



DEPARTAMENTO DE
MICroBiologia
UNIVERSIDADE DE SÃO PAULO



Vírus oncogênicos

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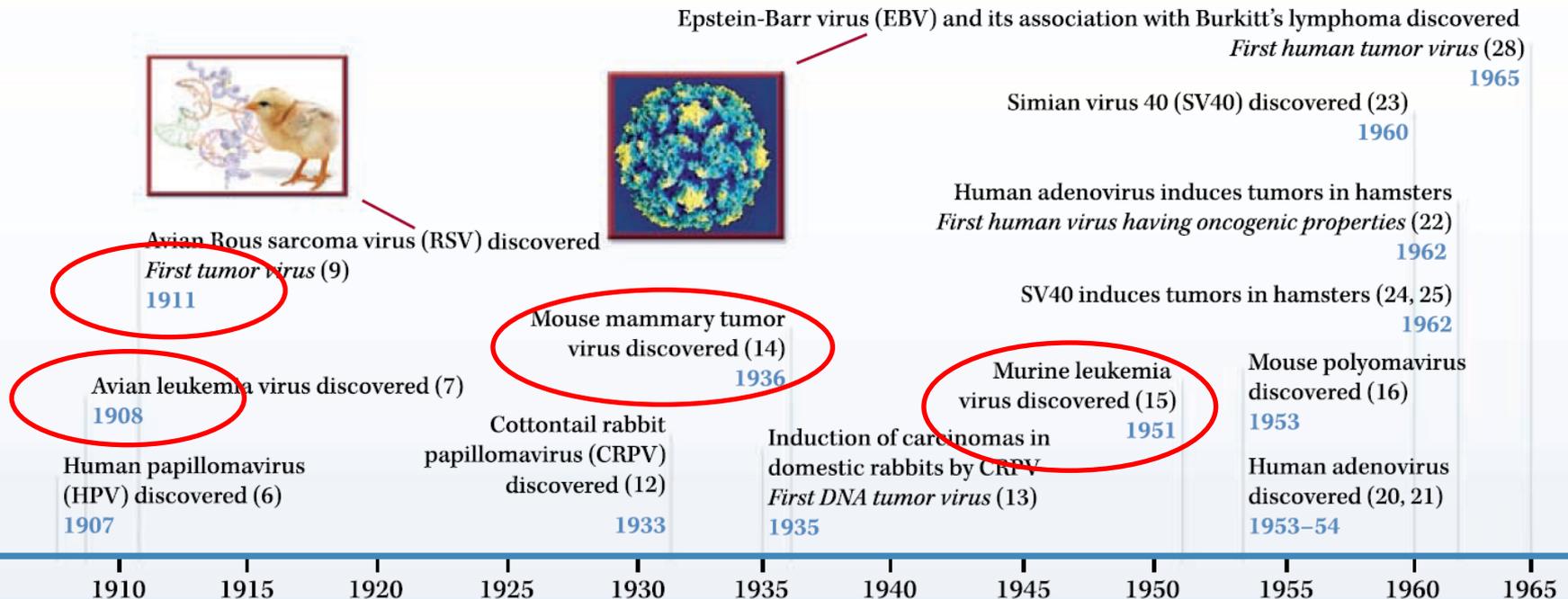
Origens do Câncer

- Alterações hereditárias
- Alterações adquiridas:
 - Fatores físicos
 - Químicos
 - **Infeções**

Vírus e Câncer: um relacionamento de longa data

Duas grandes épocas históricas...antes y após os retrovírus de transformação aguda.

Key Dates in the History of Tumor Virology (1907–Present)



Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

- Lições aprendidas de retrovírus animais.



Peyton Rous in 1923.



Transplante de tumor de segunda geração em galinha.

Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

- Retrovírus de transformação aguda transduzem oncogenes.

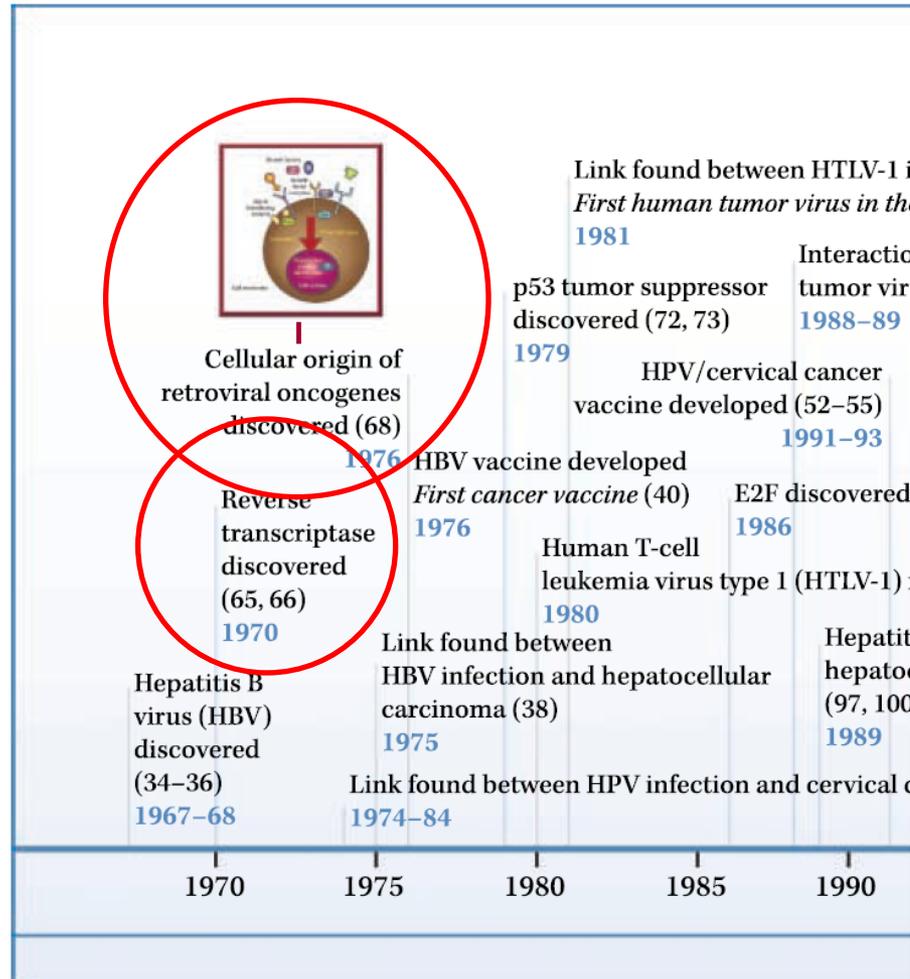
Genomes of transducing retroviruses

Avian transducing retroviruses

Mammalian transducing retroviruses



Vírus e Câncer: um relacionamento de longa data

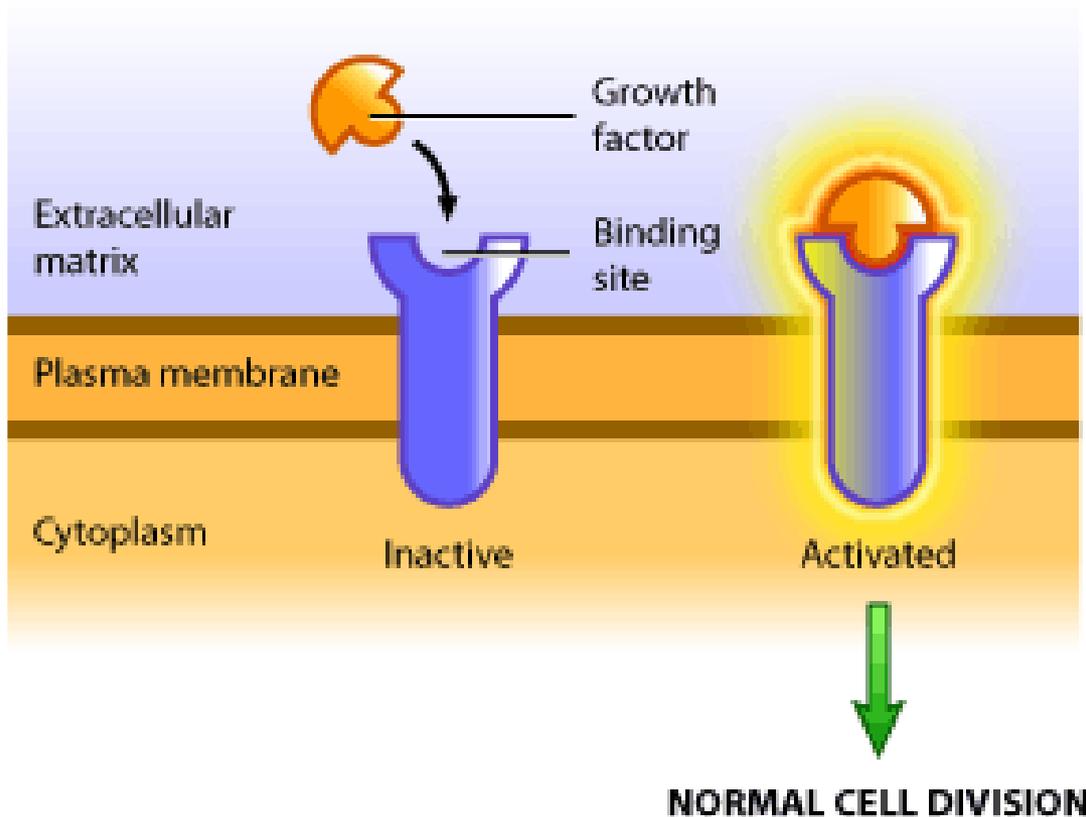


Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

- **Retrovírus de transformação aguda.**

Proto-oncogene celular

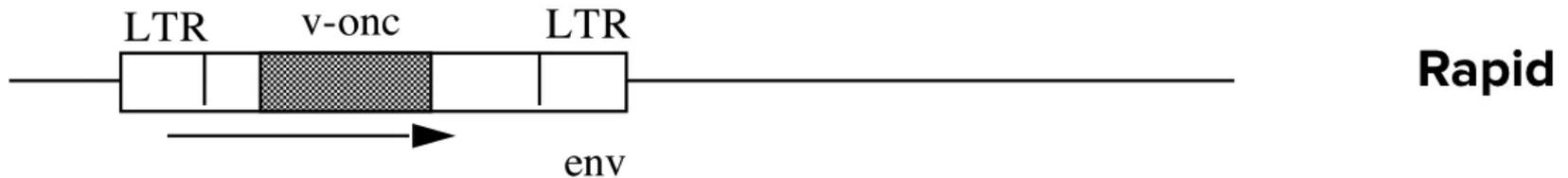


Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

- Retrovírus de transformação aguda transduzem oncogenes.

TRANSDUCING



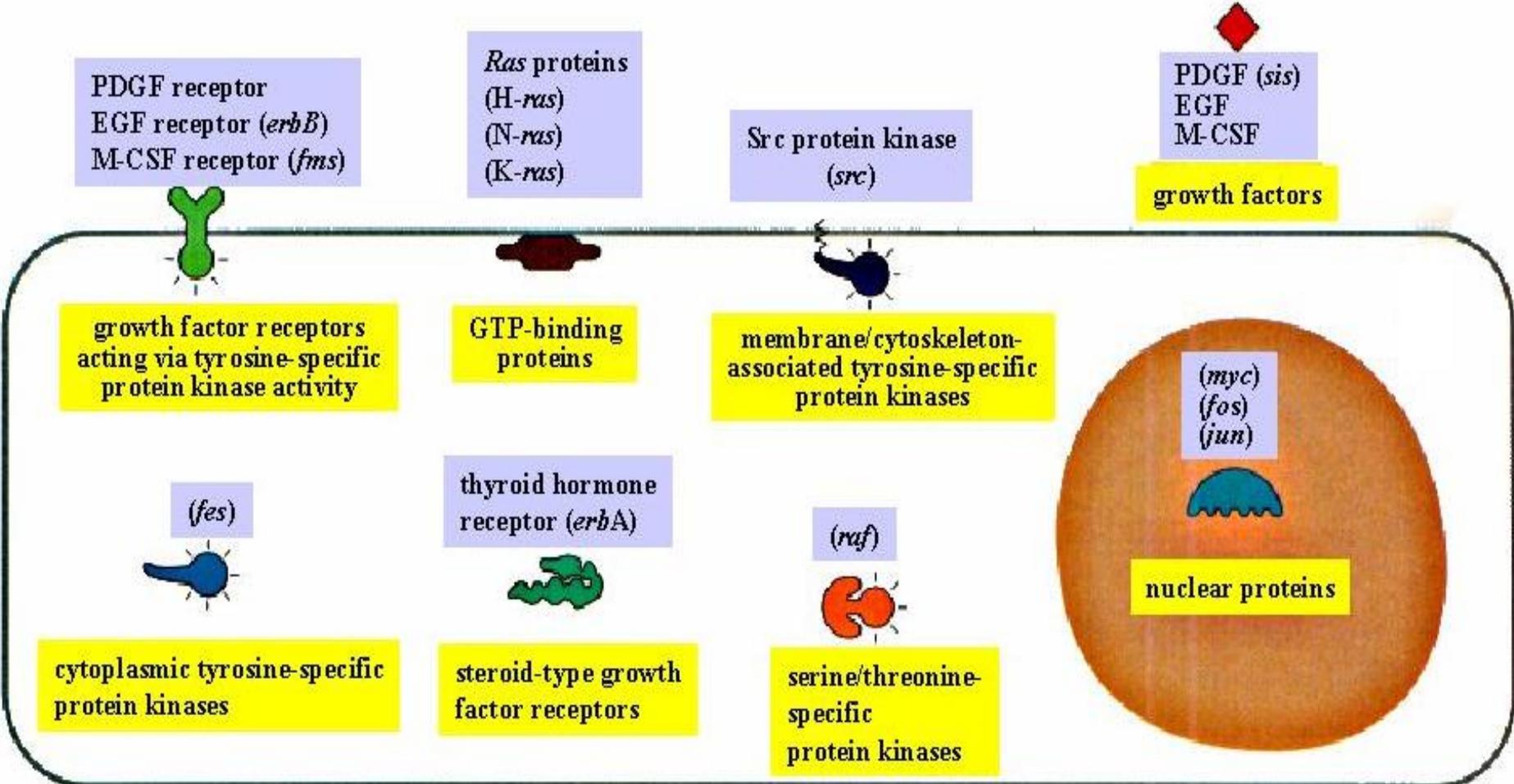
- Carregam oncogenes (até dois) de origem celular.
- Causam tumores de forma rápida em 100% dos indivíduos infectados.
- Como consequência de carregar um gene “celular” podem perder a capacidade de replicar.
- Contribuíram com o descobrimento dos proto-oncogenes celulares com o conceito de cooperação entre oncogenes.

Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

- **Retrovírus de transformação aguda: identificação de oncogenes**

Proto-oncogene vs oncogene



Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

- **Retrovírus de transformação aguda: identificação de oncogenes**

Table 2 | **Oncogenes first identified in retroviruses as drivers in human cancer**

Oncogene	Mechanism of activation	Cancer type	Refs
MYC	Increased transcription	Burkitt's lymphoma	64,186
	Increased transcription	B cell lymphoma	187,188
	Amplification	Neuroblastoma	65,189
	Amplification	Medulloblastoma	190–192
EGFR	Mutation	Glioblastoma	128,193
	Mutation	Non-small-cell lung cancer	130–133
RAS	Mutation	Pancreatic cancer	194–196
RAF	Mutation	Melanoma	197

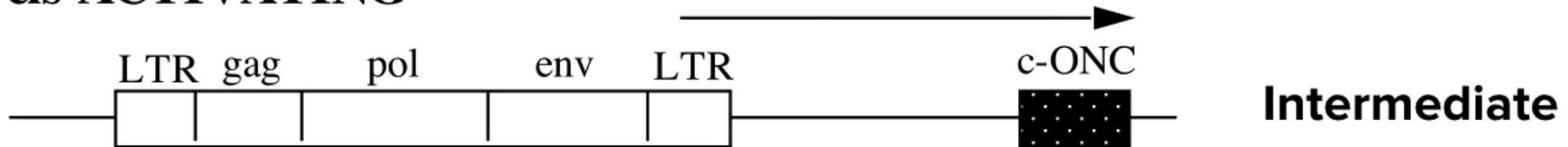
EGFR, epidermal growth factor receptor.

Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

Retrovírus de Transformação “LENTA”

cis-ACTIVATING

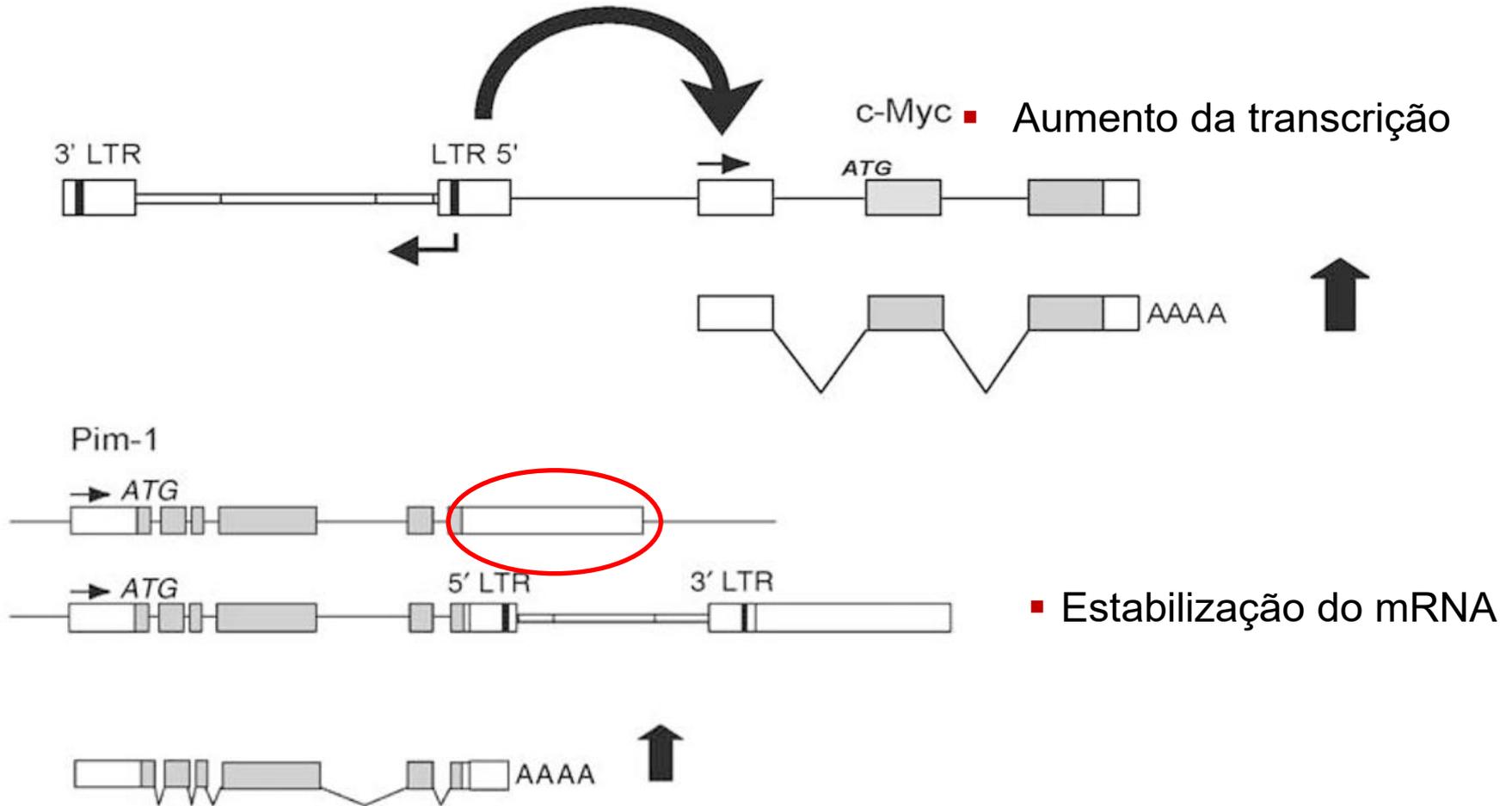


- **NÃO** apresentam oncogenes de origem celular.
- Causam tumores em uma pequena proporção dos indivíduos infectados e após longos.
- Capacidade de replicar normal.
- Contribuíram com a identificação do fenômeno de **mutagênese insercional**.

Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

Retrovírus de Transformação “LENTA” Mutagênese Insercional



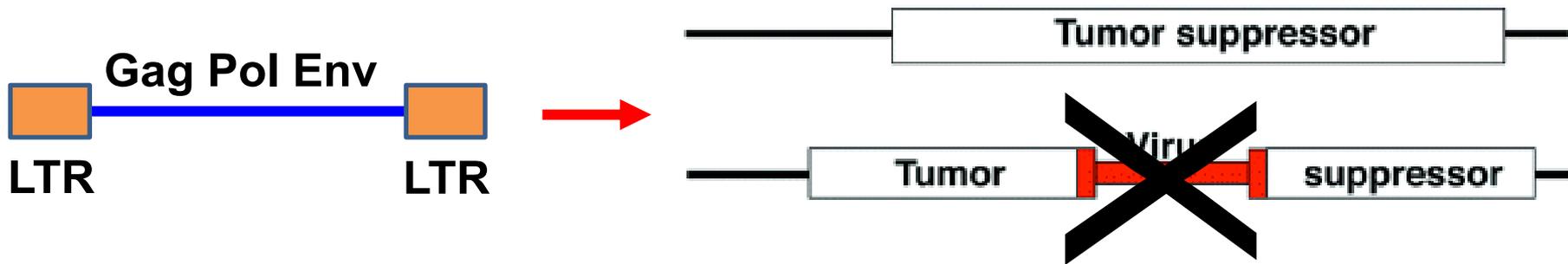
- Independente de proteínas codificadas pelo genoma viral

Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

Retrovírus de Transformação “LENTA”

Mutagênese Insercional

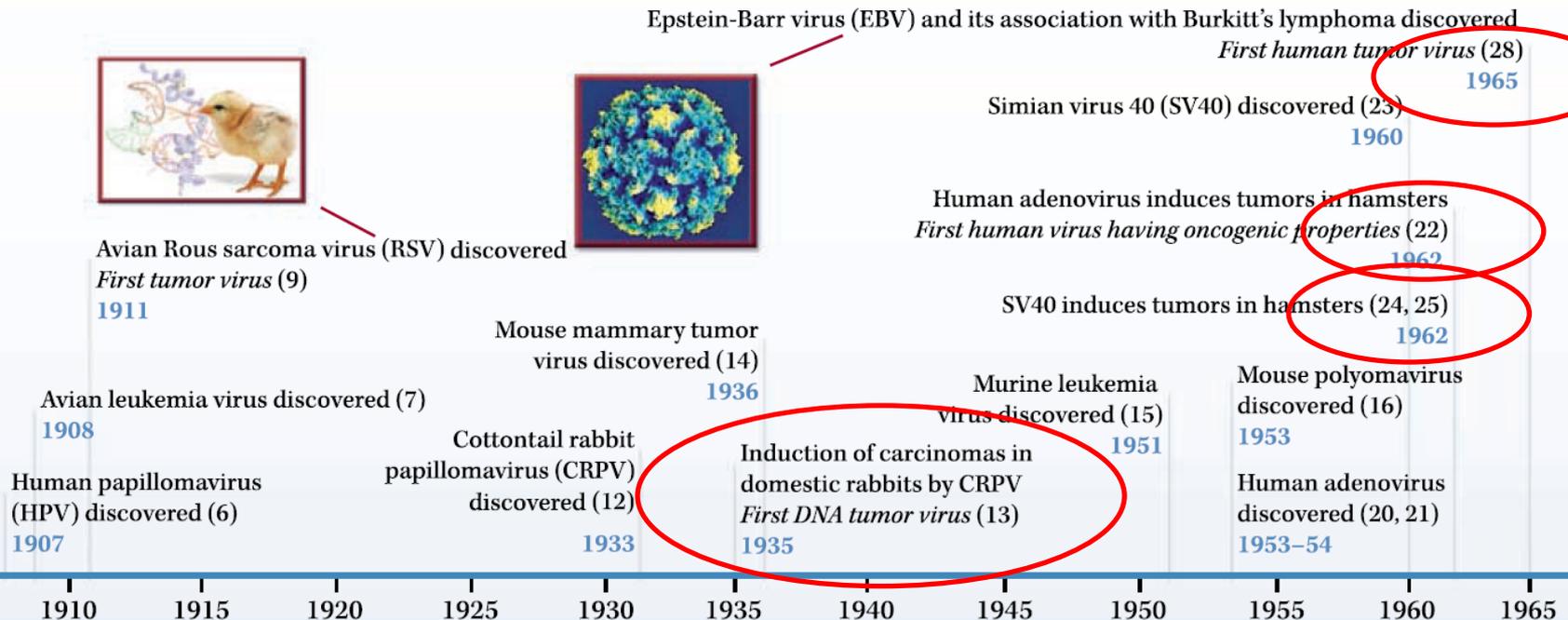


- Independente de proteínas codificadas pelo genoma viral

Vírus e Câncer: um relacionamento de longa data

Mas...apenas retrovírus...e em animais

Key Dates in the History of Tumor Virology (1907–Present)



Vírus e Câncer:

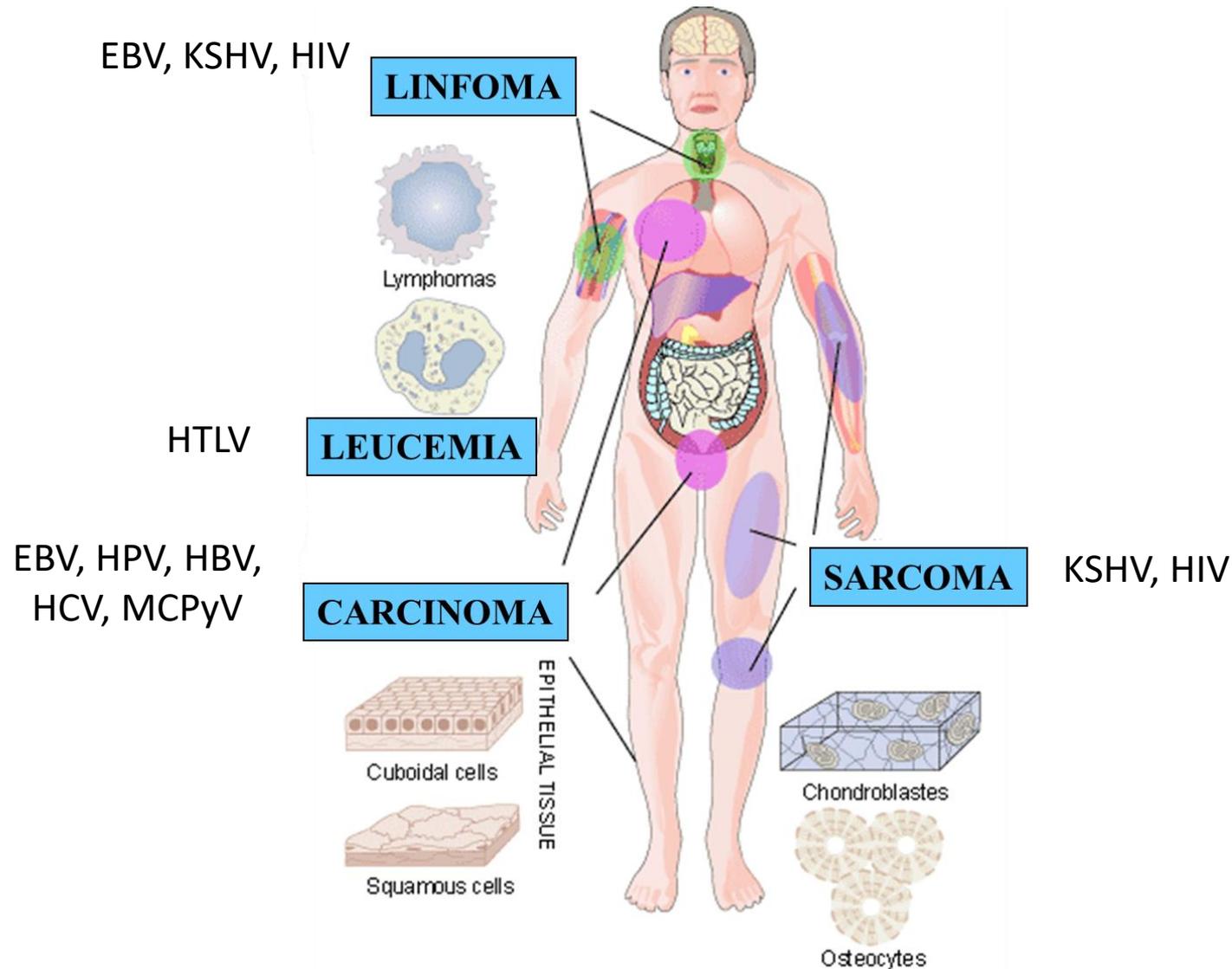
Seis famílias virais envolvidas (até o momento...)

