Tumors associats a les infeccions virals

Guillem Sirera 21-03-2024

Fight Infections Foundation

Germans Trias i Pujol Hospital

Infectious Agents, Associated Cancer

Epstein-Barr virus

Merkel cell polyomavirus (MCPyV)

Hepatitis B virus

Hepatitis C virus

Kaposi sarcoma herpes virus

Human immunodeficiency virus type 1

Human papillomavirus type 16

Human T-cell lymphotropic virus type 1

World Health Organization (WH)

- **2020, the global burden of cancers caused by infection was estimated at 15.4%**

- **Cancer-causing infections are responsible for approximately 30% of cancer cases in low- and lower-middle-income**

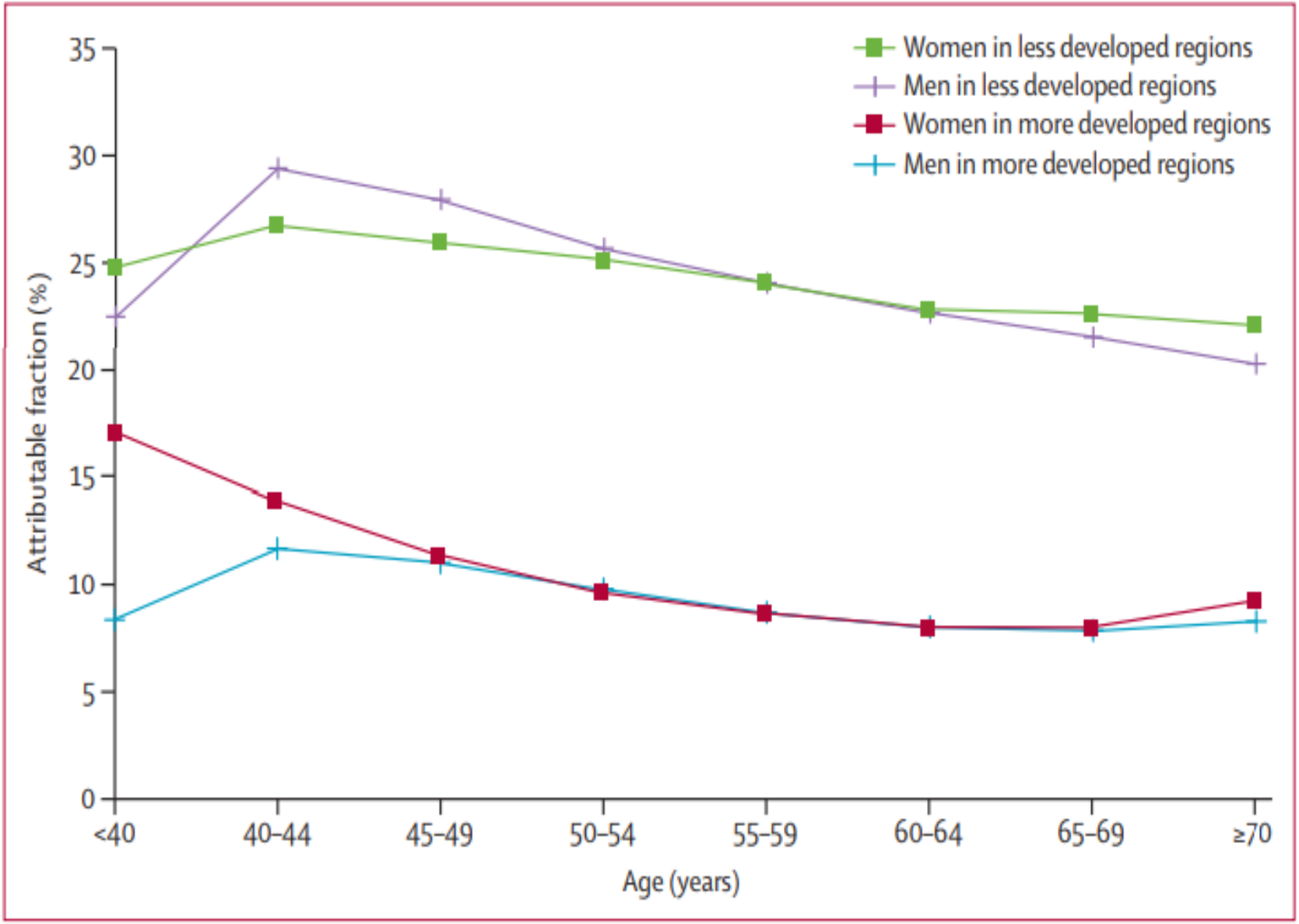


***Figure 3*: Proportion of cancer cases in 2012 attributable to infection, by sex, age group, and development status**

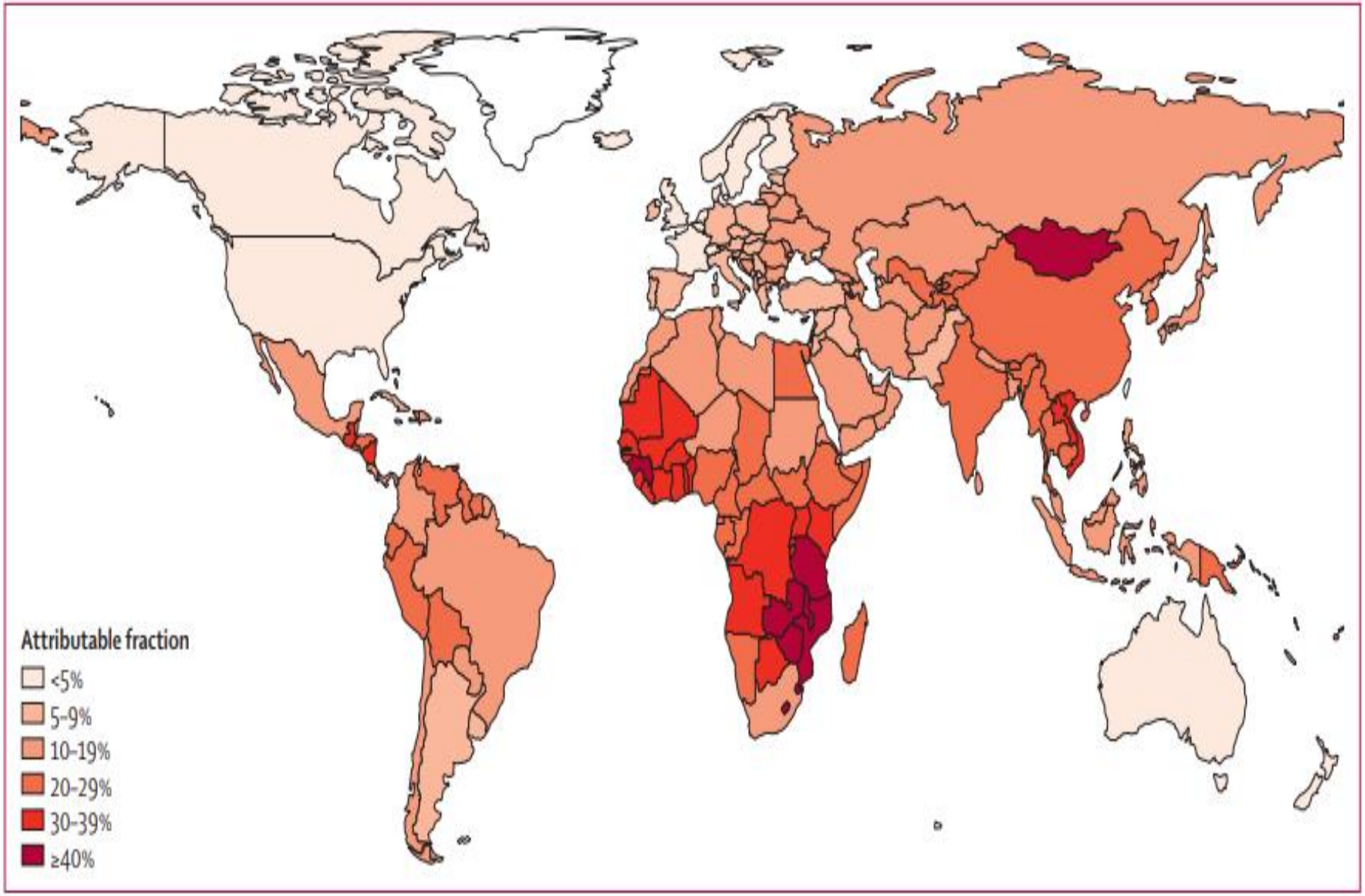


Figure 1: Attributable fraction of cancer related to infection, 2012

Number of new cancer cases attributable to specific viral infections by gender

Virus	Total	Females	Males
HPV	636,000	570,000	66,000
HBV	420,000	120,000	300,000
HCV	165,000	55,000	110,000
EBV	120,000	40,000	80,000
KSHV	43,000	15,000	29,000
HTLV	2,900	1,200	1,700

Prevalence of viruses in virus-associated cancers

Virus	Cancer	Geographical area	Attributable fraction (%)
HPV	Cervix	World	100
HPV	Penile	World	51
HPV	Anal	World	88
HPV	Vulvar	World	48
HPV	Vaginal	World	78
HPV	Oropharynx	North America	51
HPV	Oropharynx	India	22
HPV	Laryngeal	World	4.6
HBV	Liver	Developing	59
HBV	Liver	Developed	23
HCV	Liver	Developing	33
HCV	Liver	Developed	20

EBV	Hodgkin's lymphoma	Africa	74
EBV	Hodgkin's lymphoma	Asia	56
EBV	Hodgkin's lymphoma	Europe	36
EBV	Burkitt's lymphoma	Sub-Saharan Africa	100
EBV	Burkitt's lymphoma	Other regions	20–30
EBV	Nasopharyngeal carcinoma	High-incidence areas	100
EBV	Nasopharyngeal carcinoma	Low-incidence areas	80
KSHV	Kaposi's sarcoma	World	100
HTLV-1	Adult T-cell leukemia and Lymphoma	World	100
MCPyV	Merkel cell carcinoma	North America	70–80[c]

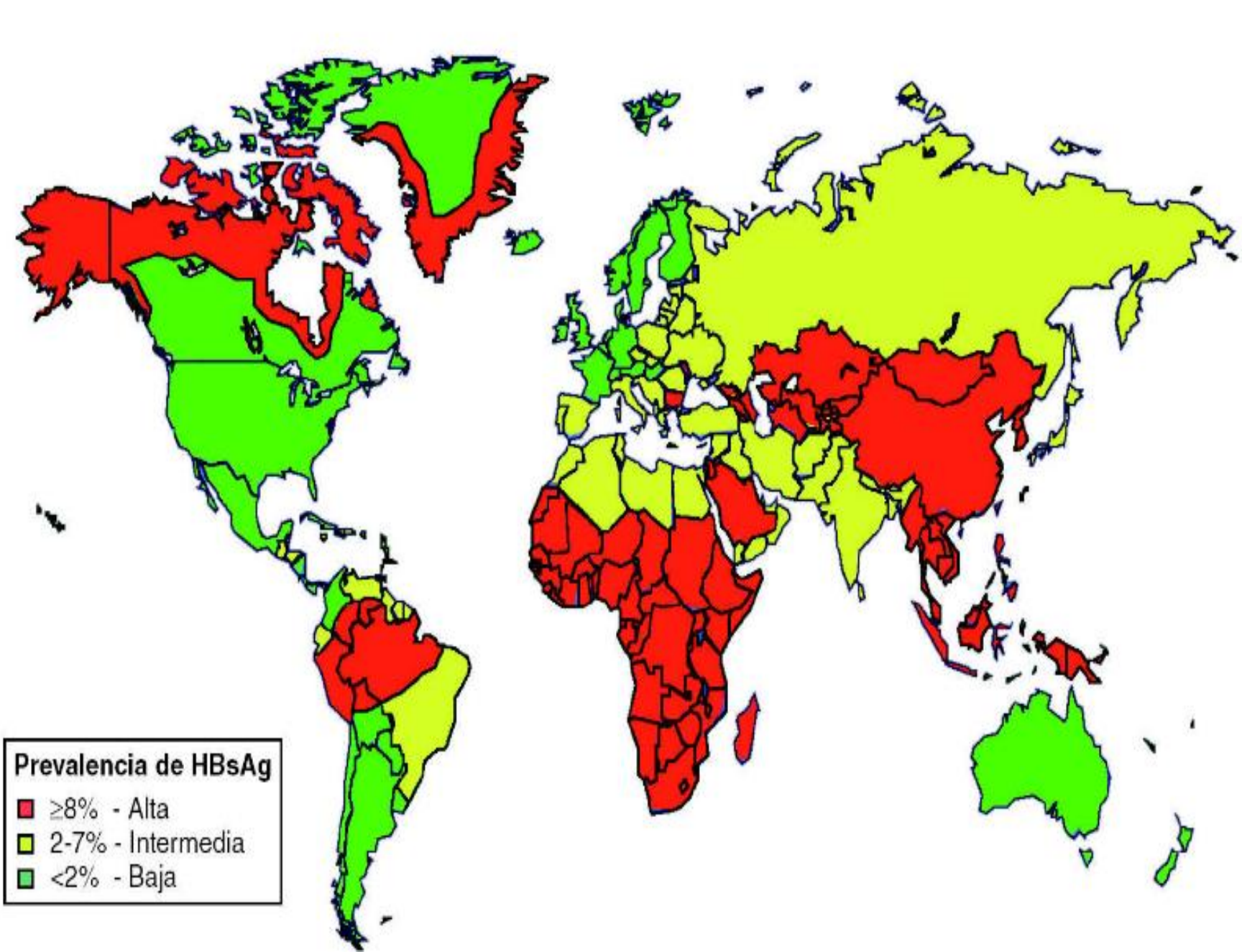
Incidence of hepatocellular carcinoma in different geographical areas and risk factors

Revista Española de Quimioterapia 2021 Emilio Bouza

Geographical region	Adjusted incidence /100,000 inhabitants		Risk factors			
	Male	Female	HCV (%)	HBV (%)	Alcohol (%)	Others (%)
Europe	6.7	2.3	60-70	10-15	20	10
Southern Europe	10.5	3.3				
Northern Europe	4.1	1.8				
North America	6.8	2.3	50-60	20	20	10 (NASH)
Asia and Africa	21.6	8.2	20	70	10	10 (Aflatox)
China	23	9.6				
Japan	20.5	7.8	70	10-20	10	10
Africa	1.6	5.3				
Worldwide	16	6	31	54	15	?

