HPV The BCN HPV Course

Jornadas sobre el VPH

21st October 2021,
Barcelona

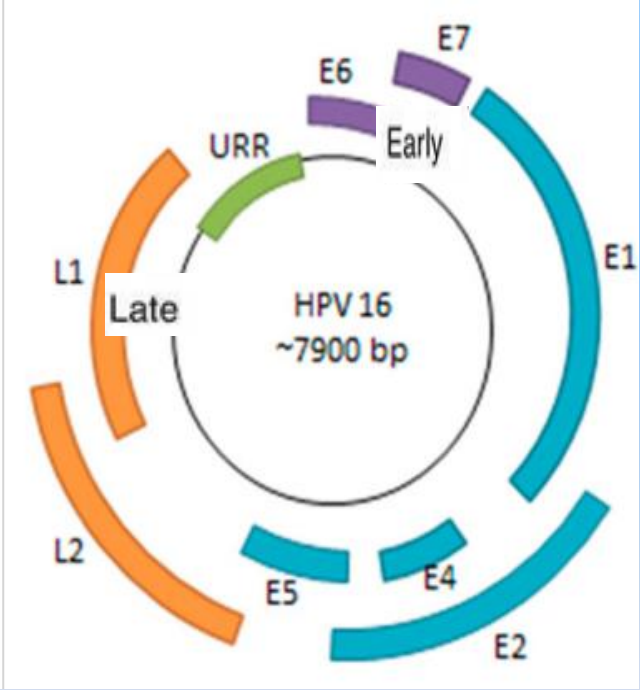
Screening in transplanted patients

Guillem Sirera

FLS, Hospital Germans Trias, Badalona

Structure of human papillomavirus and function of its viral proteins

Viruses **2017**, *9*(8), 229



GENES	ACTIVITY
L1	Major Capsid protein
L2	Minor Capsid protein
E1	Replication of Viral genome and its maintenance
E2	Initiation of viral DNA replication; regulates transcription of E6 and E7
E4	Release of viral particles
E5	Enhances growth factor signaling pathways
E6	Inhibits p53 and causes loss in cell cycle regulation
E7	pRb mediated deregulation of cell cycle

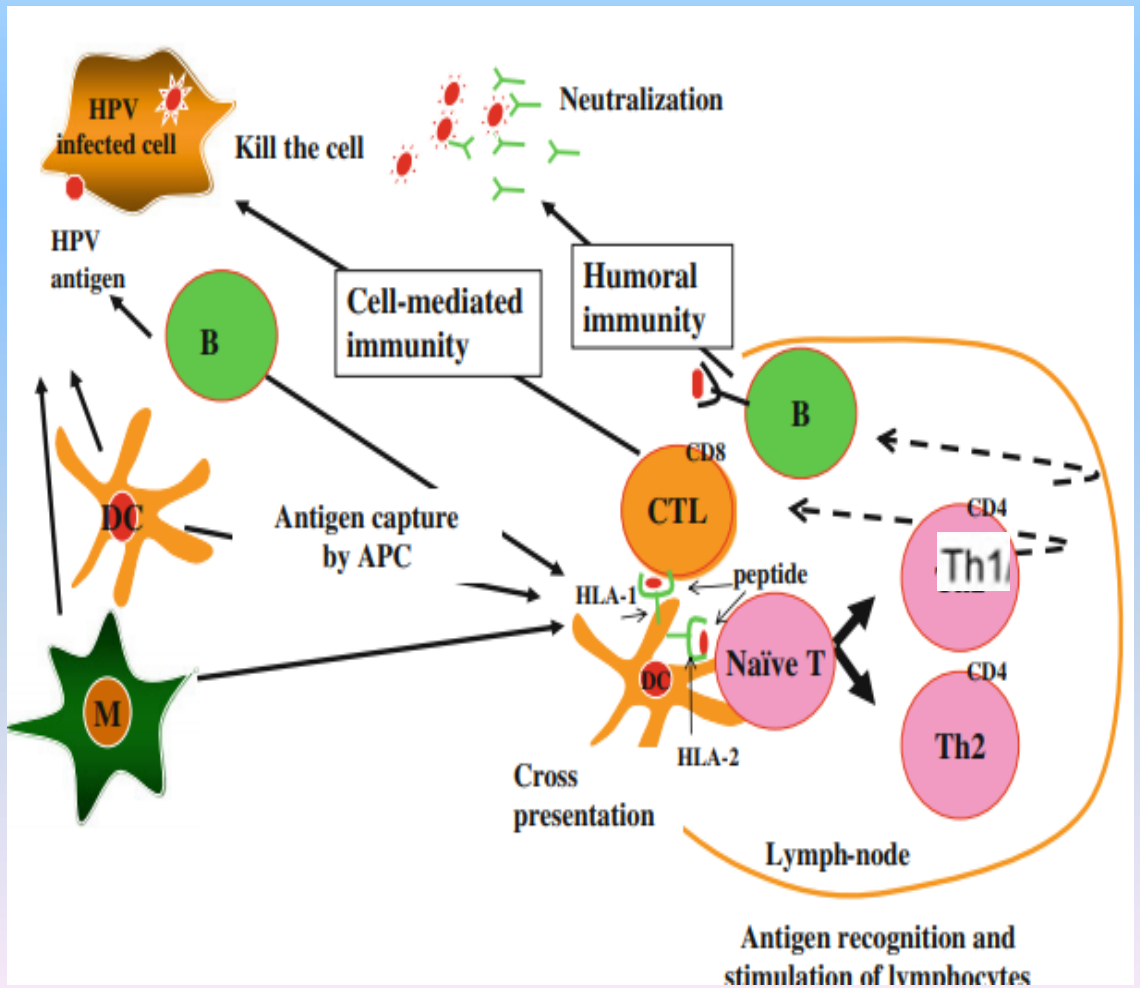
The human papillomavirus family and its role in carcinogenesis

Tommasino, M. (2014) Seminars in Cancer Biology

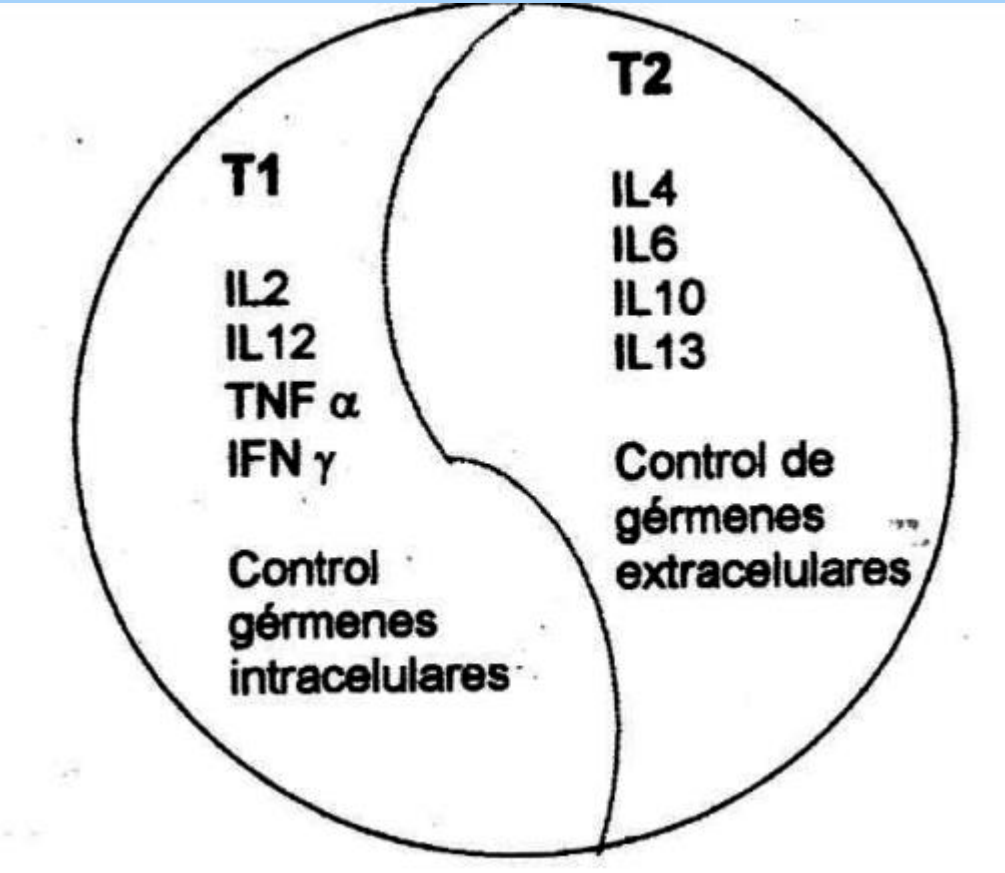
		HPV type	Disease (% attributed cases)
Alpha	mucosal lhigh-risk	HPV16	Cervical squamous cell carcinoma (~50) Cervical adenocarcinoma (~35) Oropharyngeal cancer (~25)
		HPV18	Cervical squamous cell carcinoma (~20) Cervical adenocarcinoma (~35)
		HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Cervical squamous cell carcinoma (~30)
	mucosal low-risk	HPV6, 11	Benign genital lesions Respiratory papillomatosis
		HPV13, 32	Oral focal epithelial hyperplasia
	cutaneous benign	HPV2,3, 27, 57	Skin warts
Mu		HPV1	Skin warts
Beta	cutaneous	HPV5 and 8	First beta HPV types isolated from SSC of EV indiviuals
		HPV9, 12, 14, 15, 17, 19-25, 36-38, 47, 49, 75, 76, 80, 92, 93, 96, 98-100, 104, 105, 107, 110, 111, 113, 115, 118, 120, 122, 124, 143, 145, 150- 152, 159	Likely associated with SCC in EV patients as well as immuno-compromised and immuno-competent individuals
Gamma		HPV4, 48, 50, 60, 65, 88, 95, 101, 103, 108, 109, 112, 115, 116, 119, 121, 123, 126-142, 144, 146-149, 153-158, 161-170	Unknown

