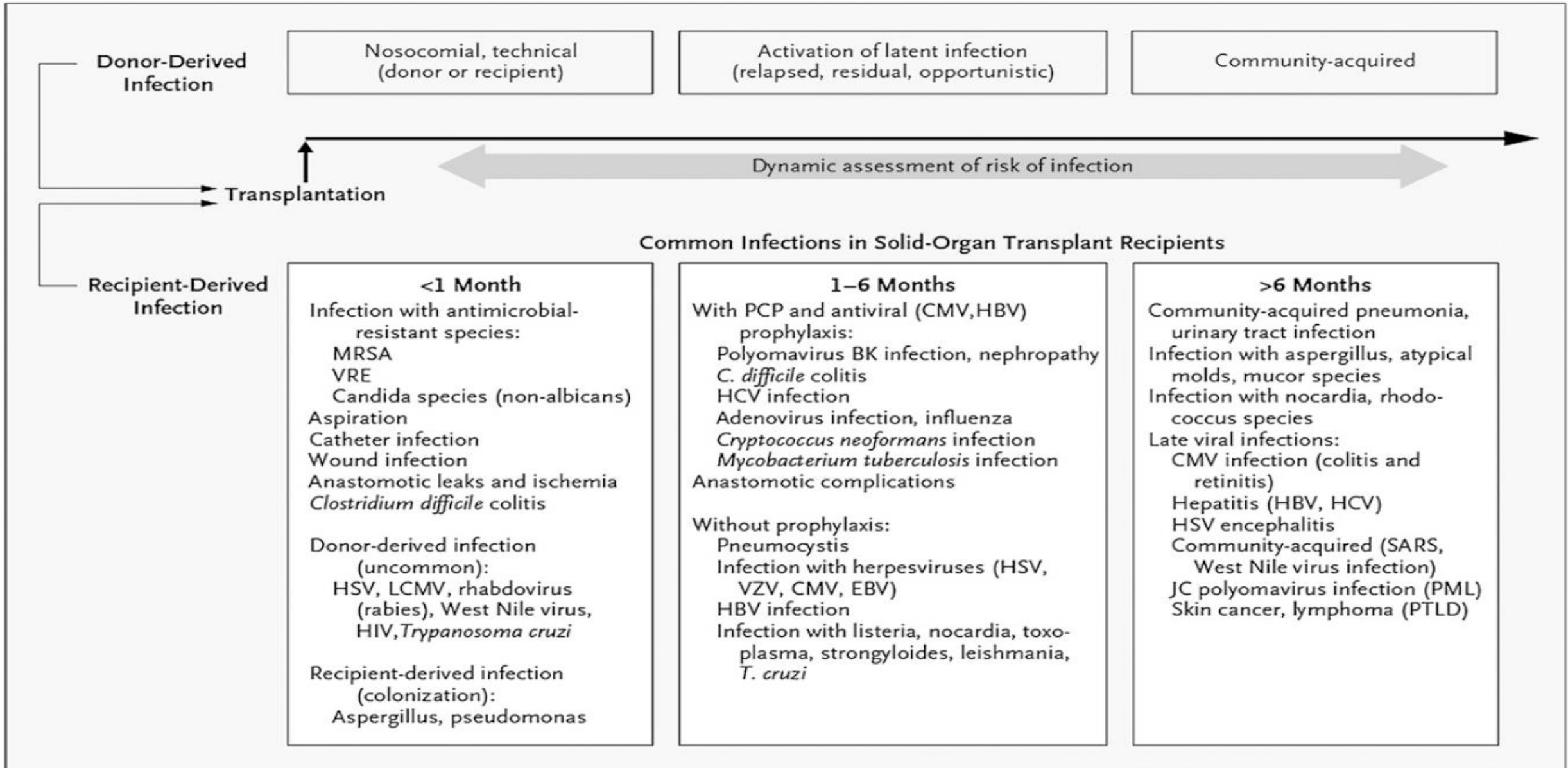
Shamila Karuthu and Emily A. Blumberg†*

Summary

Infections are a major cause of morbidity and mortality in kidney transplant recipients. To some extent, these may be preventable. Careful pretransplant screening, immunization, and post-transplant prophylactic antimicrobials may all reduce the risk for post-transplant infection. However, because transplant recipients may not manifest typical signs and symptoms of infection, diagnoses may be confounded. Furthermore, treatment regimens may be complicated by drug interactions and the need to maintain immunosuppression to avoid allograft rejection. This article reviews common post-transplant infections, including prophylactic, diagnostic, and treatment strategies, providing guidance regarding care of kidney transplant patients with infection.