HBV

Transmission	Risk Factors	Disease Course	Vaccine Target Populations	Other Control Strategies
• Perinatal • Parenteral • Sexual	• Maternal HBV infection • High endemicity area • Risky sexual practices • Injection drug use • Healthcare worker • Skin piercing and tattoos	• Acute infection, which may self-resolve • Chronic infection, which can progress to cirrhosis or liver cancer • Asymptomatic disease	• Infants and children • Health care workers • Other high-risk groups including drug users, HIV+ individuals and those with underlying liver disease	• Safe sex practices • Skin piercing and tattooing safety • Blood product screening • Needle exchange • Education of healthcare workers • Treatment of HBV infected patients


Prevalencia de HBsAg
≥8% - Alta
2-7% - Intermedia
<2% - Baja

Journal of Hepatology 2023

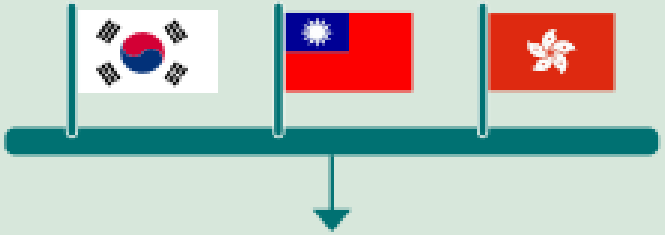
Objective

To compare the risk of HCC development associated with tenofovir disoproxil fumarate (TDF) *vs.* entecavir (ETV) treatment in patients with CHB, using individual patient data (IPD)

Methods

Systematic literature review (SLR) of published SLRs, electronic databases and key congress proceedings

20 eligible studies identified; **11 studies from 3 countries contributed IPD** to the meta-analysis



Meta-analysis performed using IPD from **42,939 eligible**

Findings

Patients receiving TDF had a significantly lower risk of developing HCC than those receiving ETV, with risk diverging after 2.5 years

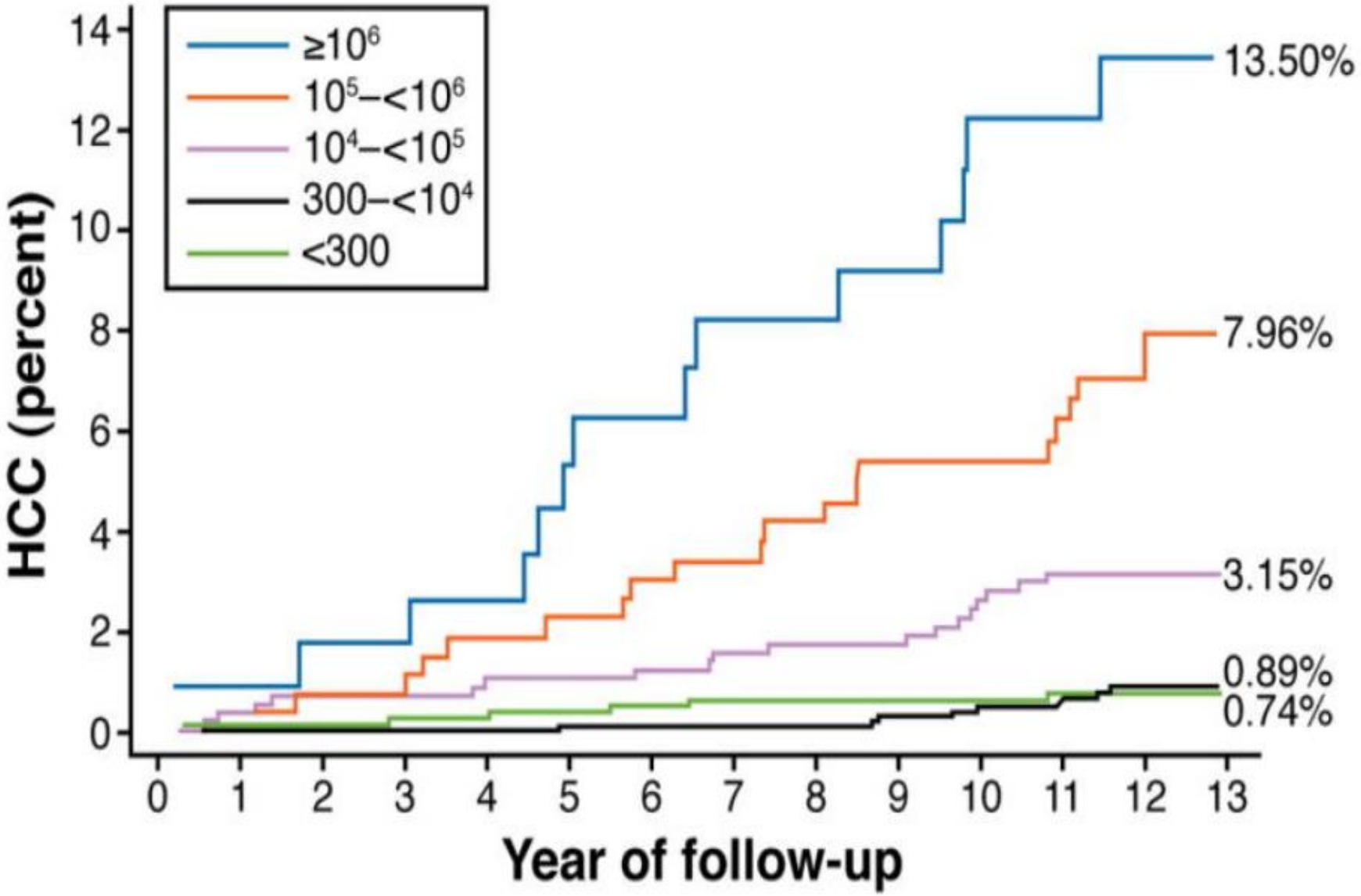
Number at risk N (%)							
ETV	35,960 (100)	35,960 (100)	29,679 (83)	24,642 (69)	19,749 (55)	13,046 (36)	4,383 (12)
TDF	6,979 (100)	6,979 (100)	5,792 (83)	4,387 (63)	2,927 (42)	1,730 (25)	751 (11)

Conclusions

Patients with CHB receiving treatment with TDF were significantly less likely to develop HCC than those receiving ETV

These findings should be considered in determining the treatment course to achieve the best long-term outcomes in patients with CHB

An association between baseline serum level of HBV DNA and future incidence of HCC. Gastroenterology 2012



VIRUS HEPATITIS D

- El VHD es un virus defectiu, que no pot replicar a les cèl·lules sense ajuda de un altre virus , el virus B.

- El 5% de tots els pacients positius per el antigen de superfície del virus de la hepatitis B (HBsAg) estan co-infectats amb el VHD.

- VHD major prevalença amb ADVP , VHC o VIH

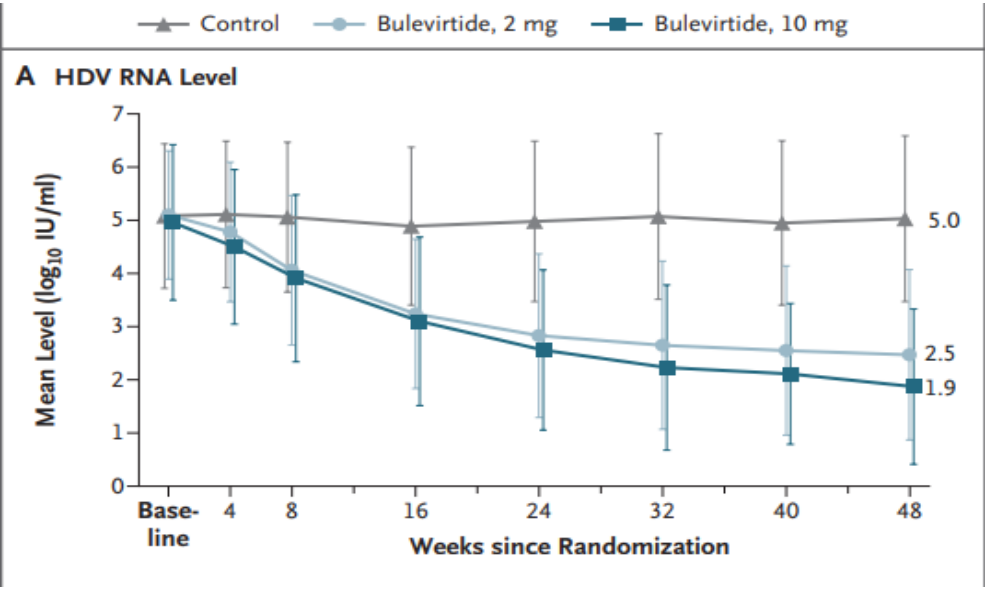
- VHD causa estimada 18% de cirrosi i un 20 % de HCC associats amb Hepatitis B

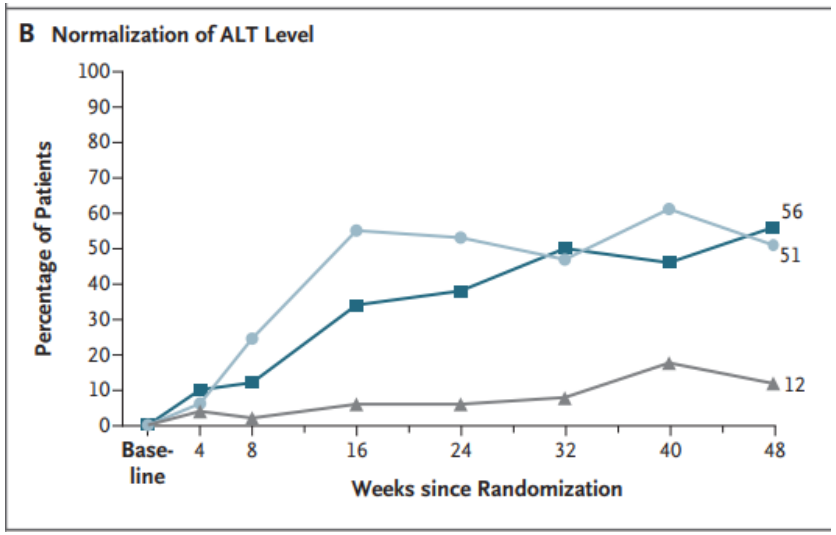
HEPATITIS D

A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D

BACKGROUND

Coinfection with hepatitis D virus (HDV) accelerates the progression of liver disease associated with chronic hepatitis B. Bulevirtide inhibits the entry of HDV into hepatocytes





CONCLUSIONS After 48 weeks of bulevirtide treatment, HDV RNA and ALT levels were reduced in patients with chronic hepatitis D

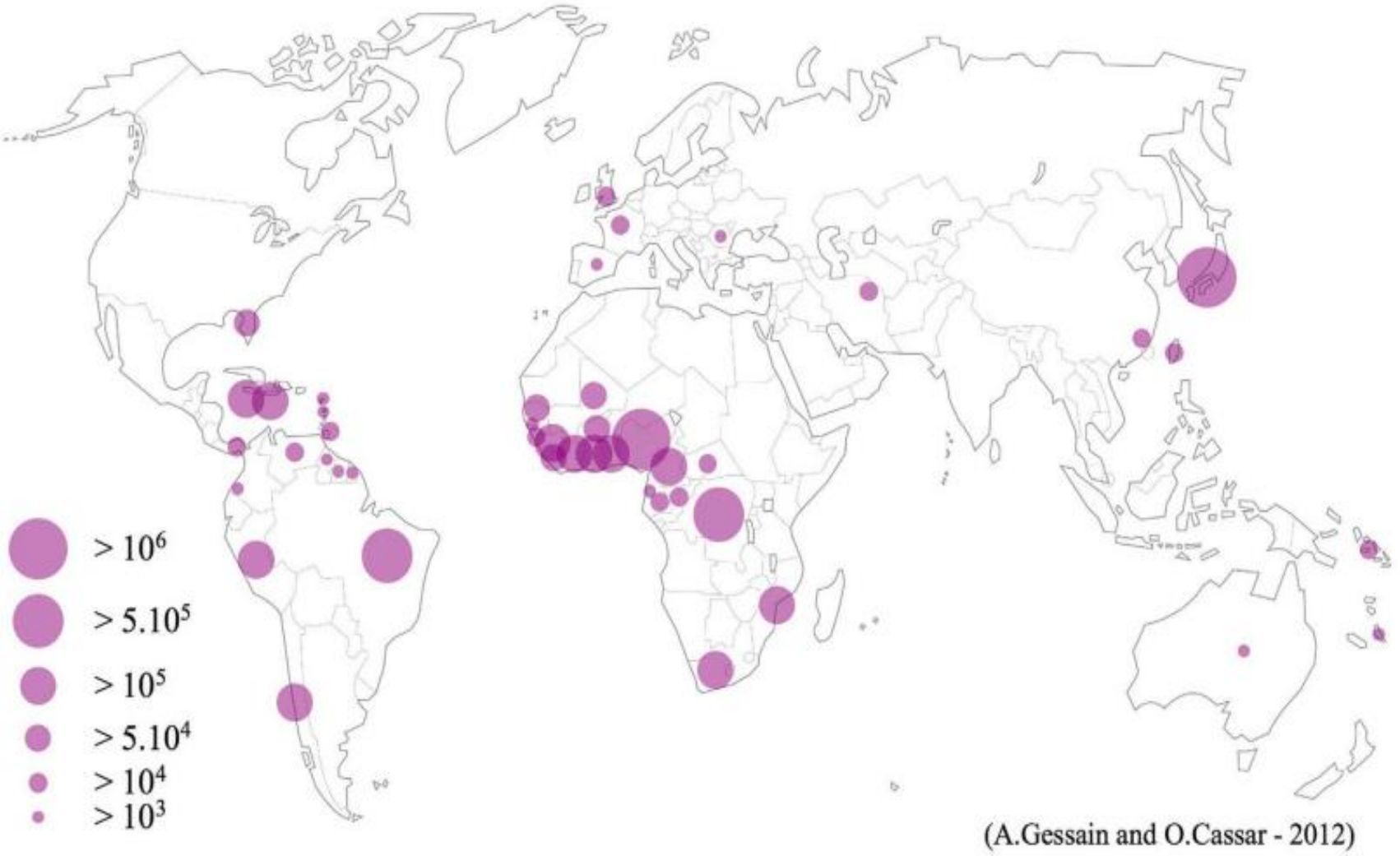
- **COMERCIALIZACIÓ A ESPAÑA 1 FEBRER 2024**

- **Nom comercial : Hepcludex**

HTLV-1 infection in humans

Transmission	Risk Factors	Malignancies	Control Strategies
• Vertical, esp. breastmilk • Sex • Blood • Organ transplant	• Geographic • Breast-feeding • Close contact • Blood transfusion • Organ transplant • Intravenous drug use	• Adult T-cell Leukemia/Lymphoma (ATL)	• No vaccine available • Screening of blood and organ donations • Management of ATL depends on clinical status