Immune responses against human papillomavirus (HPV) infection

Journal of Infection and Chemotherapy, 2012

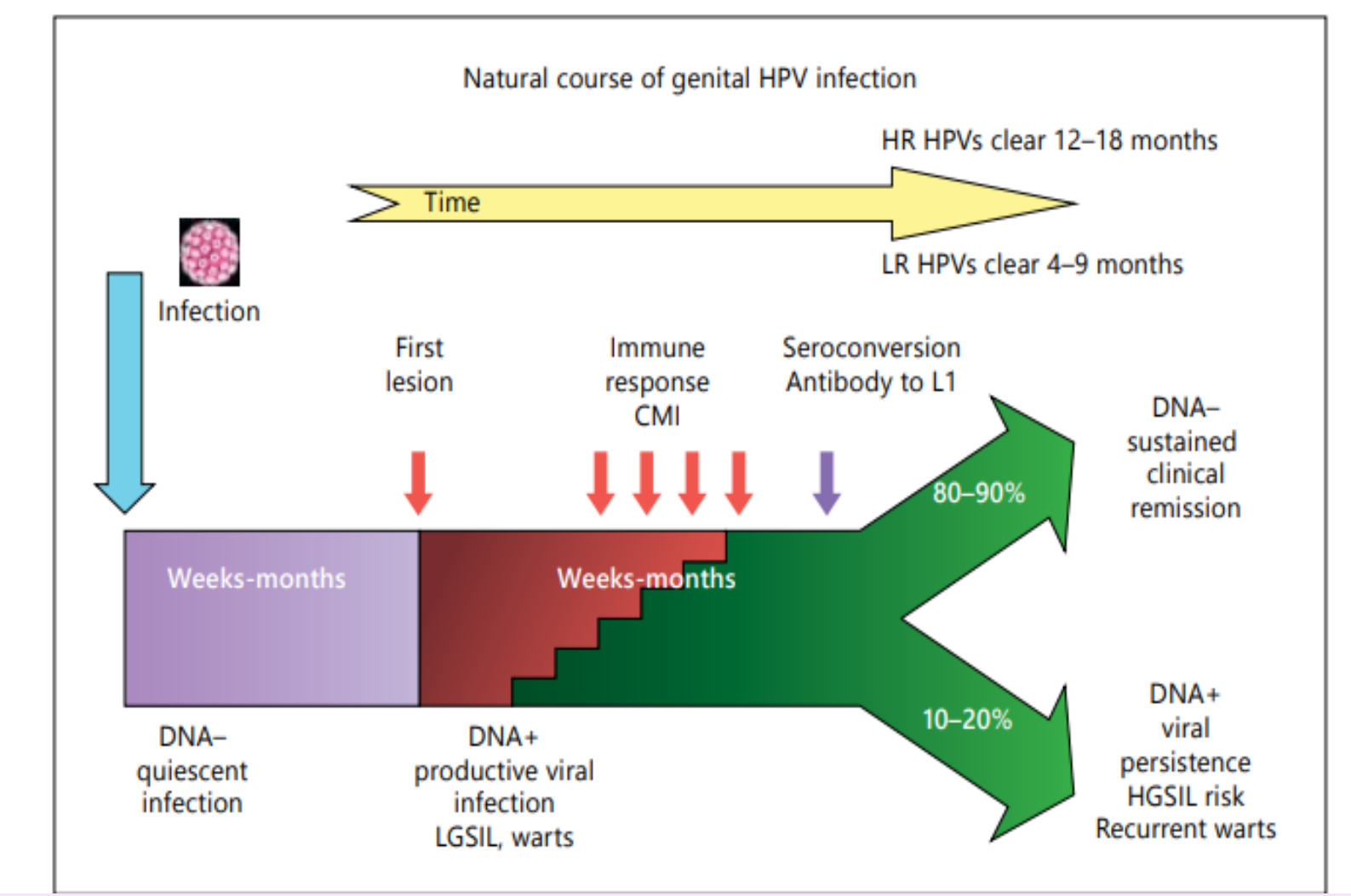


Acta Med Colomb Vol. 24 N°5 ~ 1999



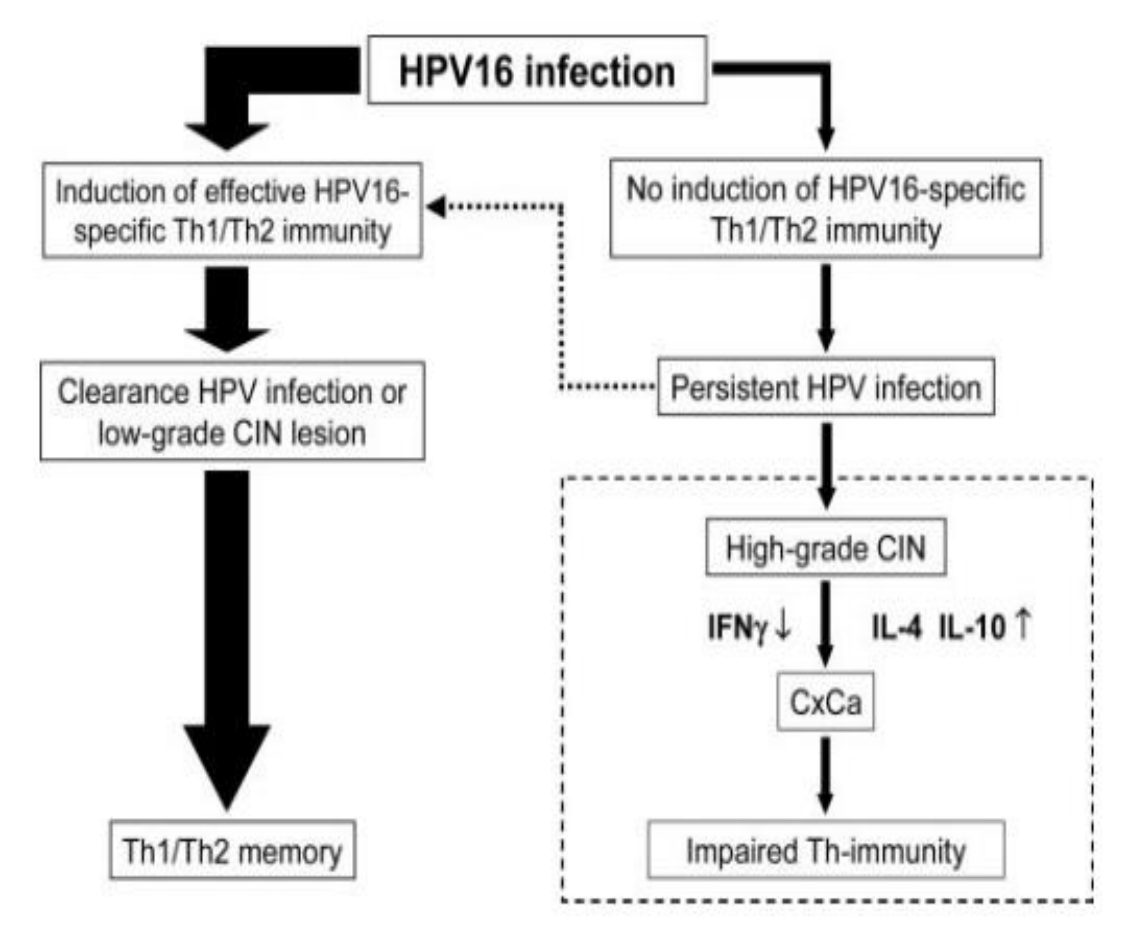
Host responses to infection with human papillomavirus

Stanley M.



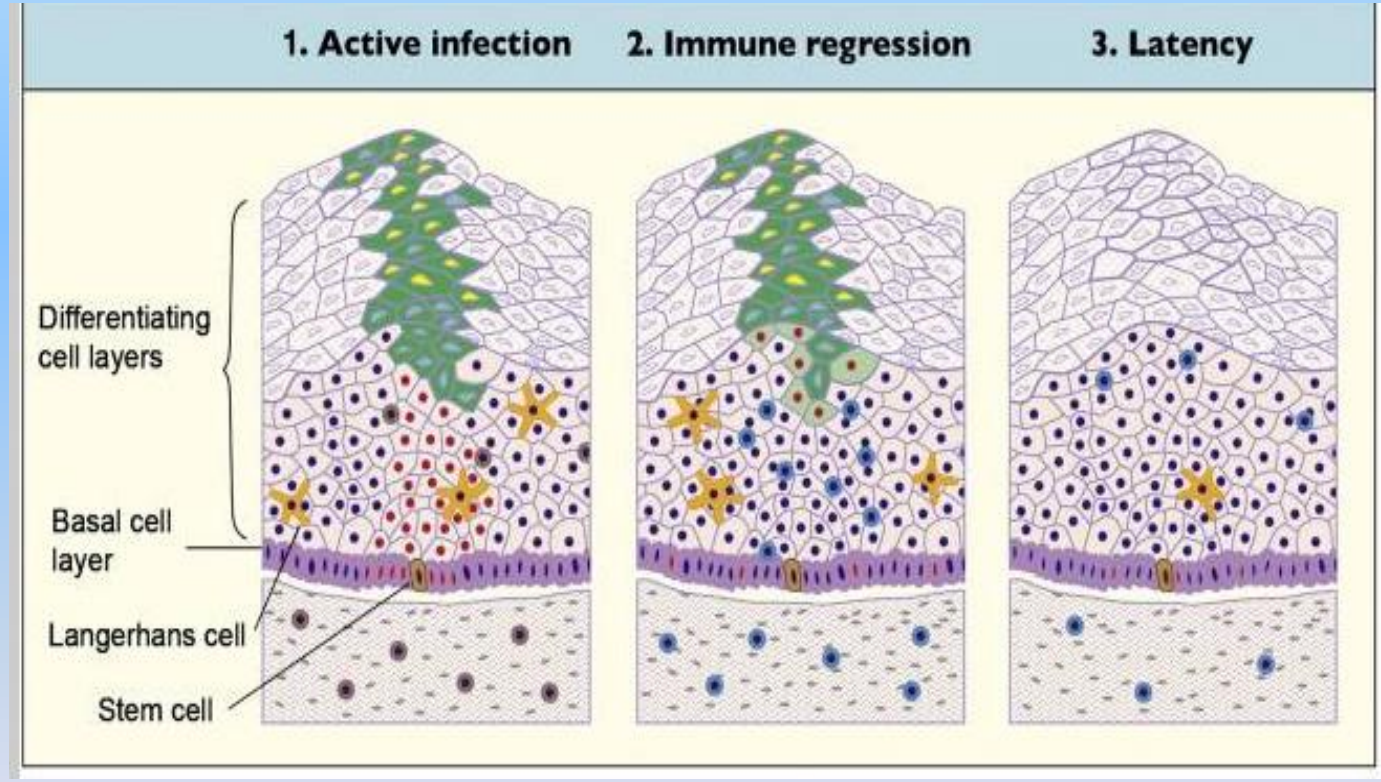
Proposed model for the association between human papillomavirus (HPV) 16-specific CD4 T-cell immunity and the development of HPV16-induced disease.

de Jong [CANCER RESEARCH 64, 5449–5455, 2004]