Clin J Am Soc Nephrol 7: 2058–2070, 2012. doi: 10.2215/CJN.04410512

Karuthu Sh,et al.Clin J Am Soc Neph 7: 2012


Donor-Derived Infection
Nosocomial, technical (donor or recipient)
Activation of latent infection (relapsed, residual, opportunistic)
Community-acquired
Dynamic assessment of risk of infection
Transplantation
Recipient-Derived Infection
Common Infections in Solid-Organ Transplant Recipients
<1 Month
Infection with antimicrobial-resistant species:
MRSA
VRE
Candida species (non-albicans)
Aspiration
Catheter infection
Wound infection
Anastomotic leaks and ischemia
Clostridium difficile colitis
Donor-derived infection (uncommon):
HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, Trypanosoma cruzi
Recipient-derived infection (colonization):
Aspergillus, pseudomonas
1–6 Months
With PCP and antiviral (CMV,HBV) prophylaxis:
Polyomavirus BK infection, nephropathy
C. difficile colitis
HCV infection
Adenovirus infection, influenza
Cryptococcus neoformans infection
Mycobacterium tuberculosis infection
Anastomotic complications
Without prophylaxis:
Pneumocystis
Infection with herpesviruses (HSV, VZV, CMV, EBV)
HBV infection
Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, T. cruzi
>6 Months
Community-acquired pneumonia, urinary tract infection
Infection with aspergillus, atypical molds, mucor species
Infection with nocardia, rhodococcus species
Late viral infections:
CMV infection (colitis and retinitis)
Hepatitis (HBV, HCV)
HSV encephalitis
Community-acquired (SARS, West Nile virus infection)
JC polyomavirus infection (PML)
Skin cancer, lymphoma (PTLD)

< 1 MONTHS

- Donor-Derived inf. (uncommon):
  - HSV
  - LCMV
  - Rhabdovirus
  - West-Nile virus
  - HIV

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1-6 MONTHS

With prophylaxis

- Polyomavirus BK inf.
- HCV infection
- Adenomavirus inf.
- Influenza

Without prophylaxis

- Inf. With Herpesviruses (HSV, VZV, CMV, EBV)
- HBV inf.

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> 6 MONTHS

- Late viral infections:
  - CMV infection (colitis & retinitis)
  - Hepatitis (HBV & hcv)
  - HSV encephalitis
  - Community-acquired (SARS, West-Nile virus infection)
  - JC Polyomavirus infection
  - Skin cancer
  - PTLD

Karuthu Sh,et al.Clin J Am Soc Neph 7: 2012

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Review Article

Viral Infection in Renal Transplant Recipients

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Viruses are among the most common causes of opportunistic infection after transplantation. The risk for viral infection is a function of the specific virus encountered, the intensity of immune suppression used to prevent graft rejection, and other host factors governing susceptibility. Although cytomegalovirus is the most common opportunistic pathogen seen in transplant recipients, numerous other viruses have also affected outcomes. In some cases, preventive measures such as pretransplant screening, prophylactic antiviral therapy, or posttransplant viral monitoring may limit the impact of these infections. Recent advances in laboratory monitoring and antiviral therapy have improved outcomes. Studies of viral latency, reactivation, and the cellular effects of viral infection will provide clues for future strategies in prevention and treatment of viral infections. This paper will summarize the major viral infections seen following transplant and discuss strategies for prevention and management of these potential pathogens.

VIRAL INFECTIONS IN RTR

- Viruses are among the most common causes of opportunistic infection after transplantation.
- The risk for viral infection is a function of:
  - The specific virus encountered
  - the intensity of immune suppression used to prevent graft rejection
  - Other host factors governing susceptibility

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VIRAL INFECTIONS IN RTR

- The effects of viral infection are classified as:
  - Direct:
    - Fever & neutropenia syndrome & invasive disease such as pneumonia, enteritis, meningitis, or encephalitis
  - Indirect:
    - Due to release of cytokines, chemokines, & growth factors in response to viral infection of the body, which deepen immunosuppression & increase risk of other opportunistic infections.
    - May alter expression of surface antigens (e.g., HLA), provoking graft rejection.
    - Causing dysregulated cellular proliferation (oncogenesis).

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Human Papillomavirus in Kidney Transplant Recipients

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I. Virology

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide. It is an important cause of cervical, vaginal, vulvar, penile, anal and head and neck cancers in kidney transplant recipients (1). These are small DNA viruses, each comprising 7900 base pairs. There are over 100 distinct HPV subtypes. Of these, there are high-risk and low-risk types, distinguished by their association with invasive cancer – high in "high-risk" and low in "low-risk". Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are designated as high-risk types. Although low-risk types such as 6 and 11 do not cause invasive cancer, they are associated with anogenital warts. Types 16 and 18 (included in all three commercially available HPV prophylactic vaccines) are the most common HPV types found in cervical cancer, accounting for 70% of these malignancies (2,

HPV

- HPV is the most common sexually transmitted infection worldwide.
- It is an important cause of cervical, vaginal, vulvar, penile, anal & head & neck cancers in RTRs.
- There are > 100 distinct HPV subtypes.
- Of these, there are high-risk & low-risk types, distinguished by their association with invasive cancer.
- Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are designated as high-risk types.
- Although low-risk types such as 6 & 11 do not cause invasive cancer, they are associated with anogenital warts.
- Types 16 & 18 (included in all 3 commercially available HPV prophylactic vaccines) are the most common HPV types found in cervical cancer, accounting for 70% of these malignancies

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HPV

- HPV-associated head & neck cancers are thought to arise in the base of the tongue & the tonsils.
- The epidemiology is distinct from the head & neck cancers associated with older age, smoking & alcohol consumption.
- There is less evidence for a direct role between HPV infection & SCC of the skin.