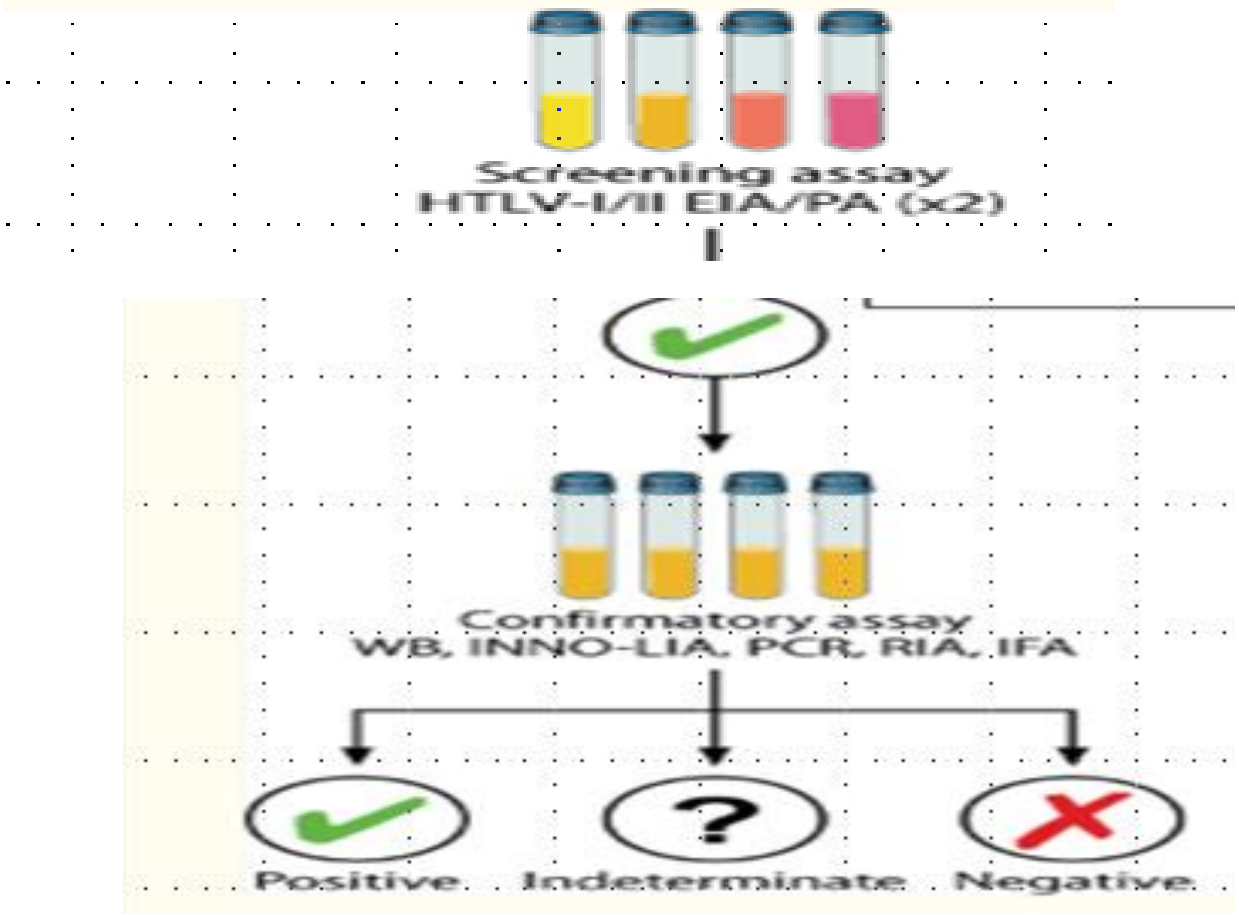
| Geographical distribution of the main foci of HTLV-1 infection



HTLV-1 infection in humans

- First retrovirus causing cancer in humans in 1979 R.Gallo
- HTLV-1 infects 10-20 million people worldwide and its main geographical distribution is Japan, the Caribbean, South America and sub-Saharian Africa.
- Only 5% of infected people develop disease
- HTLV-1 positive serology have a 2-5% risk of developing ATL over their lifetime

HTLV-1 Testing and Diagnosis Algorithms



- **The risk is greater in males and typically appears 4-5 decades after infection in subjects who acquire it in childhood, with rare occurrence in those who become infected in adulthood**

- **The HTLV-1 genome is composed of a single strand of RNA that is integrated into the cell. It then expresses 2 oncogenic proteins: the transcriptional transactivator protein (Tax) and the HBZ protein**

- **ATL is characterised by a clonal proliferation of CD4+ T cells with the HTLV-1 integrated**

Entidades clínicas relacionadas con la infección por el HTLV-1

HTLV-1

Fuerte asociación

Paraparesia espástica tropical/ mielopatía asociada al HTLV (TSP/HAM)
Leucemia/linfoma de células T del adulto (LLTA)
Uveítis
Artropatía
Dermatitis infecciosa

Probable asociación

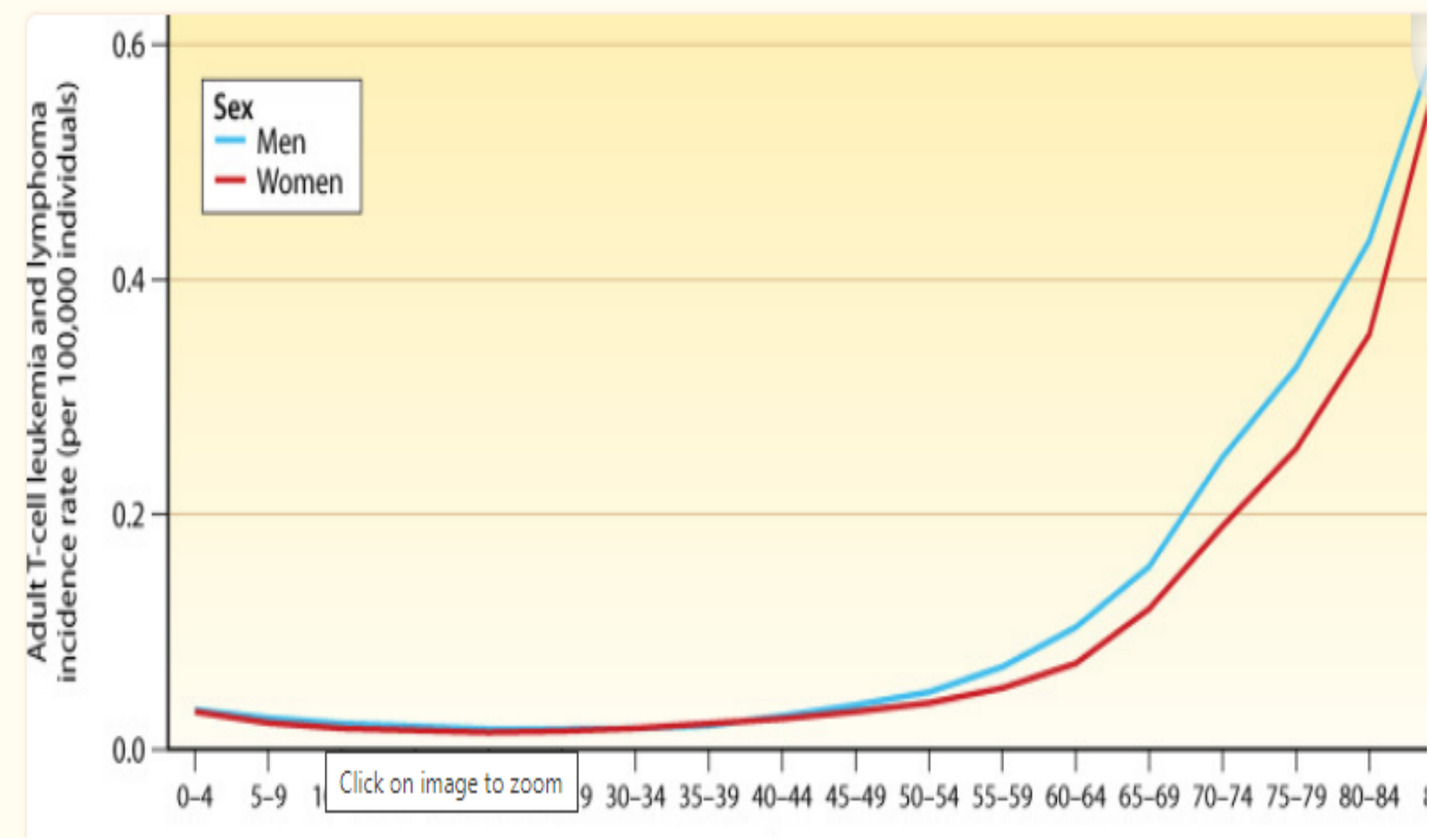
Esclerosis múltiple
Polimiositis
Síndrome seco
Alveolitis linfocitaria
Síndrome hipereosinofílico
Superinfección por *Strongyloides stercoralis*

Adult T-cell leukaemia-lymphoma (ATL)

Shimoyama Classification

Subtype	Affectation	Leukaemia cells	Hypercalcaemia	LDH	Survival
Acute leukaemia (60%)	Lymphadenopathy Extranodal Visceromegalies	Yes	Yes	Elevated	6 months
Lymphoma (20%)	Lymphadenopathy Extranodal Visceromegalies	No (< 1%)	Yes	Elevated	10 months
Chronicle (15%)	Skin, liver, spleen, lung, lymphadenopathy	Occasionally	No	< 2.5	24 months
Indolent (5%)	Skin, lung	Occasionally (>5%)	No	< 1.5	Years

ATL incidence by age and sex in 2018.



TRACTAMENT HTLV-1. MALALTIES ASSOCIADES

- ✓ La quantificació de la carrega viral pro-virica te valor pronòstic .
- ✓ Tractament antiviral : AZT, lamivudina , raltegravir resultats no concloents.

OPCIONS TERAPEUTIQUES LIMITADES PER LA TSP/HAM Y LLTA: :

- ➢ Glucocorticoides fase inicial TSP/HAM
- ➢ LLTA ; supervivència 1 any :
- ➢ -Quimio + zidovudina+ Interferon ALFA , millor que quimio
- ➢ Trasplant alogènic
- ➢ .-MOGAMULIZUMAB (ANTI CCR4) . LENALIDOMIDA

PROFILAXIS HTLV-1

- **Gestants seropositives :**

  Contraindicat lactància.

- **Seropositius : Utilitzar Preservatiu**

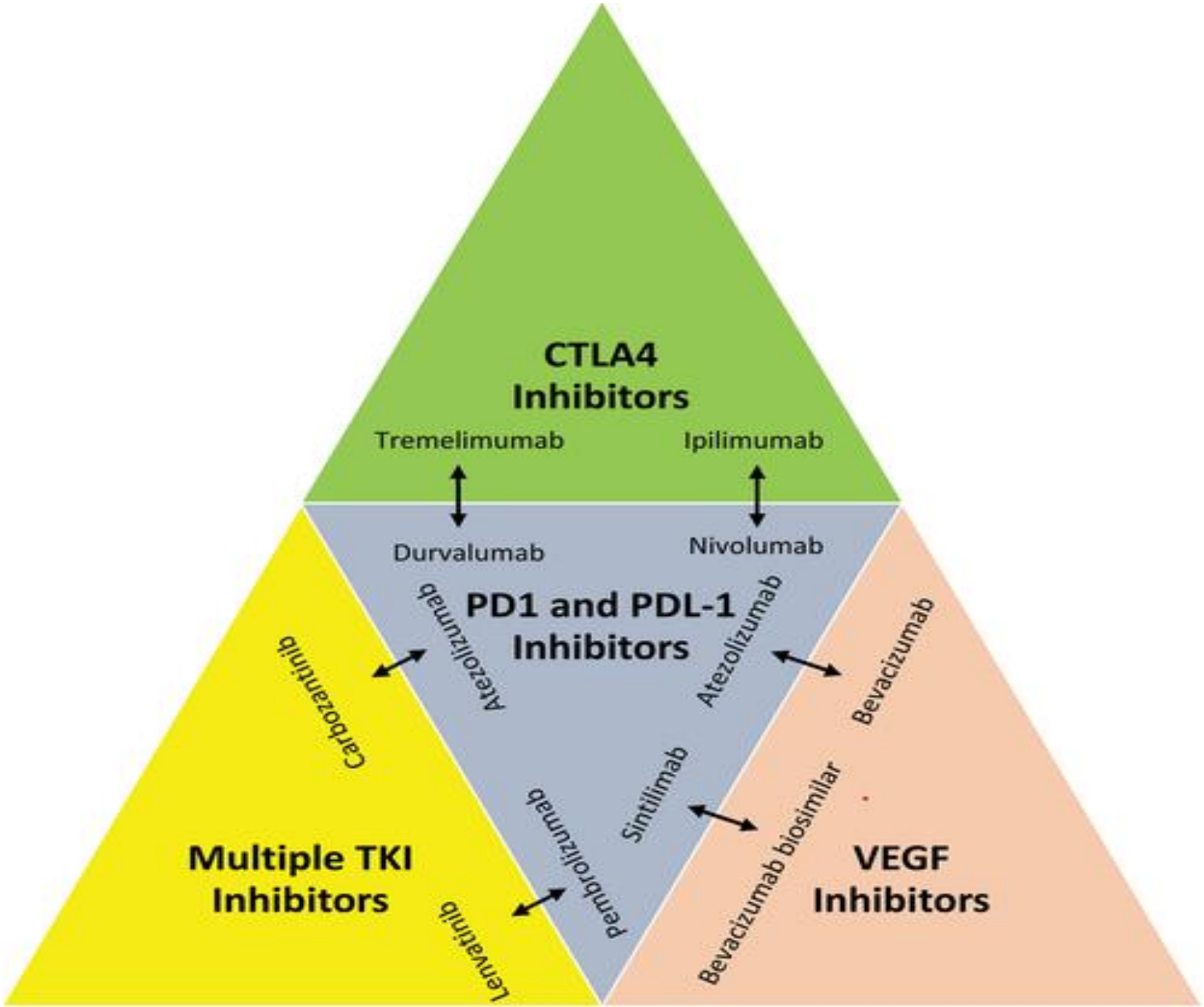
- **Cribat rutinari en bancs de sang en àrees endèmiques i en no endèmiques: emigrants provinents de àrees endèmiques.**

- **Donants òrgans sòlids**

HCV

Transmission	Risk Factors	Disease Course	Control Strategies
• Perinatal • Parenteral • Sexual	• Maternal HCV infection • High endemicity area • Injection drug use • Risky sexual practices • Healthcare worker • Skin piercing and tattoos	• Acute infection, which may self-resolve • Chronic infection, which can progress to cirrhosis or liver cancer • Asymptomatic disease	• Treatment of HCV infected patients • Education of healthcare workers • Blood product screening • Needle exchange • Safe sex practices • Skin piercing and tattooing safety • No vaccine available

Combination of immunotherapies in HCC.