Immune clearance, latency and possible reactivation

John Doorbar et al. Vaccine 2012: 30,5



Cells driven into cell cycle

E4 expression + virus assembly

E4 expression + genome amplification

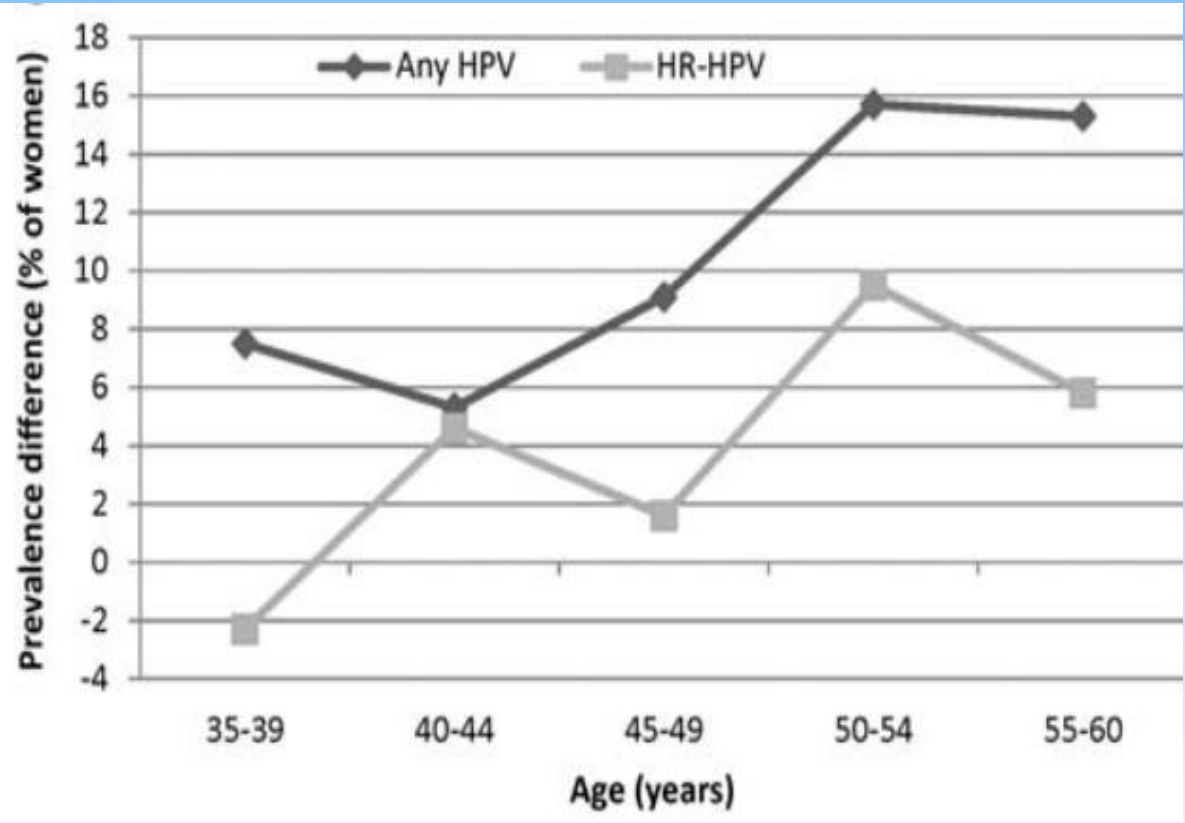
T cells

Active T cells

Relative difference in prevalence proportions of any HPV and HR-HPV between subjects with ≥5 lifetime sex partners

Patti E. Gravitt, The Journal of Infectious Diseases 2013

An increase in HPV prevalence at older ages, which may be secondary to reactivation of “latent” infection.



Natural History and Possible Reactivation of Human Papillomavirus in Human Immunodeficiency Virus–Positive Women

Howard D. Strickler, Joel M. Palefsky
Journal of the National Cancer Institute, Vol. 97, No. 8, April 20, 2005

1848 VIH + and 514 VIH - women

Semiannual visits

Techniques: PCR VPH /CERVIX CITOLOGY

AIM OF THE STUDY: HPV infection and SILs prevalence, persistence and incident.

RESULTS:

High risk with < 200 CD4 y > 100.000 copias/ml

Incident detection of human papillomavirus (HPV) in sexually active and inactive women

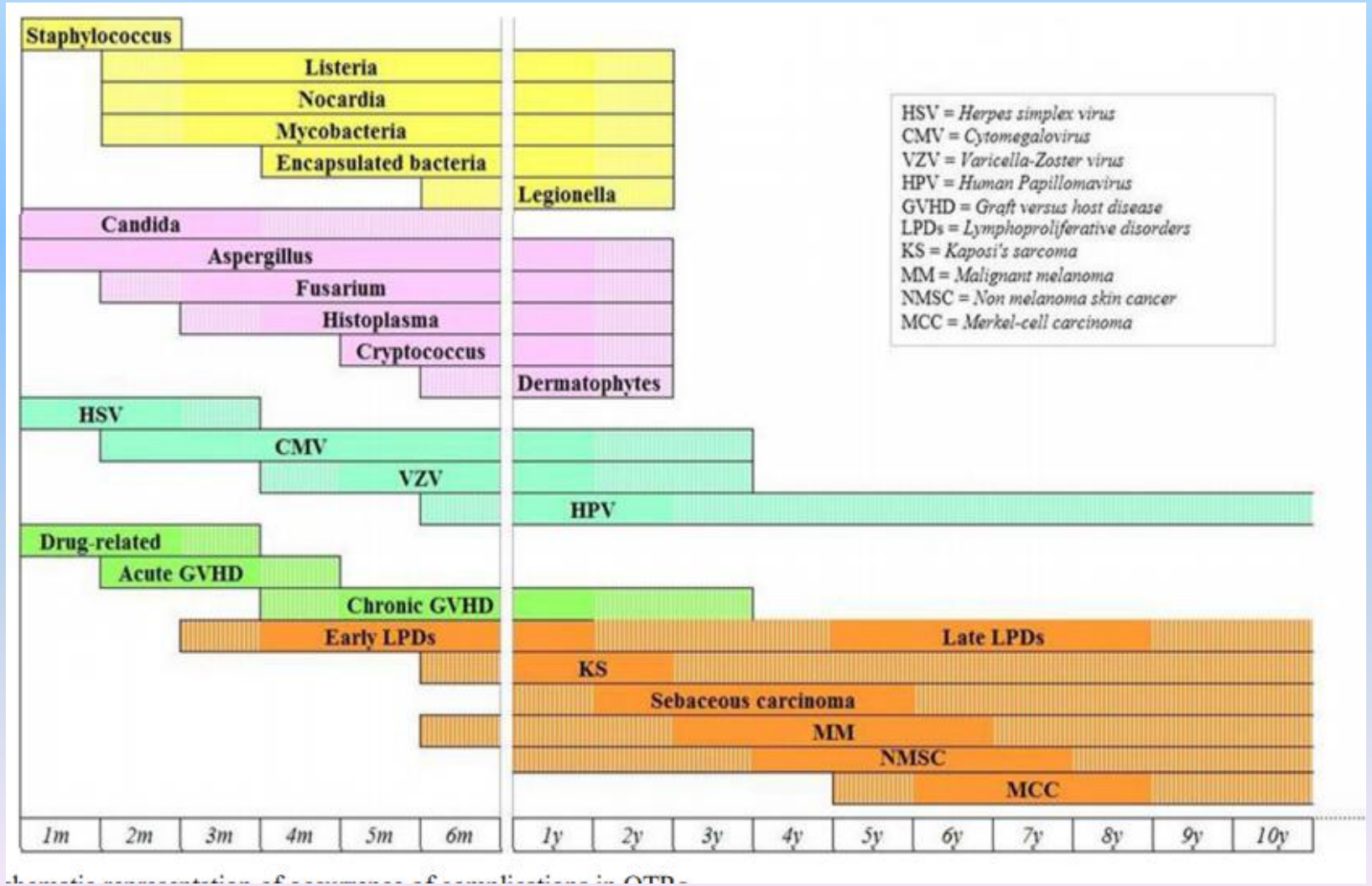
Sexual activity	HIV-positive women			HIV-negative women
	<200†	200–500†	>500†	
Sexually active for at least past 18 mo	13/42 (31)	25/141 (18)	14/112 (13)	14/174 (8)
No sexual activity for at least past 18 mo	7/32 (22)	6/65 (9)	3/46 (7)	2/43 (5)

CONCLUSION:

In HIV-positive women, plasma HIV RNA level and CD4+ count appear to have a strong association with incident detection of HPV, some of which may reflect HPV reactivation (e.g., in sexually inactive women).

Schematic representation of occurrence of complications in OTRs

Naldi, L Clinic Rev Allerg Immunol 2017



Infection and transplantation

EFFECTIVE IMMUNOSUPPRESSION

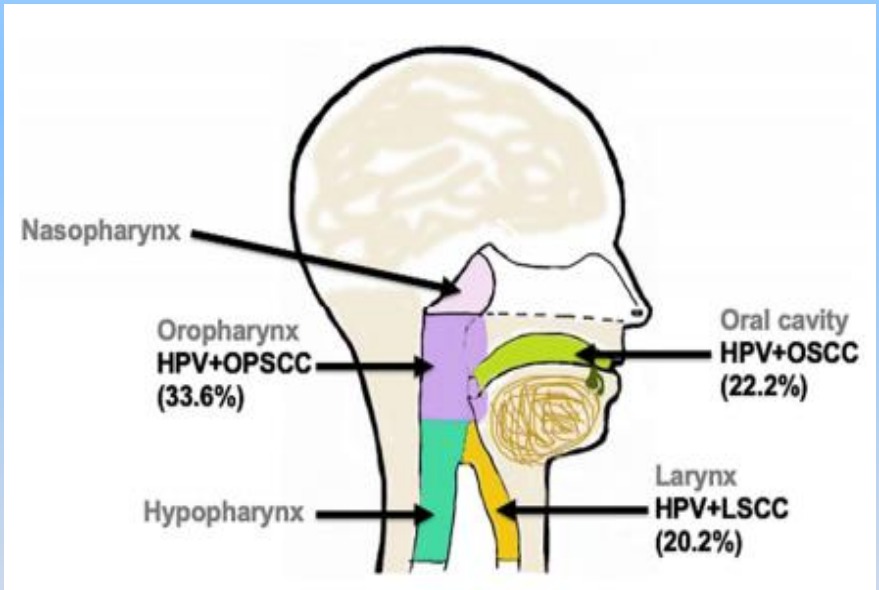
Graft failure **Infection**

HPV CANCER AND TRANSPLANTATION

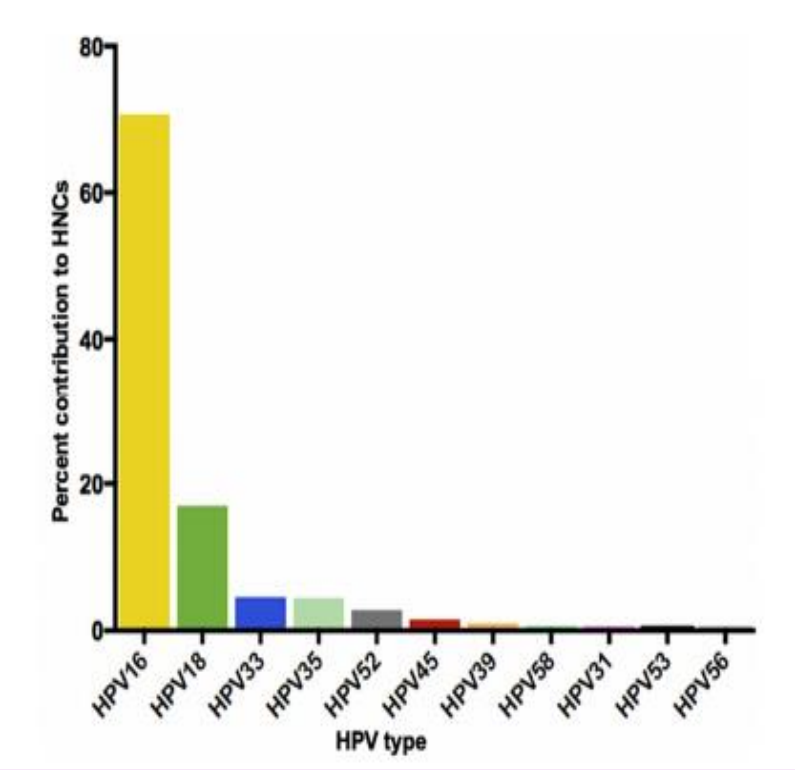
1. Head and neck squamous cell carcinoma