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HPV

- The prevalence of warts is linked directly to the duration of immunosuppression.
- In patients who have been transplanted 4-5 years ago, the proportion of patients with warts reaches as high as 50-92%.
- Compared to the general population, RTRs have more numerous warts with a higher diversity of HPV types.
- Given that most lesions appear in sun exposed areas among transplant patients, ultraviolet light is thought to be a risk factor in this population.

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HPV VACCINES FOR RTR

Vaccine	Who to give	When to give	How to give	Adverse effects
Nonavalent (HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58; Gardasil 9, Merck, Whitehouse Station, New Jersey)	Routinely offer to boys and girls 11-12 years old Can vaccinate ages 9-26	Pre-transplant preferred. Also safe post transplant (non-infectious)	Three doses at months 0, 2 and 6	Minimal Mild to moderate localized pain, erythema, swelling
Quadrivalent (HPV types 6, 11, 16, 18; Gardasil, Merck, Whitehouse Station, New Jersey)	Routinely offer to boys and girls 11-12 years old Can vaccinate ages 9-26	Pre-transplant preferred. Also safe post transplant (non-infectious)	Three doses at months 0, 2 and 6	Minimal Mild to moderate localized pain, erythema, swelling
Bivalent (HPV types 16, 18; Cervarix, GlaxoSmithKline, Rixensart, Belgium)	Routinely offer girls 11-12 years old Can vaccinate ages 9-26	Pre-transplant preferred. Also safe post transplant (non-infectious)	Three doses at months 0, 1 and 6	Minimal Mild to moderate localized pain, erythema, swelling

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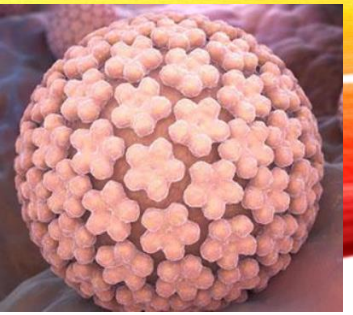

HPV

- Guidelines recommend screening in women from ages 21 until 65.
- Many transplant centers recommend that RTRs undergo the same screening protocol as HIV-infected women.
- For the first year following transplantation, a cervical Pap test should be performed every 6 months.
- If these are both normal, the screening interval can be increased to once yearly.

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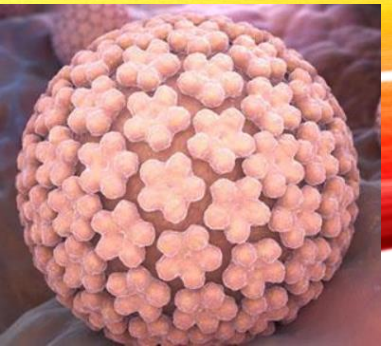

HPV

- It may be reasonable to reset the screening intervals back to twice yearly for one year if the patient has been treated for rejection, particularly if AT agents are used.
- Use of high-risk HPV testing is recommended for women aged ≥30 ys in conjunction with a Pap test in the general population. If both tests are negative, the screening interval can be increased to every 3 - 5 ys.
- Among immunocompromised women such as KTRs, most are screened every 6-12 ms.

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Immunogenicity of Quadrivalent Human Papillomavirus Vaccine in Organ Transplant Recipients

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Abstract

Go to:

Solid organ transplant recipients are at risk of morbidity from human papillomavirus (HPV)-related

DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

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%)