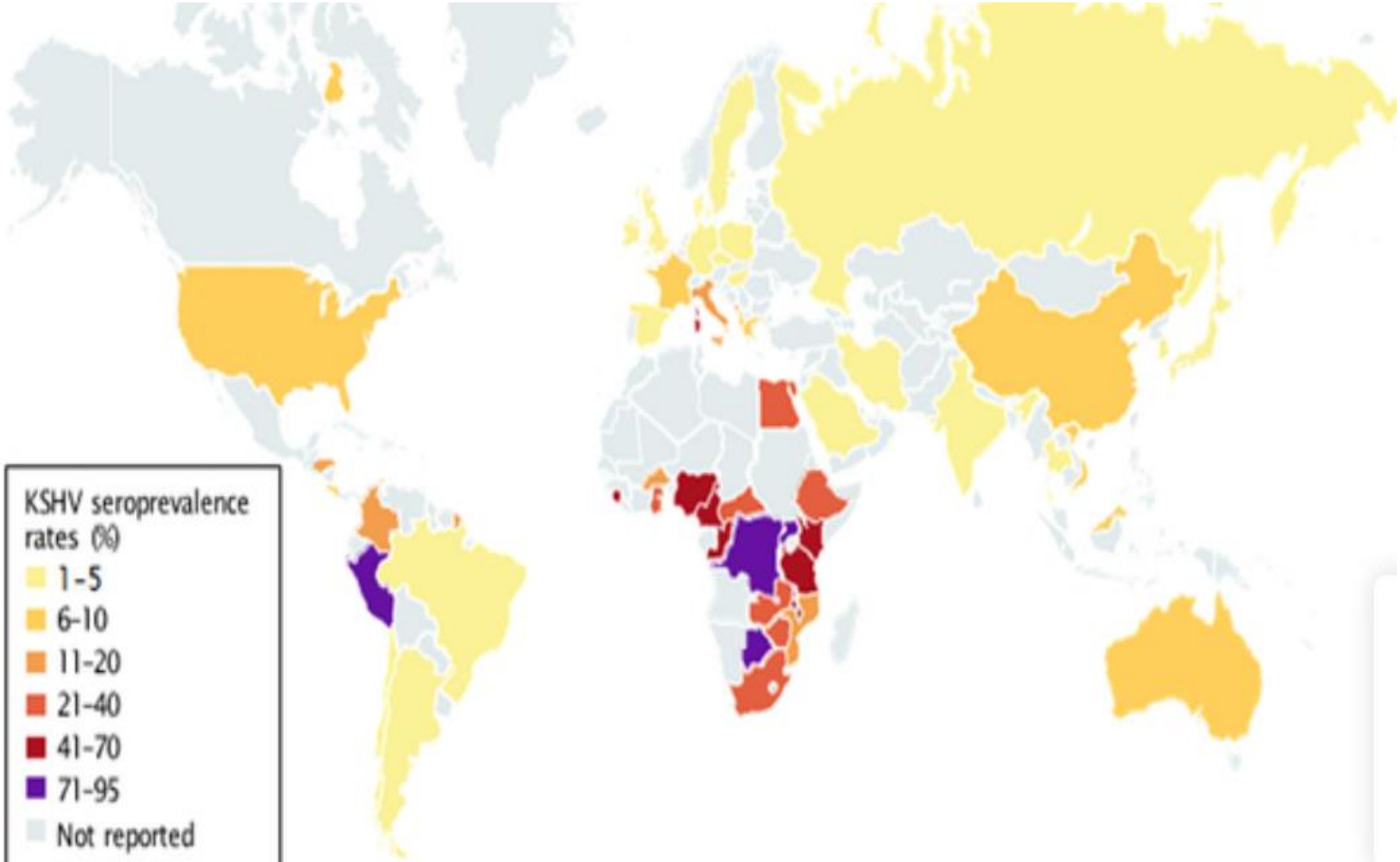
HHV-8.

- **The cause of KS was not known until 1994 when, on led to the discovery of the KS herpesvirus (KSHV; also known as human herpesvirus-8 (HHV-8)**

HHV-8.

Transmission	Risk Factors	Malignancies	Control Strategies
• Saliva (primary) • Sex • Blood • Organ transplant *Routes of transmission not fully understood	HHV-8 Infection • Geographic • Close contact • Blood transfusion • Organ transplant Malignancy • Immunosuppression • HHV-8 genotype	• Kaposi Sarcoma (most common) • KS-Associated Herpesvirus Inflammatory Cytokine Syndrome • Multicentric Castleman's Disease • Primary Effusion Lymphoma • Diffuse Large B-cell Lymphoma • Germinotropic Lymphoproliferative Disorder	• No vaccine available • No specific prevention strategies recommended • No specific control strategies recommended • Management depends on specific malignancy and patient factors

Geographical prevalence of KS and seroprevalence of KSHV.



Comparison of the epidemiological forms of KS

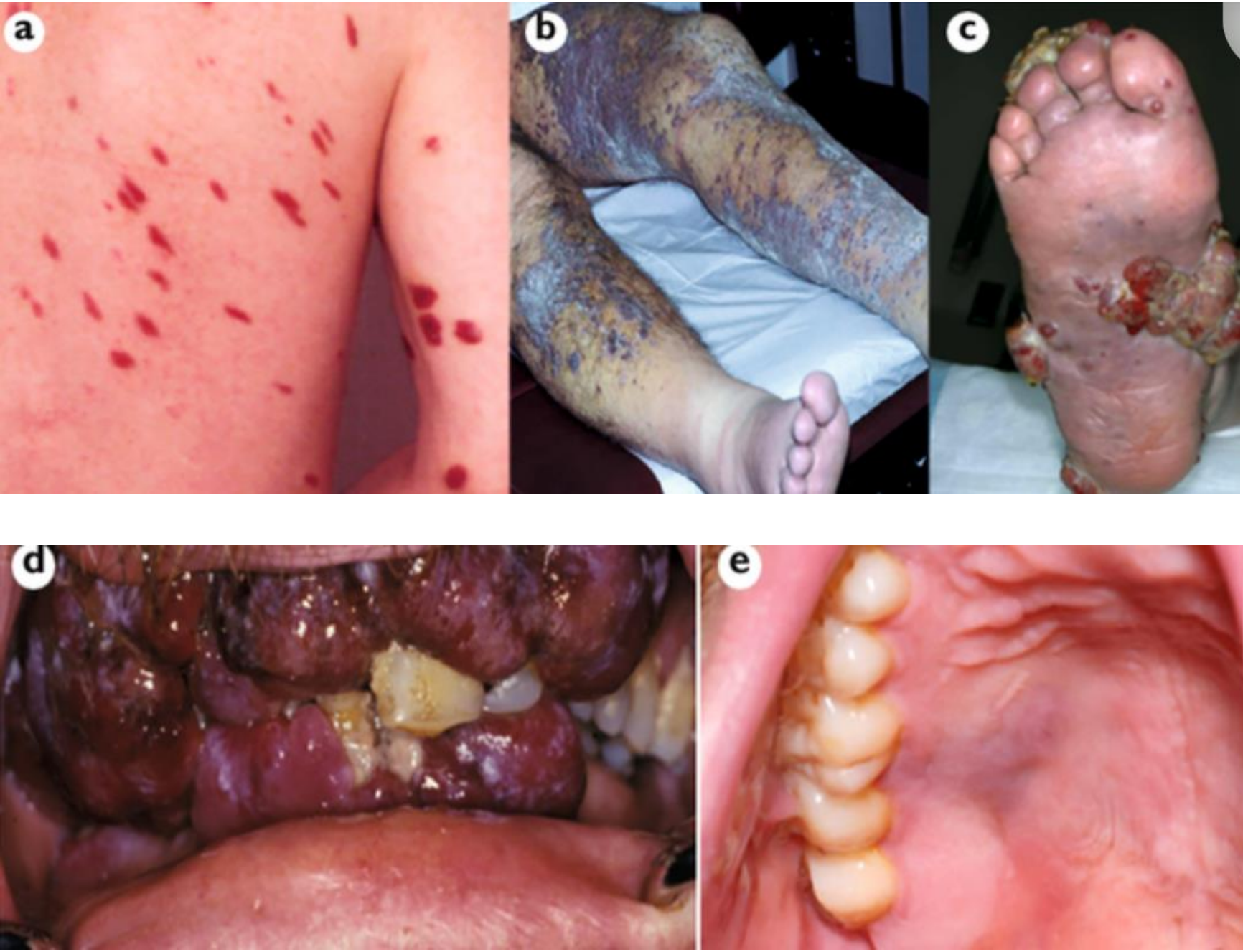
KS
AIDS-related (also known as epidemic)

Iatrogenic

Endemic

Classic (also known as sporadic KS)

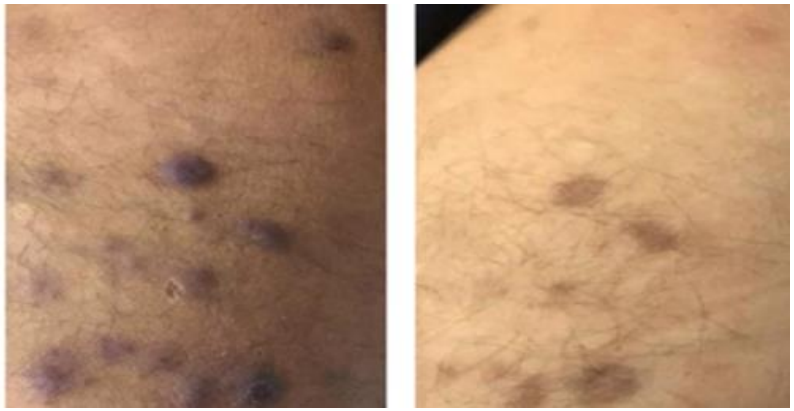
MSM without HIV infection


a
b
c
d
e

TREATMENT

- In advanced-stage KS, chemotherapy with pegylated liposomal doxorubicin or paclitaxel is the most common treatment

- Pilot studies of the use of immune checkpoint inhibitors in KS (anti-PD-L1) have been promising both in patients with HIV and in patients who are HIV seronegative.

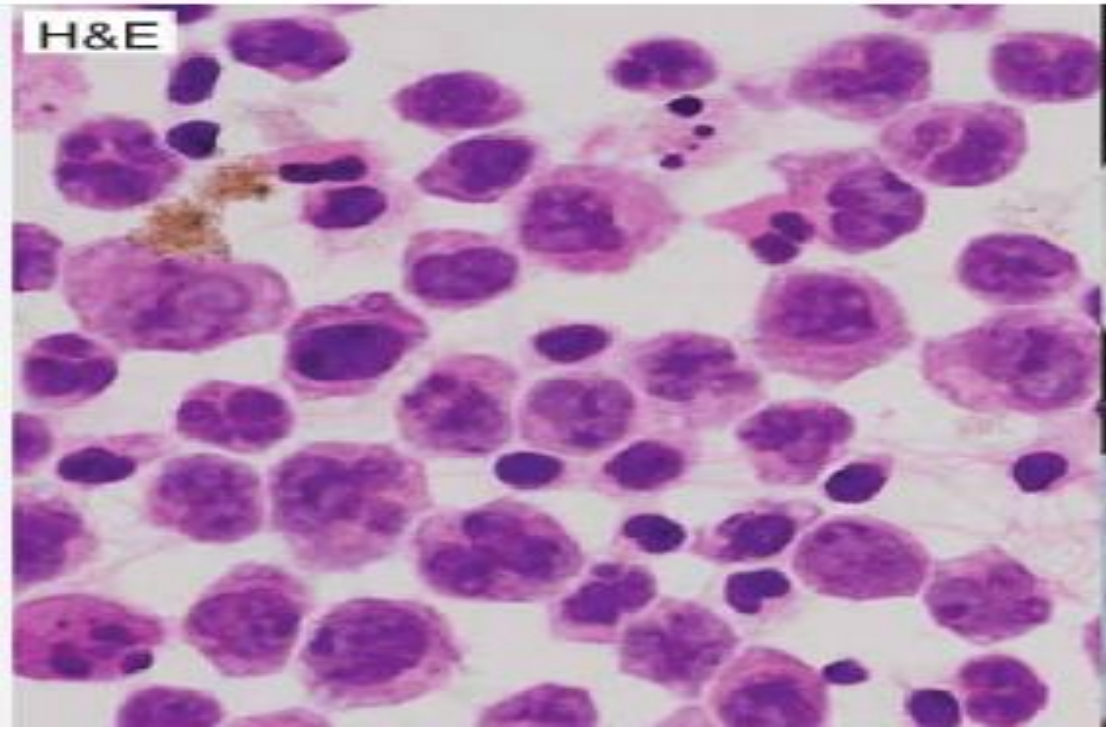


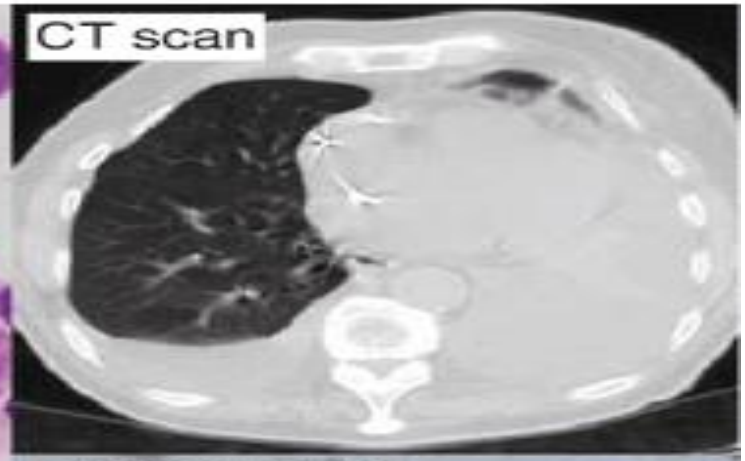
Diseases caused by KSHV

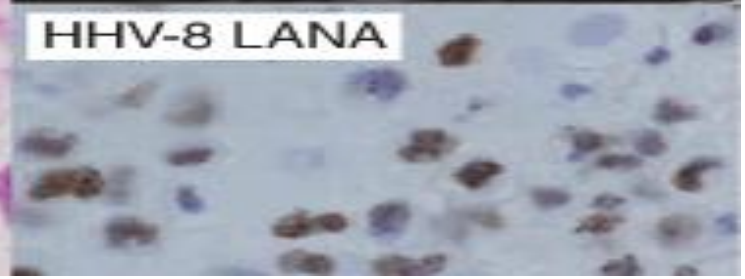
- **Primary effusion lymphoma (PEL) is a B cell lymphoma that most commonly affects body cavities, including the peritoneal, pleural and pericardial cavities**