Ebenezer Tumban. Viruses 2019, 11, 922

Distribution of human papillomavirus-associated head and neck cancers (HPV + HNC) between anatomical sites

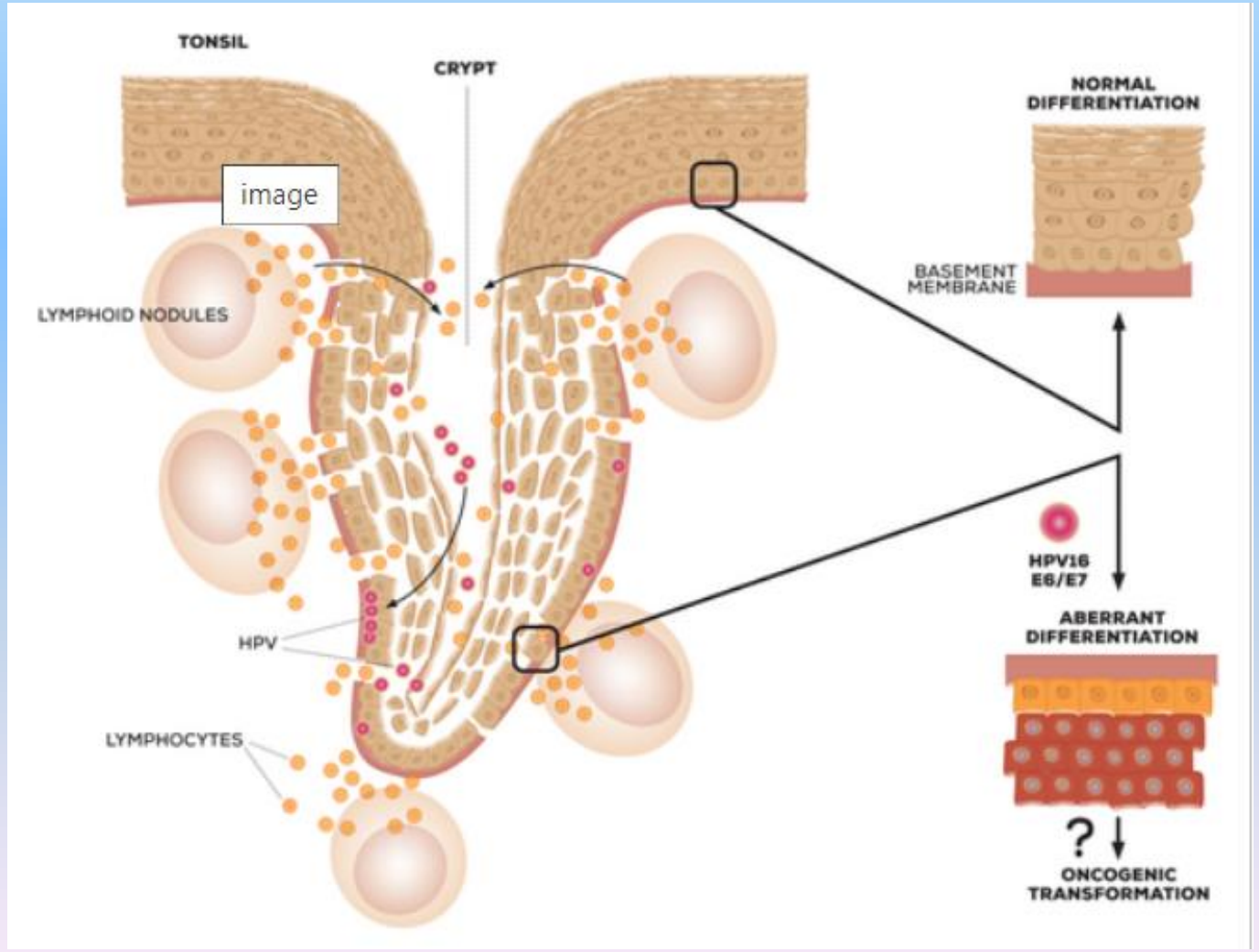


The prevalence/contribution of human papillomavirus types



Human papillomavirus (HPV) in oropharyngeal carcinogenesis

Tara A. Berman, Cancer June 2017



Characteristics and long-term outcomes of head and neck squamous cell carcinoma after solid organ transplantation

Samer Alsidawi Oral Oncology , 2017 , 72, 104–109

1995 and 2010: **33 patients** who had received a solid organ transplant (kidney, liver, heart, lung or pancreas).

RESULTS:

- The median time to diagnosis of HNSCC after transplant was 5.9 years.
- The primary site was: oral cavity in 15 patients, oropharynx in 10, larynx in 3, hypopharynx in 2, parotid in 2 and unknown in 1 patient.
- The 5-year overall survival rate was: 37 % locally advanced disease.
- Seventy five percent of patients with oropharyngeal tumors were HPV-positive and they had better outcomes (5-year overall survival rate of 67%).
- In multivariate analysis, age 60 years was a negative predictor of survival (HR 2.7; 95% CI, 1.1–6.5; P = 0.03).

Samer Alsidawi Oral Oncology, 2017 , 72, 104–109

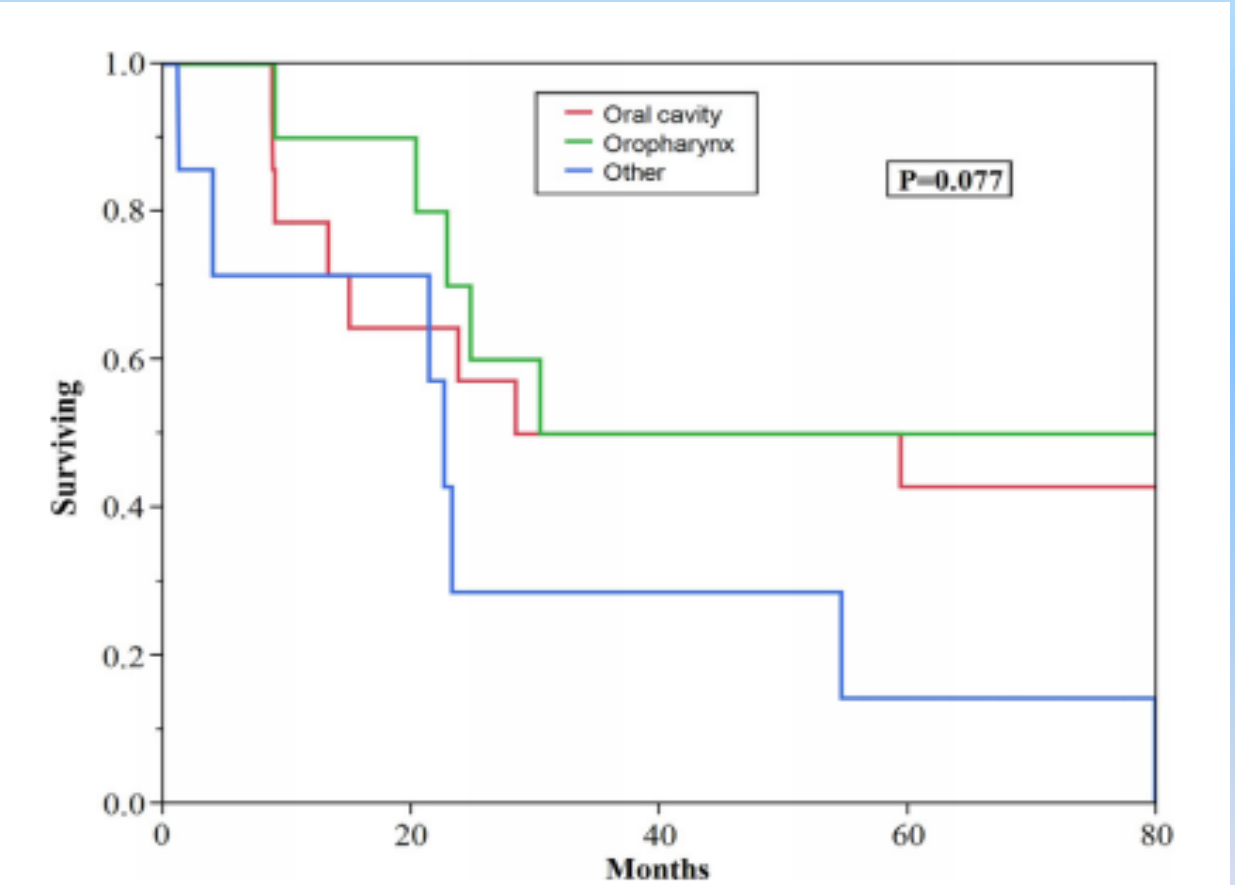
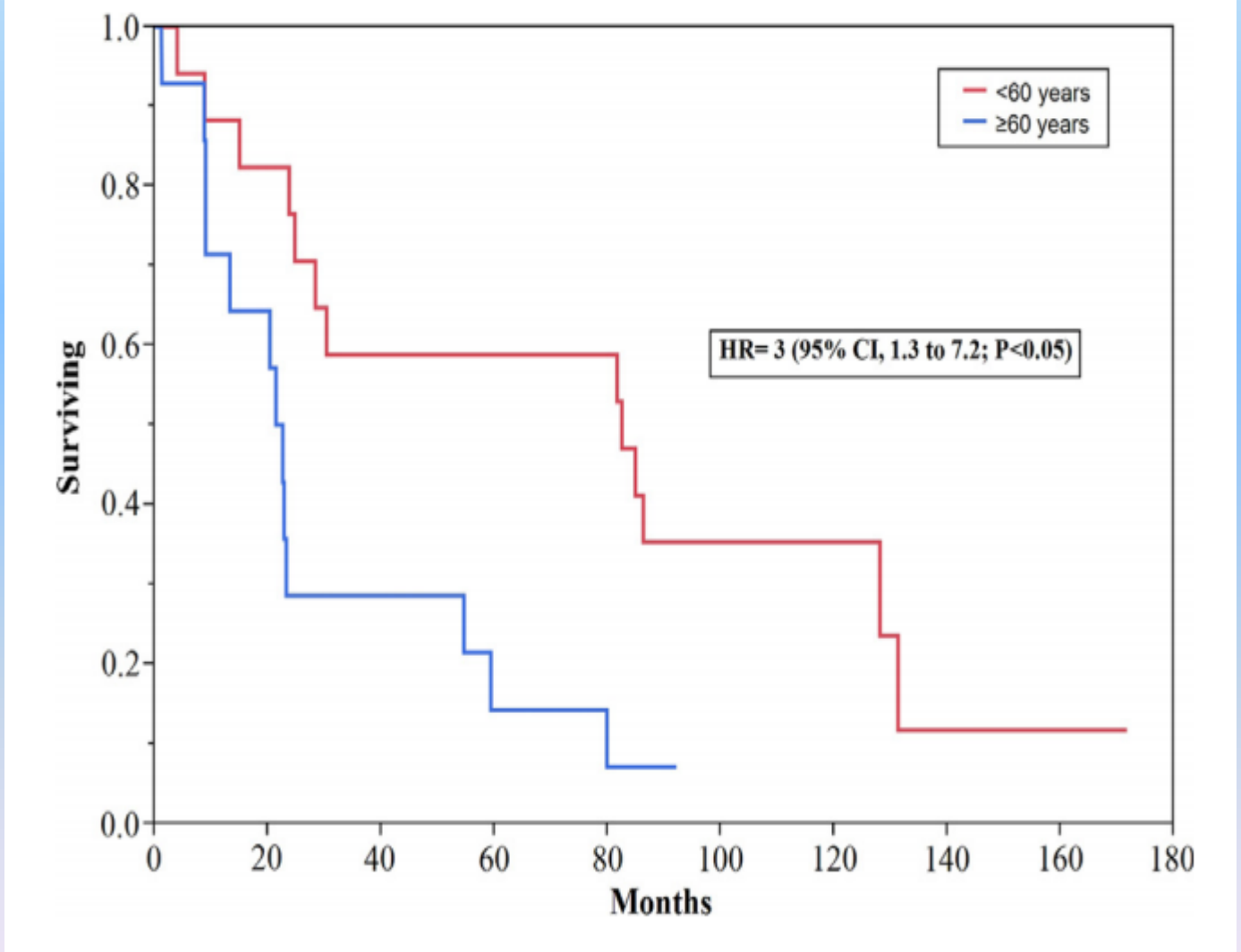