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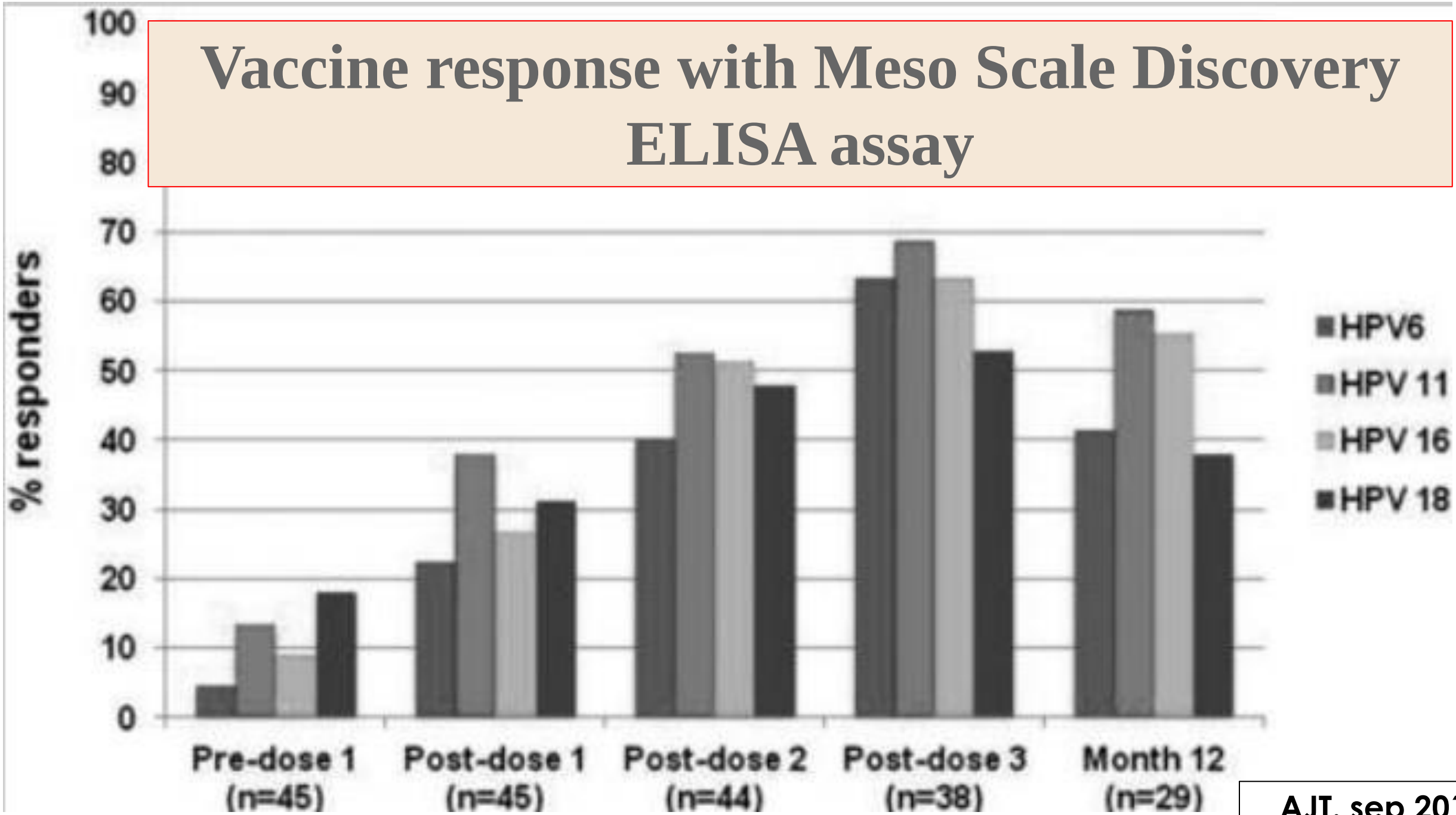
Vaccine response with Meso Scale Discovery ELISA assay



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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

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CONCLUSION

- We found suboptimal responses in posttransplant recipients.
- As with other vaccines, pretransplant vaccination may be more beneficial.
- 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.

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Sirolimus-Based Immunosuppression for Treatment of Cutaneous Warts in Kidney Transplant Recipients

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Keywords. human papillomavirus, kidney transplantation, sirolimus, viral infections, warts

Dermatological complications, especially skin infections, are very common following organ transplantation, and result in a lot of distress in the recipient. Herpes zoster, herpes simplex, and human papillomavirus infections are common infections in kidney transplant recipients, and therapeutic management is usually disappointing in immunosuppression state. We report here 2 cases of kidney transplant recipients who developed diffuse human papillomavirus-induced cutaneous warts with no response to conventional treatments. According to similar reports in organ transplant recipients, we modified the immunosuppressive regimen by converting to sirolimus, which led to a rapid relief from cutaneous warts in both patients. This evidence along with other case reports suggest that conversion to sirolimus may be considered as an effective strategy in cases of giant or multiple viral warts in kidney and perhaps other transplant recipients.