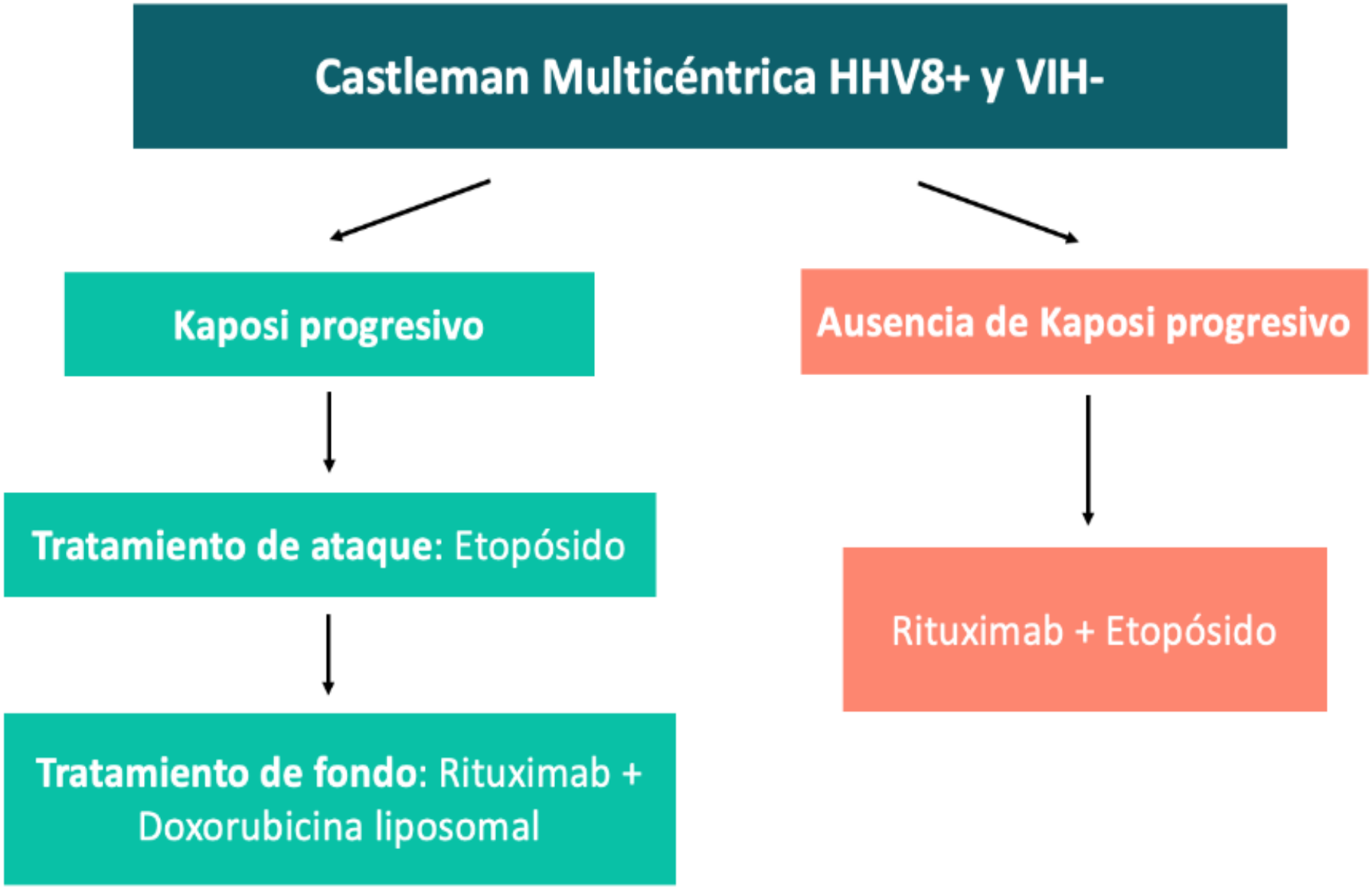
- **Multicentric Castleman disease (MCD) is a lymphoproliferative disorder presenting with generalized lymphadenopathy) and systemic symptoms.**

Primary effusion lymphoma








Castleman Multicéntrica HHV8+ y VIH-
Kaposi progresivo
Ausencia de Kaposi progresivo
Tratamiento de ataque: Etopósido
Tratamiento de fondo: Rituximab + Doxorubicina liposomal
Rituximab + Etopósido

KSHV-positive diffuse large B cell lymphoma

KSHV inflammatory cytokine syndrome (KICS) :

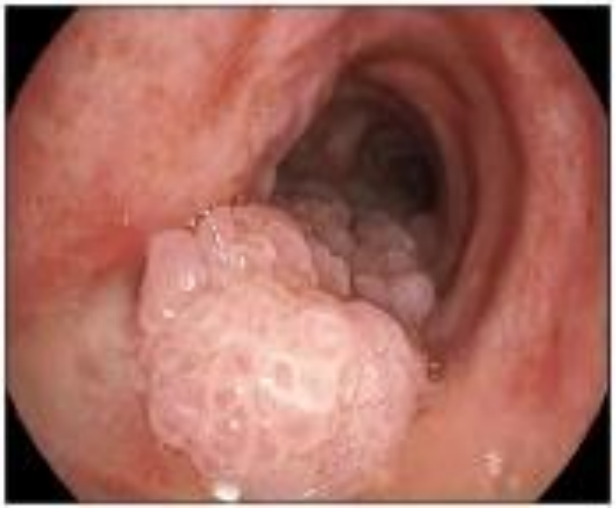
- **This is a syndrome that in some ways mimics severe sepsis with associated acute respiratory distress syndrome, possibly requiring a ventilator and vasopressor support.**

- **However, unlike severe sepsis, antibiotics provide no benefit.**

- **High KSHV viral load and interleukin-6 can cause cytopenia, fevers, cachexia, hyponatremia, and hypoalbuminemia**

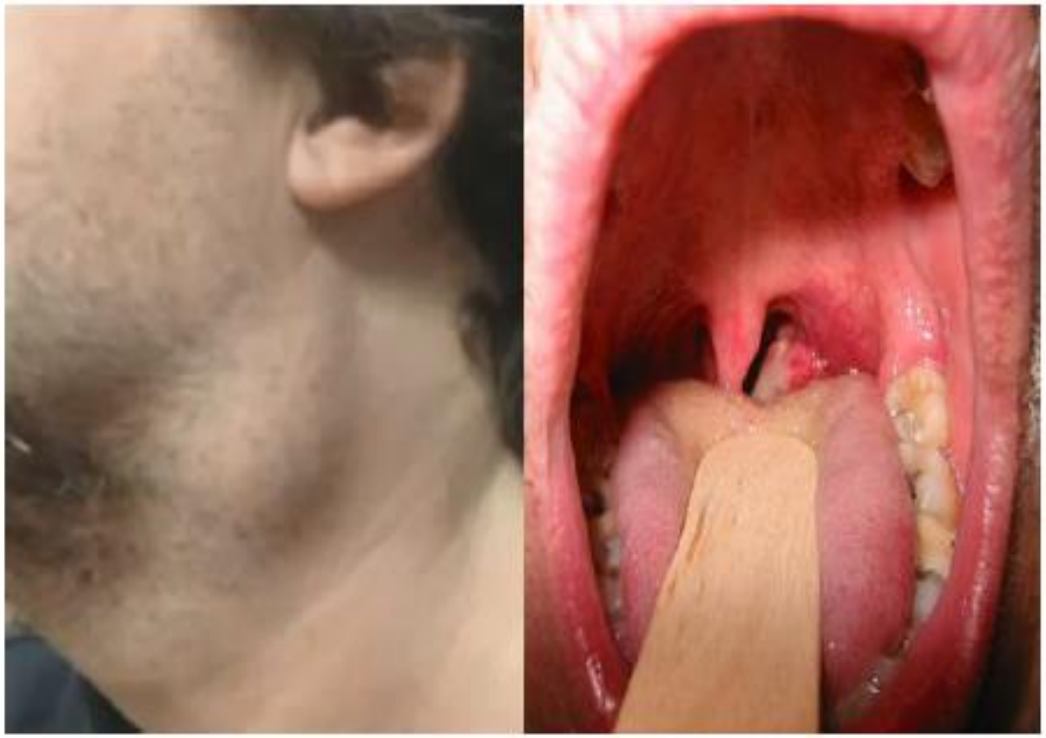
HPV

Transmission	Risk Factors	Disease Course	Vaccine Target Populations	Other Control Strategies
• Sexual • Skin Contact	• Sex - vaginal, anal, and oral • Skin contact	• Asymptomatic infection • Can clear spontaneously (immune response) • Can progress to cervical, vulvar, vaginal, penile, anal, or oropharyngeal cancer	• Males and females prior to sexual debut • Given at older ages in some risk populations • Recommended at ages 9-14 for females by WHO (451)	• Safe sex practices • Screening programs • Monitoring of detected abnormalities • Treatment of pre-malignant and malignant lesions