Fig. 2. Median overall survival in post-transplant patients with head and neck cancer based on primary tumor location. Other = larynx, hypopharynx, salivary, unknown primary.

Samer Alsidawi Oral Oncology, 2017 , 72, 104–109.

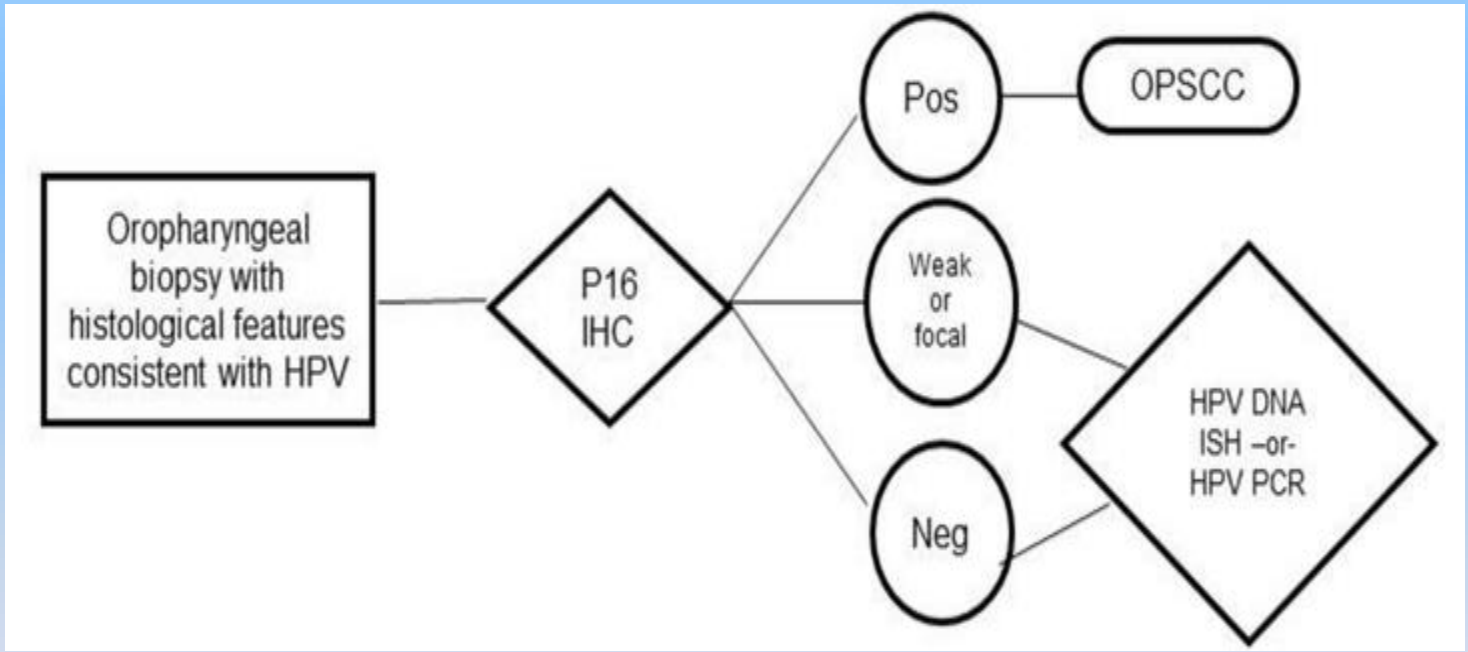


Previous studies that evaluated outcomes of head and neck cancer after solid organ transplant.

Study	Incidence (%)	N	Transplant to Malignancy in years	Estimated Survival Rates
Duvoux et al. (1999)	N/A	11	N/A	87% at 5 years
Preciado et al. (2002)	0.6	23	8.4	13% at 5 years
Coordes et al. (2014)	0.86	13	N/A	82% at 5 years
Nelissen et al. (2014)	1.8	16	5.27	62% at end of study
Deeb et al. (2012)	0.5	17	4–5.5	55% at 1 year
Nure et al. (2013)	1.5	5	3.25	N/A
	1.6	33	7	34% at 5 years
Schiefele et al. (2005)	0.9	48	7.8	58% at 5 years
Roithmaier et al. (2007)				
Rabinovics et al. (2014)	0.4	30	7.3	74% at 5 years
Öhman et al. (2015)	1.1	17 oral and 39 lip cancers	6.6–9.4	27% and 61% at 5 years for oral and lip respectively
Piselli et al. (2015)	1.2	32	N/A	35.2% at 10 years

Algorithm for diagnosis of oropharyngeal squamous cell carcinoma

EILEEN M. BURD

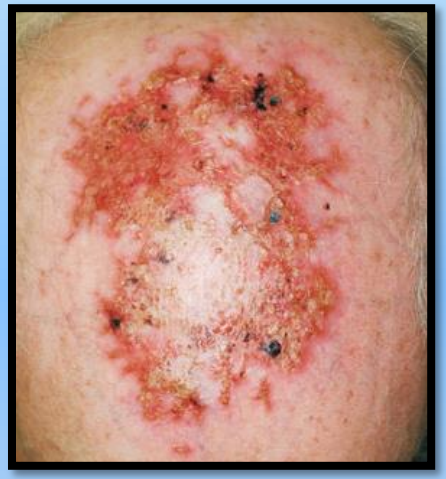


HPV CANCER AND TRANSPLANT

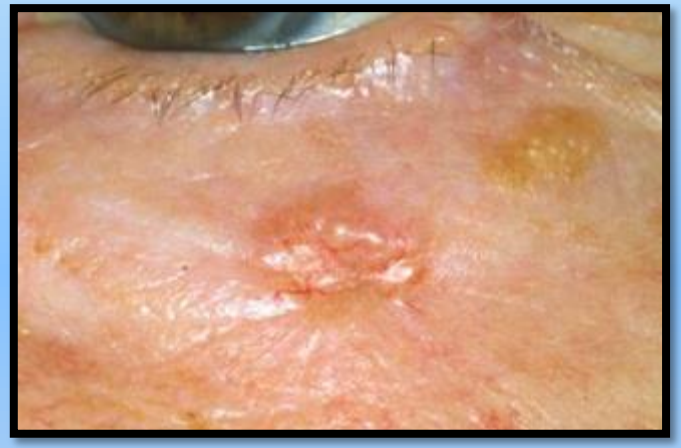
2. Skin squamous cell carcinoma

Advances in Experimental Medicine and Biology

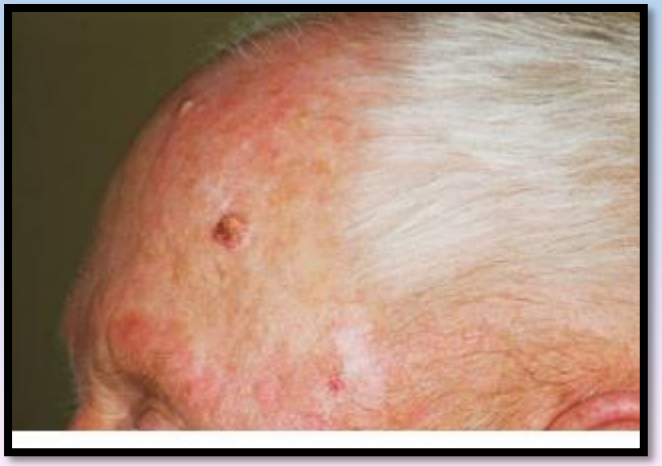
Reichrath, J. 2020



Actinic keratoses



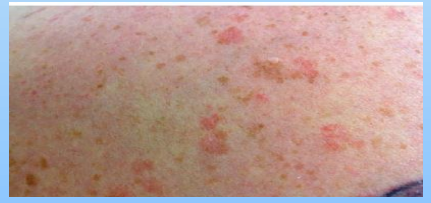
Basal cell carcinomas



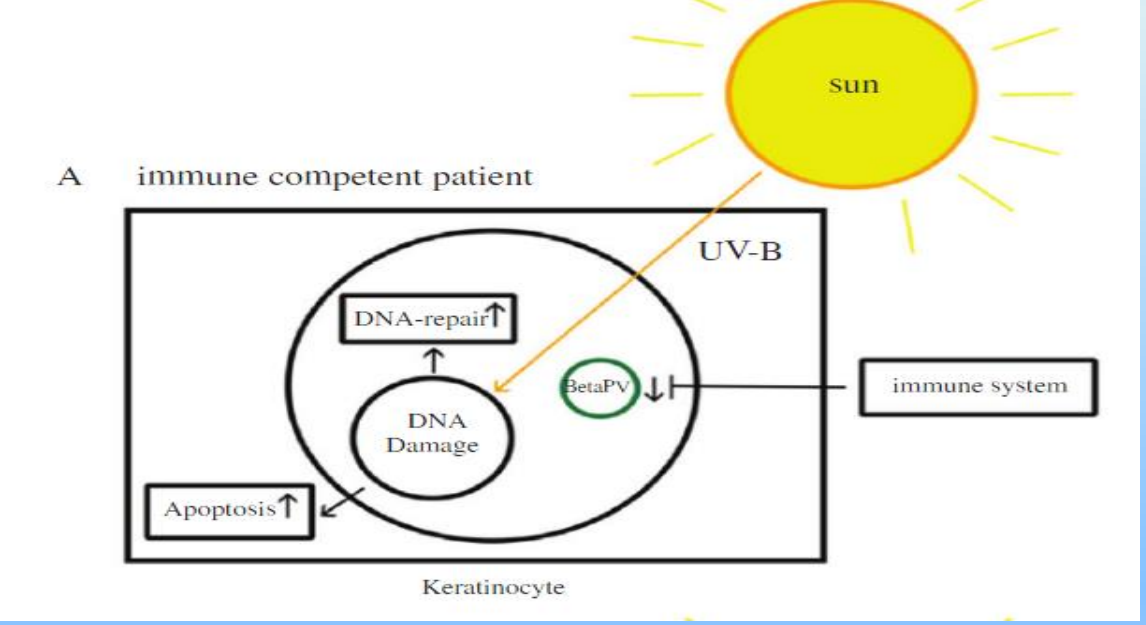
Invasive cutaneous squamous cell carcinoma