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www.ijkd.org

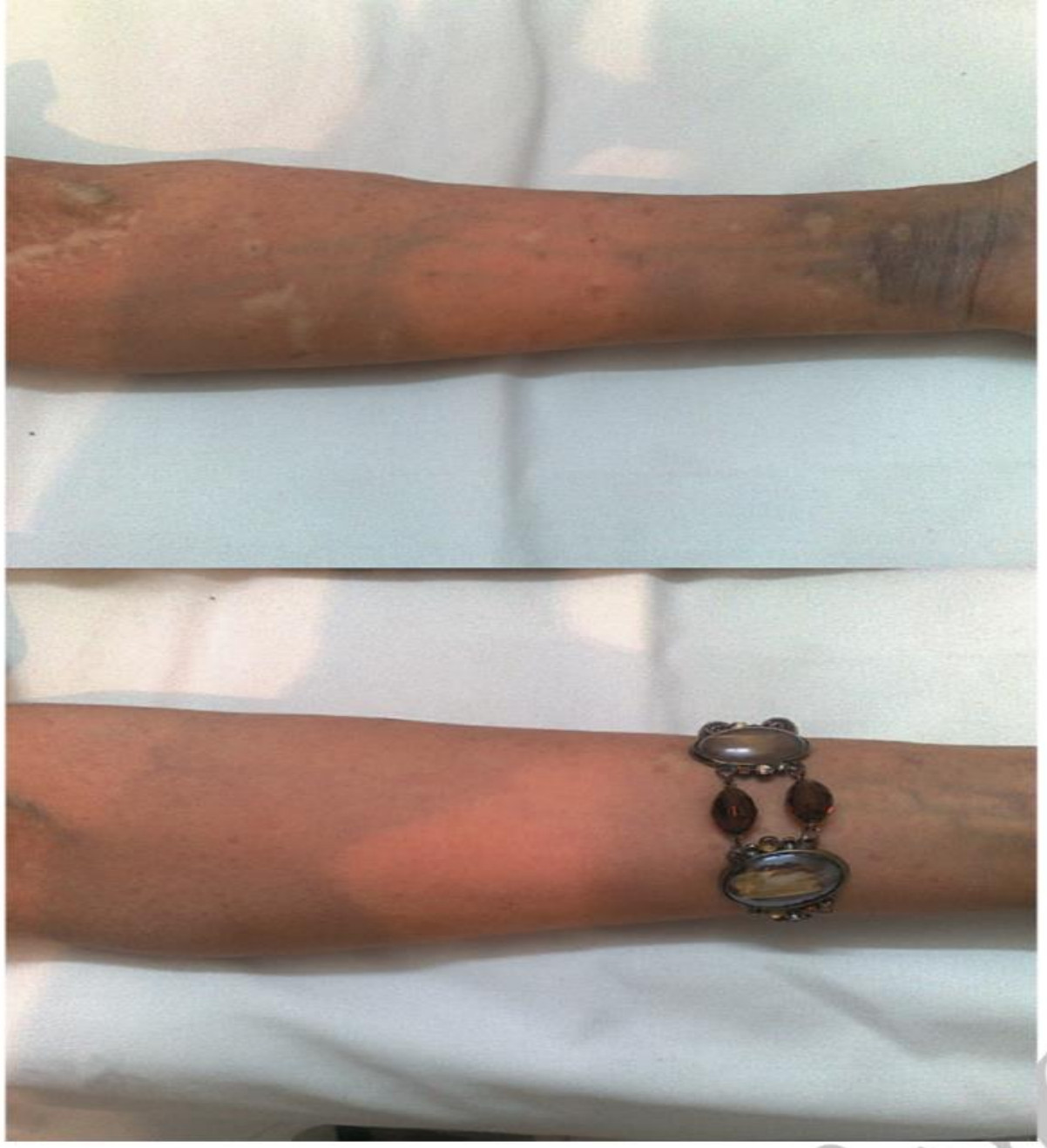

Figure 1. Top, Warts in a kidney transplant recipients. **Bottom**, improvement of the warts after conversion of cyclosporine to sirolimus.