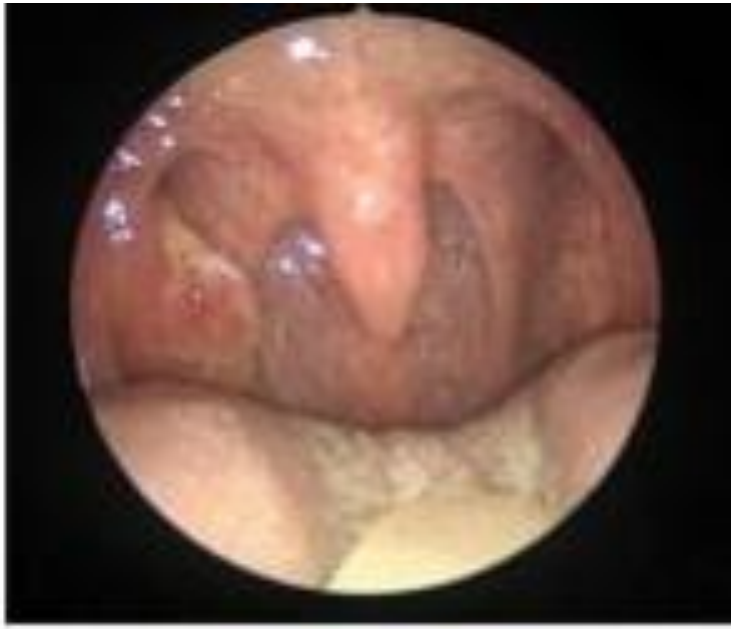


Respiratory Papillomatosis

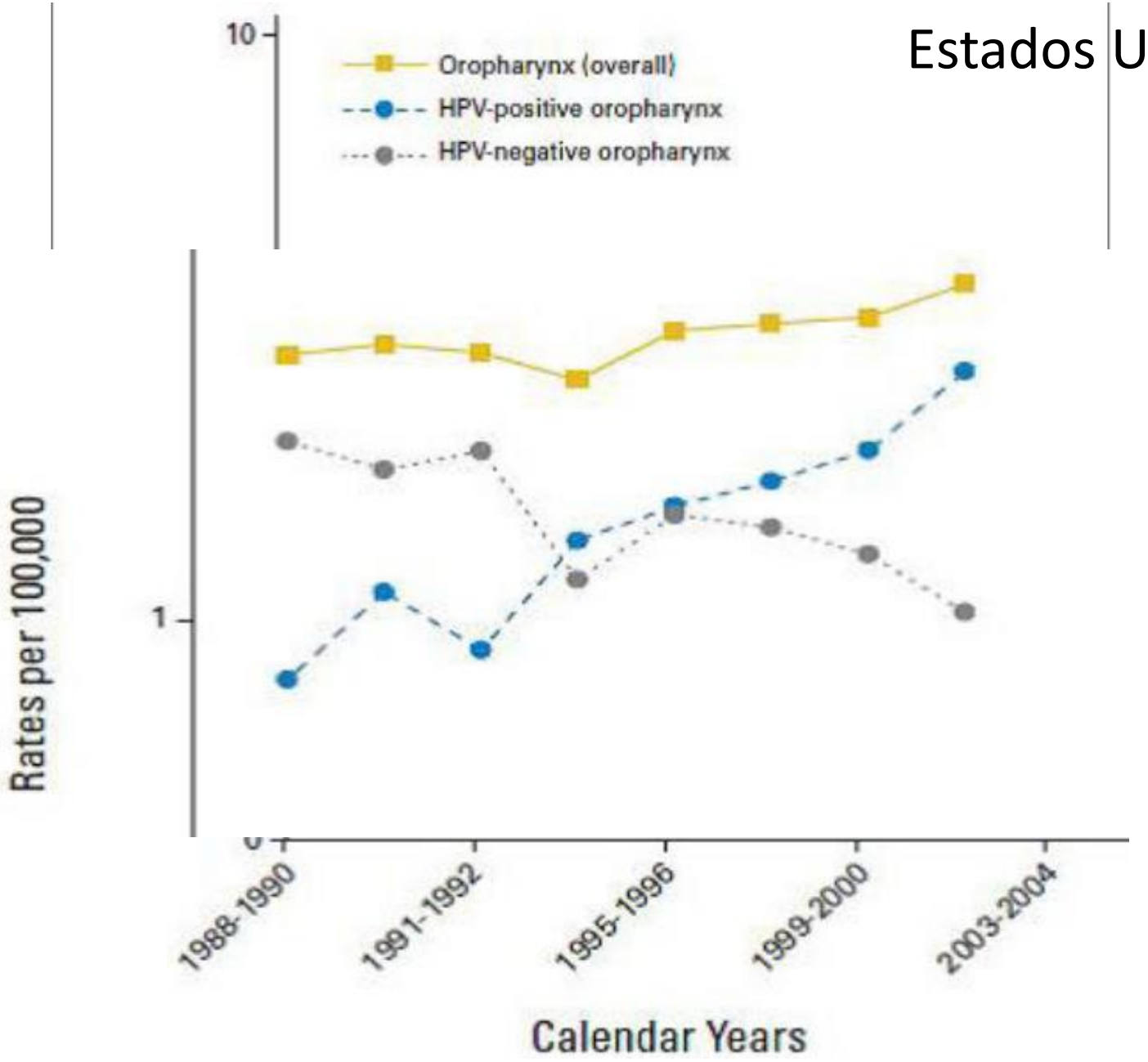
Cancer Amigdala



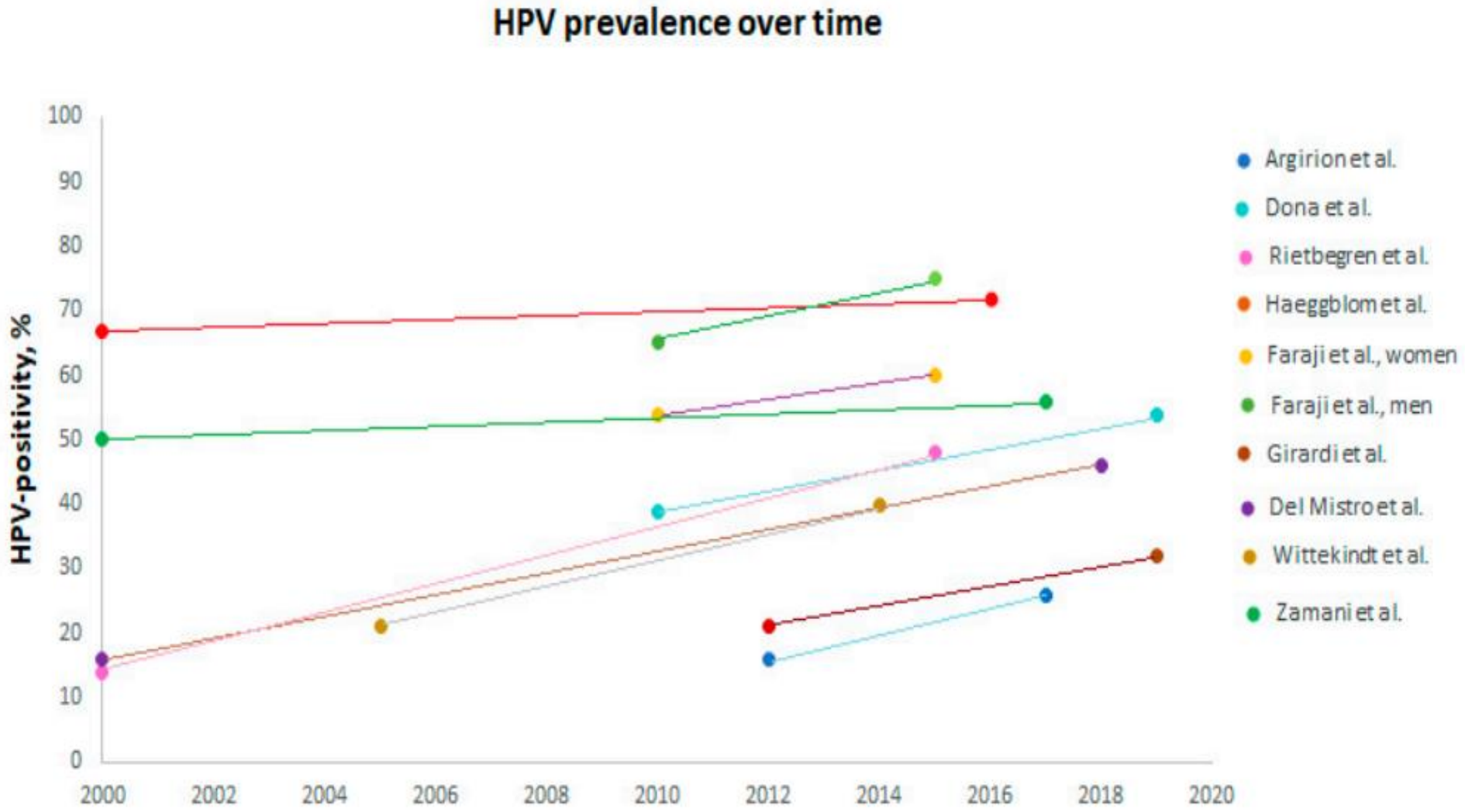
Cancer Amigdala



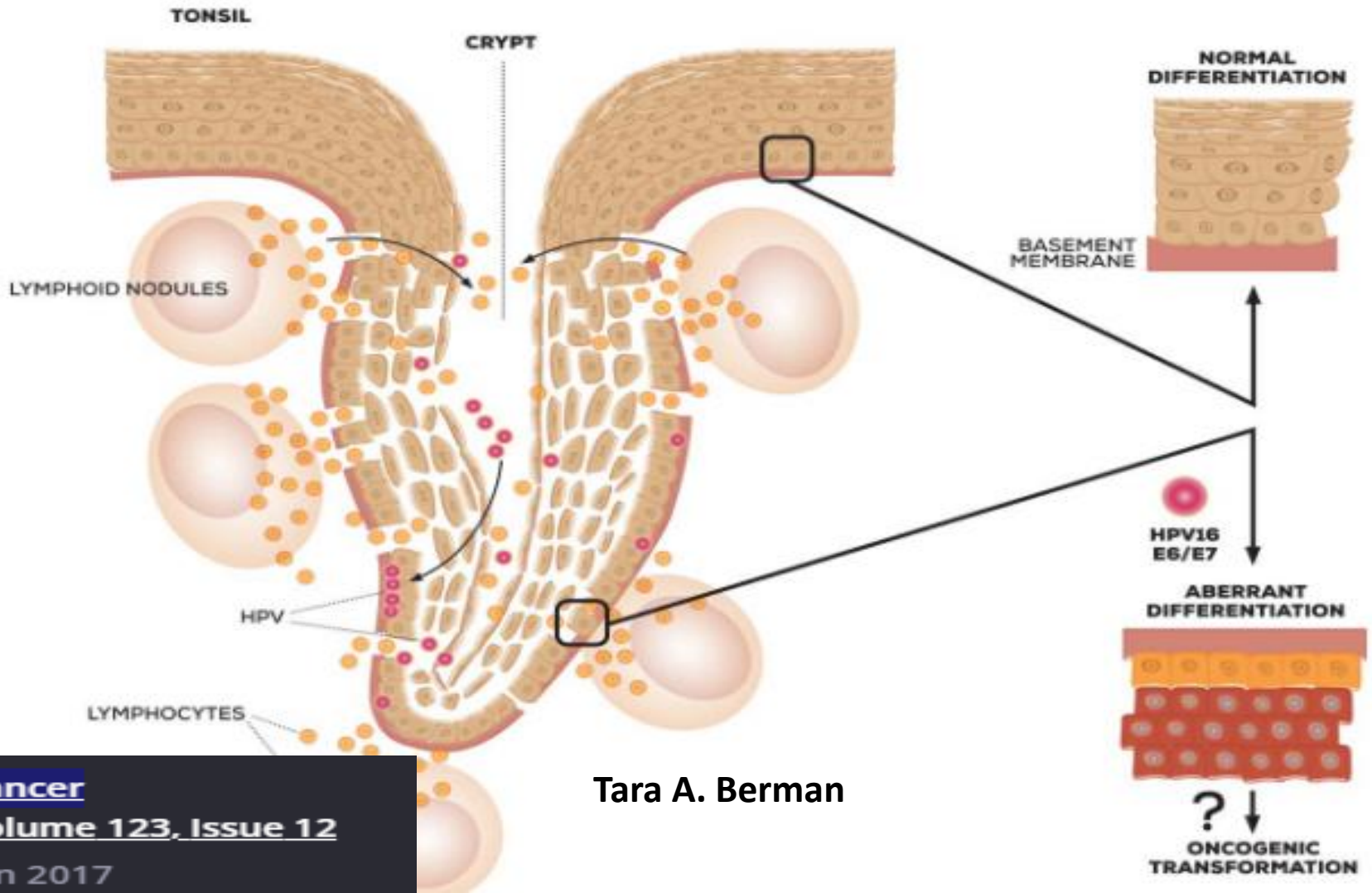
Estados Unidos



HPV-positivity in patients with OPSCC over time worldwide



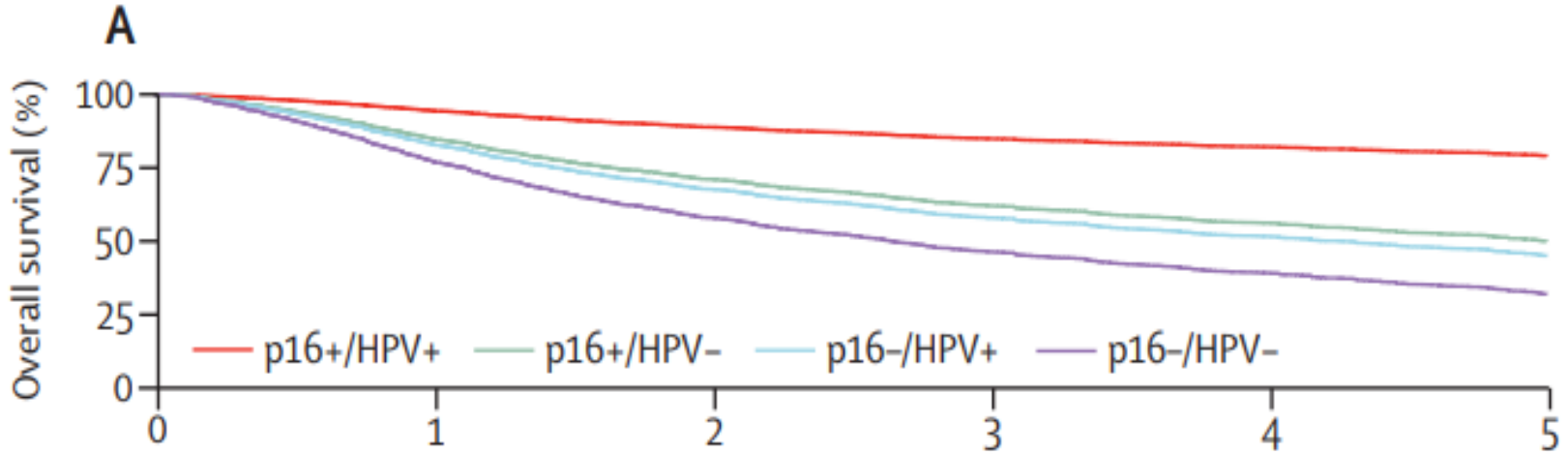
Human papillomavirus (HPV) in oropharyngeal carcinogenesi



Cancer
Volume 123, Issue 12
Jun 2017

Tara A. Berman

5-year adjusted overall survival

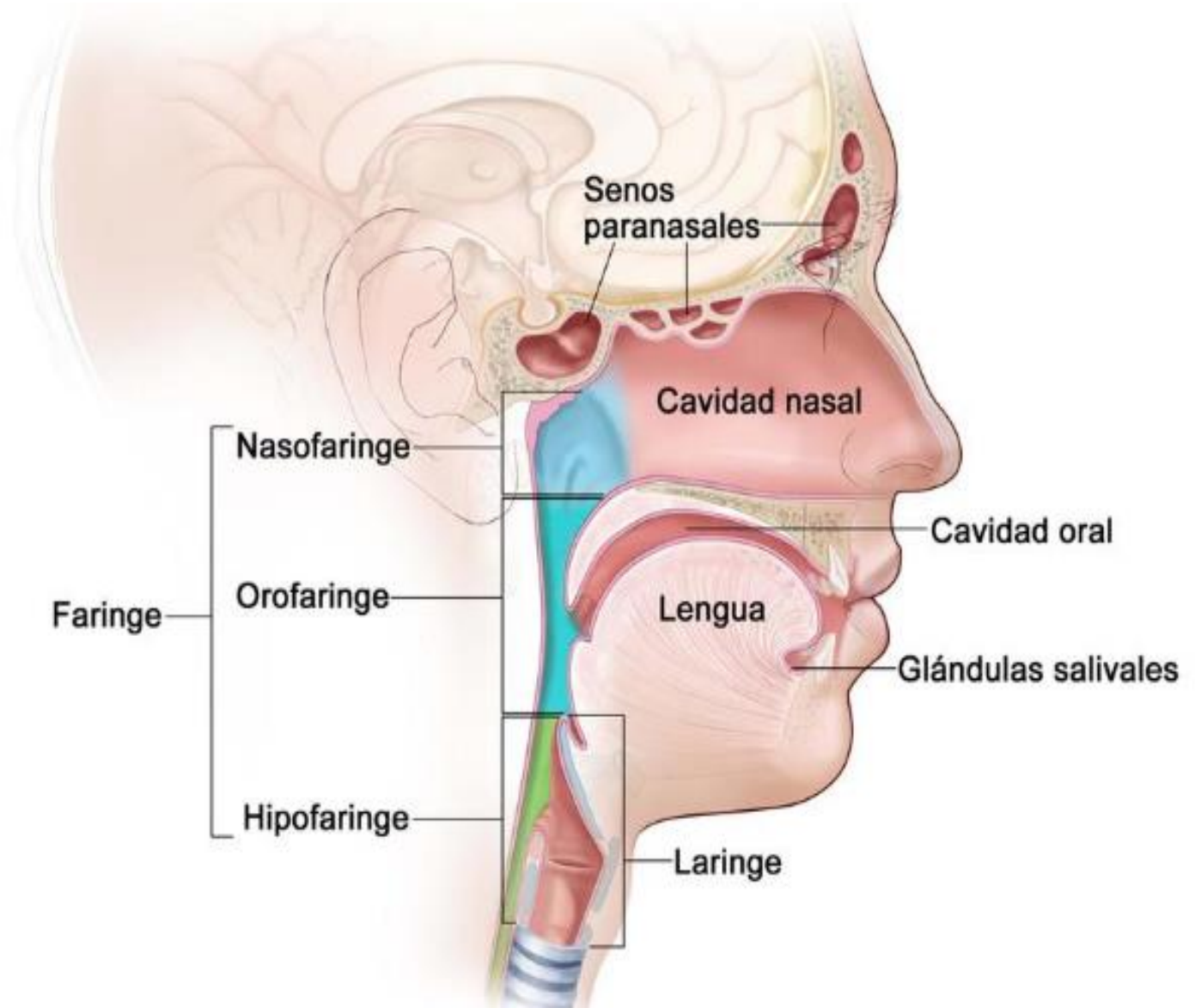


Number at risk (number censored)						
p16+/HPV+	3220 (1)	2927 (168)	2434 (517)	1966 (892)	1644 (1153)	1166 (2737)
p16+/HPV–	364 (0)	304 (17)	240 (43)	190 (68)	148 (91)	98 (226)
p16–/HPV+	240 (0)	184 (17)	138 (35)	108 (48)	92 (59)	59 (144)
p16–/HPV–	3058 (1)	2332 (108)	1702 (250)	1316 (392)	1057 (504)	804 (1424)

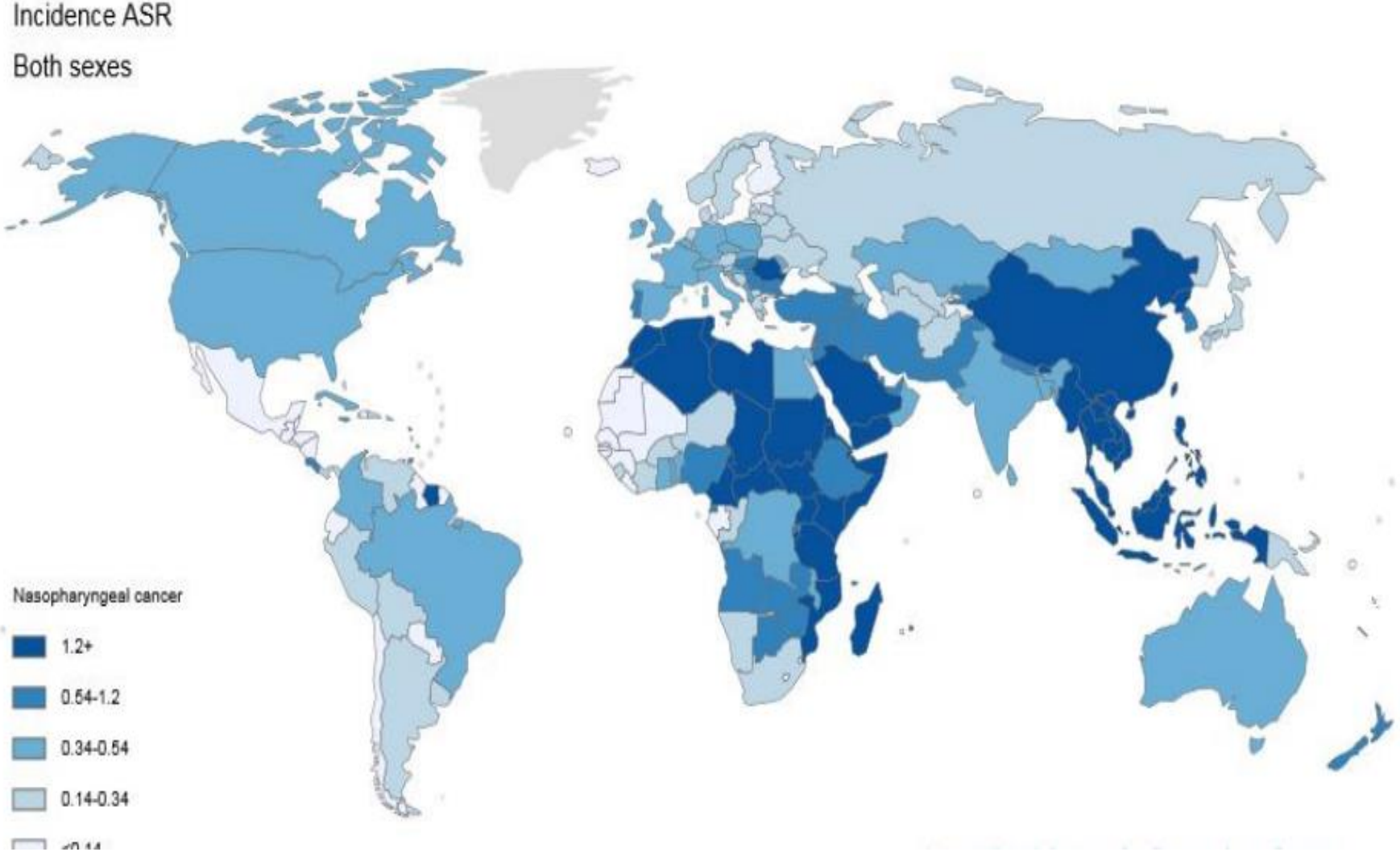
EBV

Transmission	Risk Factors	Example Malignancies	Control Strategies
• Saliva (primary) • Sex • Blood • Organ transplant	• Geography • Close contact • Blood transfusion • Organ transplant • Immunosuppression • Fomites	• Burkitt's Lymphoma • Hodgkin Lymphoma • Nasopharyngeal Carcinoma • Post-transplant Lymphoproliferative Disorder • T-cell Lymphoma • B-Lymphoproliferative Disease • T/NK cell Lymphoma • Primary Effusion Lymphoma • Gastric Carcinoma	• No vaccine available • No specific prevention strategies recommended • No specific control strategies recommended • Management depends on specific malignancy and patient factors