Evidence supporting a role of beta-HPV in skin carcinogenesis

Bandolin Rev Me Virol 2014

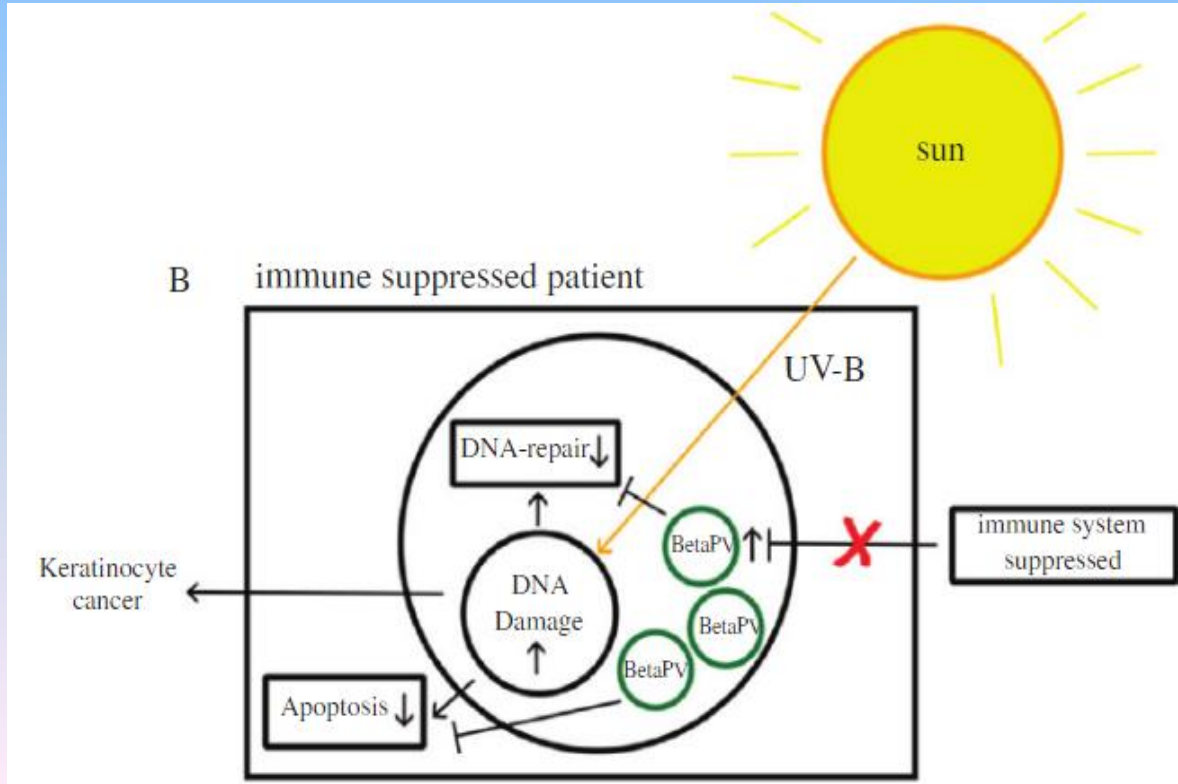


1. **Epidermodysplasia verruciformis patients**
   - 1922 Lewandowsky and Lutz
   - High susceptibility to beta-HPV infections,(HPV 5, 8) benign wart-like cutaneous lesions. Skin carcinogenesis
2. **Solid Organ Transplant Recipient**
   - 100-fold increased risk of developing KC (mainly SCC) due to drug induced immunosuppression.
   - Beta-HPV DNA isolated in 80% of SCC (vs 40% of SCC in immunocompetent population).
   - Positivity to beta-HPV DNA in hair follicles, anti-beta-HPV serum IgG, multiple beta-HPV species and high viral load are correlated with increased risk of developing SCC.



Koen D Quint

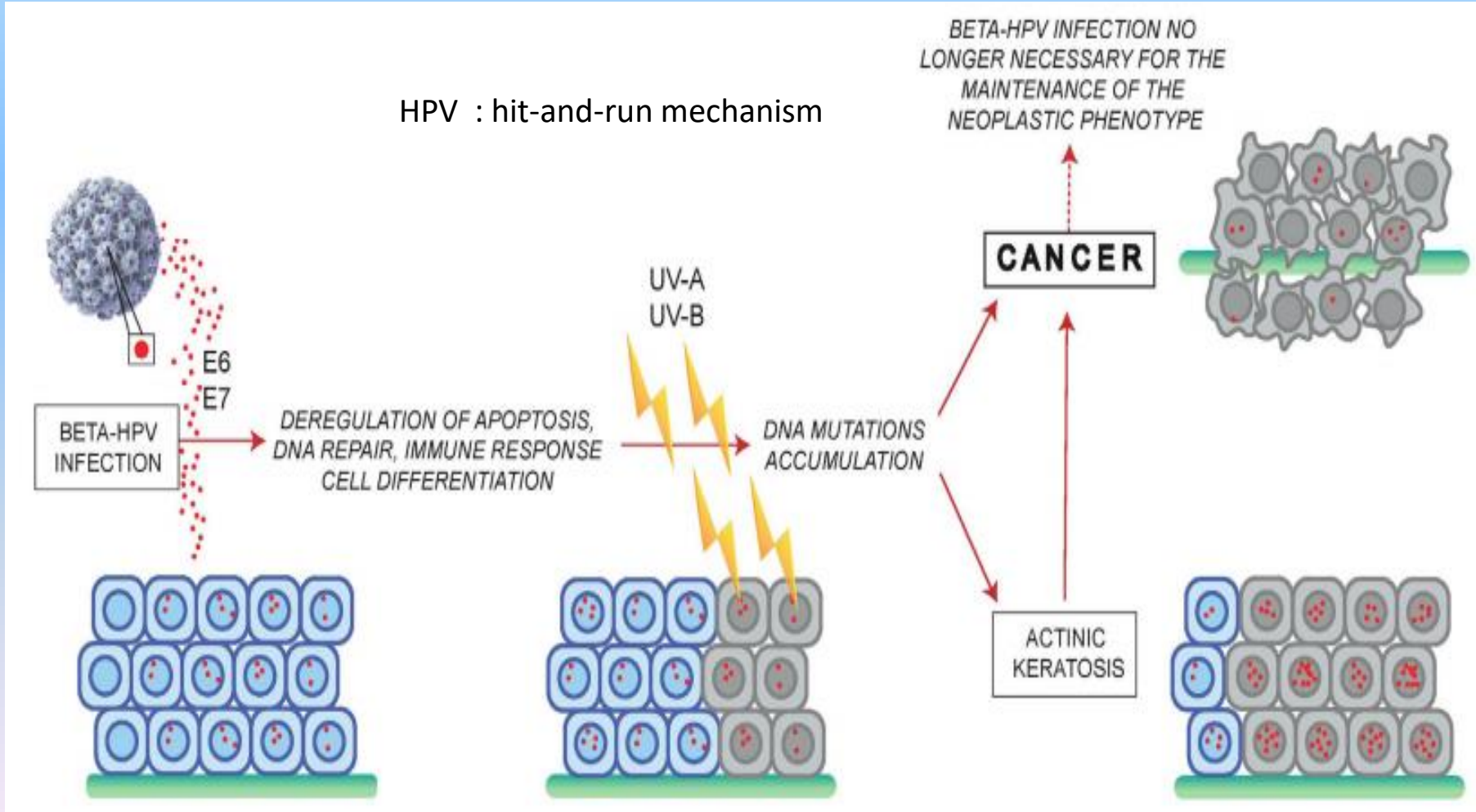
J Pathol 2015; 235: 342–354



Mechanisms of oncogenesis in beta-HPV induced skin carcinogenesis

Luigia Bandolin Rev Med Virol 2020

HPV : hit-and-run mechanism



SKIN CANCER

1. **Dose-dependent effect of immunosuppression**
   Increased risk of SCC established for CNIs, azathioprine, mTOR inhibitors and prednisolone.

2. **Increasing number of immunosuppressants prescribed**

3. **Duration of use of immunosuppressants**
   High accumulated dose of azathioprine increased risk of SCC 5.4-fold after 1 year of follow-up, rising to 8.9-fold after 5 years.

4. **Age 50 years at transplantation**

5. **Duration of time since transplantation**
   Heart: 31% of recipients had NMSC at 5 years and 43% at 10 years in an Australian cohort; Kidney: 25% NMSC cumulative incidence at 5 years, 38% at 10 years, and 70% at 20 years.

6. **Cumulative UV radiation exposure**

7. **Male sex**

8. **Pre-transplant NMSC**

Lauren D. Crow Transplant International 2019

- The International immunosuppression & Transplant Skin Cancer Collaborative (ITSCC) and Transplant Skin Cancer Network (TSCN) identified specific risk factors for development of skin cancer: age >50 at time of transplant, white race, male sex, and thoracic organ transplantation.

- **Prevention**: Control by dermatologist. Caucasian high risk within 2 years. Photoprotection.

Skin cancer rates by transplant organ type.

Organ	Rate*	95% CI
Lung, heart-lung	3520.94	3014.07–4113.04
Heart	1633.79	1345.59–1983.71
Kidney	1280.02	1158.19–1414.67
Liver	1196.32	1041.86–1373.69
Pancreas, kidney-pancreas	639.25	385.38–1060.35

*Rates of skin cancer, including SCC, Merkel cell carcinoma, and melanoma, per 100 000 person-years, based on TSCN

HPV CANCER AND TRANSPLANT

3. Gynecologic cancers

Gynecologic cancers and solid organ transplantation

John B. Liao Am J Transplant. 2019; SIR per cancer site

Author	Year	Transplant type	No. studied	Location	Cervix	Invasive vulva/vagina
Adami	2003	All SOT	5931	Sweden	2.0 (0.7-4.7)	23.9 (11.9-42.8)
Kasiske	2004	Kidney >65	35 765	US	5.7[b]	8.8[b]
Vajdic	2006	RTR	10 180	Australia	2.5 (1.3-4.3)	22.2 (13.9-33.6)
Grulich	2007	All SOT	31 977	meta-analysi	2.1 (1.4-3.3)	22.8 (15.8-32.7)
Villeneuve	2007	RTR	11 155	Canada	1.5 (0.6-3.4)	
Serraino	2007	All SOT	2875	Italy	3.3 (0.7-9.7)	
Collette	2010	All SOT	37 617	UK	2.3 (1.4-3.5)	
Engels	2011	All SOT	175 732	US		
Krynitz	2012	Kidney Liver Heart ± Lung	7 952 1221 1012	Sweden	2.4 (1.2-4.4) 2.6 (0.1-15) 7.5 (0.9-27)	14 (8.4-23) 6.9 (0.2-39) 11 (0.3-62)
Cheung	2012	Kidney	4895	Hong Kong	7.2 (3.9-13.4)	–
Madeleine[d]	2013	All SOT	72 035	US	1.0 (0.8-1.3)	7.3 (5.6-9.2)
Na	2013	Liver, heart, lung	4644	Australia	–	33.2 (13.3-68.3)
Hortlund	2017	All SOT	6794 12 420	Denmark Sweden	2.6 (1.6-4.5) 2.5 (1.5-4.1)	7.0 (3.5-14.1)[e] 11.1 (7.3-17.1)[e]
Nordin	2017	Liver	4246	Nordic[f]	1.1 (0.13-4.0)	2.9 (0.4-10.5)[e]

SOLID ORGAN TRANSPLANTED

54 articles that examined the relationship between SOT (kidney, liver, pancreas, heart, lung) and HPV, SIL, and CC published between 1990 and 2018.