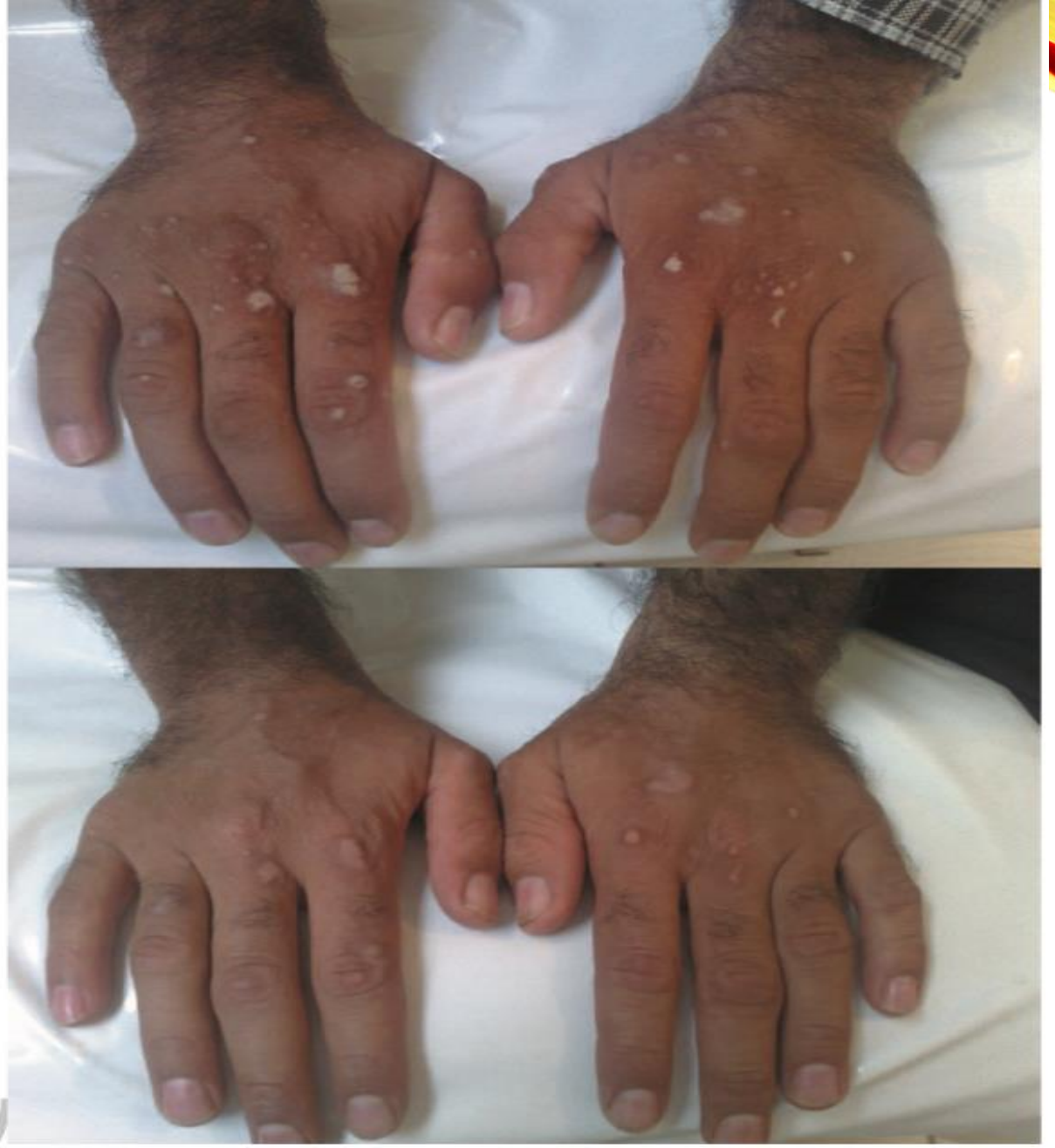

Figure 2. Top, Warts in a kidney transplant recipients. **Bottom**, improvement of the warts after conversion of cyclosporine to sirolimus.

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Reactivation of Latent HPV Infections After Renal Transplantation

F. Hinten, L. B. Hilbrands, K. A. P. Meeuwis, J. IntHout, W. G. V. Quint, A. J. Hoitsma, L. F. A. G. Massuger, W. J. G. Melchers, J. A. de Hullu

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Abstract

Female renal transplant recipients (RTRs) have an increased risk for developing human papillomavirus (HPV)–related (pre)malignant lesions of the genital tract. This study aims to assess the genital prevalence of HPV before and after renal transplantation (RT). In female patients who were counseled for RT at the Radboud University Medical Center Nijmegen, the Netherlands, gynecological examination was performed at first visit, and 1

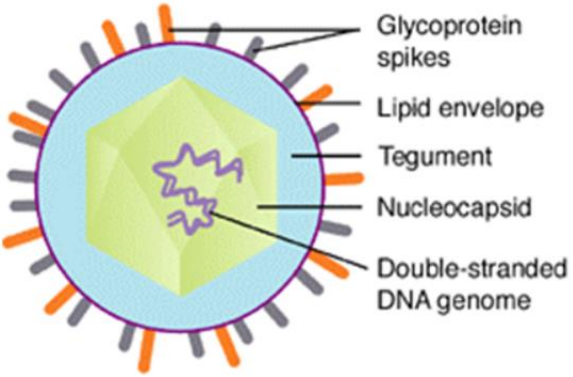
Figures References Related Infor

Reactivation of Latent HPV Infections After Renal Tx

- **In 65 patients who underwent RT, the hrHPV prevalence as assessed with the highly sensitive SPF_{10} -$LiPA_{25}$ test increased significantly from 19% before to 31% after RT (p = 0.045).**
- **Conclusion:**
  - **Activation of latent HPV infections may contribute to the increased risk of HPV-related (pre)malignant lesions in female RTRs.**

HPV SUMMARY

- Using a foundation of Pap testing, & careful & methodical routine PE, many precancer lesions can be identified & treated before progression to cancer.
- It is unfortunate that screening guideline uptake for HPV cancers in the KTRs is low.
- This is a silent epidemic that deserves our close attention & advocacy.