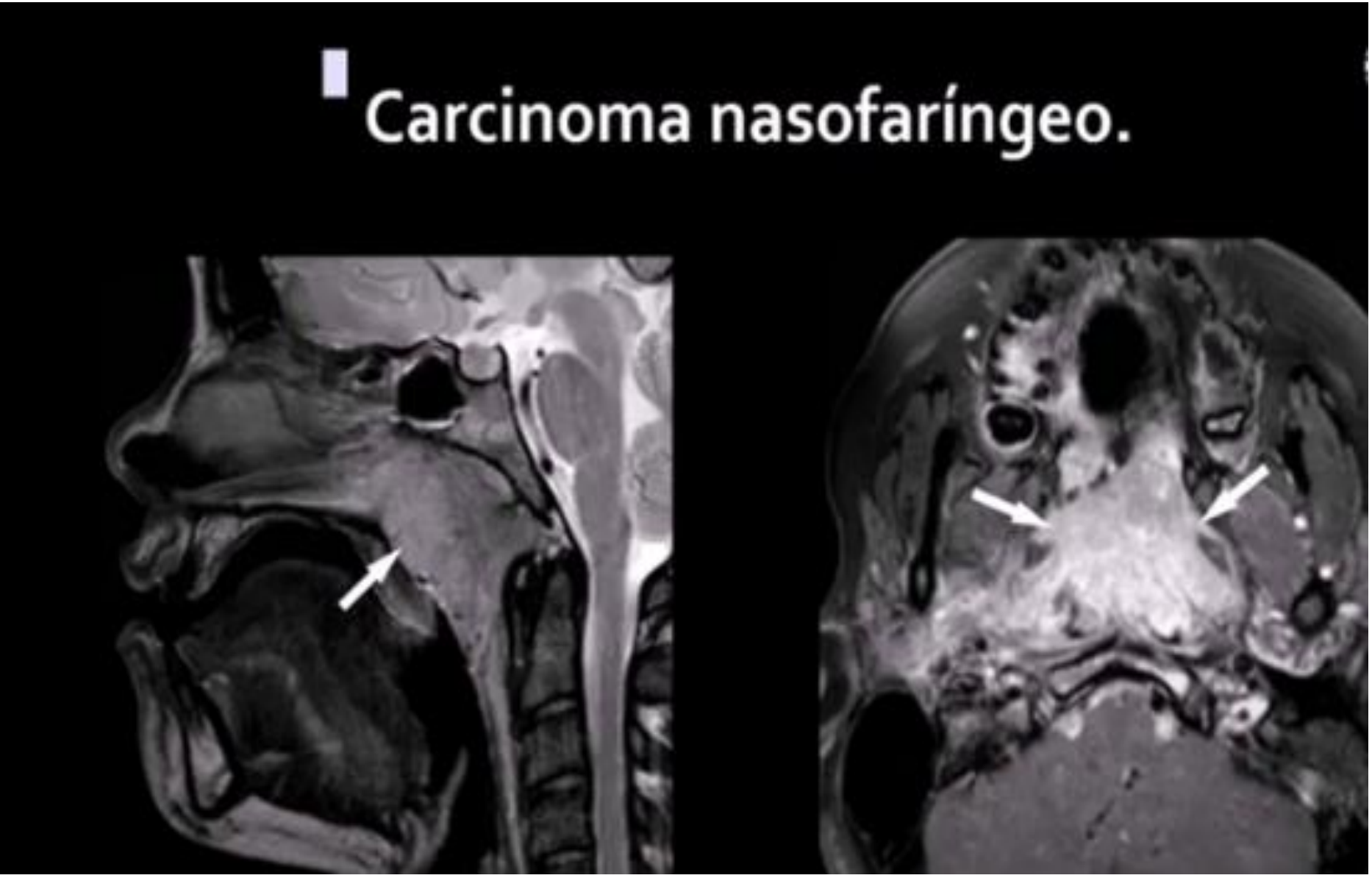
Càncer Nasofaringi



✓Mayor incidencia en Asia y Norte de África

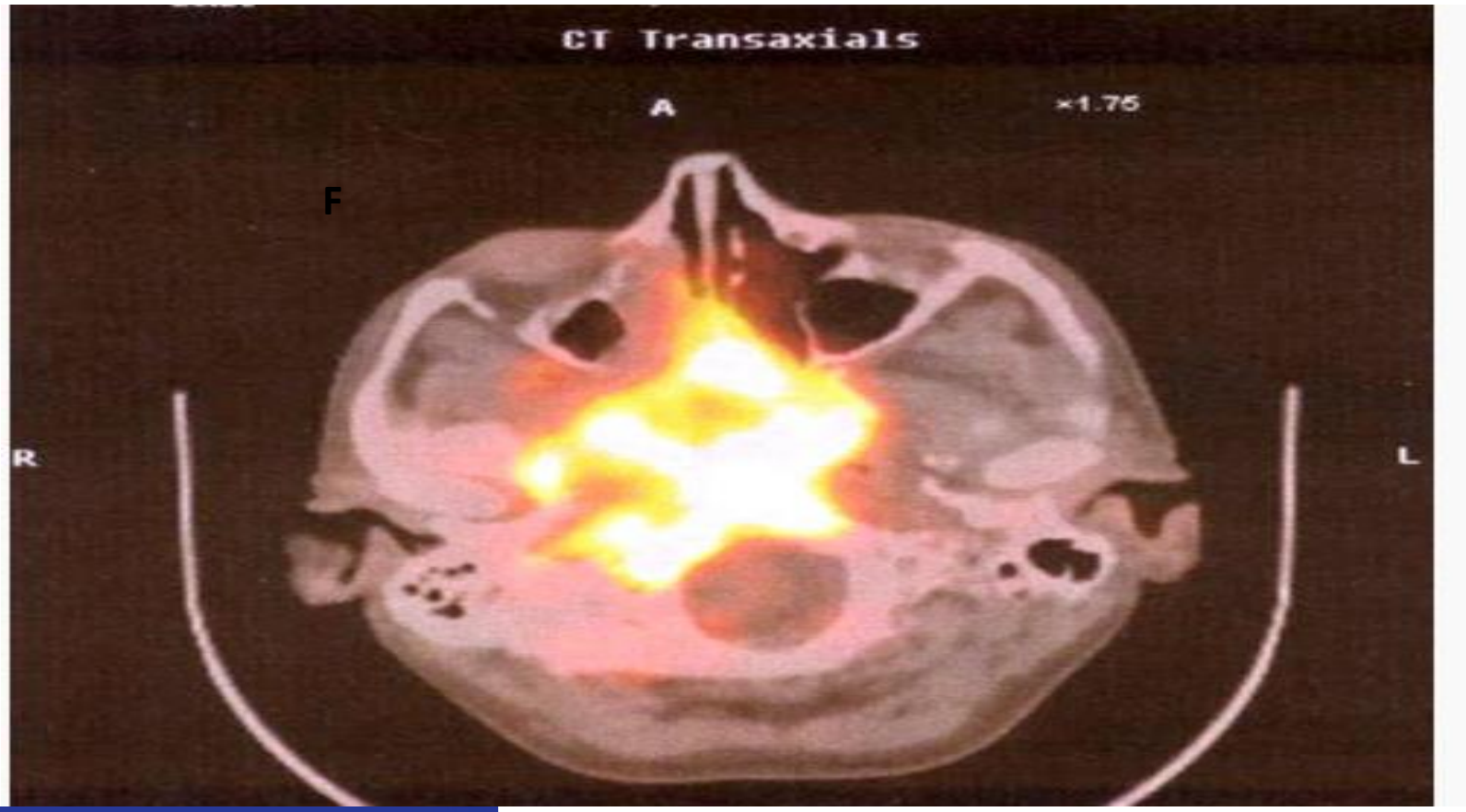


Carcinoma nasofaríngeo.



Fatal Fast-Evolution of Nasopharyngeal Squamous Cell Carcinoma in an HIV Patient with EBV and HPV (-16 AND -33) in Blood Serum

2008



The Open AIDS Journal

Guillem Sirera

Survival estimates according to viral status

Clinical Outcome	EBV Positive (n=26)	HPV Positive (n=18)	EBV/HPV negative (n=17)	*P*
Overall survival at 5 yr – % (95% CI)	71.6% (47.1-86.2)	47.9% (23.6-68.7)	17.6% (4.3-38.3)	0.003
Progression-free survival at 5 yr – % (95% CI)	63.1% (38.6-80.0)	34.2% (12.7-57.3)	11.8% (2.0 -31.2)	0.001
Locoregional control at 5 yr – % (95% CI)	87.3% (54.6-97.0)	48.1% (18.6-72.7)	26.4% (4.6-56.1)	0.002

Merkel cell carcinoma

Merkel cell carcinoma is a rare skin cancer with neuroendocrine differentiation.

The risk factors :

- **-Sun exposure**
- **-Advanced age**
- **-Immunosuppression :**
  - ✓ **Transplant recipients**
  - ✓ **Patients with lymphoproliferative neoplasms**
  - ✓ **Patients with HIV**

Was first described in 1972 by Toker as a trabecular skin carcinoma

Epidemiology :

- **In the European Union, between 1995 and 2002, its annual incidence rate was 0.13 per 100,000 inhabitants, but higher in groups aged 65 years or older.**

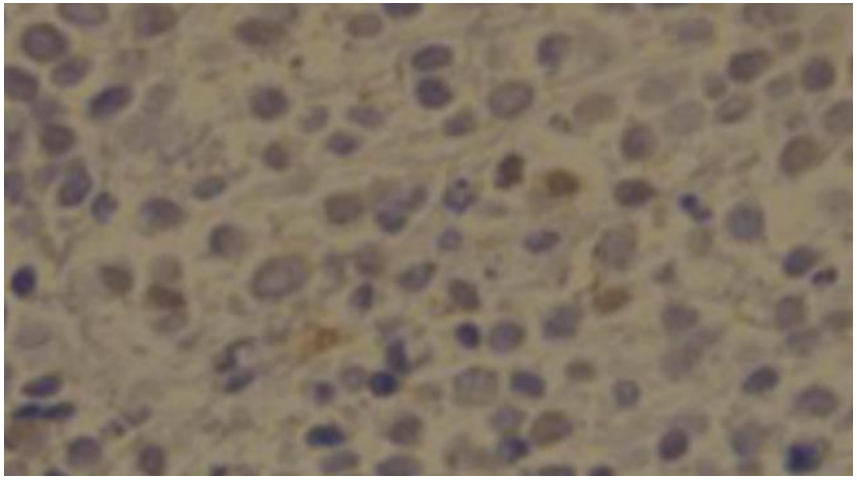
- **In the United States, the incidence rate was 0.79 per 100,000 inhabitants in 2011**

- **In an Australian study, with a rate of 1.6 per 100,000 inhabitants in the state of Queensland between 2006 and 2010, more frequent in males (2.5 per 100,000) than in females (0.9 per 100,000)**

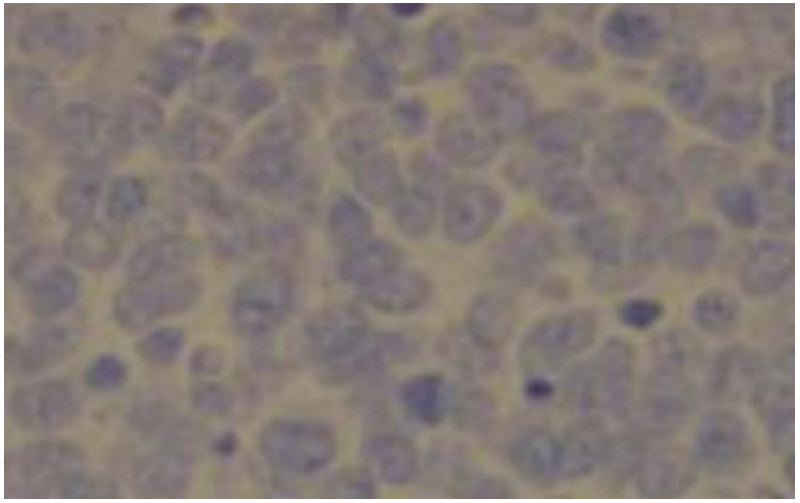
➢ In 2008,

- **Feng et al. first described the association between a novel polyomavirus and MCC, identifying viral DNA in 8 of 10 Merkel tumors, suggesting that viral infection could be an early event in the pathogenesis.**