CERVICAL CANCER (CC) RISK

- CC rates in women with SOT of any organ to expected rates in the general population show SIRs ranging from 2.0 to 6.6.5.

- The increased risk of invasive CC likely begins shortly after transplant and persists throughout the years after transplant

- **Madeleine et al**. used the US Scientific Registry of Transplant Recipients from 1987 to 2009 to examine the risk of HPV-associated cancers in 73,035 women with SOT:
  - The IRR for **heart and lung transplant** recipients was 1.8 (95% CI = 0.8–3.7) and for **liver transplant** recipients was 1.2 (95% CI = 0.6–2.3) compared with the risk associated with renal transplant patients.

- 160 Italian women after **liver transplantation** for an average of 7.2 years and reported an overall SIR of 5.7 (95% CI = 0.1–31.9) for CC..

SQUAMOUS INTRAEPITHELIAL LESION RISK

- **Silverberg**: This risk of CIN 2+ was also associated with the degree of immune suppression based on the number of immunosuppressant medication classes with RRs of 2.0 (95% CI = 0.7–5.5), 3.1 (95% CI = 1.6–6.1), and 4.9 (95% CI = 3.0–7.9) for 0, 1 to 2, and 3 or more medication classes, respectively.

- **SIL in lung transplant patients**, following 166 Australian women with annual cervical cytology screening after transplantation. Ten percent developed cervical abnormalities (7 had LSILs and 6 had HSILs).

- **For LSIL, the incidence was 42.2 per 1,000 women** screened after transplant compared with 8.3 per 1,000 in the general population, **for HSIL**, **the incidence was 30 per 1,000** women screened posttransplant compared with 6.2 per 1,000 in the general population.

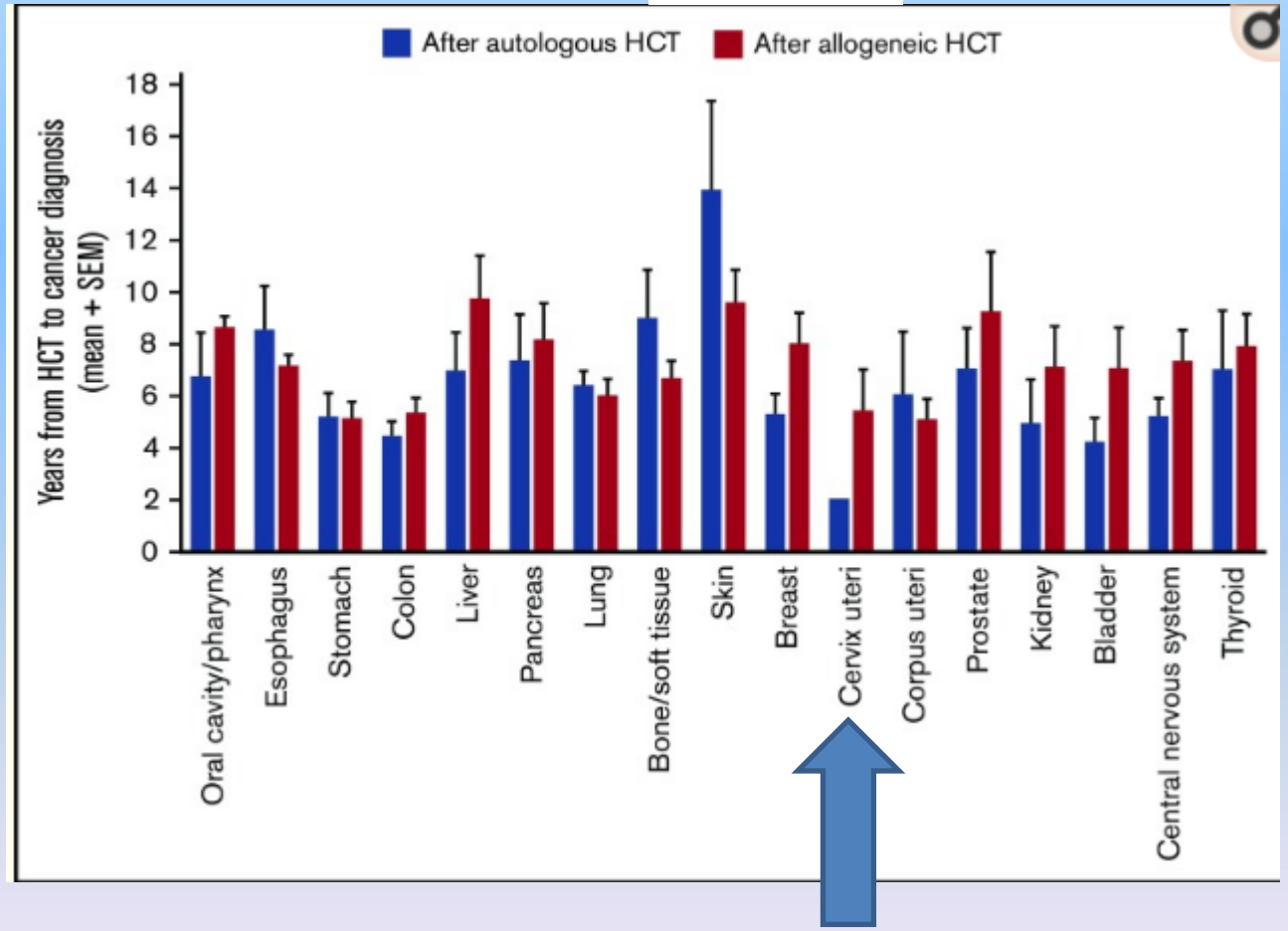
HPV AND Allogeneic HSCT

- 27 articles that examined the relationship between hematopoietic stem cell transplant and HPV, SIL, and CC published between 1990 and 2018.

Outcomes of patients who developed subsequent solid cancer after hematopoietic cell transplantation

Blood Adv. 2018 Aug 14;

Yoshihiro Inamoto,



Risks factors and timing of genital human papillomavirus (HPV) infection in female stem cell transplant survivors: a longitudinal study

D Shanis Bone Marrow Transplantation (2017)

- **Between 1994 and 2014, 109 females underwent HCT of whom 82 surviving transplant for >1 year.**
- The cumulative proportions of any genital HPV infection at 1, 3, 5, 10 and 20 years were 4.8%, 14.9%, 28.1%, 36.7% and 40.9%.
- Pre-transplant HPV disease was strongly associated with any posttransplant HPV.
- Having either extensive or genital cGvHD was associated with increased risk of any HPV disease and a higher risk for severe genital dysplasia (CIN II–III/VIN II–III).
- But no one developed HPV-related genital cancer.
- Persistent, multifocal or severe HPV disease occurred more frequently than in healthy populations.

Moscicki, A.-B 2019

RISK GROUP CATEGORY:

Solid organ transplant, Allogeneic hematopoietic stem cell, Genital GVHD or chronic GVHD.

CERVICAL CANCER SCREENING RECOMMENDATIONS:

- Cytology is recommended if younger than 30 years.
- Co-testing is preferred, but cytology is acceptable if 30 y or older.
- If using cytology alone, perform annual cervical cytology. If results of 3 consecutive cytology results are normal, perform cytology every 3 y.
- If using co-testing, perform baseline co-test with cytology and HPV. If result of cytology is normal and HPV is negative, co-testing can be performed every 3 y.
- If transplant before the age of 21 y, begin screening within 1 y of sexual debut.
- Continue screening throughout lifetime (older than 65 y). Discontinue screening based on shared discussion regarding quality and duration of life rather than age.
- Screen patients on dialysis and posttransplant similarly.

HPV CANCER AND TRANSPLANT

4. Anal cancer

Risk of genital warts in renal transplant recipients—A registry-based, prospective cohort study

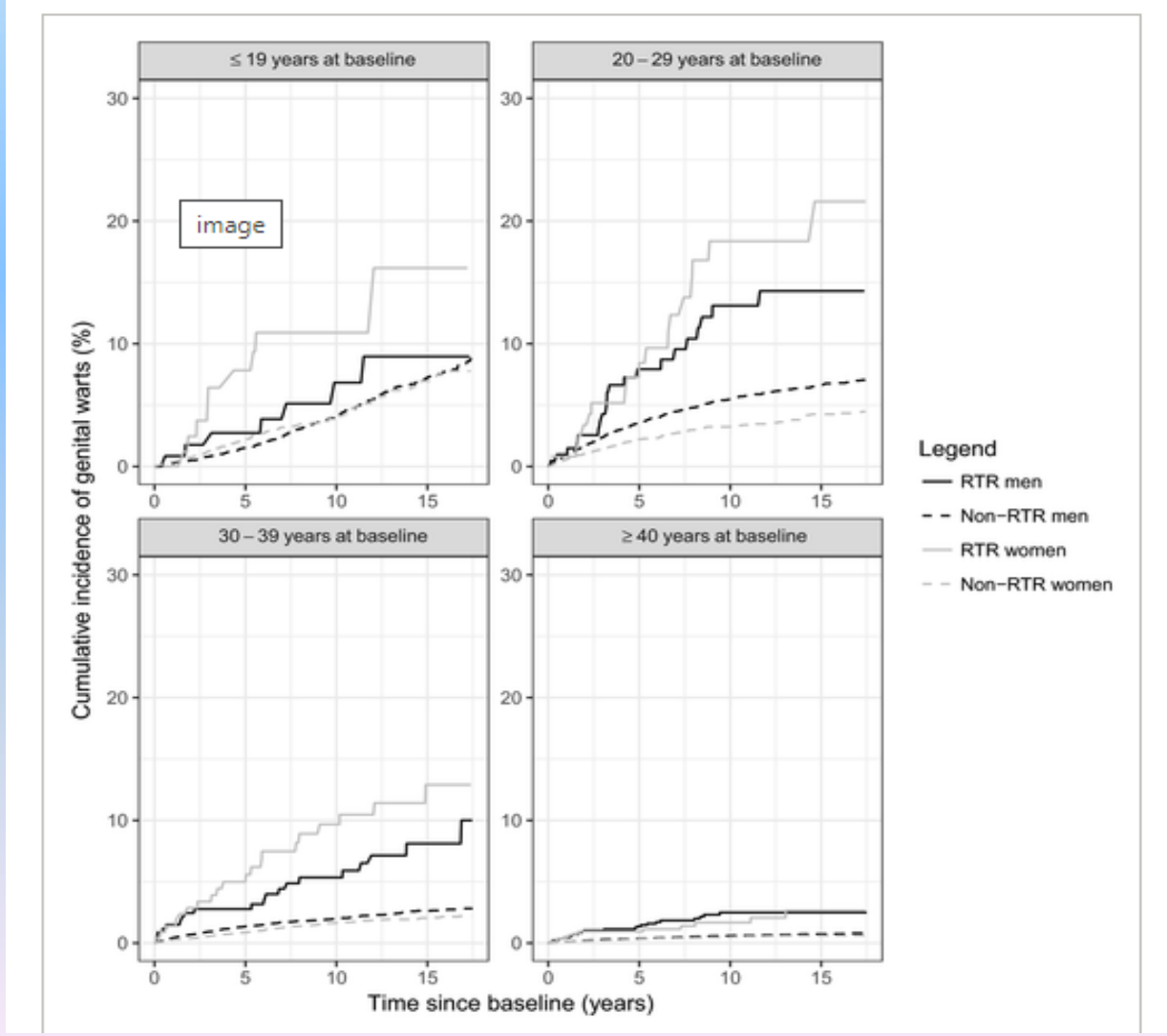
Helle Kiellberg Larsen Am J Transplant 2019 Jan