VZV OR HH3

- 90% of adult solid organ transplant recipients are VZV seropositive pretransplantation, & thus VZV reactivation in this group will cause herpes zoster.
- The remaining 10% are VZV seronegative & are thus at risk of primary infection.
- The incidence of VZV in renal transplant recipients is lower than HSV & is approximately 4 - 12%.
- VZV causes a spectrum of disease in solid organ transplant recipients, ranging from localized dermatomal zoster (involving a few adjoining dermatomes) to multidermatomal or disseminated zoster with or without visceral involvement

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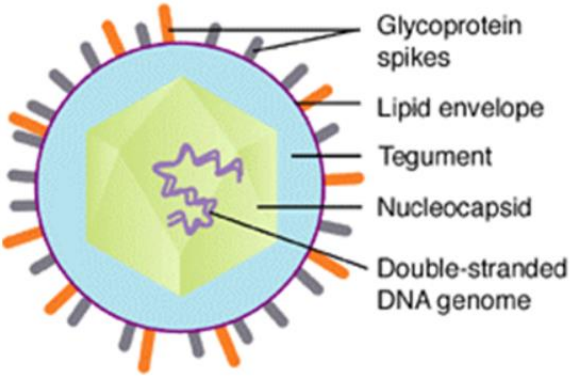

VZV OR HH3

- Pretransplant screening for previous VZV infection should be performed & na¨ıve patients should be vaccinated with live attenuated varicella vaccine before transplant whenever possible to avoid primary VZV infection after transplantation, an often severe disease with a high mortality rate.
- Due to the fact that the VZV vaccine is a live vaccine, the vaccine should not be given it if transplant is expected within 4-6 ws.

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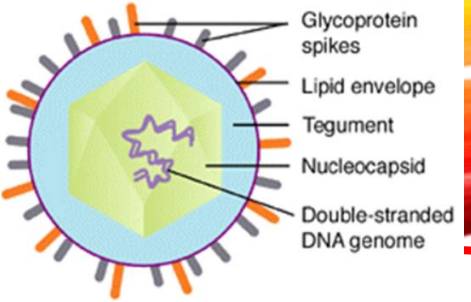

VZV OR HH3

- A VZV naïve transplant patient who is exposed to someone infected with varicella should receive:
  1. Varicella Ig within 96 hs of exposure.
  2. If VZIG is not available, or the patient presents >96 hs following exposure, acyclovir may be considered for postexposure prophylaxis.
- Posttransplant prophylaxis against reactivation of VZV & also HSV is recommended to prevent severe recurrences & consists of ganciclovir in patients needing CMV prophylaxis.
- Those patients who do not require CMV prophylaxis can receive valacyclovir or acyclovir for approximately 1-3 ms posttransplant

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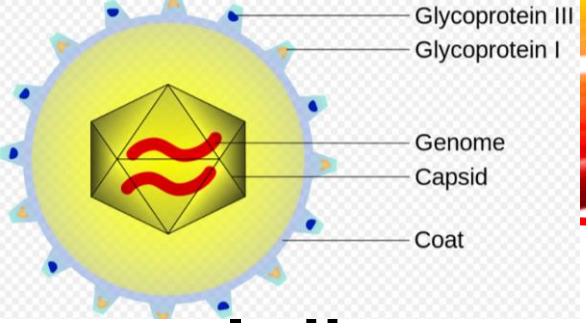

CMV OR HHV5

- Is the most common opportunistic infection in kidney tx recipients, occurring in 8 - 32% of patients.
- Risk factors for it include:
  1. Donor seropositivity (especially if the recipient is seronegative)
  2. Use of induction immunosuppression (T cell–depleting Abs)
  3. Simultaneous Kidney-pancreas transplantation
  4. Older donors (>60 ys)
  5. Presence of allograft rejection
  6. Concurrent infection from other viruses
- Antilymphocyte Ab is associated with a 2-5 fold increase in rate of CMV.

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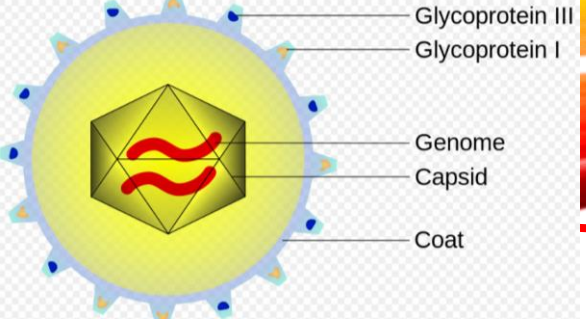

CMV OR HHV5

- **CMV infection** is defined as evidence of CMV replication regardless of symptoms.
- **CMV disease** requires both evidence of infection as well as symptoms, including viral syndrome with fever or malaise, leukopenia, thrombocytopenia, or evidence of tissue invasion (e.g., pneumonitis, hepatitis, retinitis, GI disease)

- CMV infection within 100 days of transplant is an independent risk factor for overall recipient mortality, & early CMV disease is associated with increased CV mortality beyond 100 days.