Merkel cell carcinoma



Immunohistochemistry slide from a patient showing a positive result for MCPyV

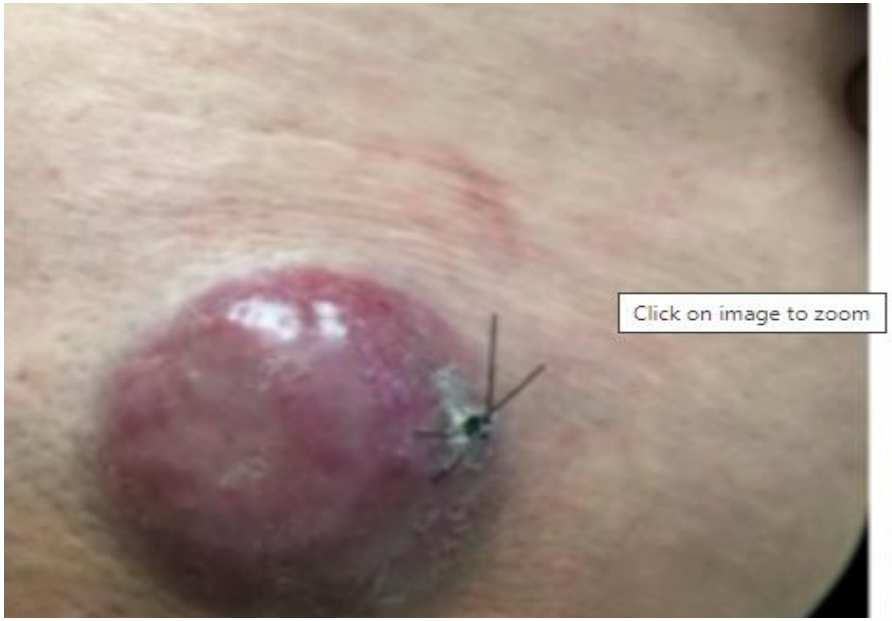


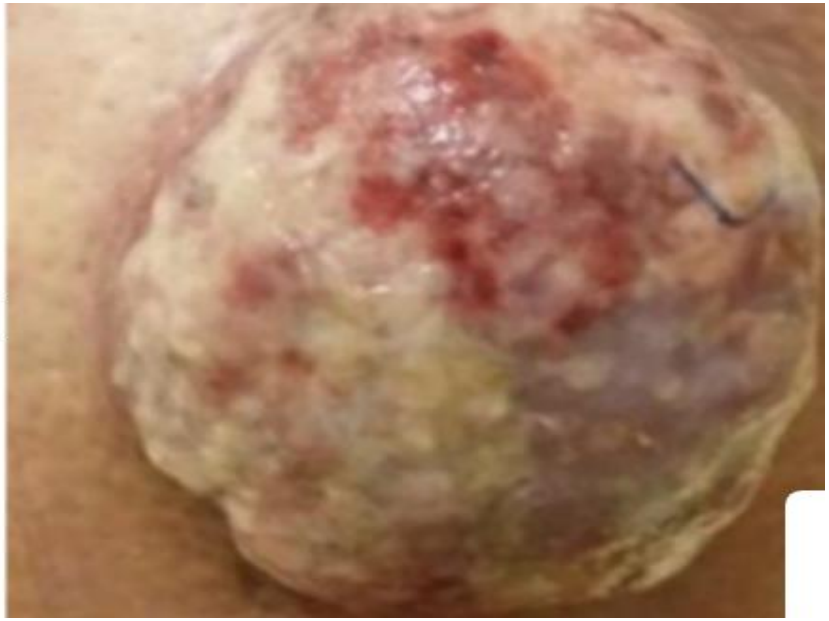
Immunohistochemistry slide from a patient showing a negative result for MCPyV

- **Cases of subclinical MCPyV infection increase with senescence, reaching a prevalence of 60% to 80% in adults**

  The skin constitutes the major viral infection site, although the virus has also been detected in peripheral blood and other organs.

- **MCPyV infection seems to be asymptomatic.**


Click on image to zoom



- **Clinically, MCC can present as a cutaneous or subcutaneous nodule, and even have a cystic appearance.**

- **The color can vary between red, pink, blue, violet, or skin color. Initially, the lesions are usually painless and solitary, but they may also ulcerate or be surrounded by satellite lesions.**

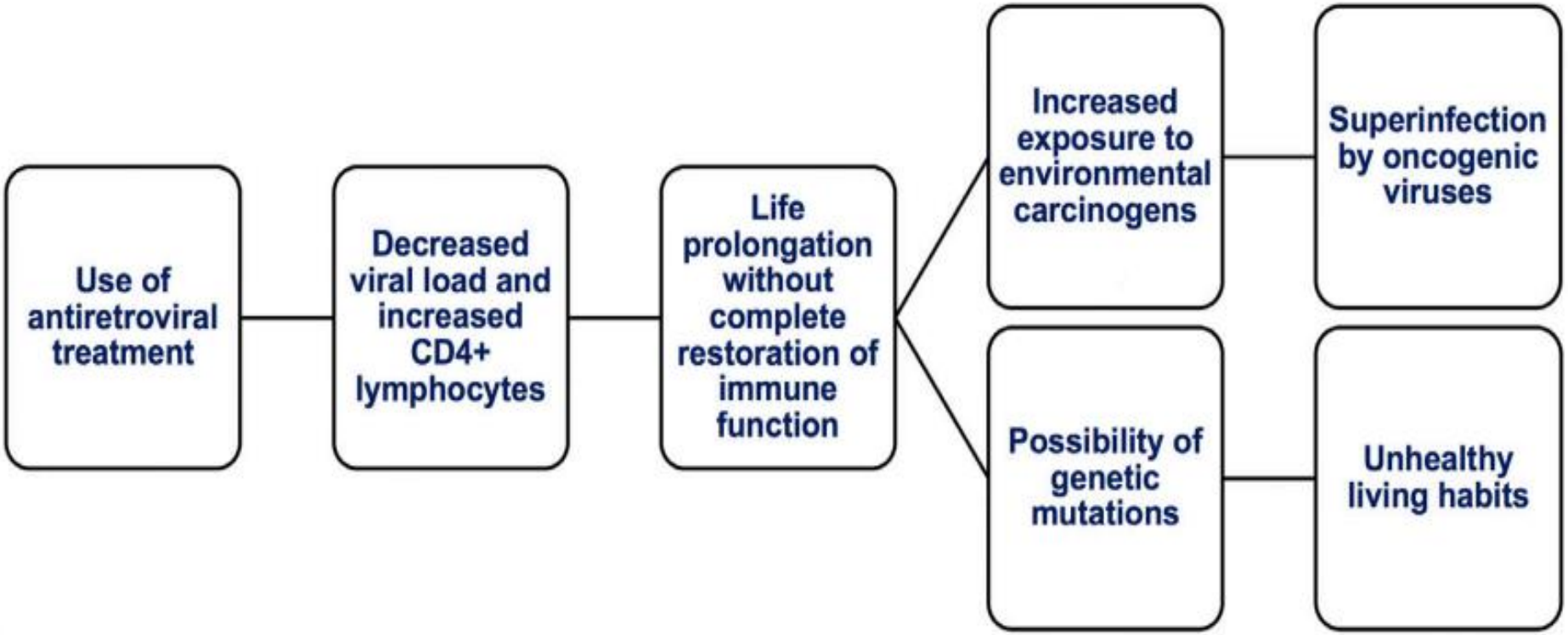
- **At diagnosis, the dimensions can vary in size but are usually smaller than 20 mm, and most cases show rapid tumor growth in a few months**

- **The first anti-PD-L1 antibody used in patients with Merkel cell carcinoma was avelumab, but pembrolizumab and nivolumab have also shown efficacy**

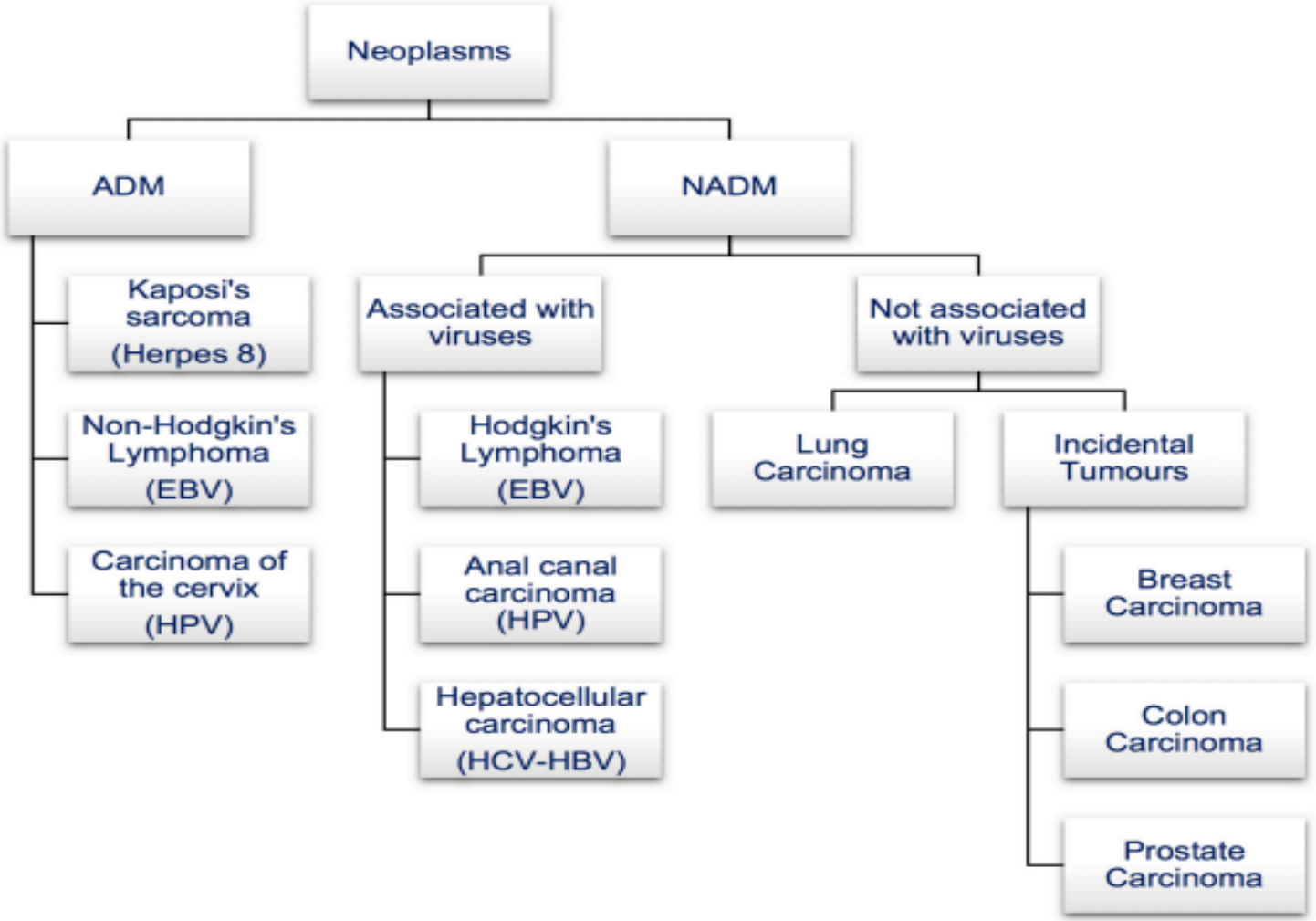
Treatment

- Surgery for the primary tumor
- Radiotherapy
- Systemic treatment
- Chemotherapy
- Immunotherapy
  - Avelumab
  - Pembrolizumab

Effects of ART on the immunity that condition the appearance of neoplasms in HIV+ patients under treatment.



Classification of the tumours that appear in HIV+ patients.



Cáncer i VIH

- **Incidencia i mortalitat per càncer més altes en VIH**
- **Diagnostic amb edad mes joves i/o estadios mes avançats**
- **Els cánceres no definitoris de SIDA son actualment mes frecuents i es preveu el seu aument .**
- **Els VIH participan menys en els programes de cribats poblacionals**
- **Existeixen poques dades de estratègies de prevenció i diagnostic**

IMPACT-NEO

- **Assaig clínic multicèntric, prospectiu aleatoritzat 1:1**
- **Avalua l'efectivitat de un programa de cribat reforçat ,`pel diagnòstic precoç de lesions pre -canceroses i càncer en VIH en comparació amb la atenció Standard recomanada per el EACS.**
- **Neoplàsies anals de cèrvix, pulmó, mama ,pròstata, hepàtiques i pell.**
- **Anàlisis primari: diagnòstics de pre-càncer i càncer en estadi precoç.**
- **Anàlisi secundari :relació cost-utilitat de cribat reforçat.**
- **Participen 22 hospitals de 10 CCAA.**
- **Inclusió homes >40 anys i dones >18 anys sense malalties actives excloent amb càncer previ, esperança de vida <5 anys, gestant i lactància**

Análisis intermedio ensayo IMPAC-Neo

Características basales de los participantes y neoplasias registradas

Características basales de los pacientes (n = 1346) [No/%]	
Edad, mediana (IQR)	**54** (44-59)
Género, hombre	1066 (**79,2%**)
Grupo de transmisión	
HSH	488 (36,25)
Heterosexual	337 (25,04)
UDI	266 (19,8)
Características clínicas VIH	
Con TAR	1232 (91,5%)
TAR y VIH < 200 copias/mL	1046 (**98,7%**)
Nadir CD4, mediana (IQR) células/uL	**237** (106-377)
Recuento CD4+, mediana (IQR) células/uL	**713** (505-496)
Recuento CD8+, mediana (IQR) células/uL	807 (580-1120)
CD4/CD8, mediana (IQR)	0,87 (0,6-1,25)
Estado basal fumador	
Actualmente o < 3 años	545 (**40,5%**)
Nunca	601 (44,6%)
Hepatitis C	231 (17,8%)
Hepatitis B	50 (3,7%)

Cánceres documentados (n = 26)	
Mama	2
Cérvix	2
Colon	1
Hígado	3
Pulmón	3
Próstata	2
Piel Basocelular (5) Epidermoide (2)	7
Amígdala Carcinoma células escamosas	1
Vejiga, carcinoma urotelial de alto grado	1
Colangiocarcinoma-Klastkin Bismuth I	1
Sarcoma partes blandas abdomen	1
No sólidos	2

Análisis intermedio ensayo IMPAC-Neo

Resultados del cribado anal y colorrectal en la visita basal

Cribados	n (%)*	Positivo, n (%)	P. adicionales, n (%)	Pré-cancer o cancer, n(%)	Otras lesiones, n (%)
Anal	**415 (71,67)**	**164 (39,5%)** 106 ASCUS (25,5) 17 HSIL (4,1); 41 LSIL (9,9)	95 **(57,9)** ¶¶	**24 (5,8%)** 19 HSIL [14 pacientes] biopsia 10 HSIL no biopsiadas	**66 (15,9%)** 44 LSIL [37 pacientes] biopsia 29 LSIL no biopsiadas
Mama	141 (85,45)	2 (1,41)	2 (1,41)	1 cáncer	
Cérvix	172 (81,51)	12 ASCUS (6,97) 6 LSIL (3,48)	7 (38,88)		4 LSIL [4 pacientes](57) 5 LSIL no biopsiados
Colorrectal	**848 (87,9)**	**77(9,1)**	60 **(77,92)** ¶¶	**15 (1,8%)** 33 adenomas[14 pacientes] 1 carcinoma	
Hígado	120 (83,91)	5 (4,16)	5 (100)	1 hepatocarcinoma	
Pulmón	189 (80,77)	27(14,3)	1 (3,7)	1 cáncer	
Próstata	656 PSA (91,11)	27 (3,3)	8 (21,62)	1 cáncer	2 adenomas
Piel	481 (83,03)	17 (3,5)	8 (47,05)	3 basocelulares	

(*) Del total de los pacientes con criterios de cribado; (¶¶) Complicaciones reportadas en 3 casos (intensidad leve, dolor y/o hemorragia)

Conclusions:

- **Els VIH que estan participant a l'assaig IMPAC-Neo, el cribat sistemàtic de neoplàsies va ser segurs i es va detectar un número apreciable de casos amb precàncer i càncer a la visita basal.**