Vírus	Família	Genoma	Via de transmissão	“Carga”
HCV	<i>Flaviviridae</i>	RNA sf+	S/P	50:
HIV	<i>Retroviridae</i>	RNA sf+	S/P/V	40:
HTLV-I	<i>Retroviridae</i>	RNA sf+	S/P	25:
HBV	<i>Hepadnaviridae</i>	DNA df (p)	S/P/V	250:
HPV	<i>Papillomaviridae</i>	DNA df	S	>30% (*)
MCPyV	<i>Polyomaviridae</i>	DNA df	C	>80%
EBV	<i>Herpesviridae</i>	DNA df	O	~90%
KSHV	<i>Herpesviridae</i>	DNA df	O/P	3-50%

C-contato; O- oral (saliva); P- parenteral; S- sexual; V- vertical. *-inf. aguda.

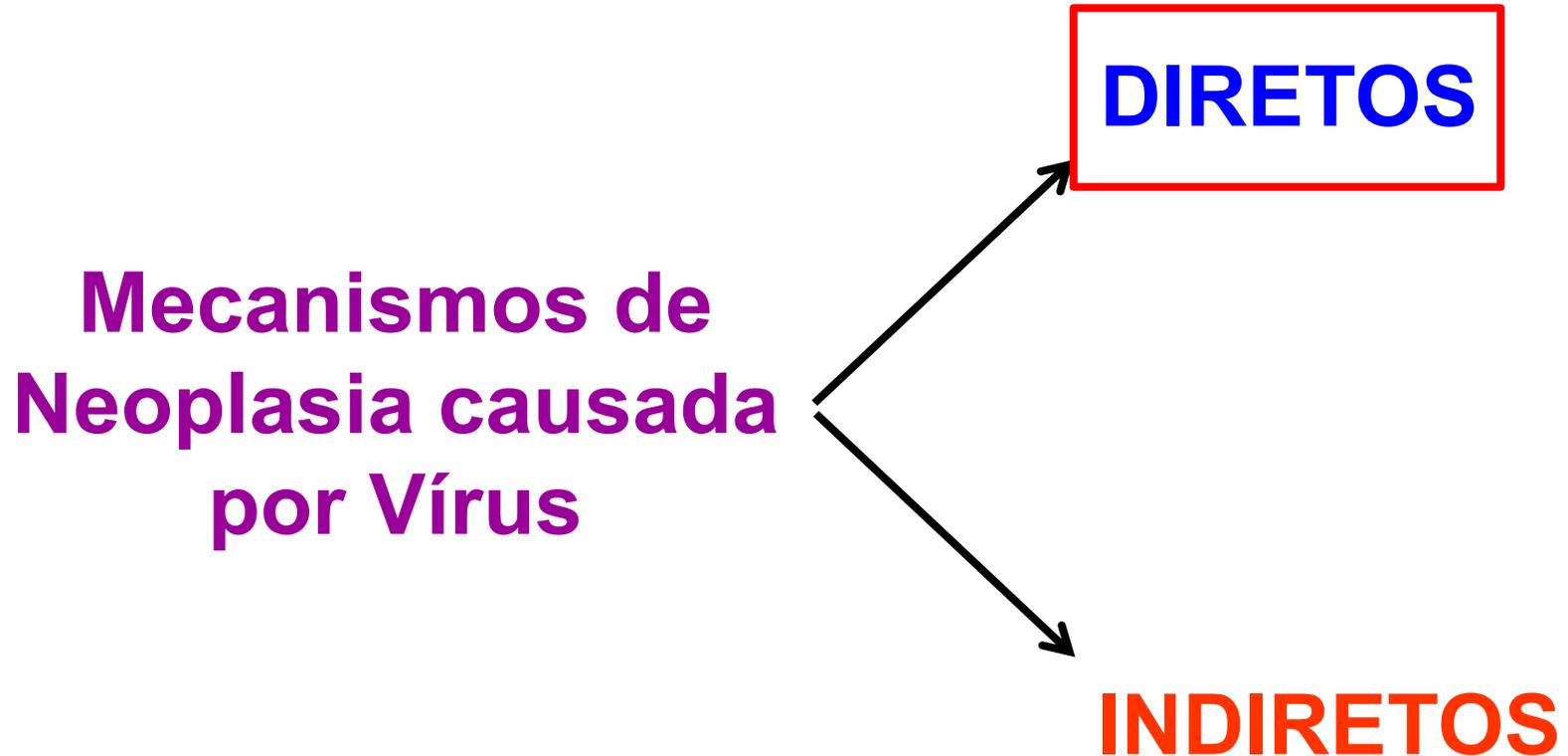
Vírus e Câncer:

Seis famílias e todos os tipos tumorais



Vírus e Câncer:

Mecanismos de carcinogênese



Vírus e Câncer:

Mecanismos **diretos de carcinogênese**

Vírus animais vs Vírus humanos

Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

Vírus animais vs Vírus humanos

- Vírus humanos não são carcinógenos completos.
- O intervalo desde a infecção até o aparecimento do tumor pode ser muito grande.
- A maioria dos indivíduos infectados não desenvolve câncer (imunocomprometidos têm risco maior).
- Efeito sinérgico entre alguns vírus e cofatores ambientais.

Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

Vírus humanos:

- Expressão de oncogenes virais sem homólogos celulares (**HPV, EBV, HTLV-1, MCPyV**).
- Mutagênese insercional (**HBV, HIV, HTLV-1, HPV**).
- “hit and run”: o genoma ou proteína virais agem como agentes mutagênicos (**HSV, CMV**).

Vírus e Câncer:

Mecanismos **diretos de carcinogênese**

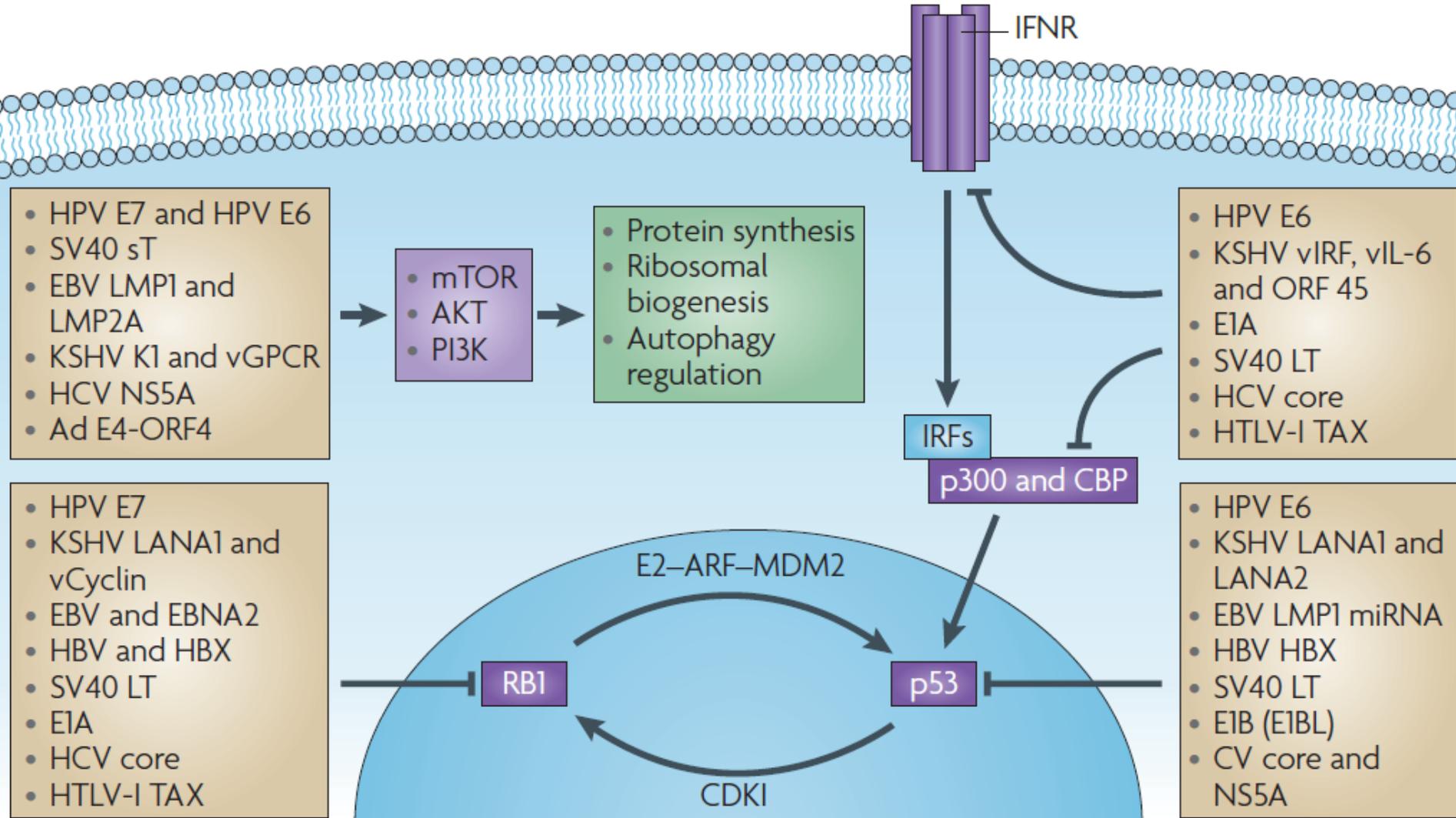
Vírus carcinogênicos em humanos:

- Expressam genes virais importantes para regular seu ciclo.
- Alguns genes virais afetam o controle do ciclo celular: são autênticos oncogenes virais.

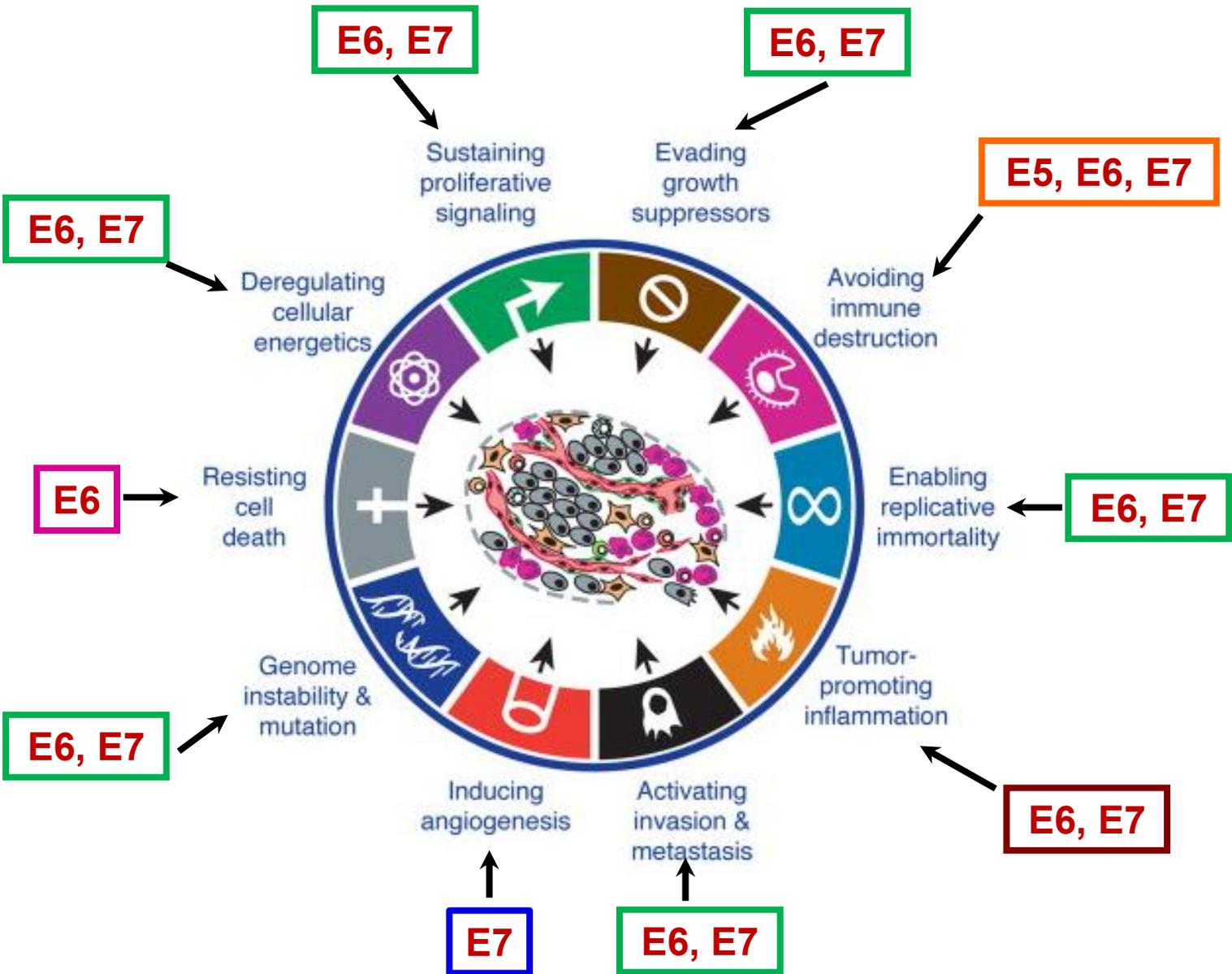
Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

Vírus humanos: **oncogenes virais e ciclo celular**



Vírus e Câncer: Mecanismos diretos



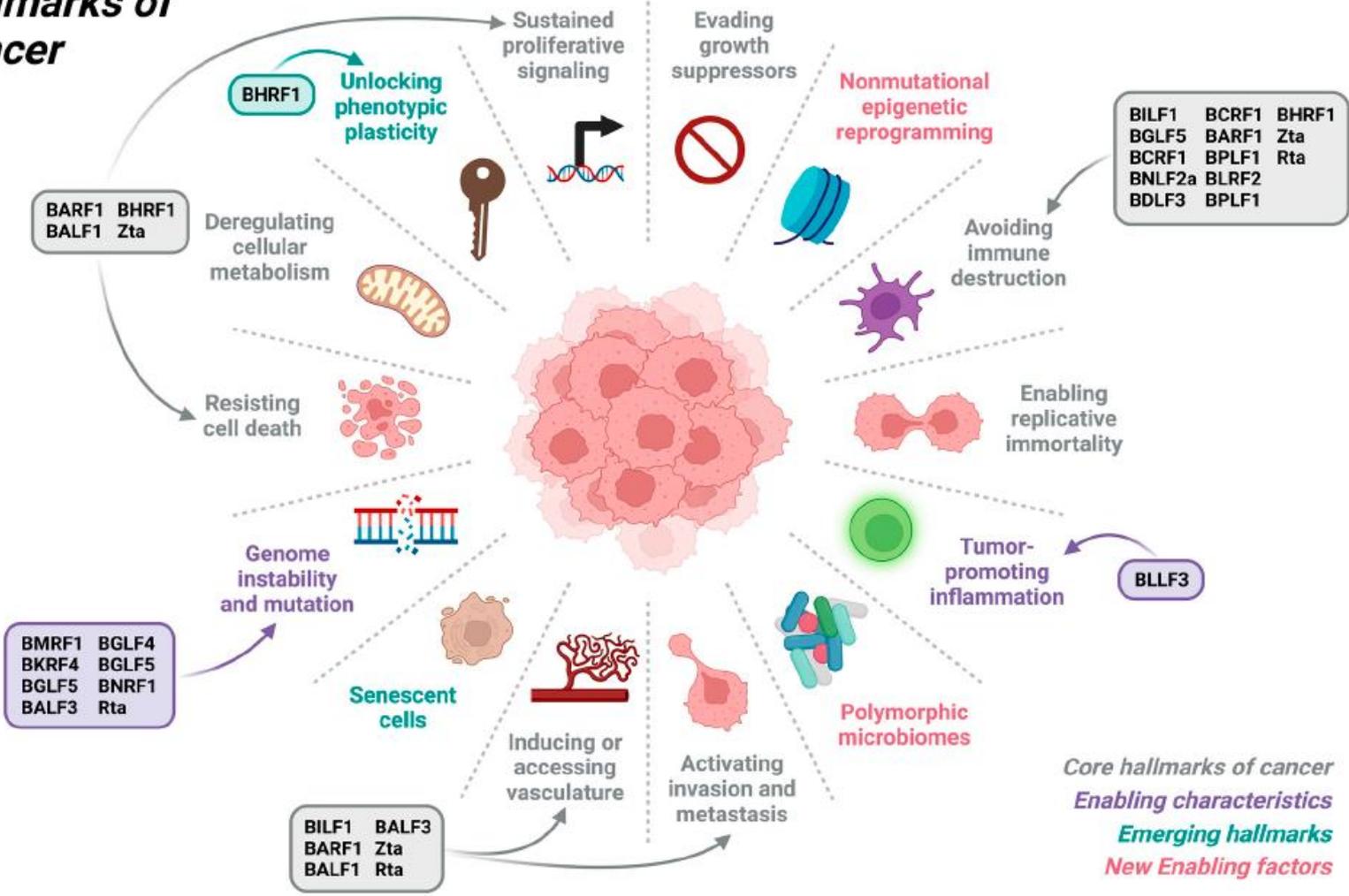
Adapted from Hanahan & Weinberg, Cell 2011, doi.org/10.1016/j.cell.2011.02.013

Vírus e Câncer:

Mecanismos diretos de carcinogênese

EBV

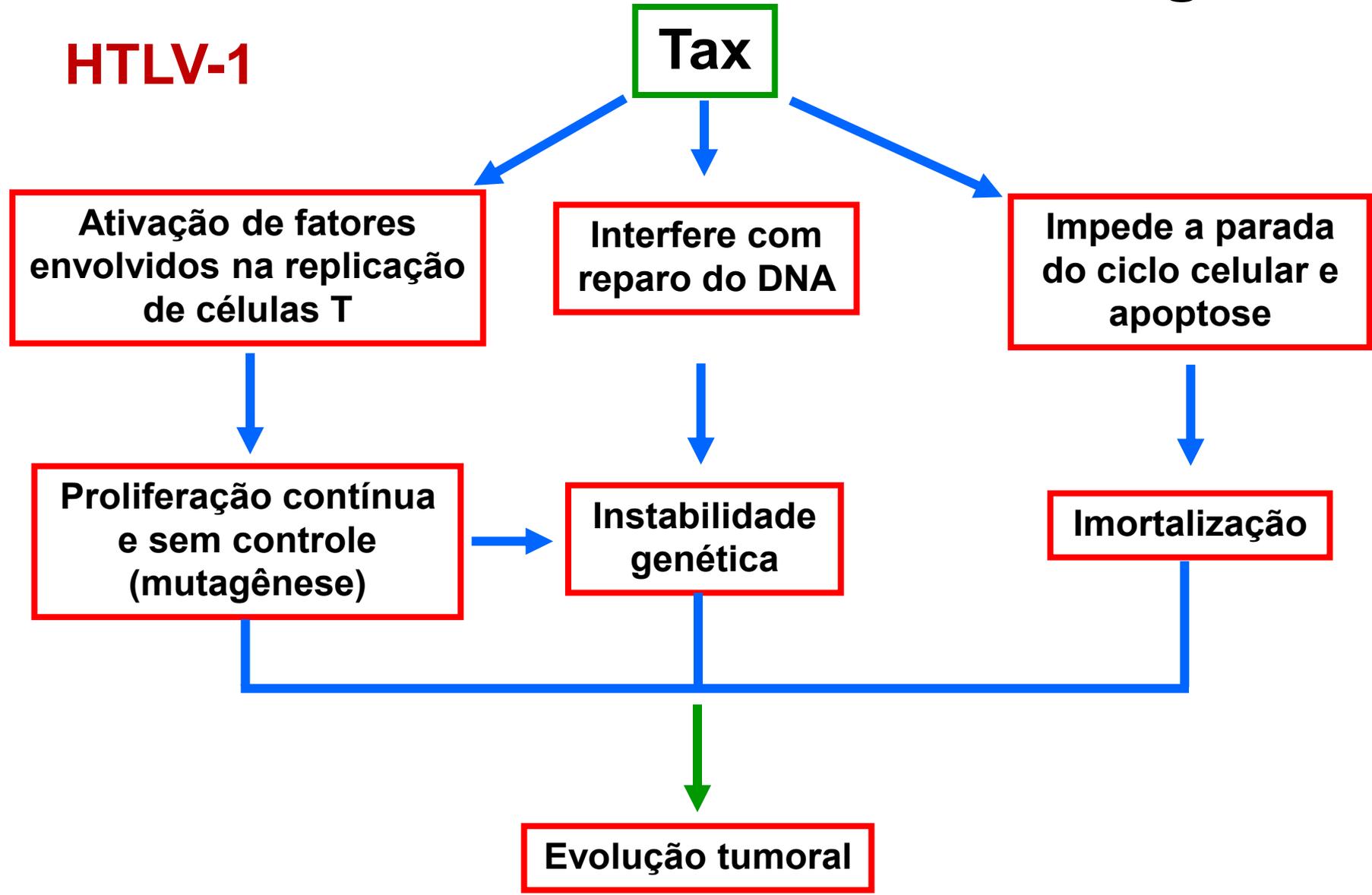
Hallmarks of Cancer



Vírus e Câncer:

Mecanismos **diretos** de carcinogênese

HTLV-1



Vírus e Câncer: Mecanismos diretos de carcinogênese

Vírus humanos: oncogenes virais afetam o ciclo celular

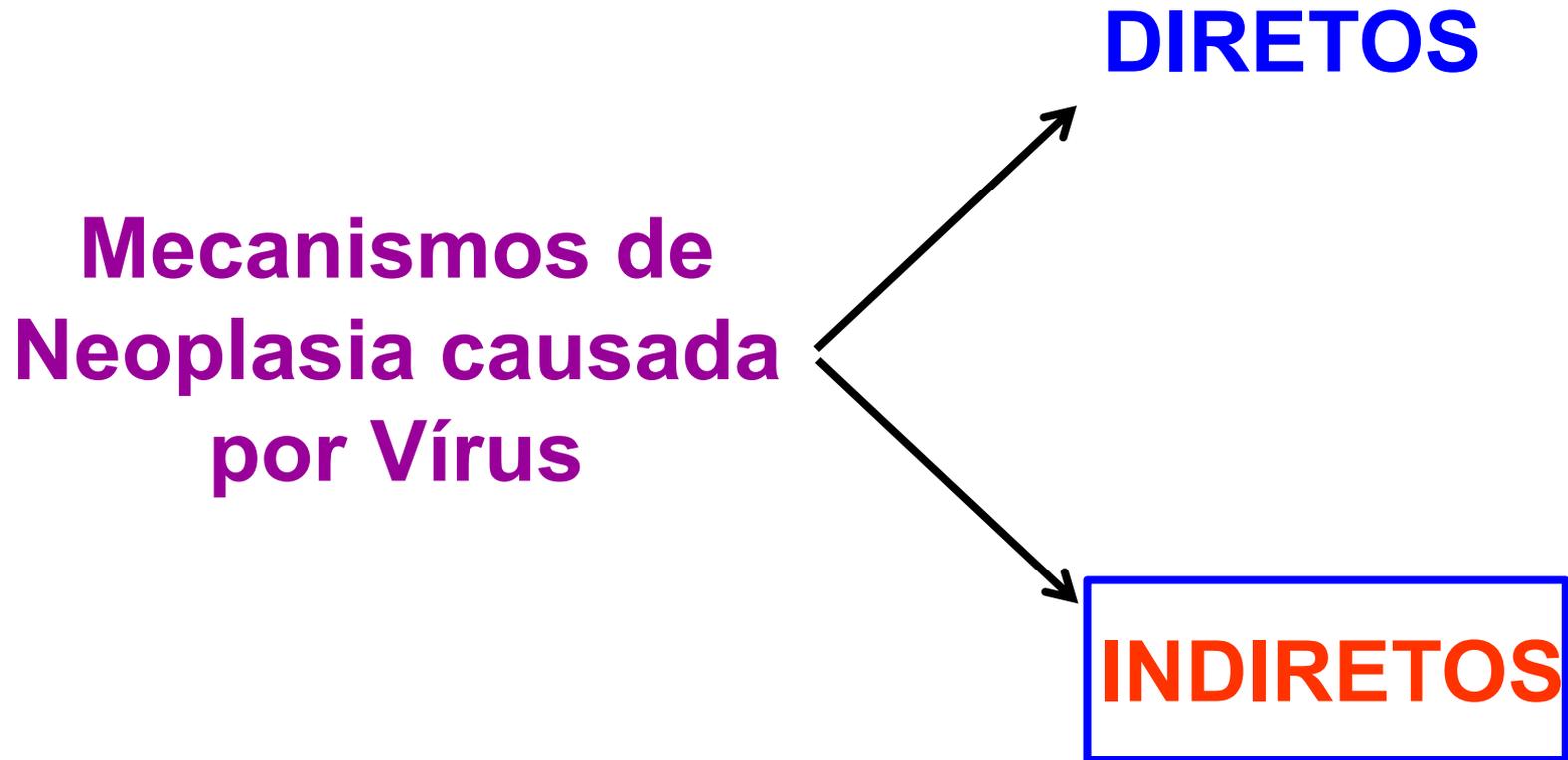
Lista representativa (no exhaustiva) de factores celulares que interaccionan físicamente con oncoproteínas virales

Vírus	Proteína Viral	Blancos celulares §
HBV	HBx	p53, CBP/p300 , Skp2, JAK/STAT, DDB1, RNA polimerase, Crm1, PI3K, Akt
HCV	core	p53 , p73, pRb , LZIP, TNFR , 14-3-3,
	NS3	p53 , H2B, H4, PKA
	NS5A	p53, TBP, CDK2, PI3K
EBV	LMP-1	TRAFs, TRADD, RIP, JAK3
HPV	E6	p53 , E6-AP, E6-BP, telomerase, c-myc, hDLG, AP-1 , hScrib, MAGI-1,2,3, TNFR, MUPP1
	E7	pRb, p107, p130, p21^{waf1} , p27 ^{kip1} , CycA, CycE , PCNA, AP-1 , HDAC, S4, TBP , IRF-1
HTLV-I	Tax	pRb , CREB, NF- κ B, SRF, CBP/p300 , p15, p16 ^{ink4a} , p21^{waf1} , CycA, CycD2, CycE , CDK4
HIV	Tat	CycT1, TFIIH, PKR, pCAF, CBP/p300 , TAFII250
KSVH	vIRF	CBP/p300
MCPyV	T Ag	pRb
JCV	T Ag	p53, pRb, p107, p130 , β -catenina

§ En negrito: factores blanco para más de un tipo viral.