32.68 RTRs / 162. 910 non-RTRs without GWs 1 year before baseline.

RESULTS:

- RTRs had higher hazard of GWs than non-RTRs (HR = 3.30; 95% confidence interval, 2.76-3.93, adjusted for sex, age, education, and income
- Hazard More pronounced in female than in male RTRs
- The hazard tended to be higher in RTRs with functioning grafts compared with RTRs on dialysis after graft failure.
- The hazard of GWs was increased <1 year after transplantation and remained increased during ≥10 years.

Cumulative incidence of genital warts in Danish renal transplant recipients (RTRs) 1996-2015 and a nontransplanted control cohort -



Risk of anal high-grade squamous intraepithelial lesions among renal transplant recipients (RT R)compared with immunocompetent controls

Larsen HK Clin Infect Dis 2020 Jun

Study the prevalence of anal high grade intraepithelial lesions (HSIL) in RTRs compared with immunocompetent controls and risk factors for anal HSIL in RTRs.

247 RTRs and 248 controls in this cross-sectional study.

RESULTS:

RTRs had higher anal HSIL prevalence than controls:

- Men : 6.5% vs 0.8%, OR adjusted=11.21, 95% CI: 1.46–291.17)
- Women: 15.4% vs 4.0%, OR adjusted=6.41, 95% CI: 2.14–24.10).
- Anal hrHPV: 33.8% vs 9.5% OR adjusted=6.06, 95% CI: 2.16– 20.27)
- Having had receptive anal sex : OR adjusted=6.23, 95% CI, 2.23–19.08)
- Genital warts: OR adjusted=4.21, 95% CI: 1.53–11.48

CONCLUSIONS : Screening for anal HSIL in RTRs should be considered.

Anogenital malignancies in women after renal transplantation over 40 years in a single center

Kim A P Meeuwis Transplantation 2012

1023 women, who underwent a renal transplantation between 1968 and 2008.

Sixteen anogenital malignancies (1.6%) were found: vulva (n=6), cervix (n=5), and anus (n=5).

The median interval between transplantation and diagnosis of malignancy was 136 months (range, 16-288 months).

A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale

Gary M. Clifford

TABLE 1 Anal cancer incidence in US transplant cancer match study 1987 to 2015, by age, gender and years since transplant

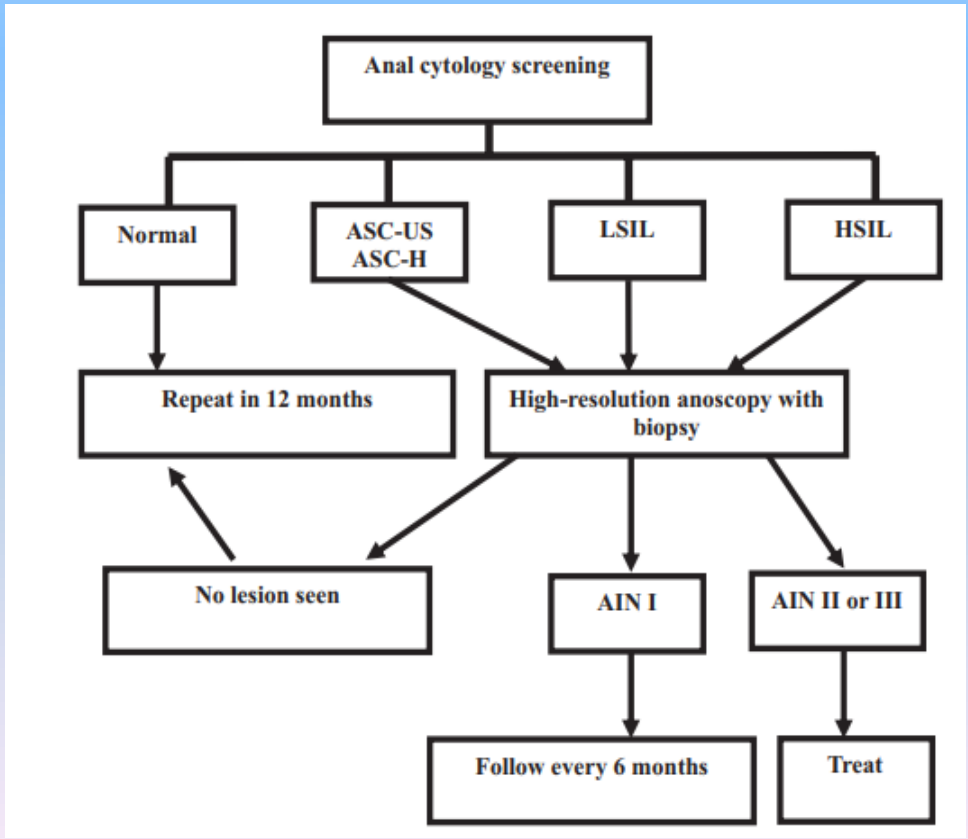
	Males			Females		
	Cases	Person-years	IR per 100 000 person-years (95% CI)	Cases	Person-years	IR per 100 000 person-years (95% CI)
All	99	1 050 327	9.4 (7.7-11.5)	128	676 462	18.9 (15.8-22.5)
Age group (y)						
<30	0	116 804	0.0 (0.0-3.2)	3	97 399	3.1 (0.6-9.0)
30-44	9	194 004	4.6 (2.1-8.8)	19	145 121	13.1 (7.9-20.4)
45-59	42	403 603	10.4 (7.5-14.1)	56	240 592	23.3 (17.6-30.2)
≥60	48	335 916	14.3 (10.5-18.9)	50	193 350	25.9 (19.2-34.1)
Years since transplant						
<5	43	657 746	6.5 (4.7-8.8)	46	412 509	11.2 (8.2-14.9)
5-9	28	278 346	10.1 (6.7-14.5)	42	183 231	22.9 (16.5-31.0)
≥10	28	114 235	24.5 (16.3-35.4)	40	80 722	49.6 (35.4-67.5)

Abbreviations: CI, confidence interval; IR, incidence rate.

Human papillomavirus infection in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Peter V Chin-Hong Clin Transplant 2019

Anal cancer screening in transplant patients



HPV VACCINE

Eur J Obstet Gynecol Reprod Biol X. 2019

Emeline Vinkenes,

Guidelines and recommendations for HPV vaccination.

Professional society, Country:	Solid organ transplant recipients (SOTR):
SST, Denmark	No recommendation.
WHO	All immunocompromised, including transplant recipients (regardless of whether they are receiving antiretroviral therapy).
CDC, USA	All immunocompromised both females and males, from 9 to 26 years of age.
IDSA, USA	All SOTR from 11 to 26 years of age(21).
PHAC, Canada	Before or after transplantation in females and males from 9 to 26 years of age(22).
AGDH, Australia	Before or after transplantation in both females and males from 9 years of age and above(23).
HSE, Ireland	Before or after transplantation in patients from 10 years of age and above(24).

Human Papillomavirus Vaccination in Male and Female Adolescents Before and After Kidney Transplantation

Corina Nailescu Front Pediatr 2020

- The quadrivalent HPV vaccine was administered to girls and boys age 9-18.
- Subjects were recruited for three groups:
  1. 18 *CKD:* chronic kidney disease stages 3, 4, and 5 not on dialysis
  2. 18 *Dialysis*
  3. 29 *KT* recipients
- The outcome consisted of antibody concentrations against HPV 6, 11, 16, and 18.
- Geometric mean titers (GMTs) and seroconversion rates were compared.
- Vaccine tolerability was assessed.

RESULTS :

- KT patients had significantly lower GMTs after vaccination for all serotypes.
- The percentages of subjects who reached seroconversion were overall lower for the *KT* group, reaching statistical significance for HPV 6, 11, and 18.

Immunogenicity And Safety Of The Nine-Valent Human Papillomavirus Vaccine In Solid Organ Transplant Recipients And HiV-Infected Adults

Lise Boey Clin Infect Dis 2020 Dec

They 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:

- Is a phase III investigator-initiated study in: **100 HIV-infected** persons (age: 18-45 years) and **171 SOT recipients** (age: 18-55 years).
- 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.
- 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.

Immune Response Following Quadrivalent Human Papillomavirus Vaccination in Women After Hematopoietic Allogeneic Stem Cell

JAMA Oncol. 2020 May; Pamela Stratton,

64 vaccinated women

Developed antibody responses to all quadrivalent HPV vaccine types p<0.001

78.3% — 23 (35.9%) were receiving immunosuppressive therapy (median age, 34 years; median 1.2 years posttransplant).

95.2% — 21 (32.8%) were not receiving immunosuppression (median age, 32 years; median 2.5 years posttransplant).

100 % — 20 (31.3%) were healthy volunteers.

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Peter V. Chin-Hong Clinical Transplantation 2019

RECOMMENDATIONS:

- Immunize all male and female transplant patients (ideally prior to transplantation) aged 9-26 (target age: 11-12) with three doses of the HPV nine-valent vaccine.
- The quadrivalent vaccine can also be used in males and females, and females can also receive the HPV-bivalent vaccine (strong recommendation, moderate-quality evidence).
- Males and females up to age 45 may also be vaccinated with three doses of the 9-valent vaccine (weak recommendation, low-quality evidence).
- Immunize transplant recipients aged 15-26 even if they already have anogenital warts (weak recommendation, low-quality evidence).
- For individuals with a known history of HPV disease, consider assessing for cervical/anal lesions prior to transplant (weak recommendation, low-quality evidence) .

GRACIAS POR SU ATENCIÓN