GIFIL

CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Starhotels Anderson

24 maggio 2024

Patogenesi dei linfomi nei pazienti con immunodeficit

Viruses and Lymphomagenesis

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CRO AVIANO

Disclosures of Riccardo Bomben

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

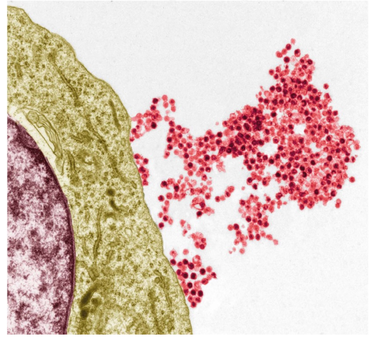
- How do viruses cause lymphomagenesis?
- Do viruses interact with each other for lymphomagenesis?
- Does lymphoma still need viruses after lymphomagenesis?

- How do viruses cause lymphomagenesis?
- **EBV**
- Do viruses interact with each other for lymphomagenesis?
- **HIV**
- Does lymphoma still need viruses after lymphomagenesis?
- **HCV**

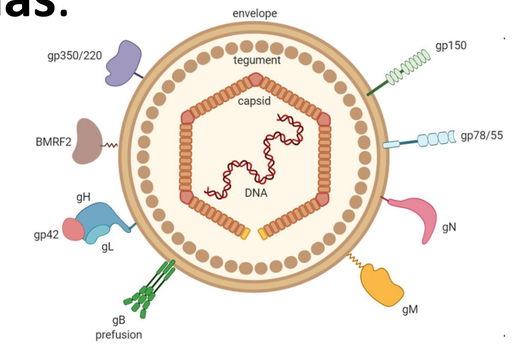
- EBV
- HIV
- HCV

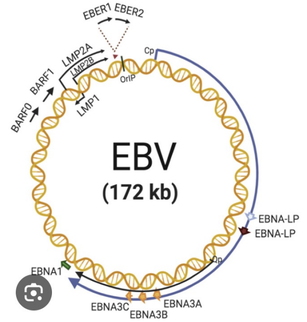
Epstein–Barr virus (EBV) a.k.a. human herpesvirus 4 (HHV4)

- originally identified in 1964 by Sir Anthony Epstein and co-workers in Burkitt's lymphoma;
- γ-herpesviridae subfamily;
- large double-stranded DNA virus;
- persists in human cells for a lifetime;
- 90-95% of the world's population sustaining an asymptomatic infection;
- a WHO class I carcinogen;
- cause 1–2% of all tumours in humans and ~200,000 new cancers per year;
- primarily associated with epithelial cell cancers and **lymphomas**.