Vírus e Câncer:

Mecanismos de carcinogênese



Vírus e Câncer:

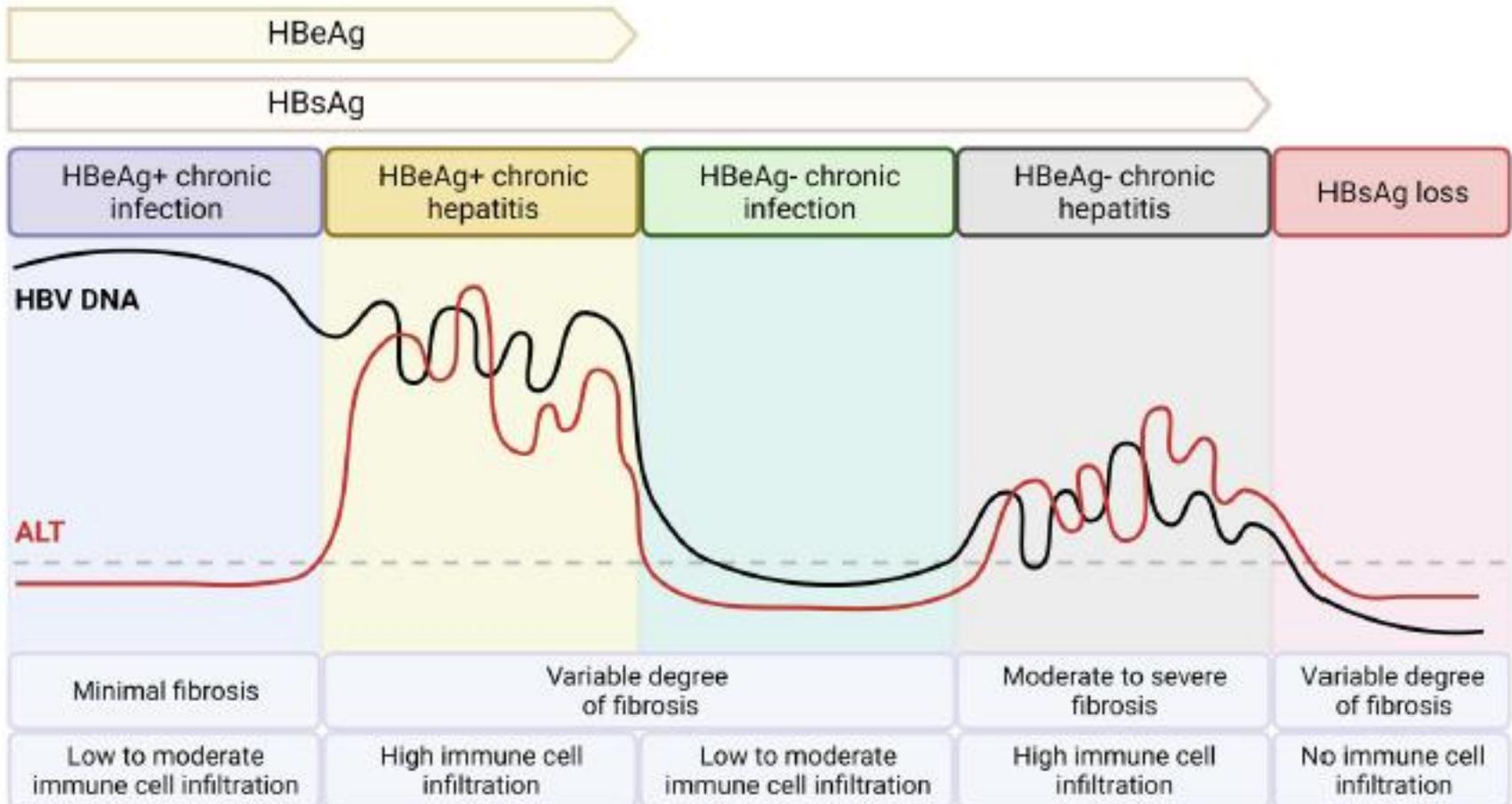
Mecanismos **indiretos** de carcinogênese

- Estímulo da proliferação celular para reposição do tecido danificado (**HBV, HCV**)
- Imunodeficiência (**HTLV-1, HIV**)
- Evasão dos sistema imune (**todos...**)

Vírus e Câncer:

Mecanismos **indiretos** de carcinogênese

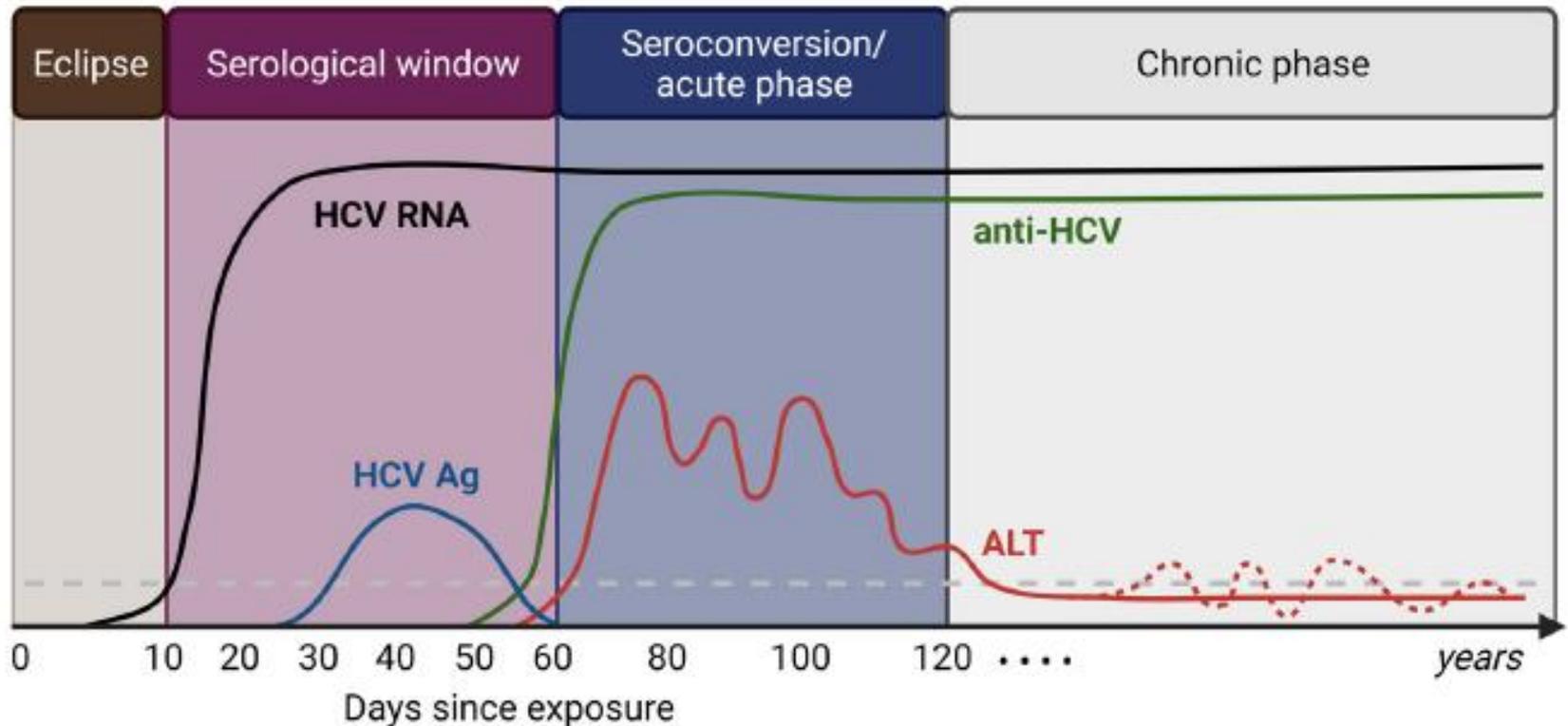
- Estímulo da proliferação celular para reposição do tecido danificado.



Vírus e Câncer:

Mecanismos **indiretos** de carcinogênese

- Estímulo da proliferação celular para reposição do tecido danificado.



Vírus e Câncer:

Mecanismos **indiretos** de carcinogênese

- Imunodeficiência

Vírus da Imunodeficiência Humana (HIV)

HIV induz o tipo de imunossupressão mais severo conhecido:

Associado a:

- Sarcoma de Kaposi (KSHV ou HHV-8)
- linfoma não-Hodgkin (EBV)
- Câncer do colo do útero (HPV)

Possível envolvimento de mecanismos [Diretos](#)

Vírus e Câncer:

Mecanismos **indiretos** de carcinogênese

Table 1 | **HIV-associated malignancies**

Tumour type	Relative risk*	Viral co-factors (prevalence of viral DNA in tumours)	Reported effects of HAART [‡] on incidence	Reported effects of HAART [‡] on outcome
<i>AIDS-defining[§]</i>				
KS	258	HHV8 (100%)	Decreased	Regression/remission
NHL	78.1	EBV, HHV8	Decreased	Improved survival/ regression
Burkitt's (classic form)	103	EBV (30%)	Unchanged/decreased	Improved survival
DLCL, centroblastic	NA	EBV (40%)	Unchanged/decreased	Improved survival
DLCL, immunoblastic	134	EBV LMP1 (90%)	Decreased	Improved survival
PCNS	175	EBV LMP1 (100%)	Decreased	Regression (anecdotal evidence)
PEL	NA	HHV8 (100%), EBV (80%)	NA	Regression (anecdotal evidence)
Uterine cervix (invasive)	8.8	HPV (100%)	Unchanged	Regression (anecdotal evidence)

DLCL, diffuse large-cell lymphoma; EBV, Epstein–Barr virus; HHV8, human herpesvirus type 8; HPV, human papillomavirus; KS, Kaposi's sarcoma; LMP1, latency membrane protein 1; NA, not available; NHL, non-Hodgkin's lymphoma; PCNS, primary-nervous-system lymphoma; PEL, primary effusion lymphoma. doi:10.1038/nrc1479

Vírus e Câncer:

Mecanismos de carcinogênese

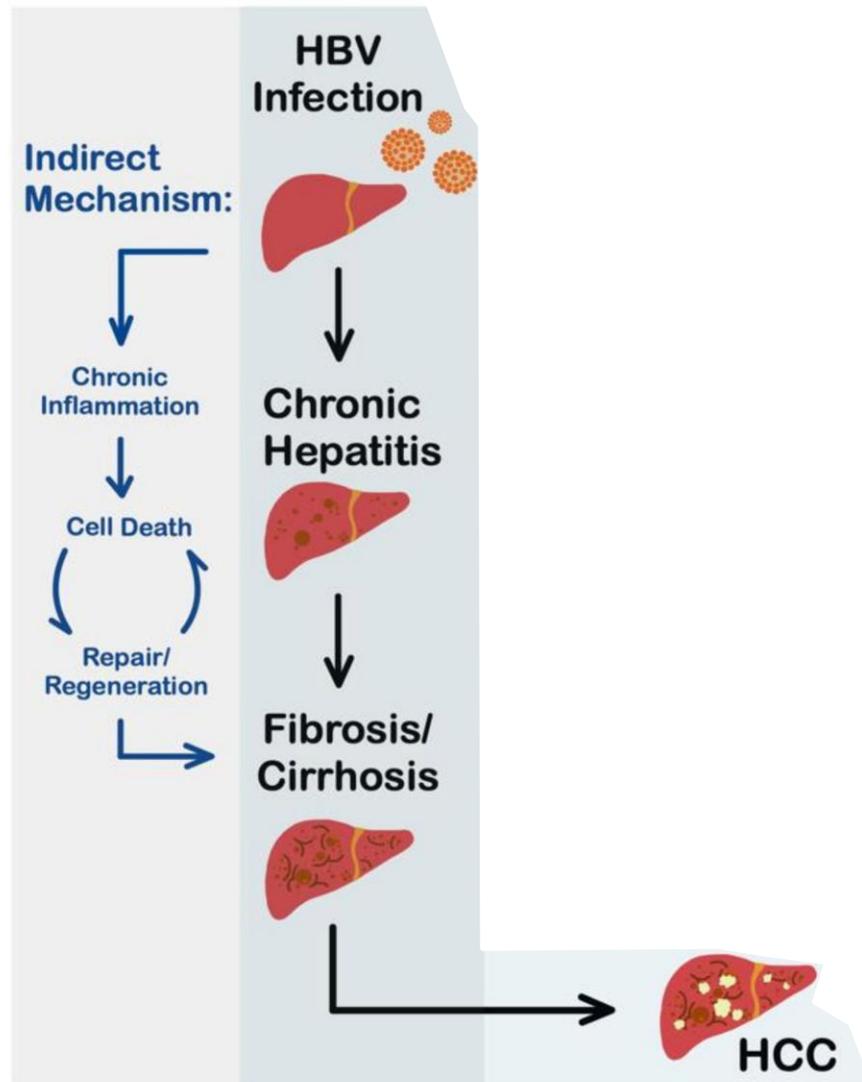
Direto vs Indireto

Muitas vezes fica difícil distinguir...

Vírus e Câncer:

Mecanismos de carcinogênese

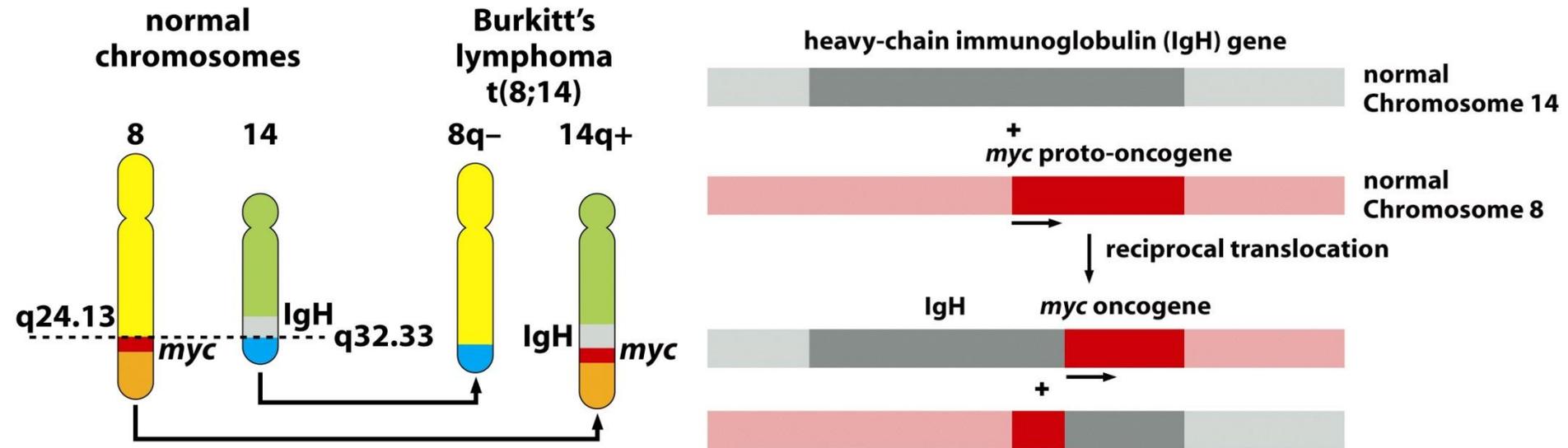
HBV e Carcinoma hepatocelular...apenas inflamação?



Vírus e Câncer:

Mecanismos de carcinogênese

Linfoma de Burkitt, caracterizado por:



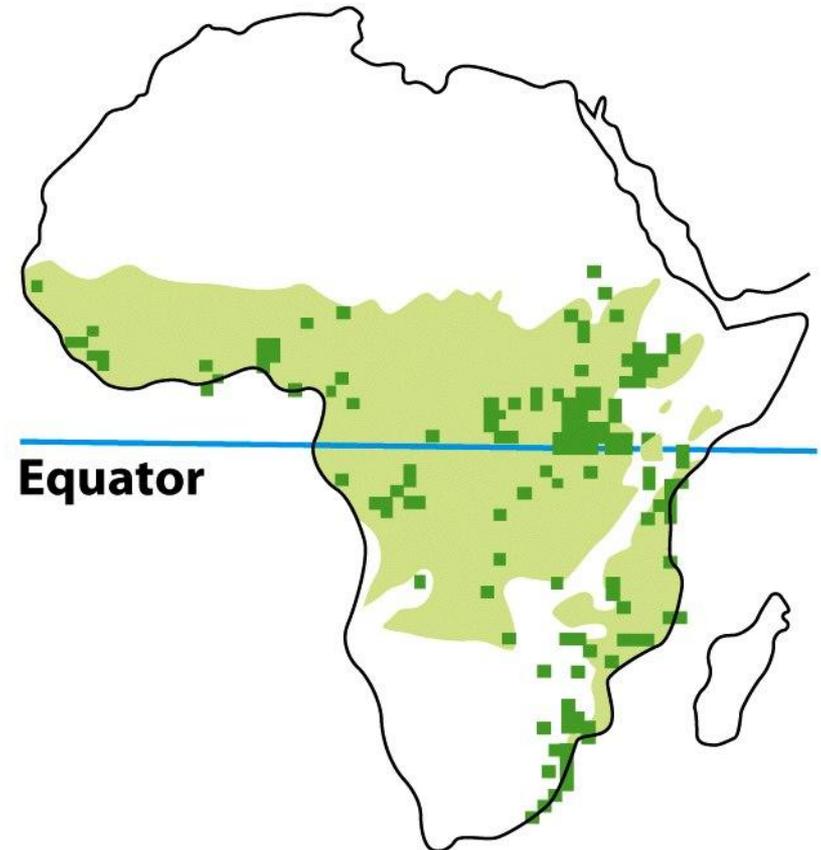
- Associado à infecção pelo Vírus Epstein-Barr (EBV)
- Diferenças geográficas e de idade de incidência notáveis.

Vírus e Câncer:

Mecanismos de carcinogênese

EBV e Linfoma de Burkitt na África: **Mecanismos complexos**

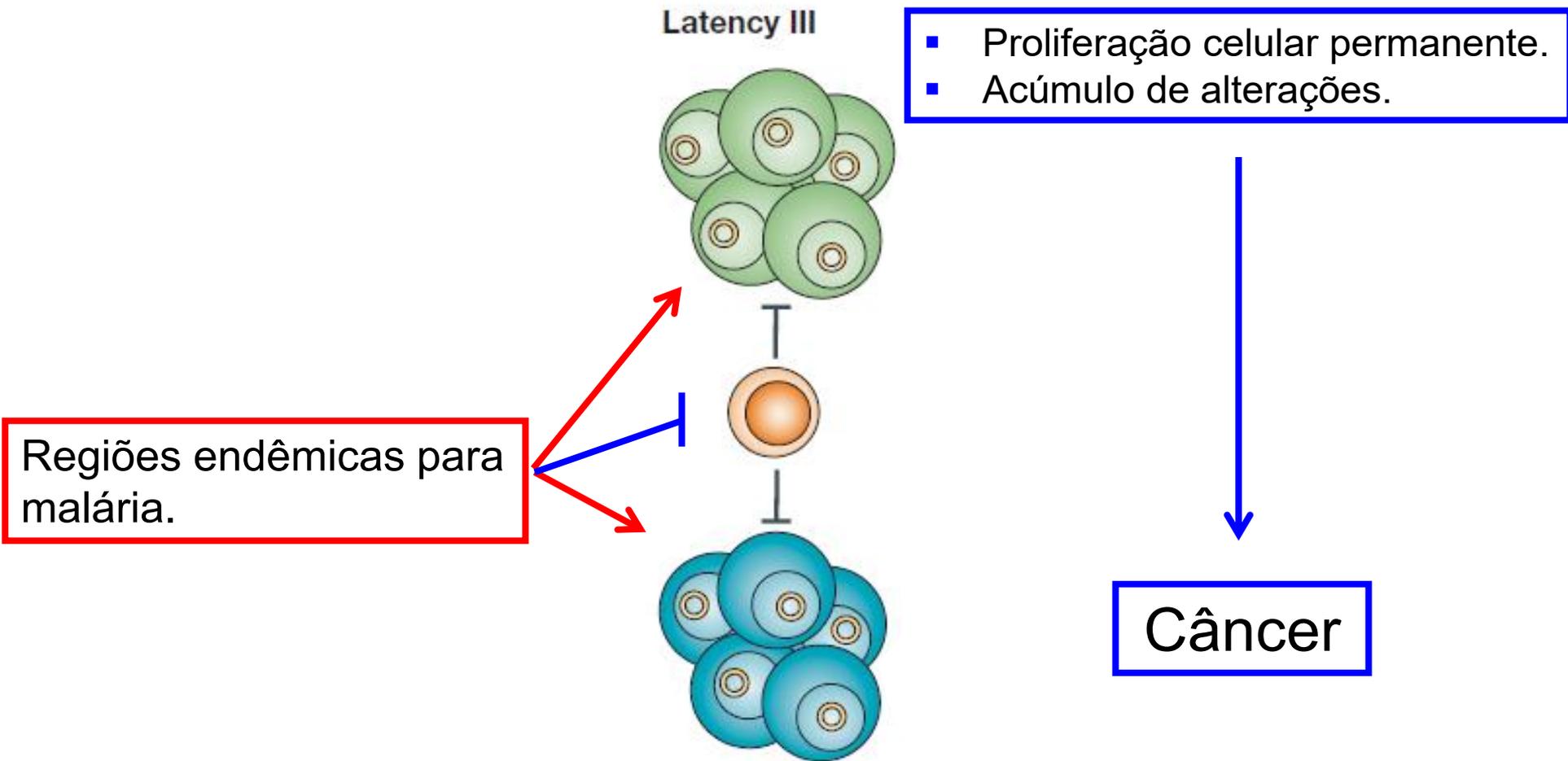
(B) Burkitt's lymphoma



Vírus e Câncer:

Mecanismos de carcinogênese

EBV e Linfoma de Burkitt na África: **Mecanismos complexos**



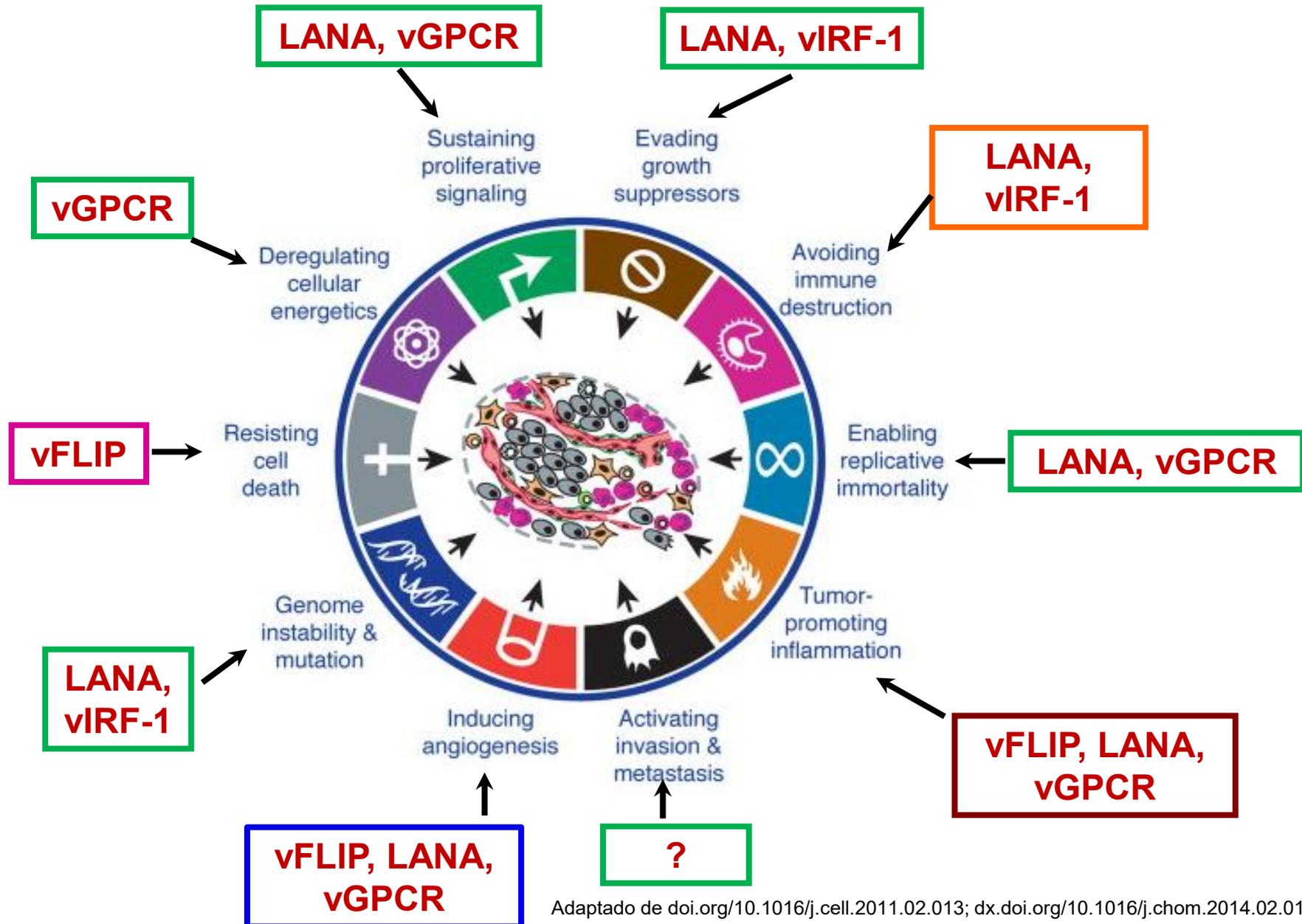
Vírus e Câncer:

Mecanismos de carcinogênese

“Take home message”

- A carcinogênese viral resulta da combinação de mecanismos diretos e indiretos.
- Os vírus oncogênicos em humanos são carcinógenos incompletos.
- A transformação celular não faz parte do ciclo viral.
- Há espaço para identificação de novos agentes e novas associações.