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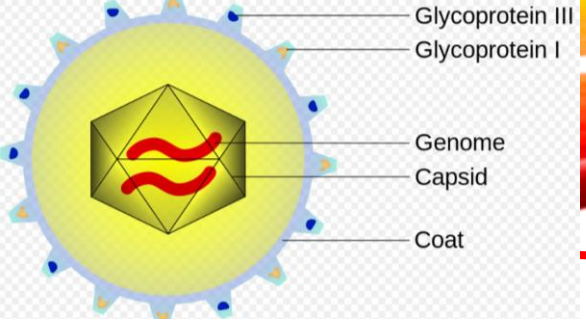

CMV OR HHV5

- More sensitive test is NAT.
- Viral load can be followed (usually weekly) to chart response to therapy.

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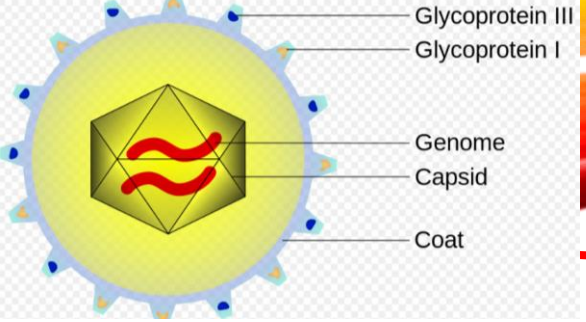

CMV OR HHV5

- Standard prophylactic guidelines:
  - Therapy in D+/R-, D+/R+, & D-/R+ using valganciclovir or oral ganciclovir (if available) for a minimum of 3 months after TX.
  - 1–3 ms after treatment with antilymphocyte Ab.
  - For the highest-risk recipients (CMV D+/R-), iv ganciclovir might also be considered.
- The optimal duration of prophylaxis is not known, but 6 ms is more effective in D+/R- RTx.

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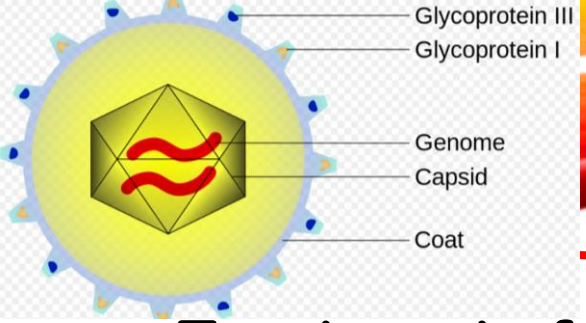

CMV OR HHV5

- Treatment of established CMV disease requires a multifactorial approach, including reduction of immunosuppressive agents, antiviral agents, & in some cases adjuvant therapy.
- Current guidelines:
  - Mild CMV disease: Valganciclovir, 900 mg twice daily, or IV ganciclovir, 5 mg/kg twice daily.
  - Life-threatening CMV disease, high viral loads, leukopenia, & impaired absorption, IV ganciclovir is preferable & maintenance immunosuppression should be decreased despite the potential risk of rejection.
  - Administration of CMV-specific hyperimmune globulin or standard IV IgG may be considered as adjuvant therapy in individuals with hypogammaglobulinemia, failure to respond to standard therapy, or severe systemic infection.

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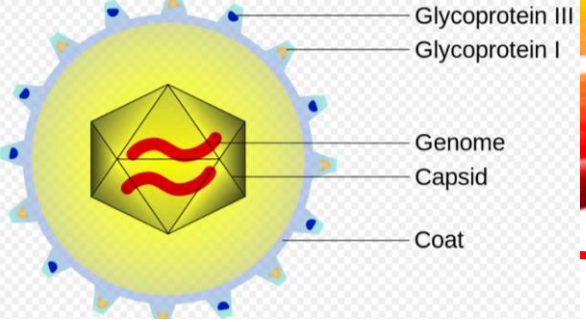

CMV

- If CMV disease worsens or the viral load increases despite 2 ws of therapy, ganciclovir resistance should be considered.
- CMV resistance is usually attributed to prolonged exposure to subtherapeutic ganciclovir (especially with oral ganciclovir).

Karuthu Sh,et al.Clin J Am Soc Neph 7: 2012

SUMMARY

- Although CMV is the most common opportunistic pathogen seen in RTRs, numerous other viruses have also affected outcomes.
- In some cases, preventive measures such as pretransplant screening, prophylactic antiviral therapy, or posttransplant viral monitoring may limit the impact of these infections.
- Recent advances in laboratory monitoring & antiviral therapy have improved outcomes.
- Studies of viral latency, reactivation, & the cellular effects of viral infection will provide clues for future strategies in prevention & treatment of viral infections.