KSHV e os “hallmarks of cancer”

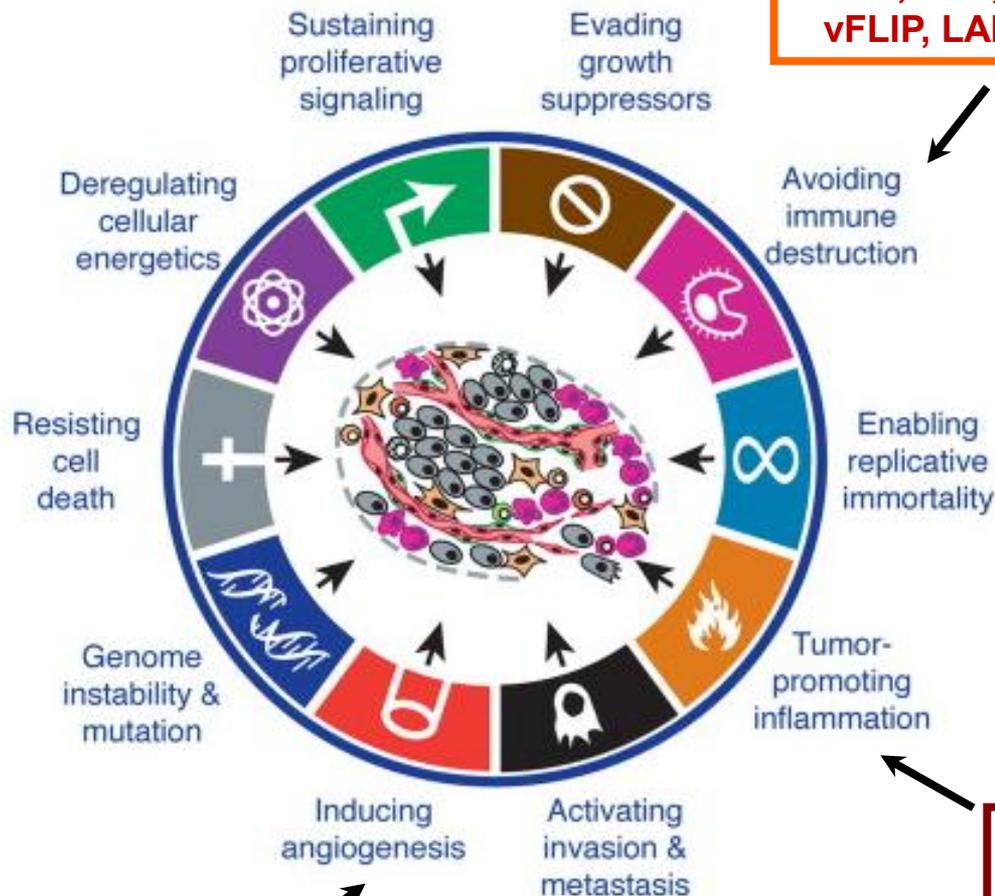


Virus e os “hallmarks of cancer”

LMP-2A, E6, E7, HBx, Core, NS3, NS5, Tax, HBZ, LANA, vGPCR

EBNA-1, E5, HBx, Core, NS3, NS5, HBZ, vFLIP, LANA, vIRF-1

EBNA-1, LMP-1, E6, HBx, Core, NS3, NS5, Tax, HBZ, vFLIP, LANA, vGPCR, vIRF-1

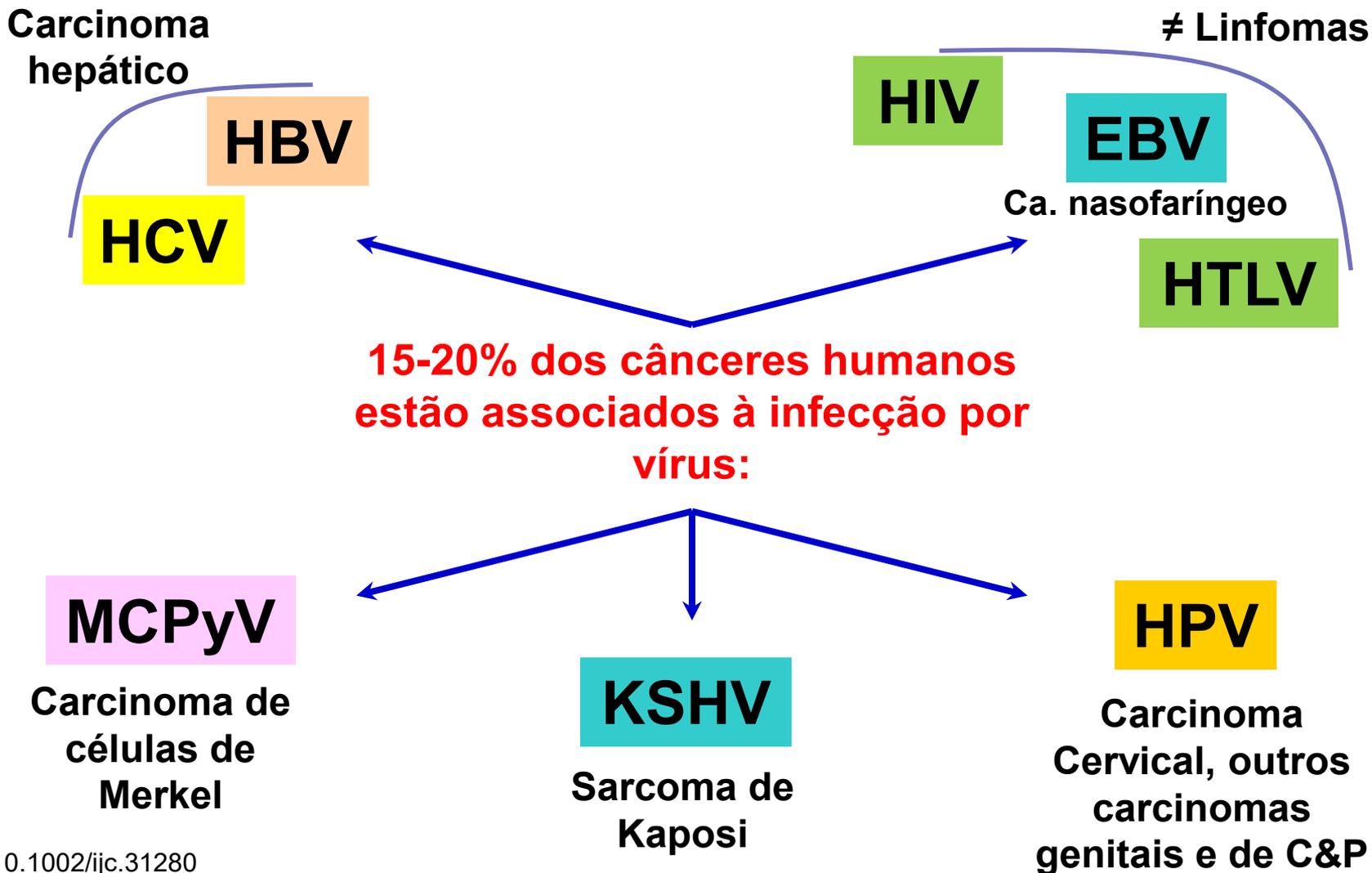


LMP-1, LMP-2A, E7, HBx, Core, NS3, NS5, vFLIP, LANA, vGPCR

LMP-1, E6, HBx, Core, NS3, NS5, vFLIP, LANA, vGPCR

Vírus e Câncer:

Seis famílias virais envolvidas (até o momento...)



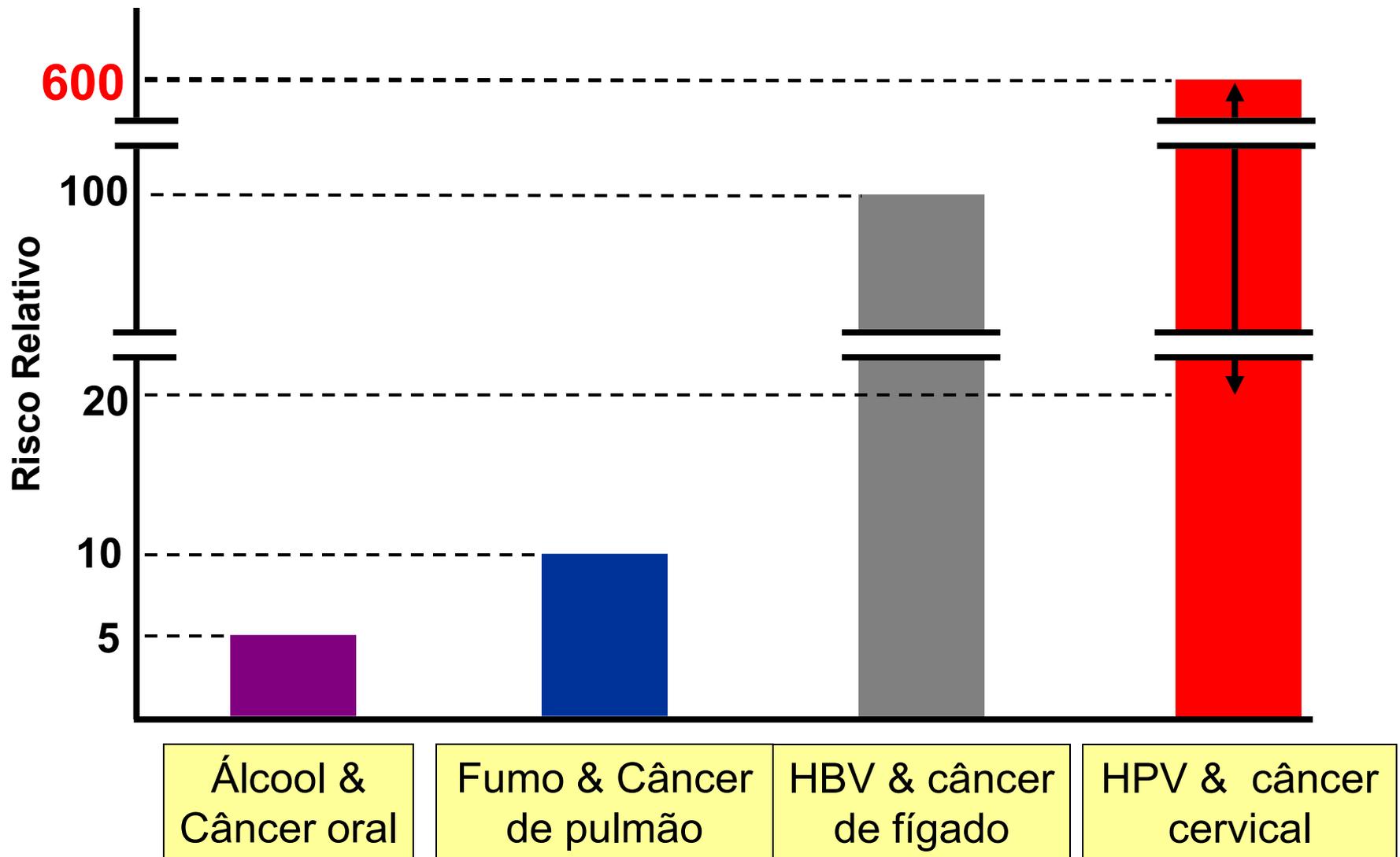
Vírus e Câncer:

Seis famílias virais envolvidas (até o momento...)

Vírus	Família	Fração atribuível	“Carga”
HCV	<i>Flaviviridae</i>	20%	70-80:
HIV	<i>Retroviridae</i>	-----	40:
HTLV-I	<i>Retroviridae</i>	100%	25:
HBV	<i>Hepadnaviridae</i>	56%	250:
HPV	<i>Papillomaviridae</i>	2-100%	>2000: (*)
MCPyV	<i>Polyomaviridae</i>	80%	>80%
EBV	<i>Herpesviridae</i>	50-85%	6300:
KSHV	<i>Herpesviridae</i>	100%	3-50%

Vírus e Câncer:

Infecções virais como fatores de risco.



**Resumindo, é bom
lembrar que:**

É bom lembrar que:

Há amplas oportunidades de intervenção!

- Tumores associados a agentes infecciosos afetam uma pequena proporção dos indivíduos infectados.
- O câncer acontece vários anos após a infecção inicial pela combinação de mecanismos diretos e indiretos.
- O agente causal foi identificado. Por tanto, sua ação pode ser prevenida!!!

Profilaxia contra vírus causadores de Tumor

Vacinas profiláticas disponíveis para HBV e HPV

- Seguras
- Bem toleradas
- Eficazes
 - ~ 50 anos de seguimento (**HBV**)
 - ~20 anos de seguimento (**HPV**)
- **Custo elevado (HPV)**
- Terapia disponível para outros vírus (**HIV, HCV, EBV, HBV**)

É bom lembrar que:

Carcinógenos de tipo 1 em humanos: HBV, HCV, HIV-1, HTLV-1, EBV, KSHV(HHV8), HPV(16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59).

Carcinógenos de tipo 2A em humanos: MCPyV, HPV68.

Carcinógenos de tipo 2B em humanos: HIV-2, HPV 5 e 8 (EV) e HPV 26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 97 (por analogia filogenética com tipos α do grupo 1), JCV, BKV.

- Outros vírus candidatos: SV40, HMTV(?), CMV e infecções esporádicas
- **15-20% dos tumores humanos tem origem viral**

É bom lembrar que:

Existem agentes infecciosos não virais

Bactéria: *Helicobacter pylori*

(Adenocarcinoma gástrico e Linfoma MALT)

Helmintos: *Opisthorchis viverrini* (colangiocarcinoma)

Clonorchis sinensis (colangiocarcinoma)

Schistosoma haematobium

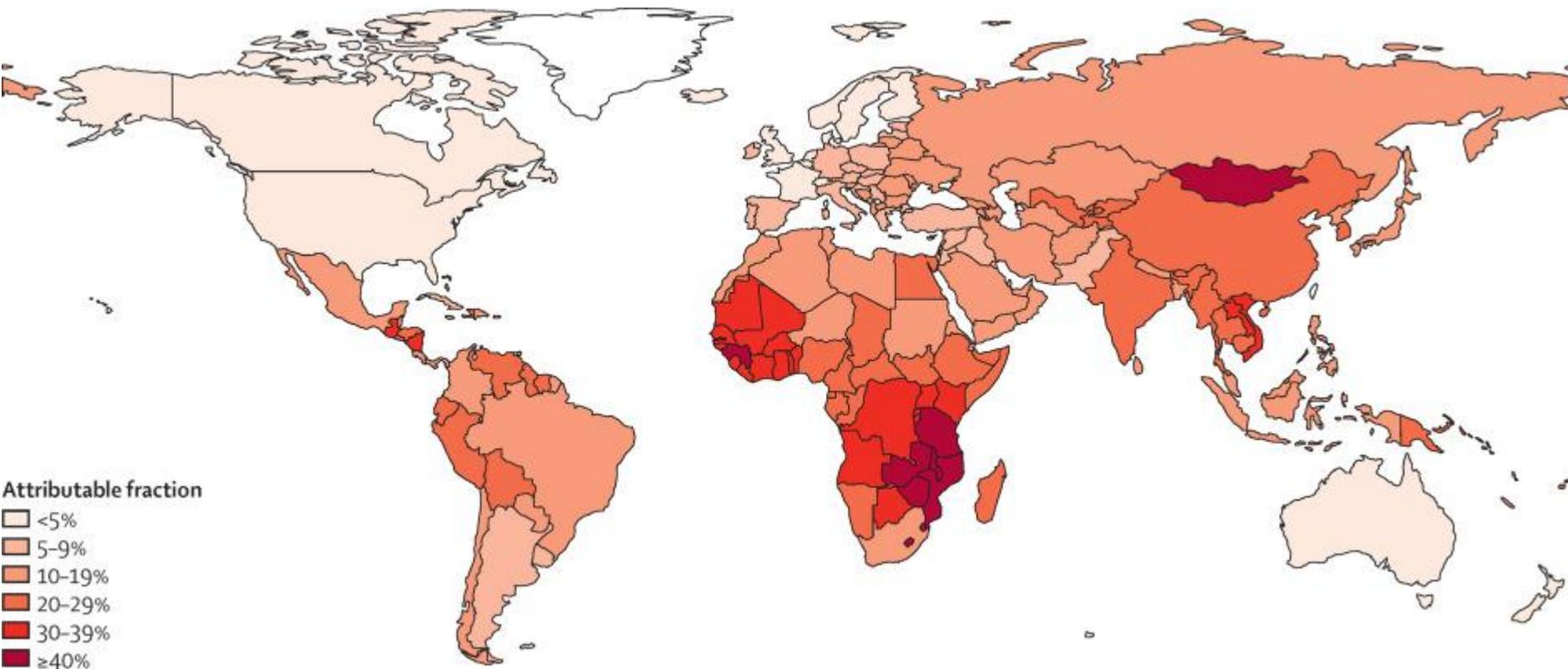
(carcinoma epidermóide de bexiga)

Agentes carcinogênicos grupo1 (IARC/OMS):

Infecção crônica por estes agentes é a **principal** causa do desenvolvimento das neoplasias a eles associadas.

É bom lembrar que:

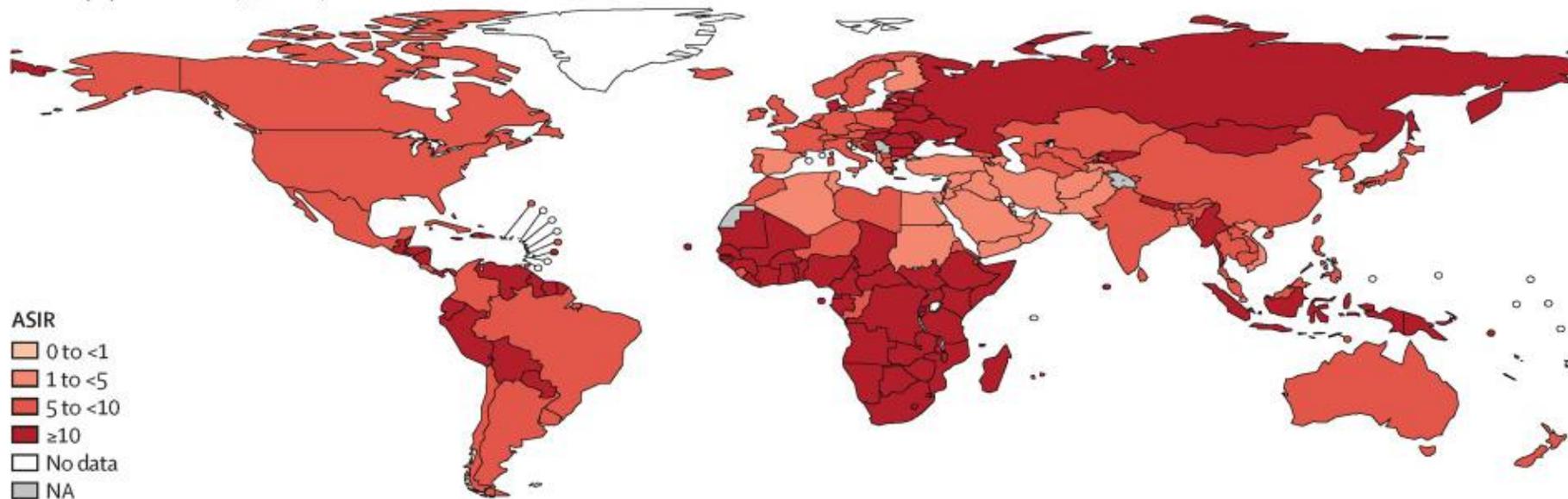
- A maioria dos tumores associados a agentes infecciosos acontece em países subdesenvolvidos



Vírus e Câncer: Vírus como fatores de risco

- Estimativa global (2018) de novos casos atribuíveis ao HPV.

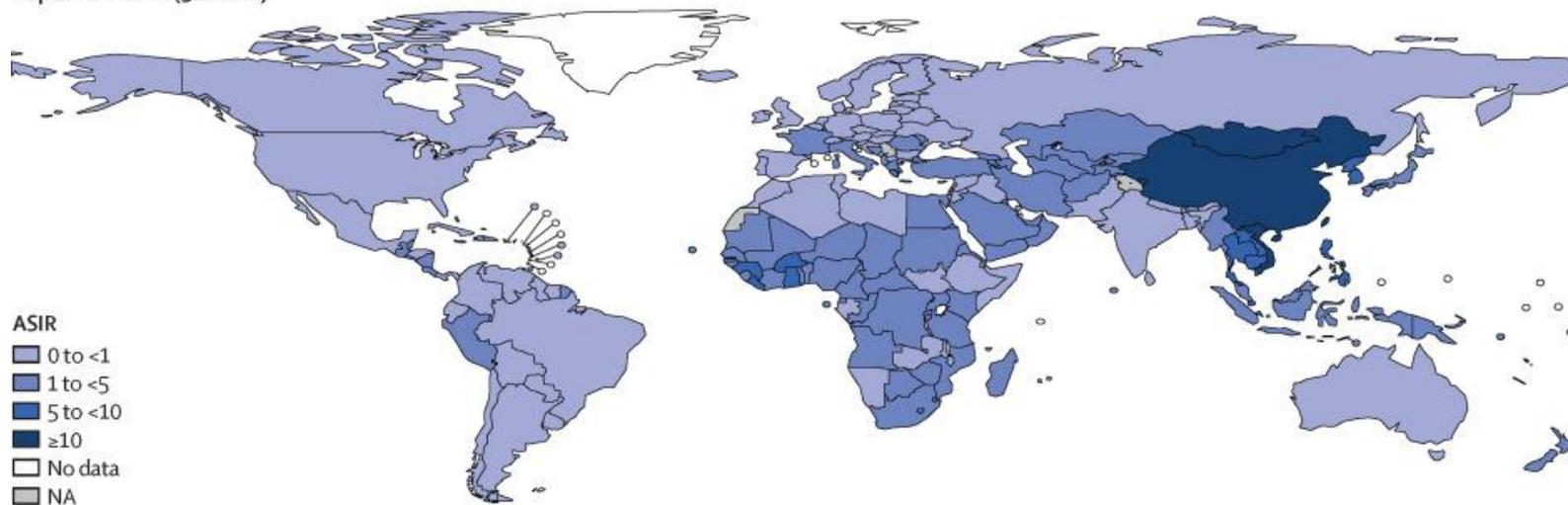
Human papillomavirus (690 000)



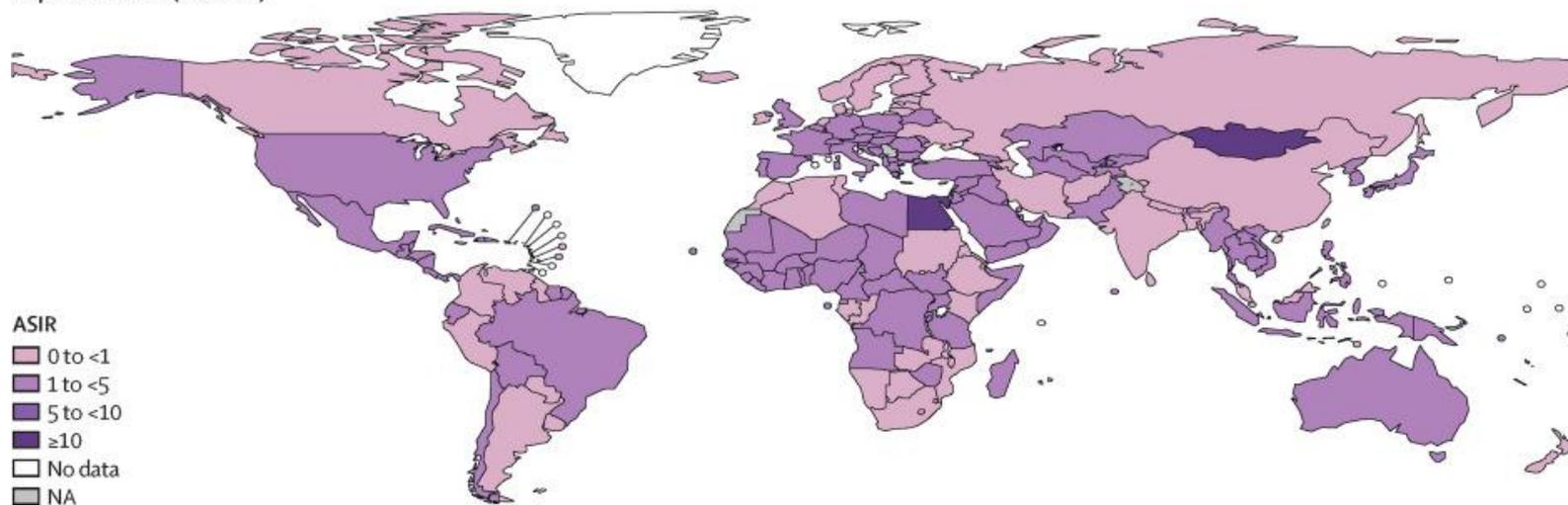
Virus e Câncer: Vírus como fatores de risco

- Estimativa global (2018) de novos casos atribuíveis ao HBV e HCV.

Hepatitis B virus (360000)



Hepatitis C virus (160000)



Obrigado!!!!!!



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UNIVERSIDADE DE SÃO PAULO



“Papillomavirus biology, epidemiology and pathogenesis

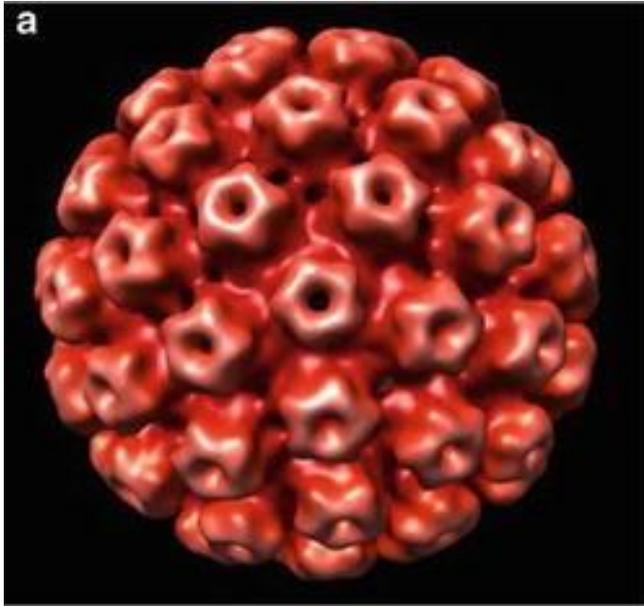
Enrique Boccardo

Laboratory of Oncovirology

Department of Microbiology - ICB/USP

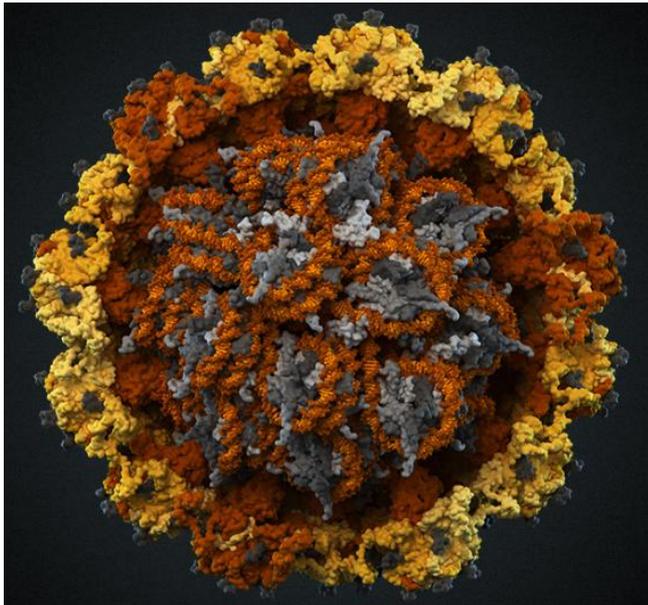
eboccardo@usp.br

Human papillomaviruses (HPV)



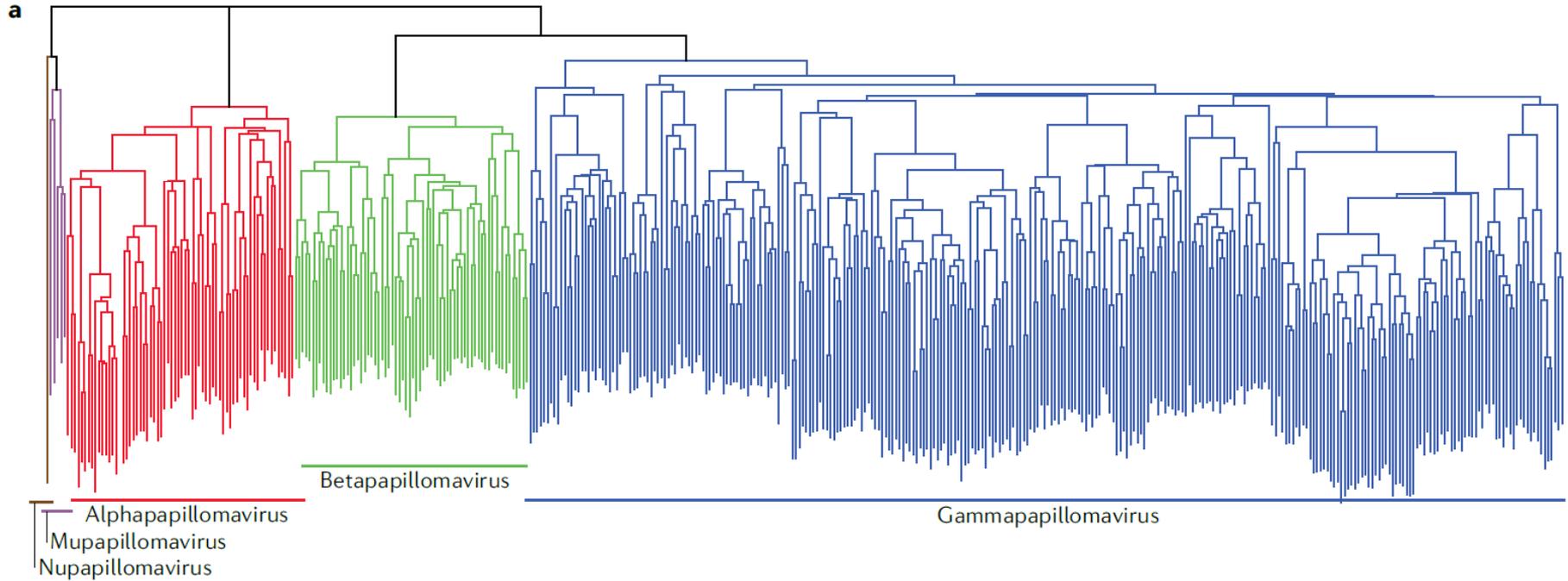
Family: *Papillomaviridae*

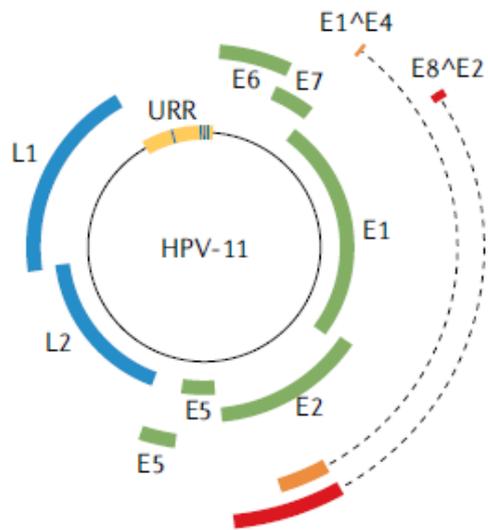
- Small non-enveloped virus (~50 nm)
- dsDNA circular genome (~8 kpb)
- Infect keratinocytes of skin and mucosa



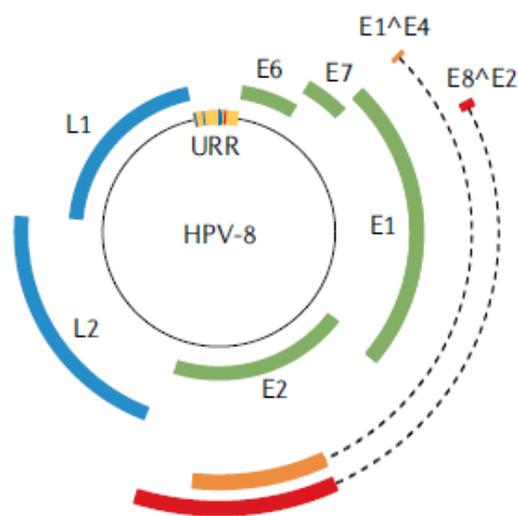
HPV classification

Family *Papillomaviridae*: 5 genera.

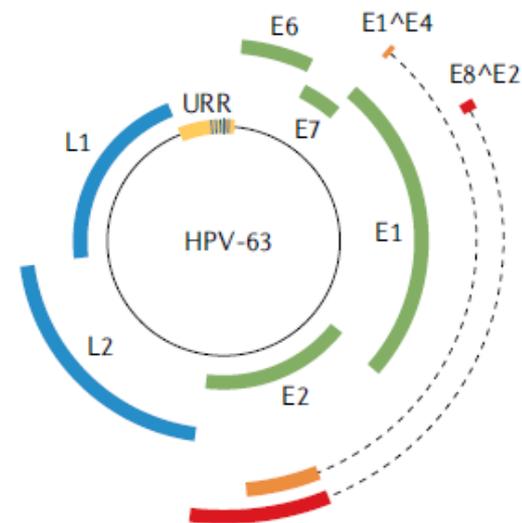




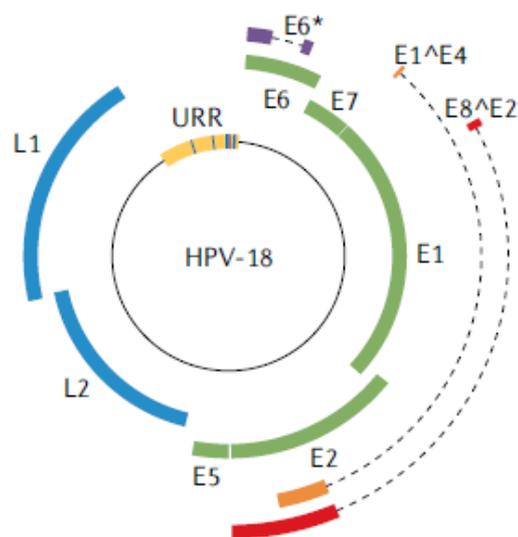
Low-risk Alphapapillomavirus



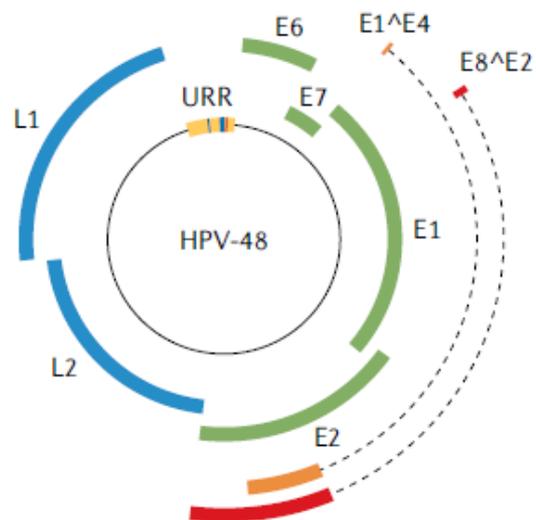
Betapapillomavirus



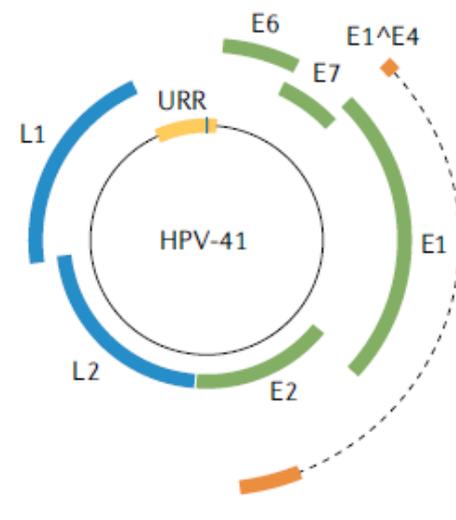
Mupapillomavirus



High-risk Alphapapillomavirus



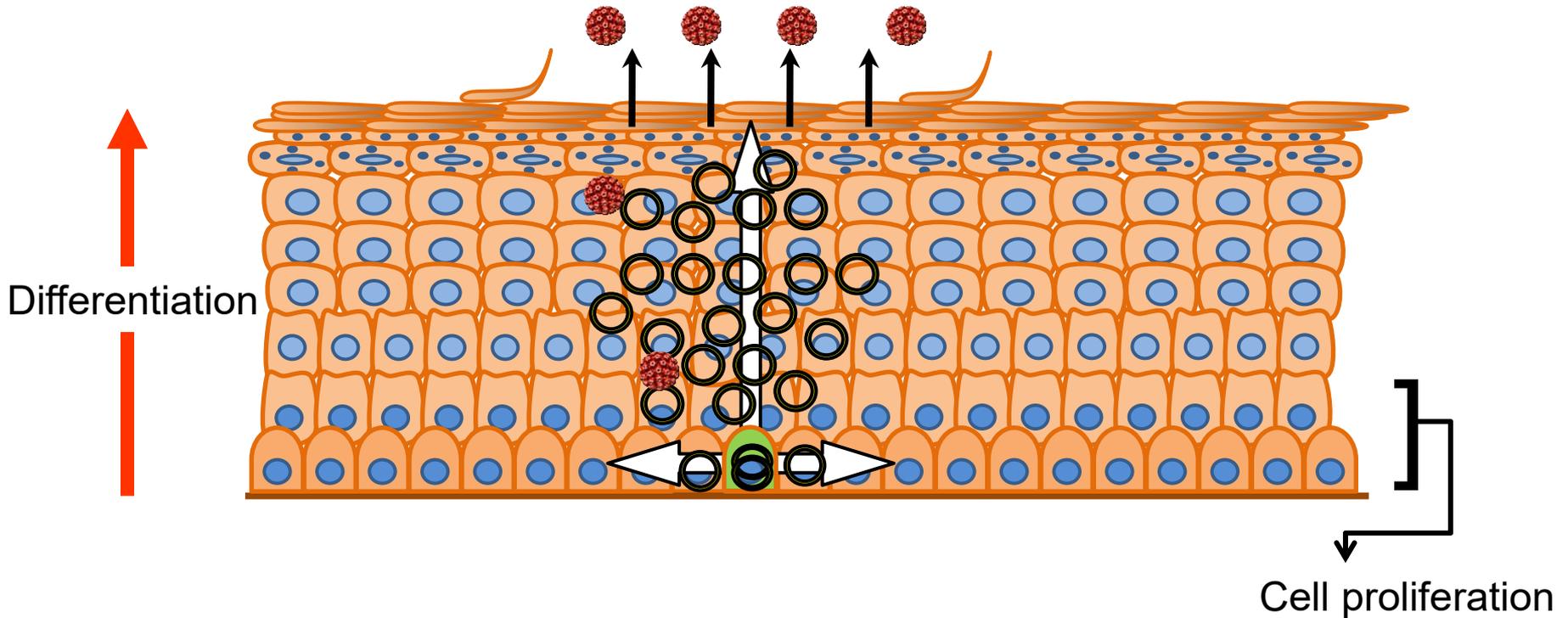
Gammapapillomavirus



Nupapillomavirus

HPV cycle

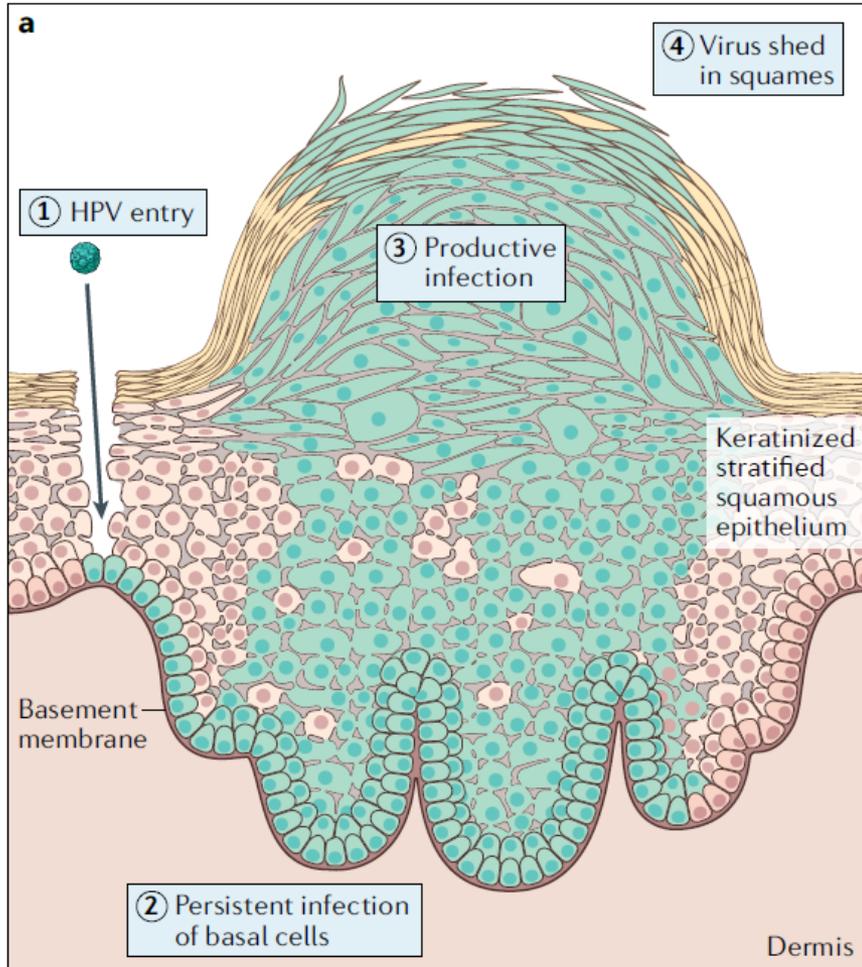
- HPV cycle is linked to keratinocytes differentiation program.



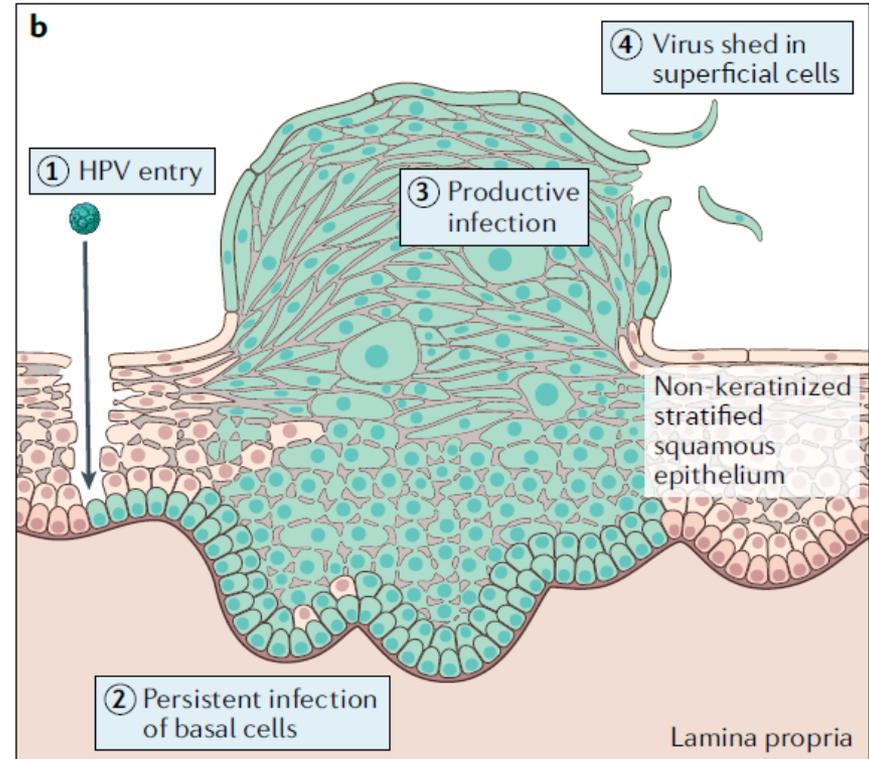
- **Clear anatomical tropism**

HPV cycle: nuances in different types

- HPV cycle is linked to keratinocytes differentiation program.



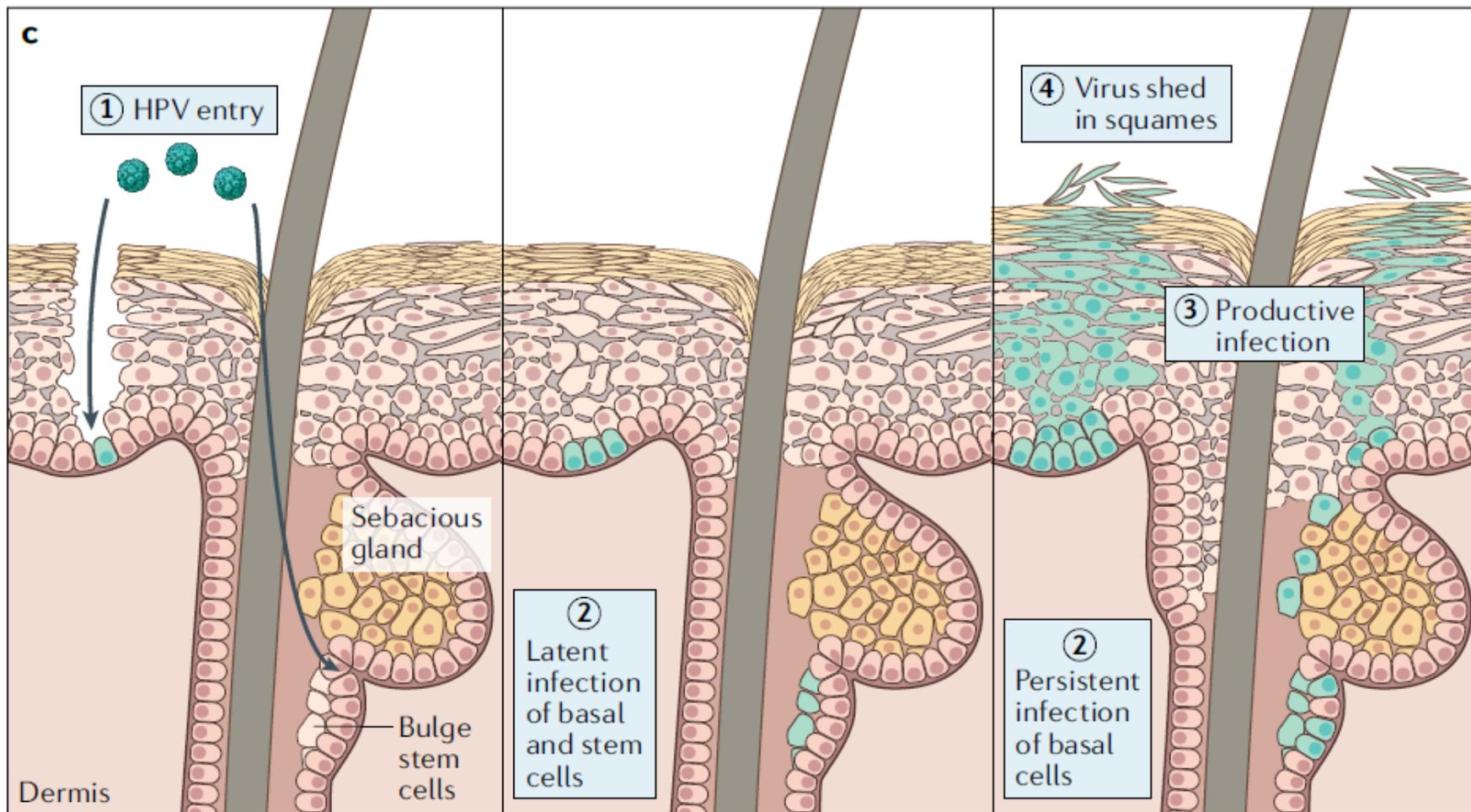
Mupapillomavirus



Alphapapillomaviruses

HPV types: nuances in cycle and tissues

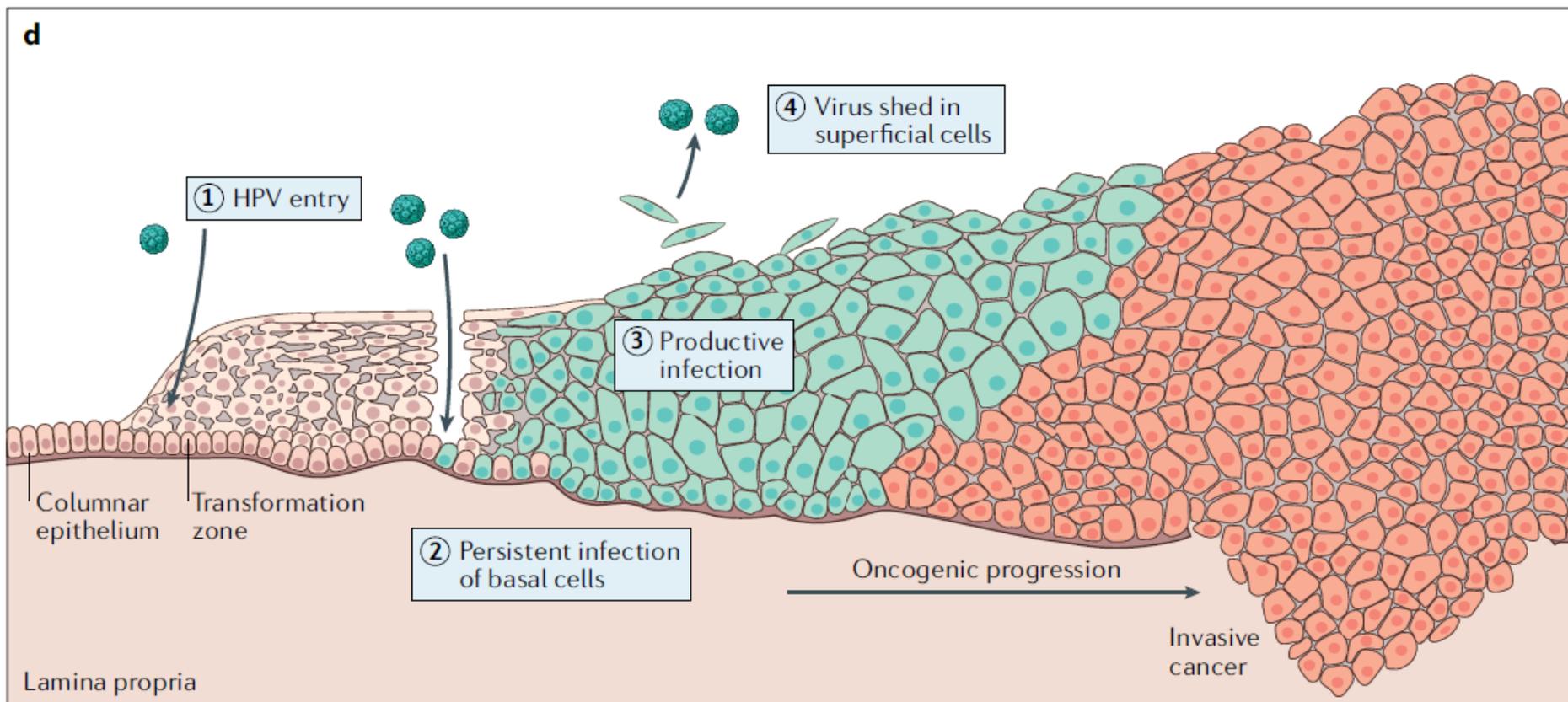
- HPV cycle is linked to keratinocytes differentiation program.



Betapapillomavirus

HPV types: nuances in cycle and tissues

- Interruption of viral cycle and disease



High-risk Alphapapillomaviruses

HPV: many types, several diseases

- However, very common...

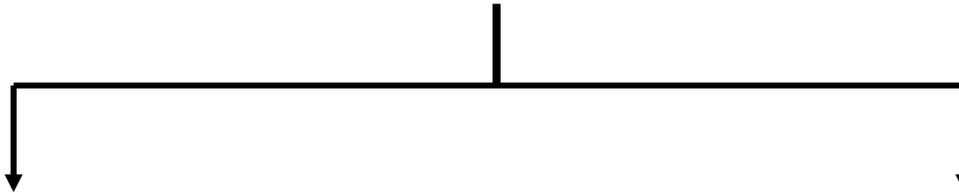


HPV classification

> 220 HPV types



~ 40 types (α genus)
Infect the anogenital tract



Low-risk

(HPV 6, 11)



**Low-grade lesions
and genital warts**

High-risk

(HPV16, 18, 31, 33, 35, 39, 45, 51,
52, 56, 58, and 59)

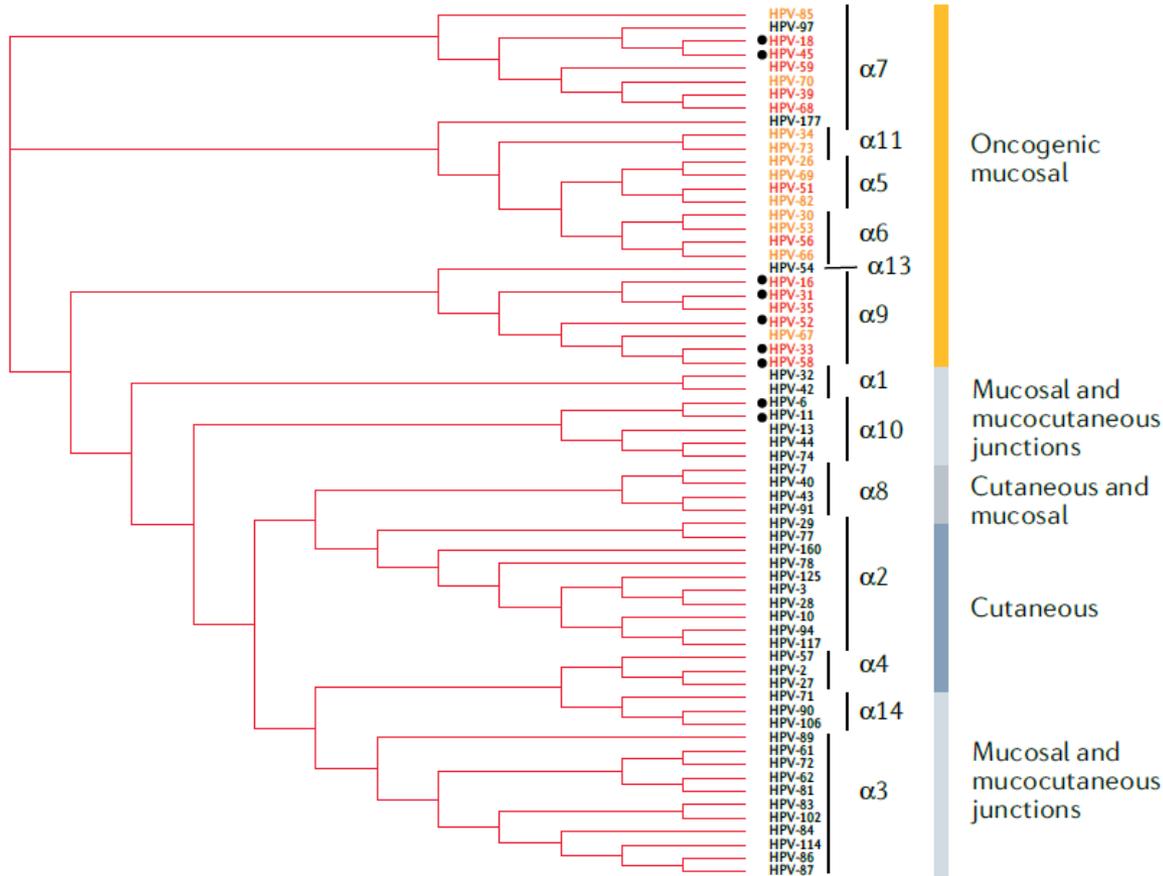


**High-grade lesions and
Invasive carcinoma**

HPV classification

α -Genus and diseases

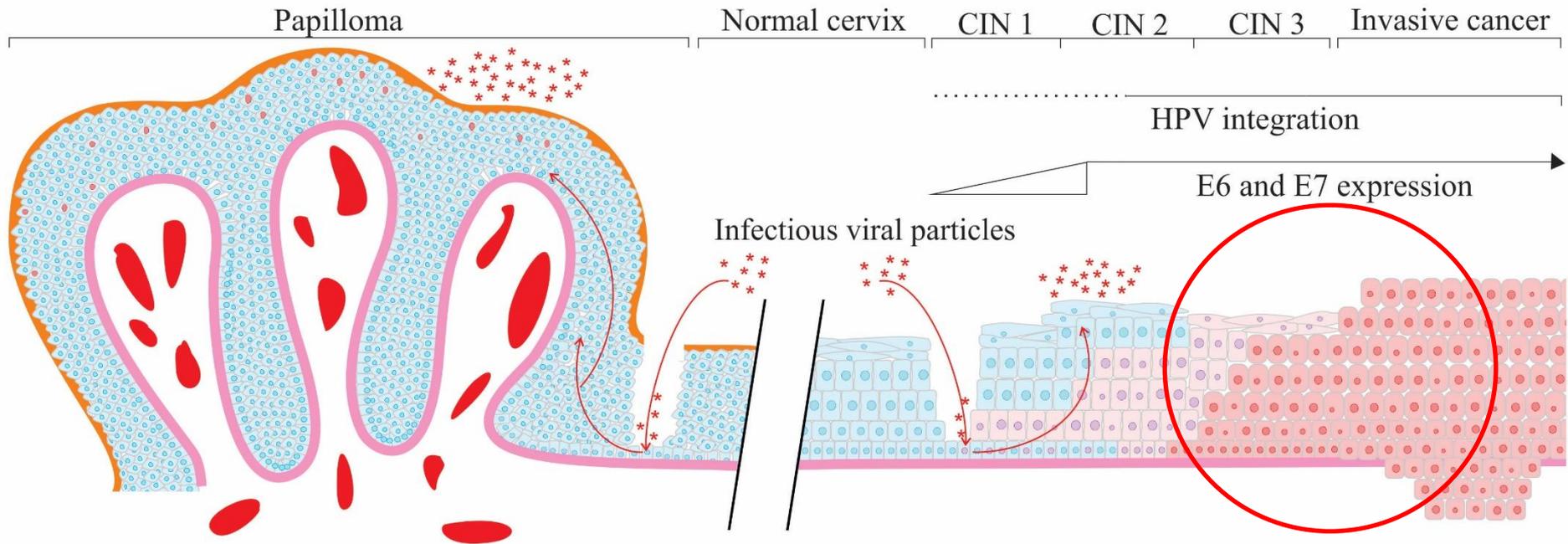
b



Species	Disease
$\alpha 5, \alpha 6, \alpha 7, \alpha 9, \alpha 11$	Anogenital cancers
$\alpha 7, \alpha 9$	Oropharyngeal carcinoma
$\alpha 1, \alpha 10$	Oral focal hyperplasia
$\alpha 1, \alpha 3, \alpha 8, \alpha 10, \alpha 13, \alpha 14$	Anogenital warts
$\alpha 4, \alpha 8$	Common warts
$\alpha 2$	Plane warts

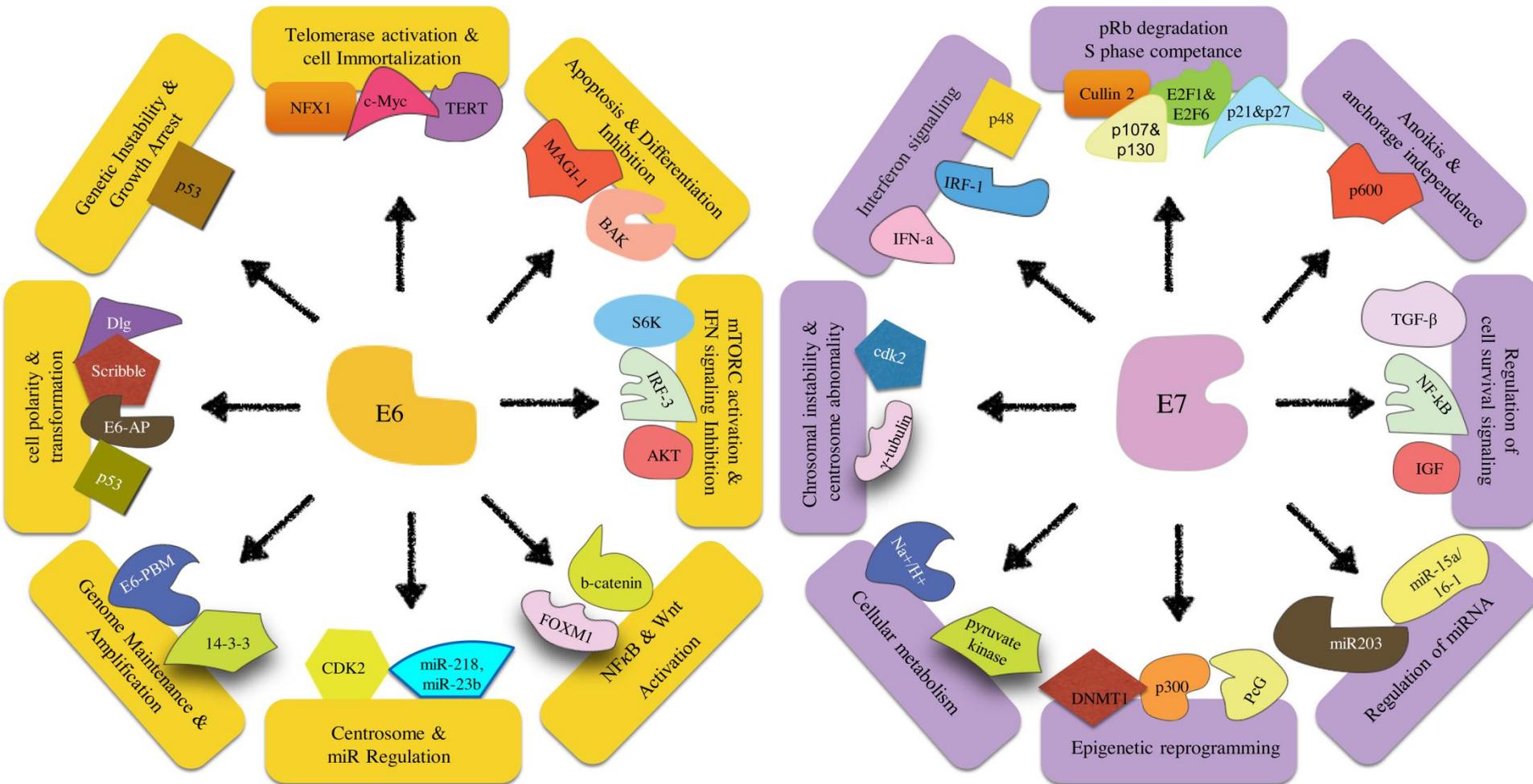
Genital HPV infections: different outcomes

- HPV infection is linked to keratinocytes differentiation program.

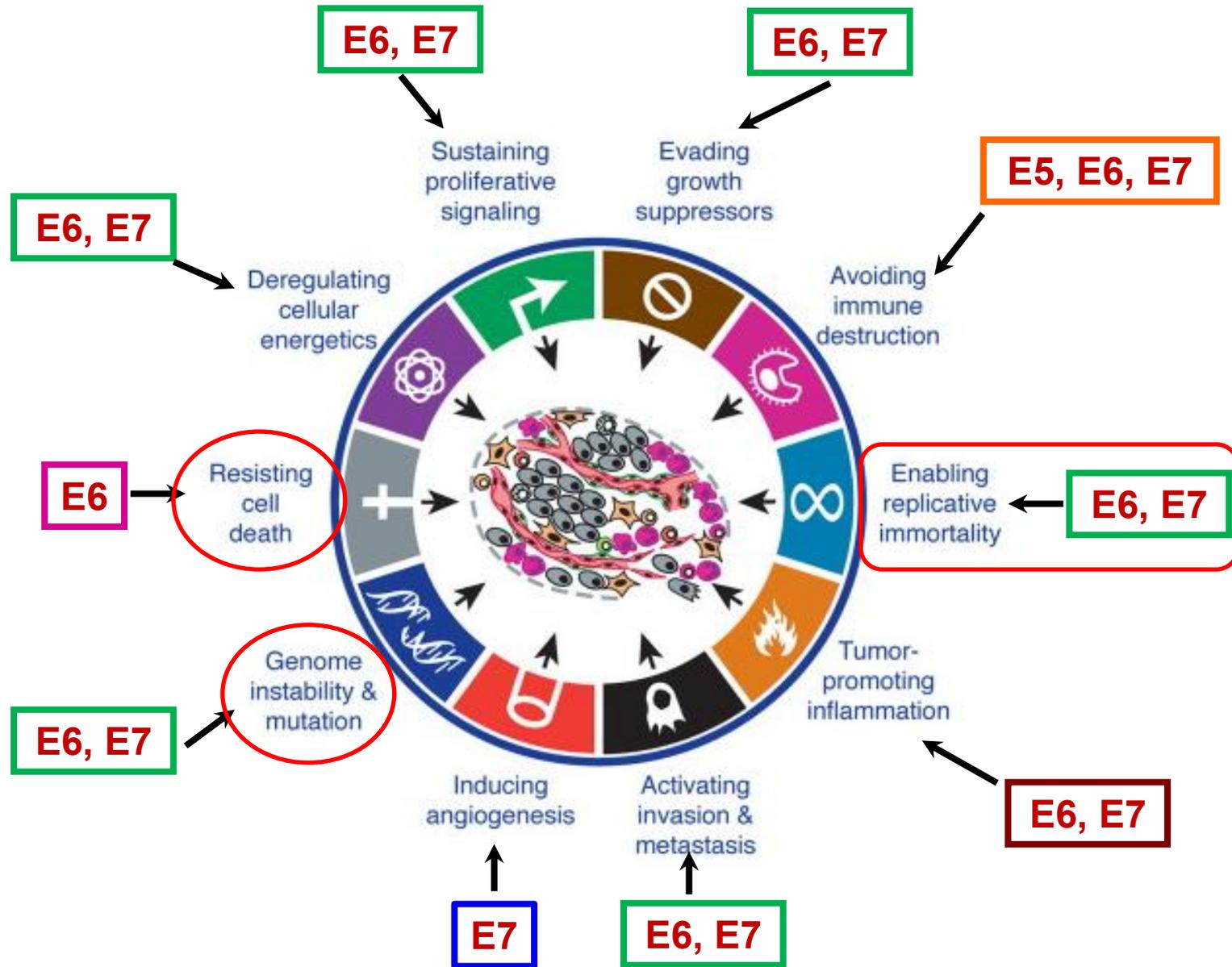


HPV oncoproteins promote cell transformation

- Generate an appropriate environment for viral replication.



HPV oncoproteins promote cell transformation



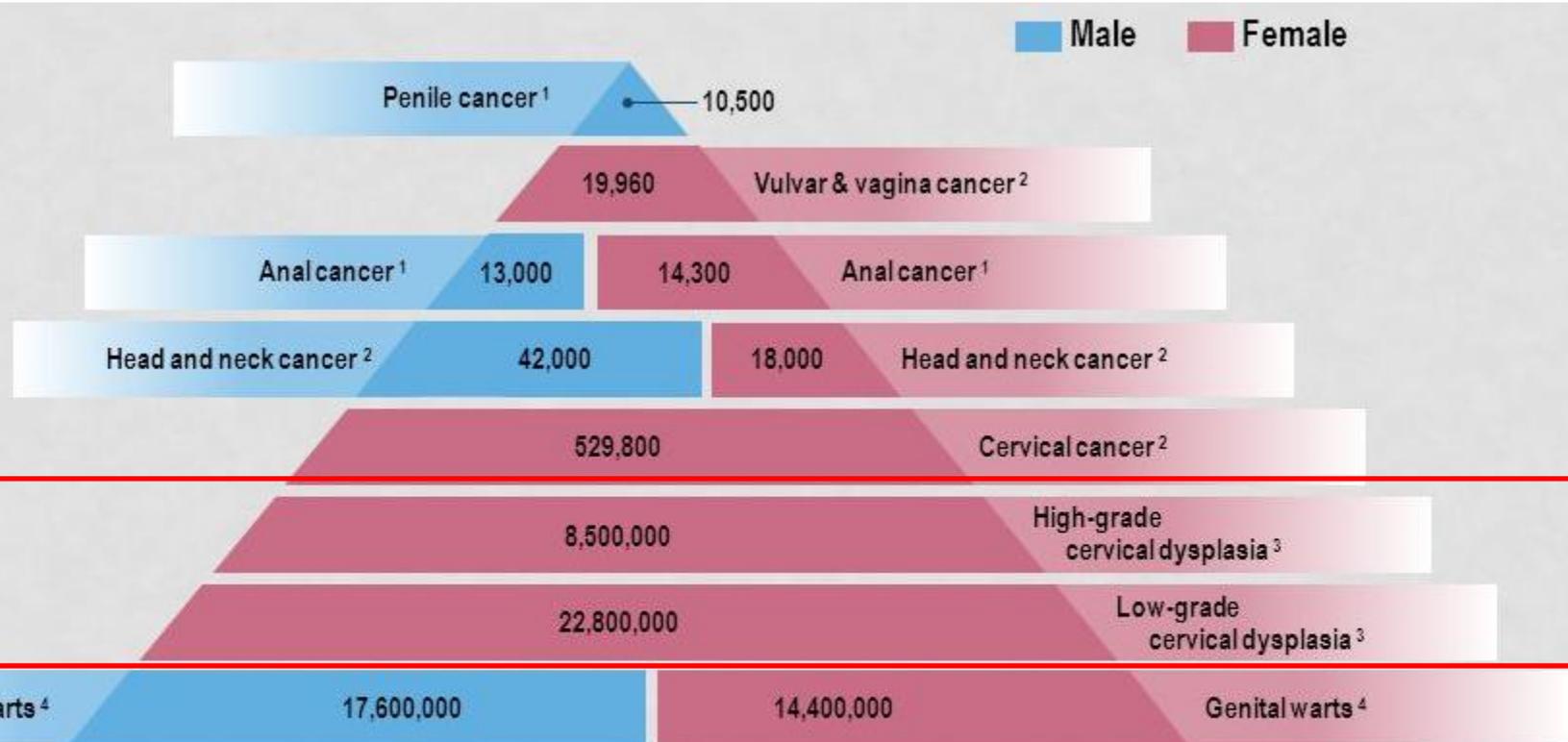
HPV burden on human populations

HPV

- ~100% Cervical carcinomas.
 - ~100% Anal carcinomas.
 - 78% Vaginal carcinomas.
 - 15-48% Vulvar carcinomas.
 - 53% Penile carcinomas.
 - 13-60% Oropharynx.
 - < 5% oral cavity and larynx.
 - 100% Genital warts.
 - 100% RRP.
- ~640.000 cases/year.
 - ~90% are cervical cancer
 - >30.000.000 cervical lesions/year
 - >30.000.000 genital warts/year
 - 4,5% of all cancers (8,6% W vs. 0,9% M).
 - 29,5% of all infectious cancers.

HPV burden on human populations

Global estimate for new cases per year



1. Parkin DM et al. Vaccine. 2006;24(Suppl 3):S3/11–S3/25. 2. WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Human Papillomavirus and Related Cancers in World. Summary Report 2010. 3. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22. 4. World Health Organization (WHO). Executive summary: the state of world health. 1995. http://www.who.int/whr/1995/media_centre/executive_summary1/en/index3.html#. Accessed June 7, 2012.

A little bit of epidemiology...

HPV infects hundreds of millions each year

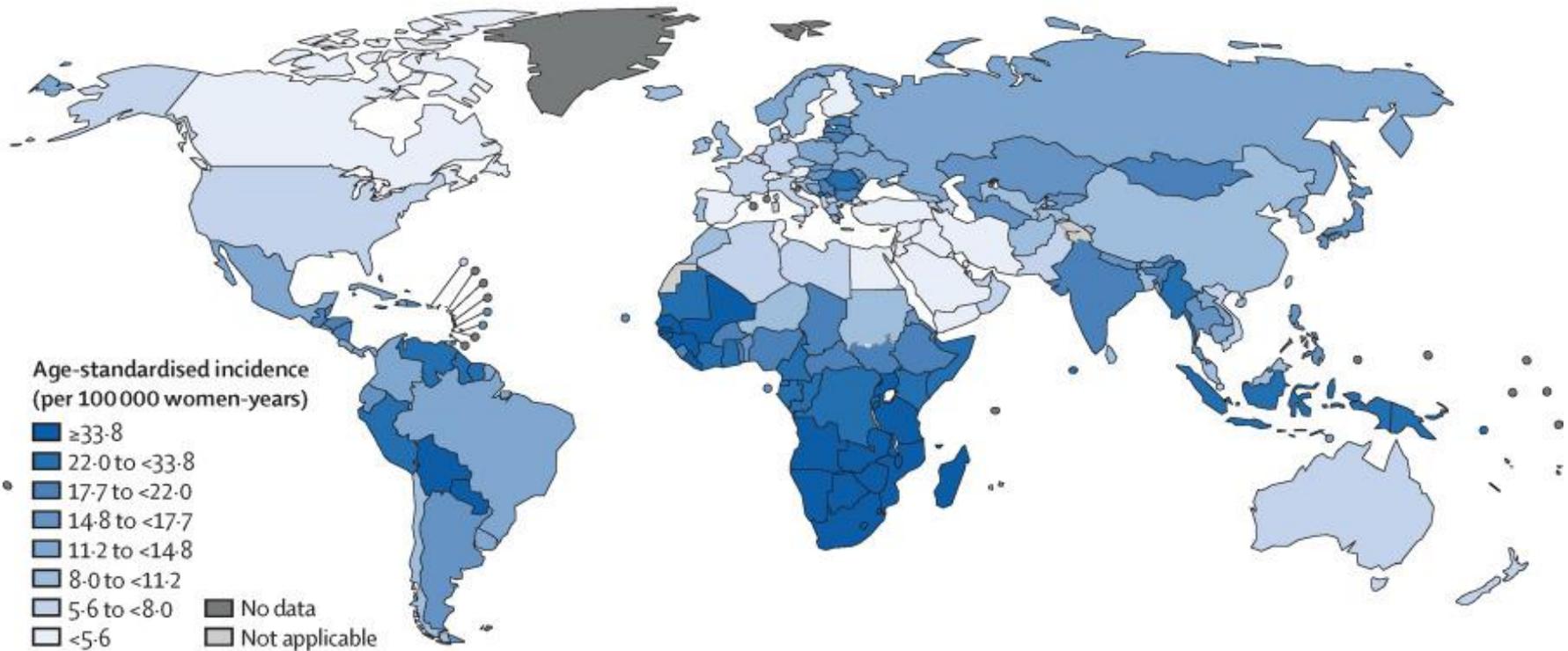
- Approximately 12% of women with normal cytology around the world are infected with some type of HPV, being more common among young women (30-50% positive)
- Among men, prevalence of HPV in the penis varies from 10 to 70% (Global prevalence ~31%).
- The probability of transmission is high (50-80%) and persists throughout life.
- Over 30 million new cases of genital warts each year and half a million new cases of cervical cancer.

HPV infections

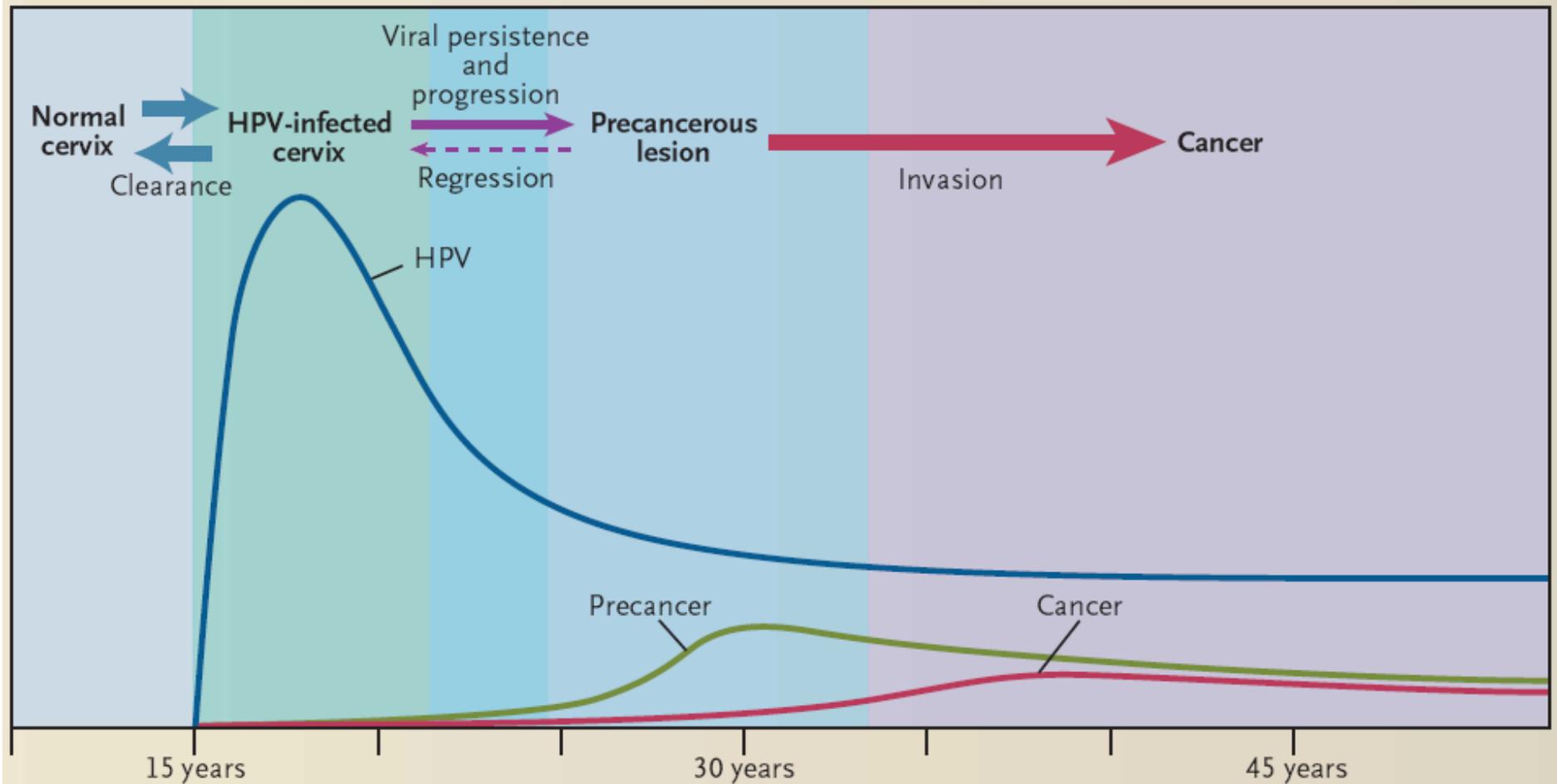
- Most infections (70-90%) are asymptomatic. No cell lysis or other cytopathic effects occur.
- Many years from initial infection and tumor development.
- Transformation requires sustained E6 and E7 expression.
- Persistent infection with HR-HPV types is the main risk factor for cervical disease.

Cervical Cancer Incidence

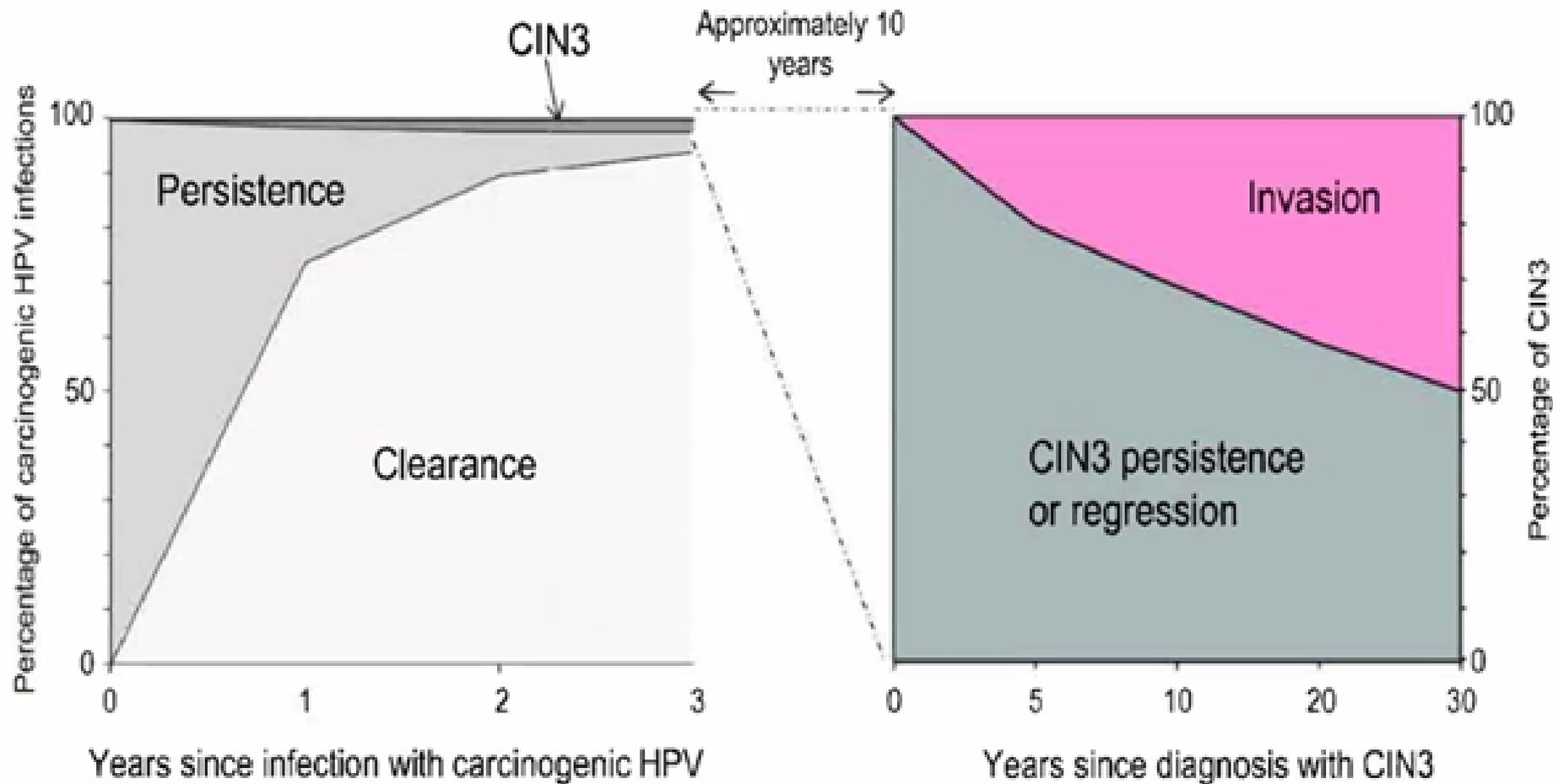
A



Natural history of HPV infection



Natural history of HPV infection



Not even HR-HPV are alike

Group *	HPV types	Comments
1	16	Most potent HPV type causes cancer of the cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and tonsil. Positive association with cancer of the larynx.
1	18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Sufficient evidence for cervical cancer
2A	68	Limited evidence in humans for cervical cancer and strong mechanistic data
2B	26, 53, 66, 67, 70, 73, 82	Limited evidence in humans for cervical cancer
2B	30, 34, 69, 85, 97	Classified by phylogenetic analogy
3	6 and 11	Inadequate epidemiological evidence and lack of carcinogenic potential in mechanistic studies

- *Carcinogenic to humans* (Group 1); *Probably carcinogenic to humans* (Group 2A); *Possibly carcinogenic to humans* (Group 2B); *Not classifiable as to their carcinogenicity to humans* (Group 3)

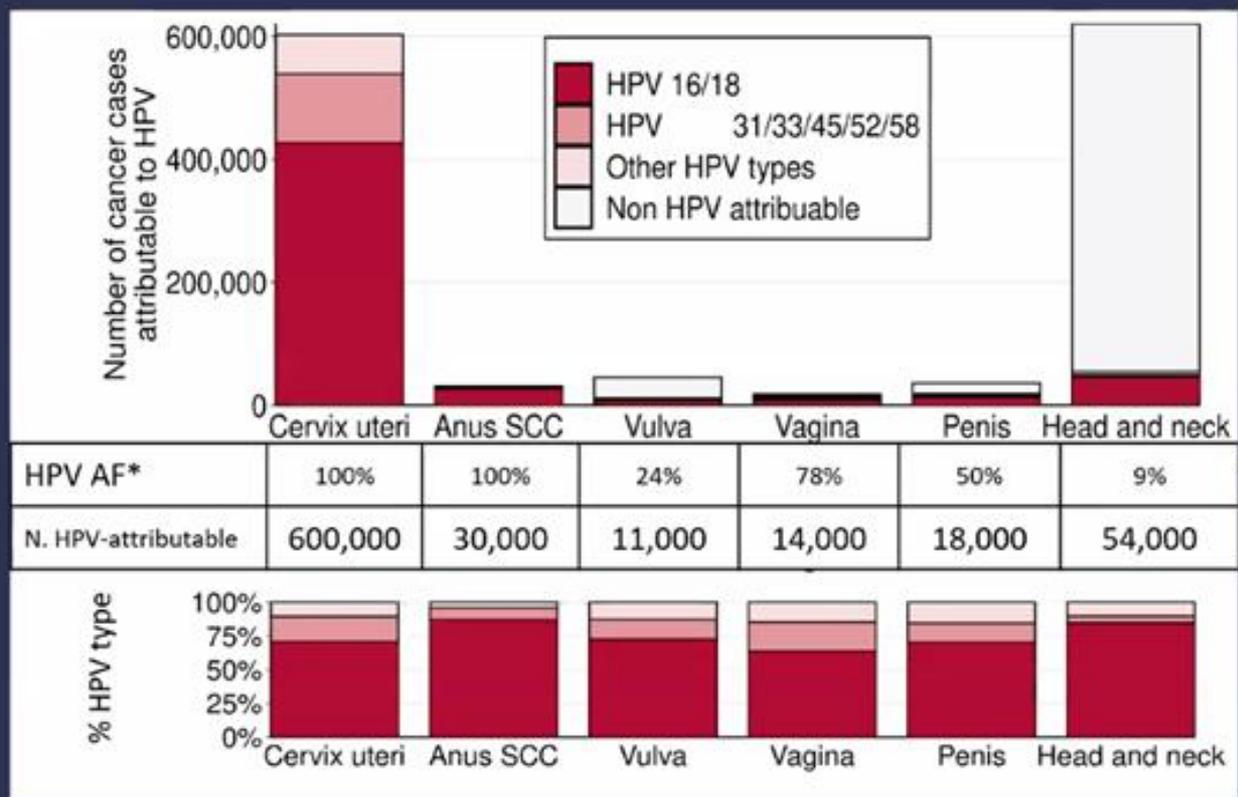
IARC Monographs Volume 100B (2012)

Not even HR-HPV are alike

HPV type	HPV species	IARC Group ^a	% HPV type prevalence in cancer	% HPV type prevalence in normal	Odds ratio	% Attributable (etiological) fraction
HPV16	α-9	Group 1	55.8	2.6	47.6	62.4
HPV18	α-7	Group 1	14.3	1	15.7	15.3
HPV45	α-7	Group 1	4.8	0.6	8.3	4.8
HPV33	α-9	Group 1	4	0.6	7.1	3.9
HPV58	α-9	Group 1	4	0.8	5.1	3.7
HPV31	α-9	Group 1	3.5	1	3.7	2.9
HPV52	α-9	Group 1	3.2	1	3.3	2.6
HPV35	α-9	Group 1	1.6	0.4	3.9	1.4
HPV59	α-7	Group 1	1.2	0.4	2.9	0.9
HPV39	α-7	Group 1	1.3	0.6	2.0	0.8
HPV68	α-7	Group 2A	0.6	0.4	1.5	0.2
HPV51	α-5	Group 1	1	0.9	1.2	0.2
HPV56	α-6	Group 1	0.8	0.6	1.3	0.2
HPV73	α-11	Group 2B	0.5	0.3	1.8	0.2
HPV26	α-5	Group 2B	0.2	0.1	4.1	0.2
HPV30	α-6	Group 2B	0.2	0.1	2.6	0.1
HPV69	α-5	Group 2B	0.2	0.1	1.4	0.1
HPV67	α-9	Group 2B	0.3	0.2	1.2	< 0.1
HPV82	α-5	Group 2B	0.2	0.1	1.2	< 0.1
HPV34	α-11	Group 2B	0.1	0.1	1.0	Not attributable
HPV66	α-6	Group 2B	0.3	0.6	0.4	Not attributable
HPV70	α-7	Group 2B	0.2	0.8	0.3	Not attributable
HPV53	α-6	Group 2B	0.5	1.1	0.4	Not attributable

Not even HR-HPV are alike

IARC estimates of global burden of HPV-related cancer in 2020



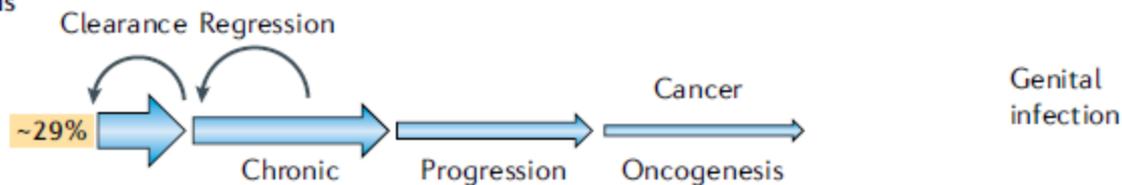
Oropharynx: 30%
 Oral cavity ~2%
 Larynx ~2%

*Attributable fractions (AF) as in de Martel et al, Lancet Global Health, 2020.

Little Summary

Prevalence of HPV infection

High-risk Alphapapillomavirus



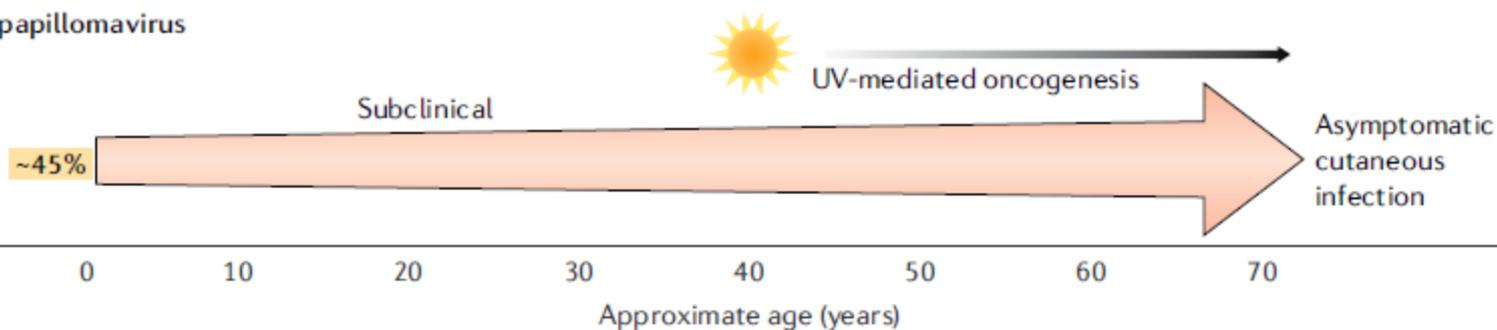
Low-risk Alphapapillomavirus



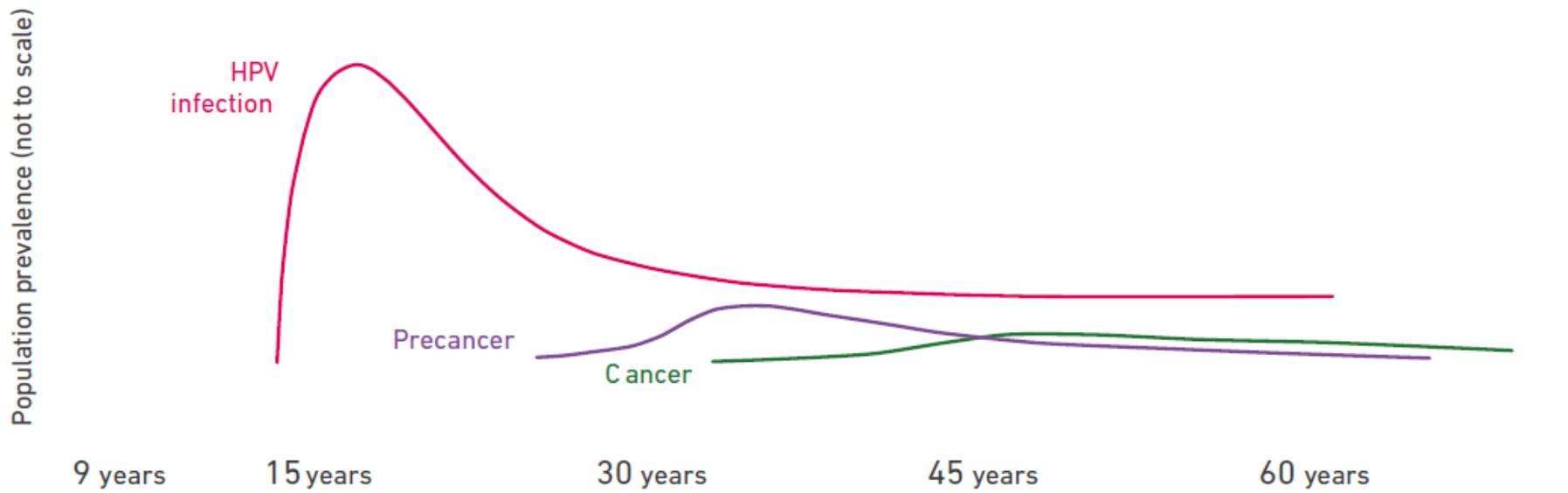
Alphapapillomavirus, Gammapapillomavirus, Mupapillomavirus and Nupapillomavirus



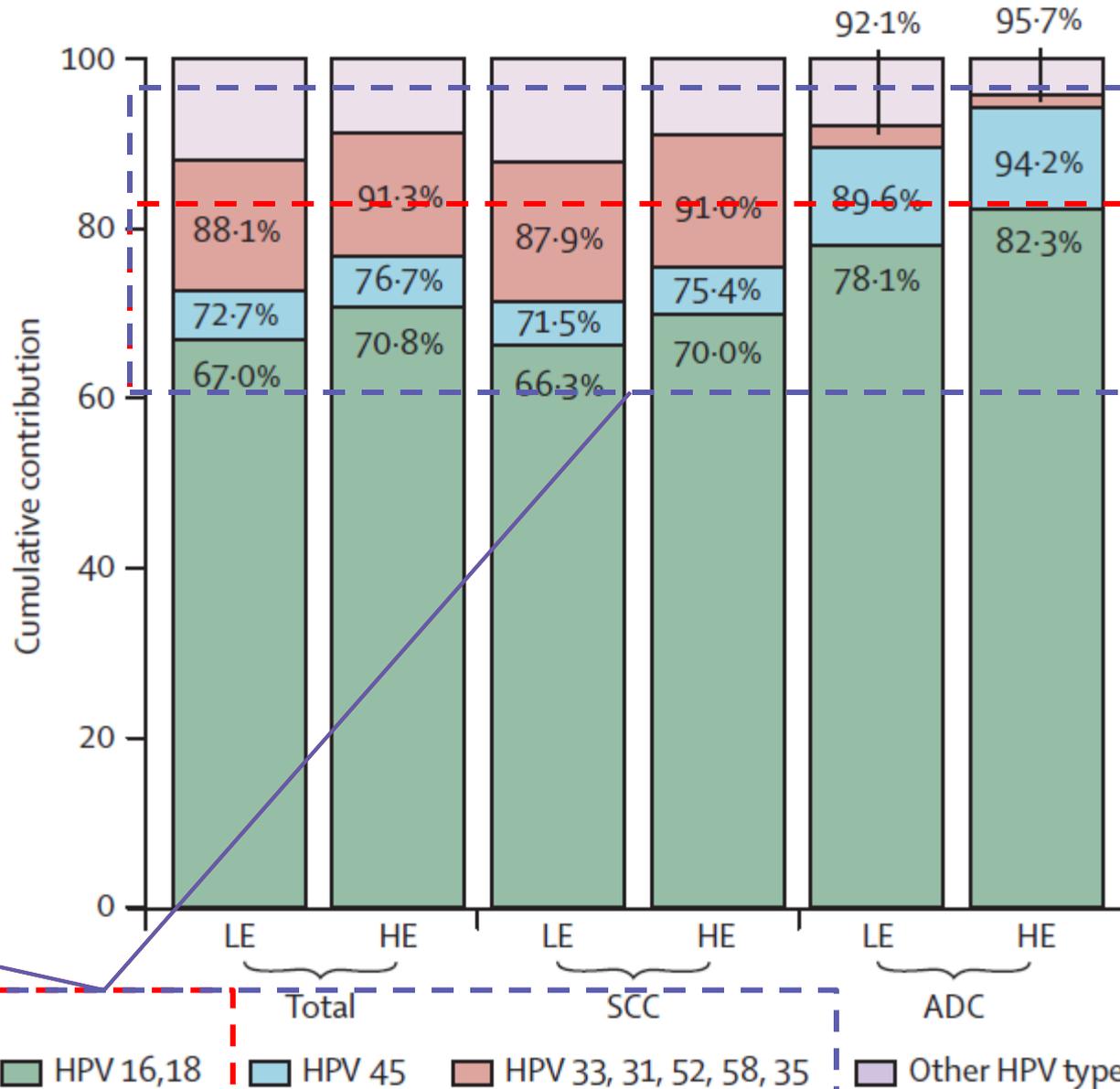
Betapapillomavirus



The fight against cervical cancer



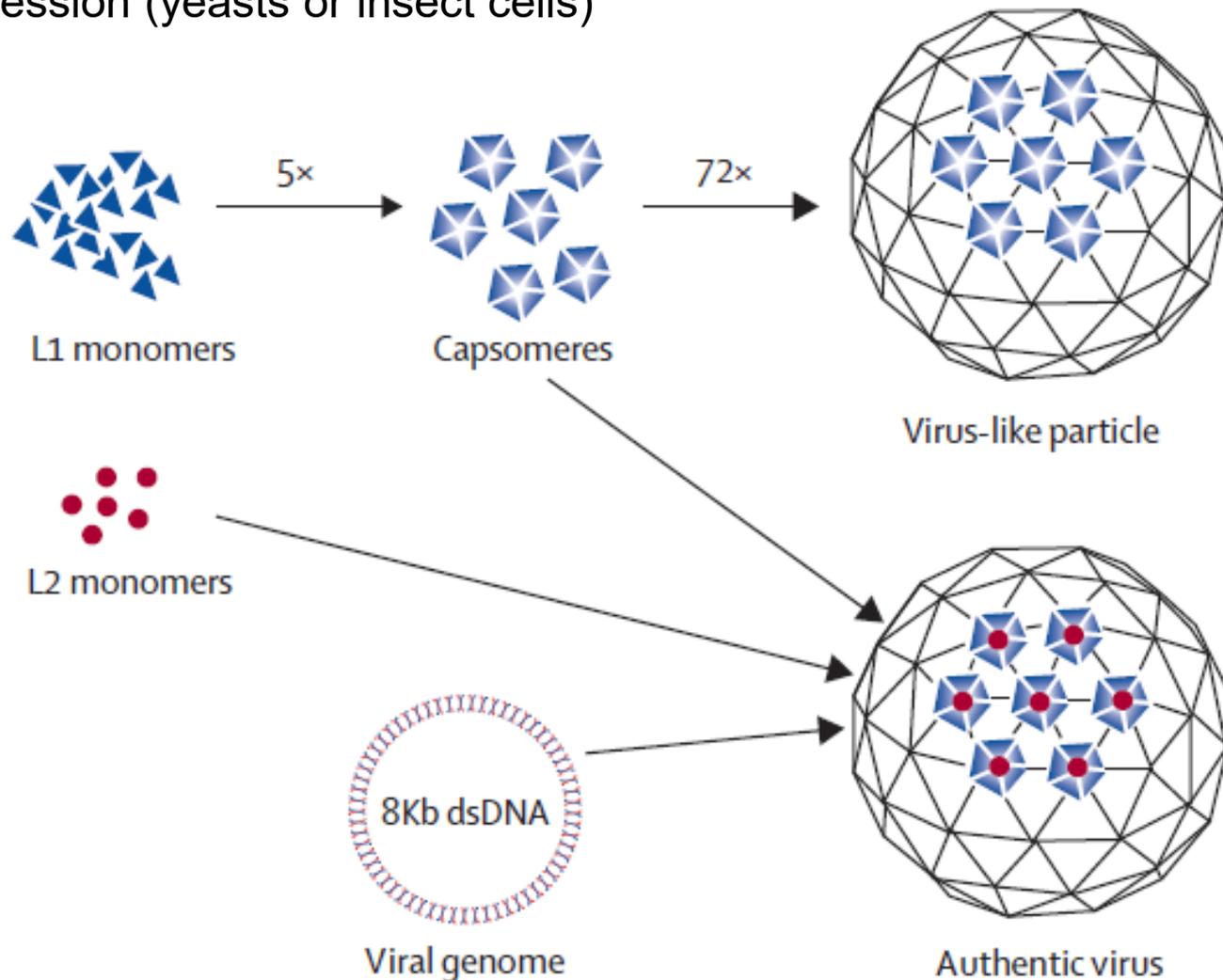
HPV types in cervical cancer



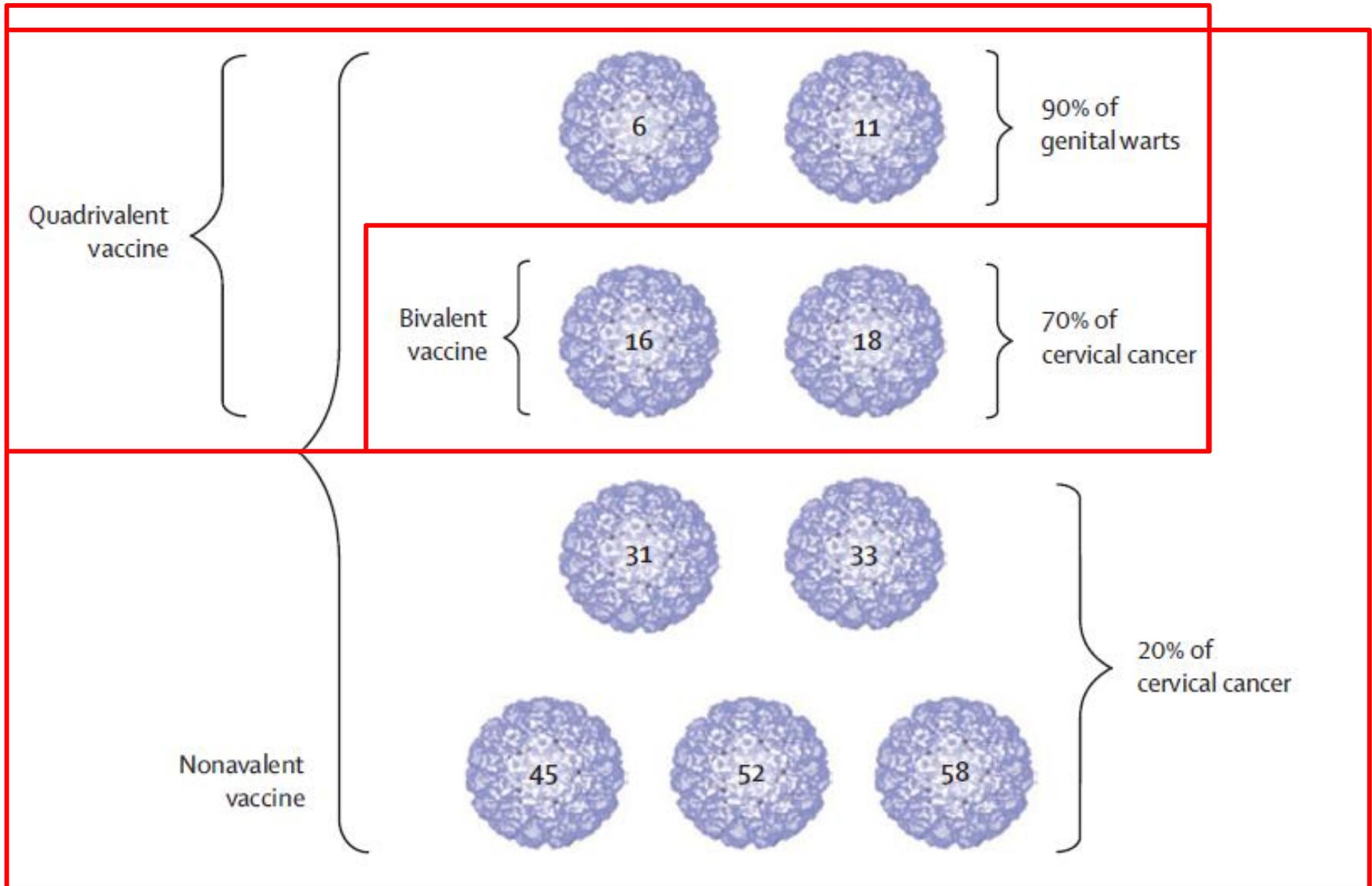
**~90% dos
CCU**

Strategy for prophylactic vaccines development: VLPs

- L1 gene expression (yeasts or insect cells)



Prophylactic vaccines: potential of protection



Licensed prophylactic vaccines

	2vHPV vaccine	4vHPV vaccine	9vHPV vaccine
Brand name	Cervarix, Cecolin, Walrinvax...	Gardasil, Silgard, Cervavax...	Gardasil 9
L1 VLPs + adjuvant	HPV-16/18	HPV-6/11/16/18	HPV-6/11/16/18/31/33/ 45/52/58
Schedule	Licensed for girls and boys aged 9–14 years as a 2-dose schedule		

Vaccination prevents HPV transmission

- Australia (2007): National Vaccination Program (4vHPV) of girls and women (12-26 yo)

Presentations with warts in men and women <21

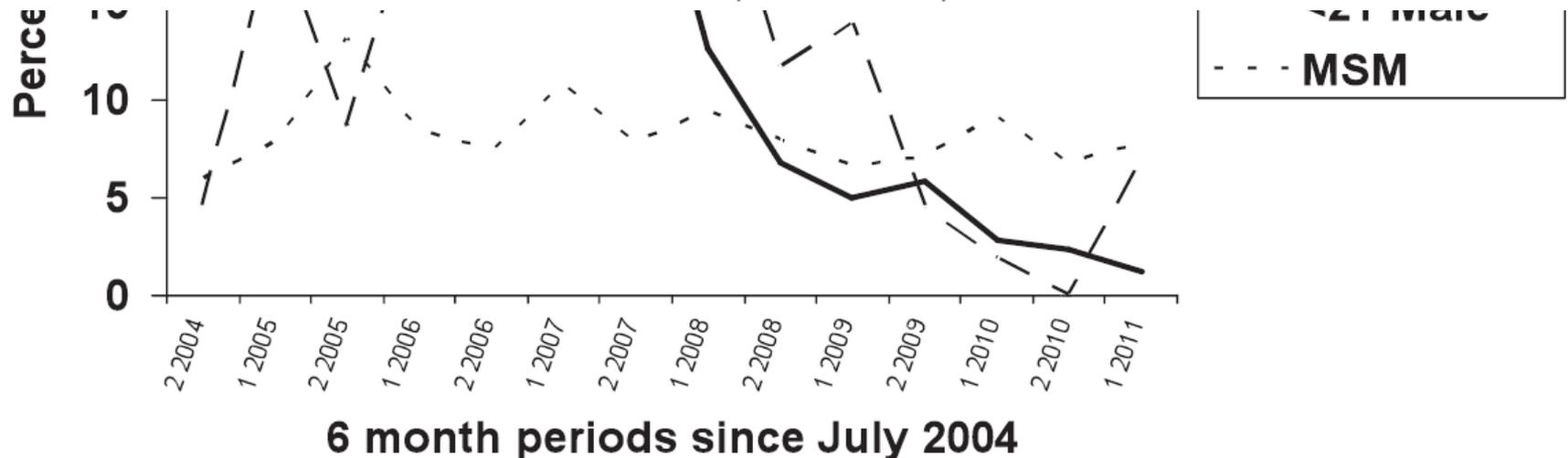
Epidemiology



ORIGINAL ARTICLE

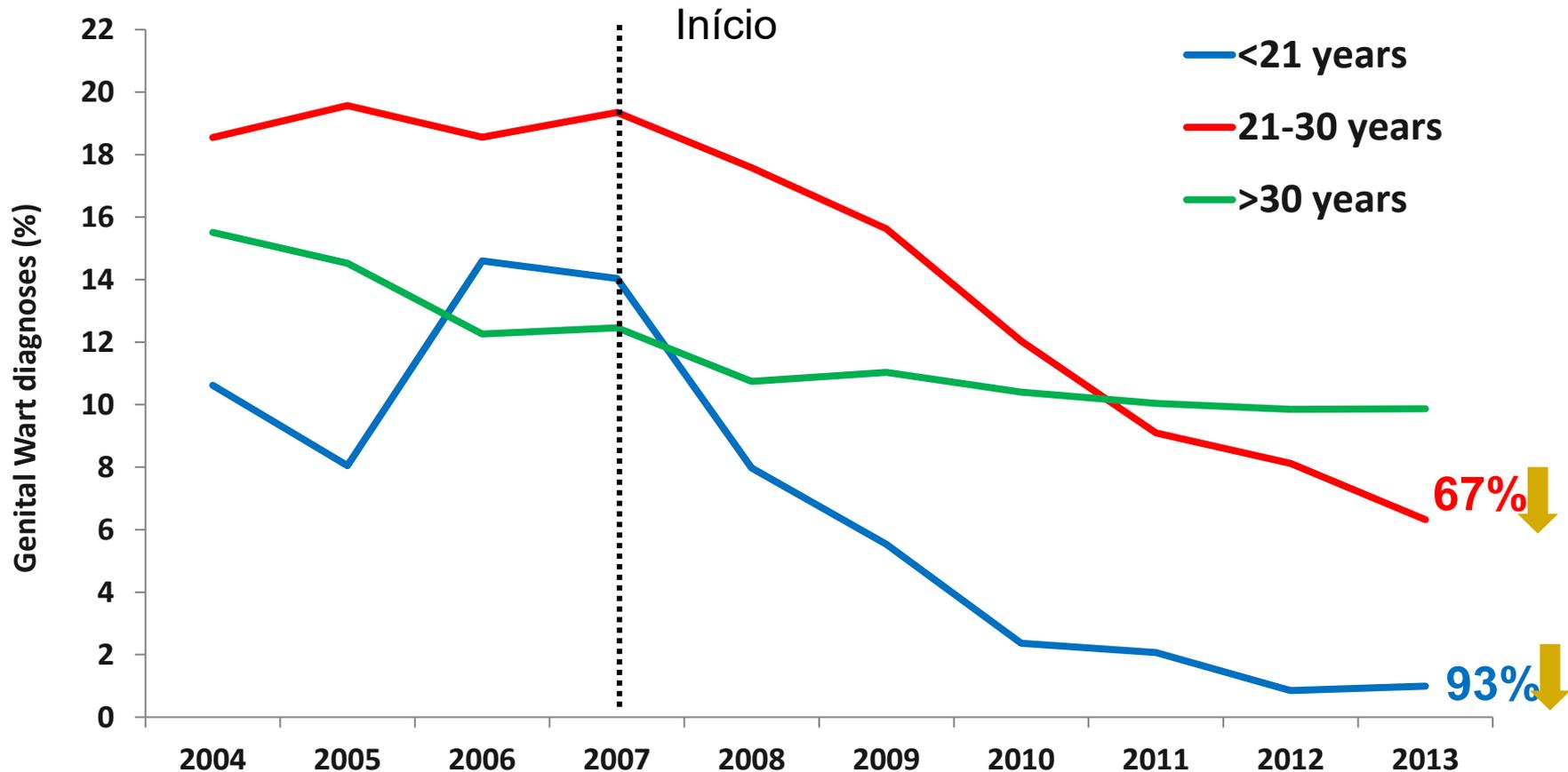
The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme

Tim R H Read,¹ Jane S Hocking,² Marcus Y Chen,¹ Basil Donovan,³
Catriona S Bradshaw,⁴ Christopher K Fairley¹



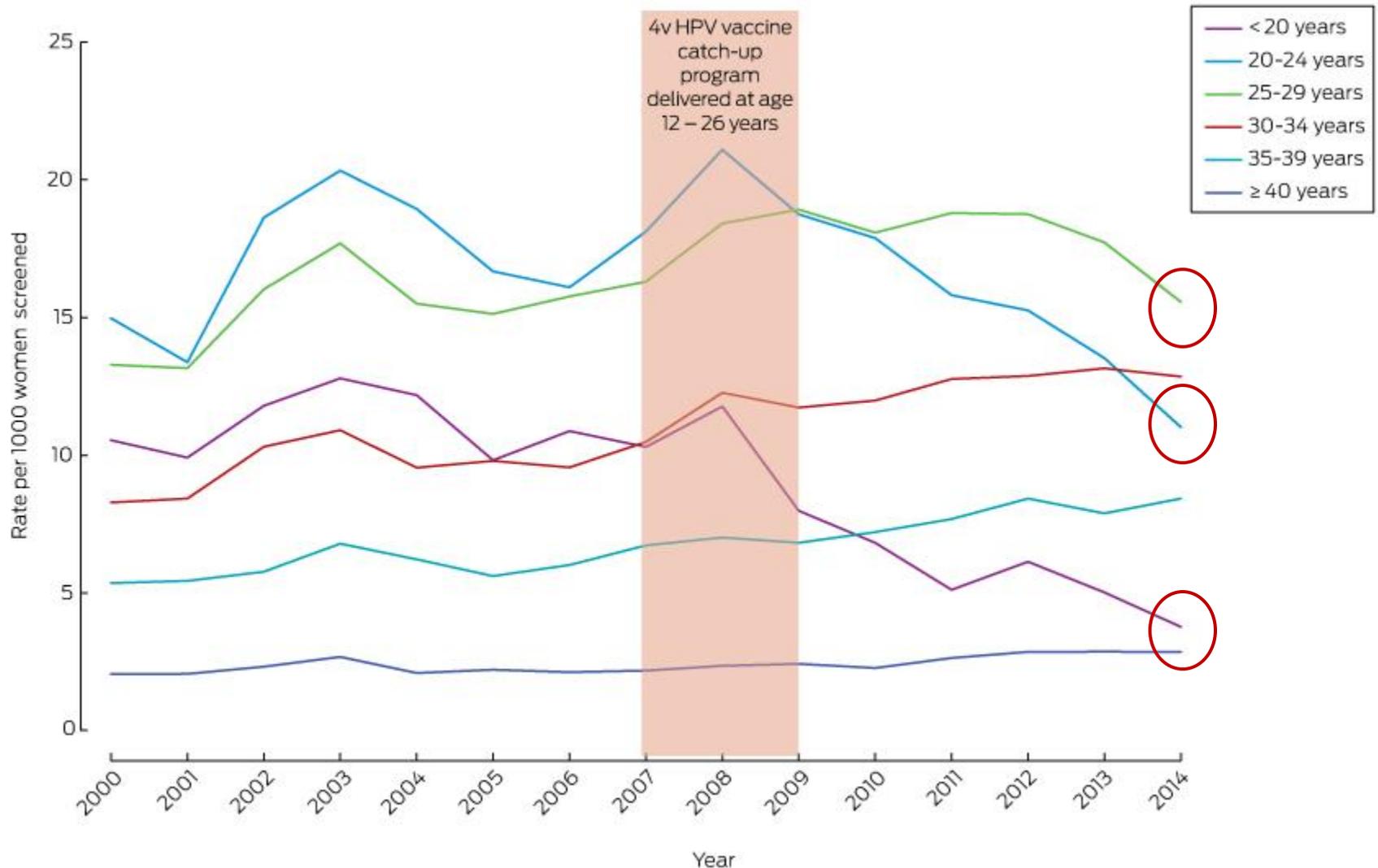
Vaccination prevents HPV transmission

- Australia (2007): National Vaccination Program (4vHPV) of girls and women (12-26 yo)
- Reduction in genital warts in heterosexual Australian men.



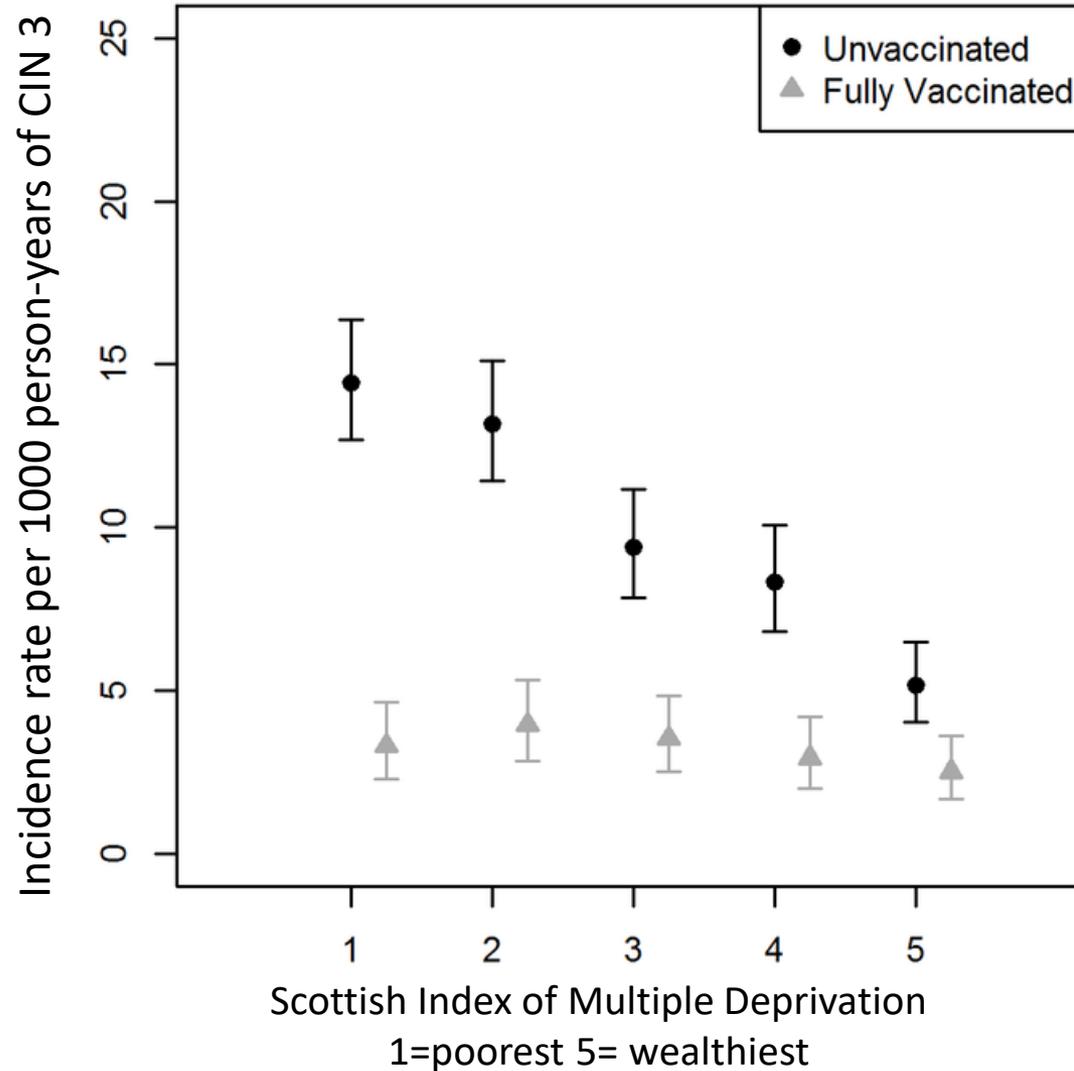
Vaccination prevents HPV transmission

- Australia (2007): National Vaccination Program (4vHPV) of girls and women (12-26 yo)
- Reduction of cervical cancer precursor lesions.

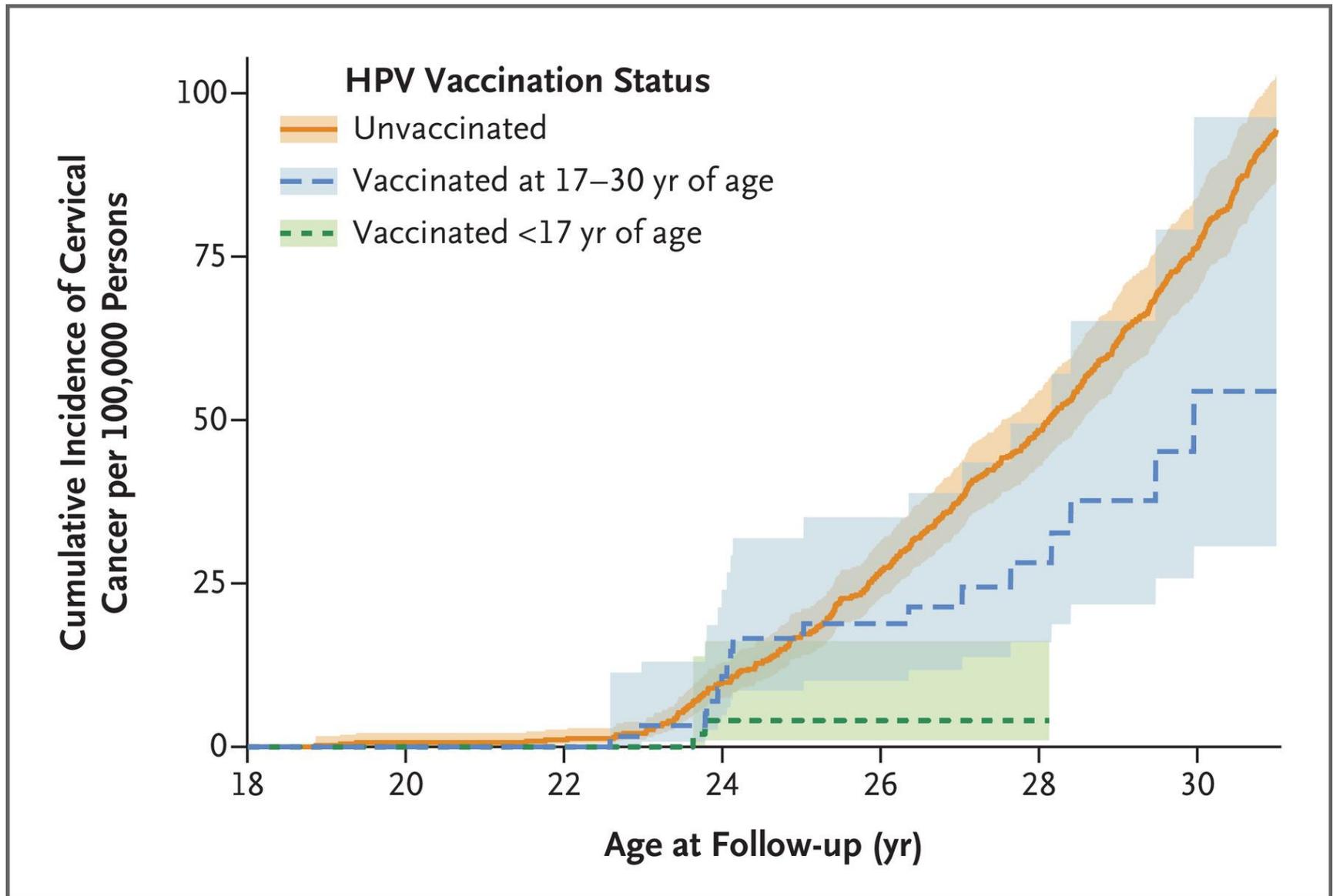


Vaccination prevents HPV transmission

- Scotland: Vaccination (2vHPV) reduce the incidence of of cervical cancer precursor lesions. Decrease in inequality.



Vaccination prevents cervical cancer



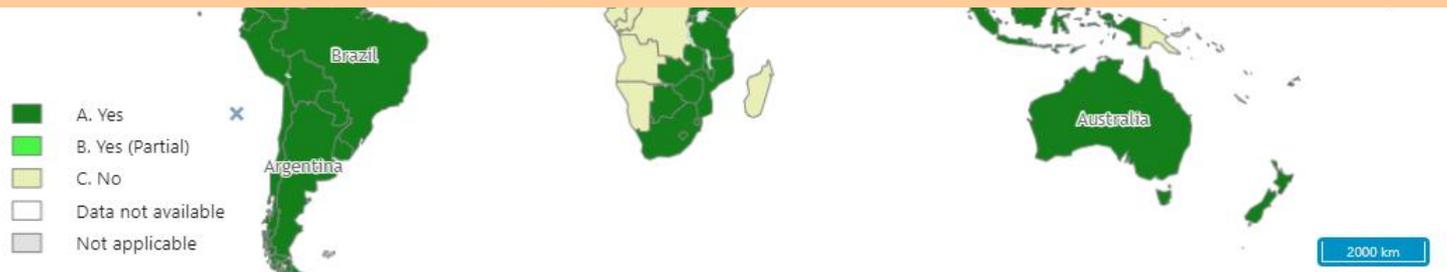
Prophylactic HPV vaccines: global reality

141 countries (73%) with HPV vaccine in their NIP for girls, and 59 countries (42%) also for boys

HPV VACCINE INCLUDED IN NATIONAL IMMUNIZATION PROGRAMME



■ Only 1 in 8 of the girls received the vaccine (mainly in developed countries).



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Prophylactic HPV vaccines: Americas

Vaccination in Brazil

Eligible population for free vaccination contra HPV^{1,2}

Population	Age	Number of doses	Dose interval
Girls and boys	9-14 yo	2 doses	0 and 6 months
With HIV/AIDS	Women and Men 9-45 yo	3 doses	0, 2, 6 months
Recipients of solid organ transplant	Women and Men 9-45 yo	3 doses	0, 2, 6 meses
Recipients of bone marrow transplants	Women and Men 9-45 yo	3 doses	0, 2, 6 meses
Oncologic patients	Women and Men 9-45 yo	3 doses	0, 2, 6 meses

1. Available at https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/c/calendario-nacional-de-vacinacao/calendario-vacinal-2022/anexo-calendario-de-vacinacao-da-crianca_atualizado_final-20-09-2022.pdf [Accessed 13 September 2023].

2. Available at <https://www.vacina100duvidas.sp.gov.br/> [Accessed 13 September 2023].



Vaccination in Brazil

Eligible population for free vaccination contra HPV^{1,2}

Publicado em 02/04/2024 11h34



Ministério da Saúde
Secretaria de Vigilância em Saúde e Ambiente
Departamento do Programa Nacional de Imunizações
Coordenação-Geral de Incorporação Científica e Imunização

NOTA TÉCNICA Nº 41/2024-CGICI/DPNI/SVSA/MS

Atualização das recomendações da vacinação
contra HPV no Brasil.

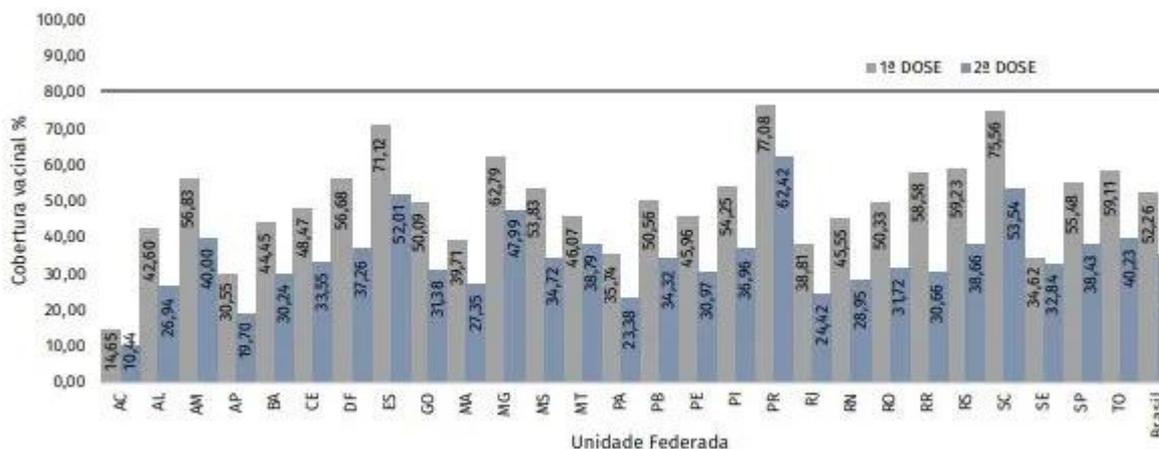
1. Available at https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/c/calendario-nacional-de-vacinacao/calendario-vacinal-2022/anexo-calendario-de-vacinacao-da-crianca_atualizado_final-20-09-2022.pdf [Accessed 13 September 2023].
2. Available at <https://www.vacina100duvidas.sp.gov.br/> [Accessed 13 September 2023].
3. <https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/notas-tecnicas/2024/nota-tecnica-no-41-2024-cgici-dpni-svsa-ms>

Vaccination in Brazil

(SI-PNI, Ministry of Health 2023)



Fonte: Sistema de Informação do Programa Nacional de Imunizações (SIPNI) - 11/1/2023



Fonte: Sistema de Informação do Programa Nacional de Imunizações (SIPNI) - 11/1/2023

Vaccination in Brazil

Atualização do painel em 25/06/2025 às 08:40:08.

Cobertura

Evolução

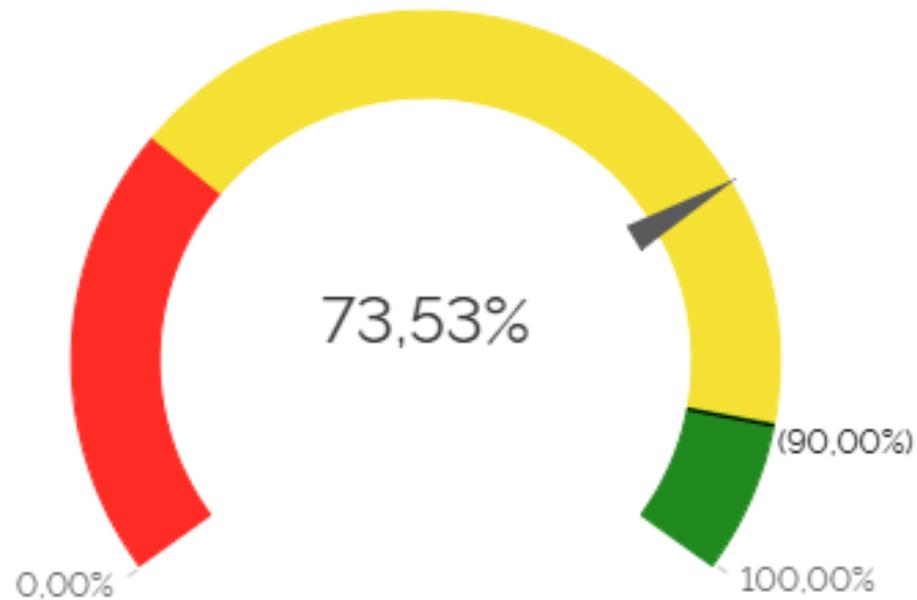
Tabelas

Feminino

Masculino

ANO
2025

Cobertura de 9 a 14 Anos - Nascidos entre 2011 e 2016



Vaccination in Brazil

Atualização do painel em 25/06/2025 às 08:40:08.

Cobertura

Evolução

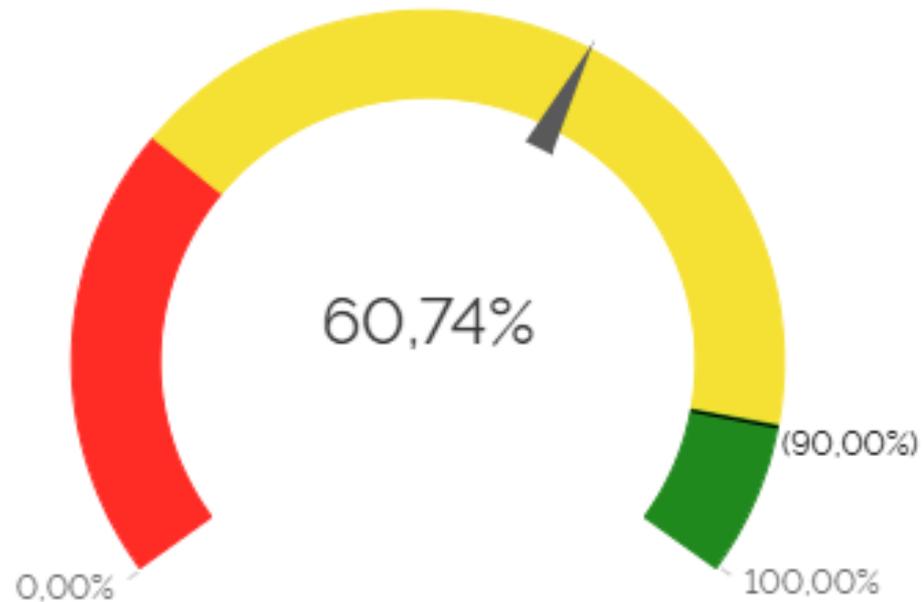
Tabelas

Feminino

Masculino

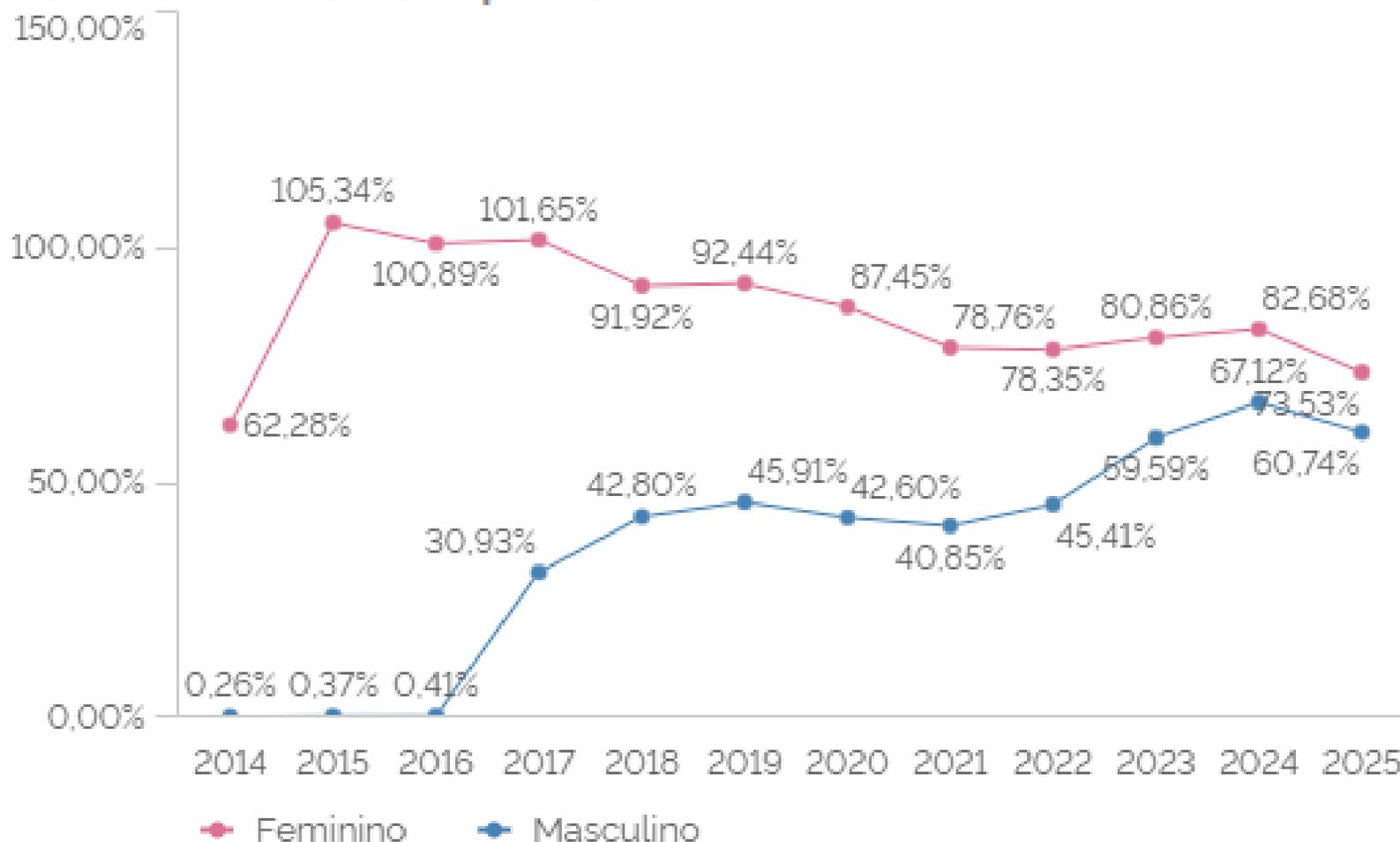
ANO
2025

Cobertura 9 de 14 Anos - Nascidos entre 2011 e 2016



Vaccination in Brazil

Cobertura de 9 a 14 Anos por Sexo



The fight against cervical cancer

WHO's initiative to eliminate cervical cancer worldwide through three actions: vaccination against HPV, screening and treatment of precancerous lesions and management of invasive cervical cancer. Goals until 2030 are:

- To achieve 90% vaccination coverage among girls up to 15 years of age;
- To achieve 70% screening coverage with a high-performance test (at 35 and again at 45 yo);
- To achieve a treatment rate of 90% for women with treated pre-cancer and women with invasive cancer.

In summary, prophylactic vaccines against HPV:

- Are effective in preventing infection.
- Are effective in preventing precursor .
- Are safe..
- But...do they reach those who need them most?
- Duration of protection?
- Do not substitute screening programs.

Obrigado