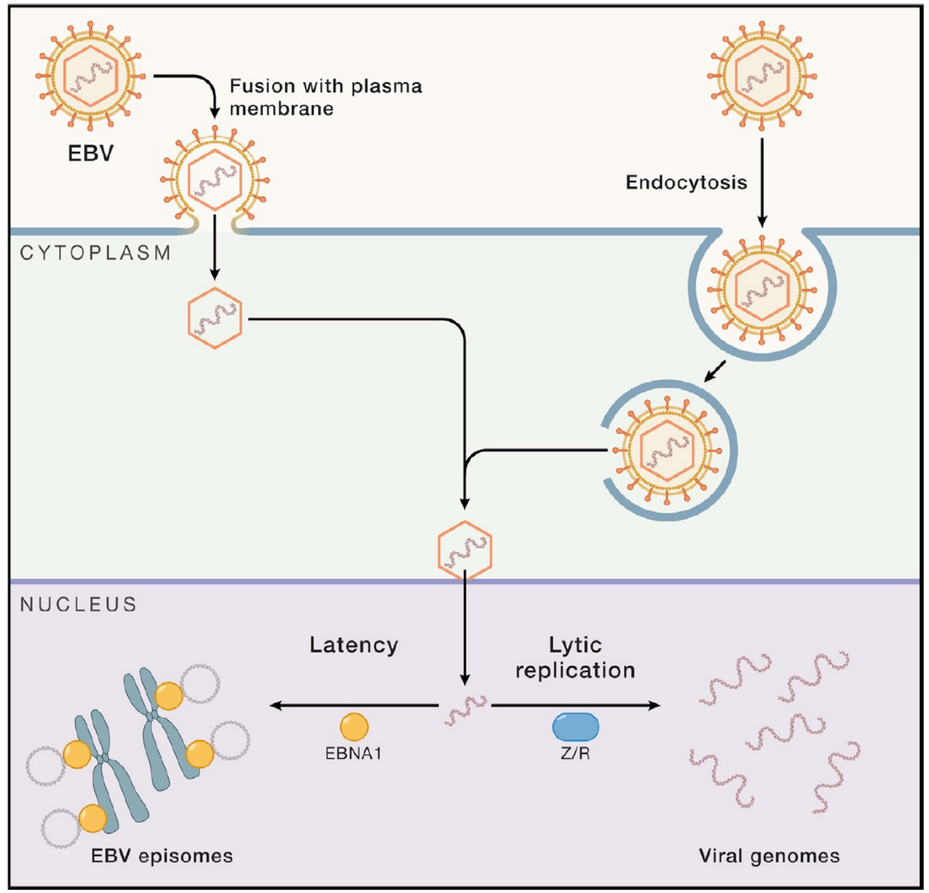
Epstein M., et al. Lancet 1964



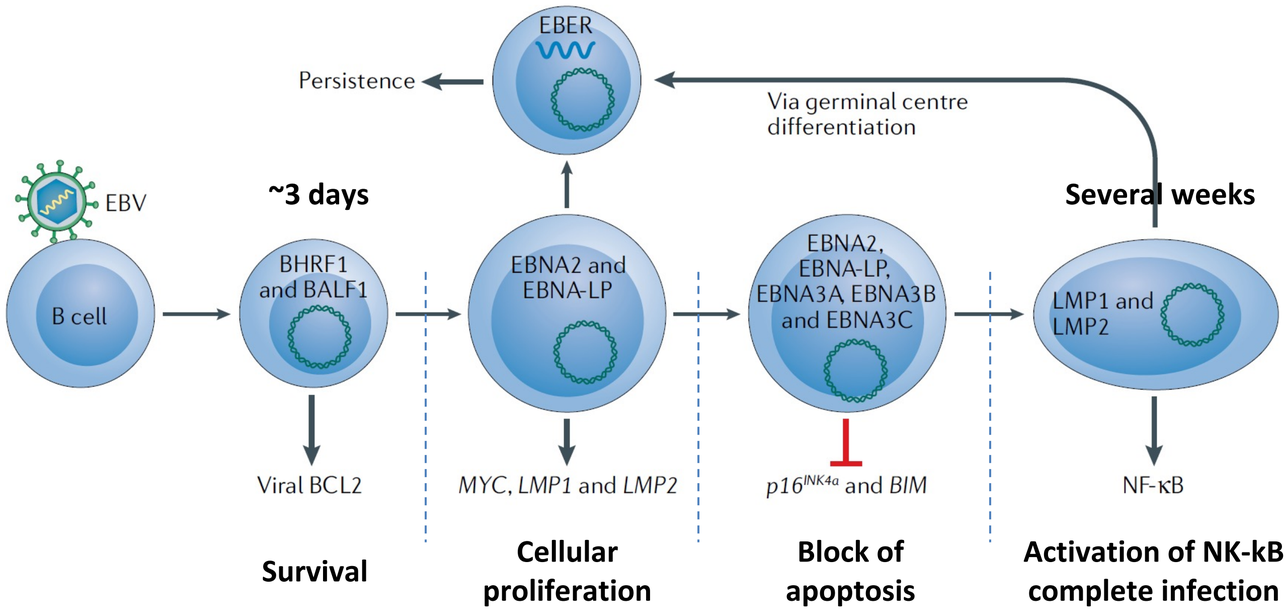


Jean-Pierre V., et al. Frontiers in Immunology 2021

The life cycle of EBV

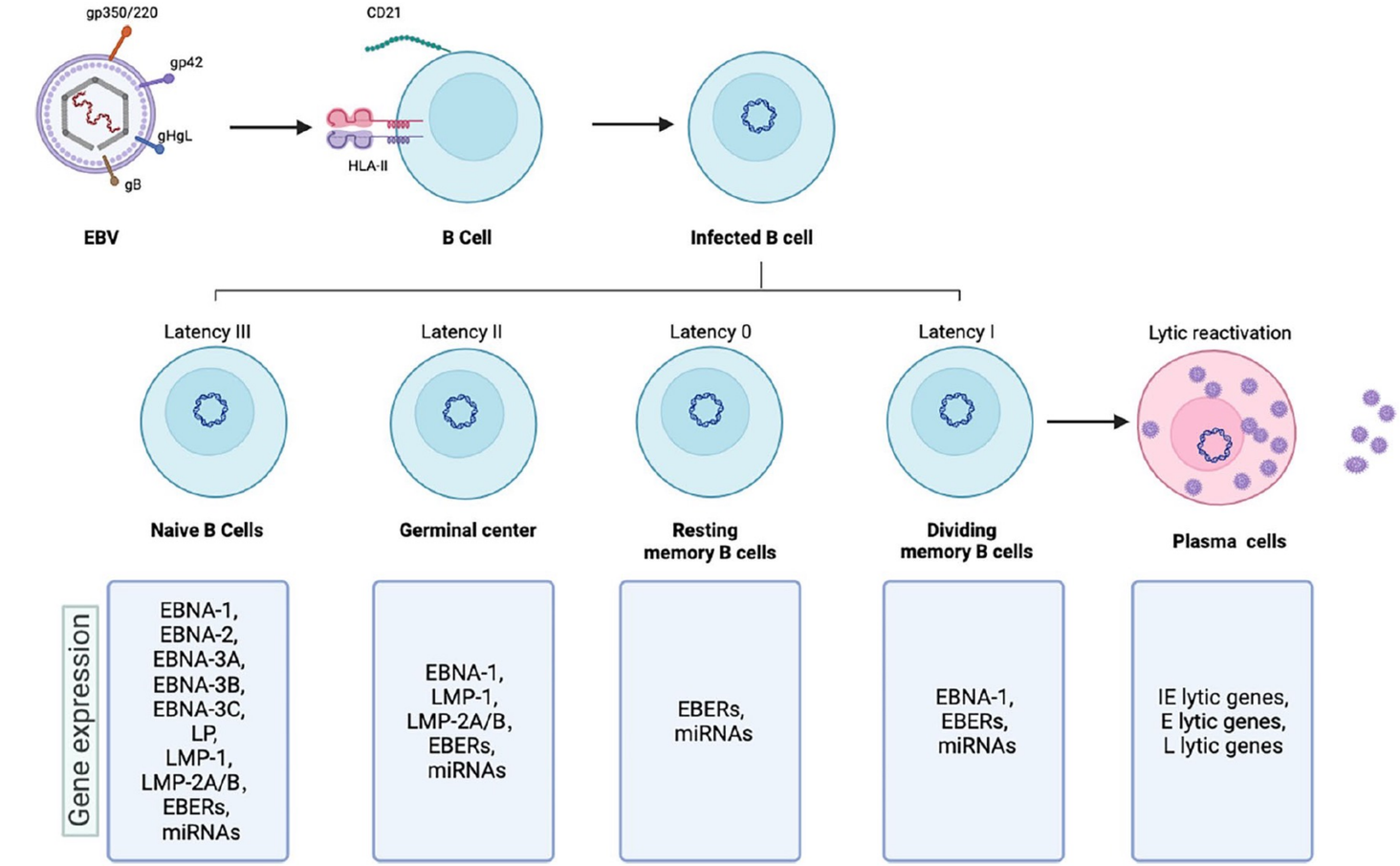


Damania B., et al. Cell 2022



Munz C., Nature Reviews 2019

Interactions of EBV with B cells



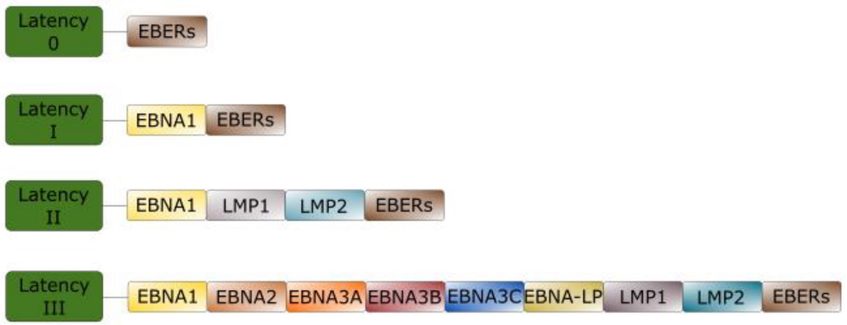
Huang W., et al. Virology Journal 2023

EBV associated cancers

Table 1. EBV-associated cancers, latency type, and viral gene expression

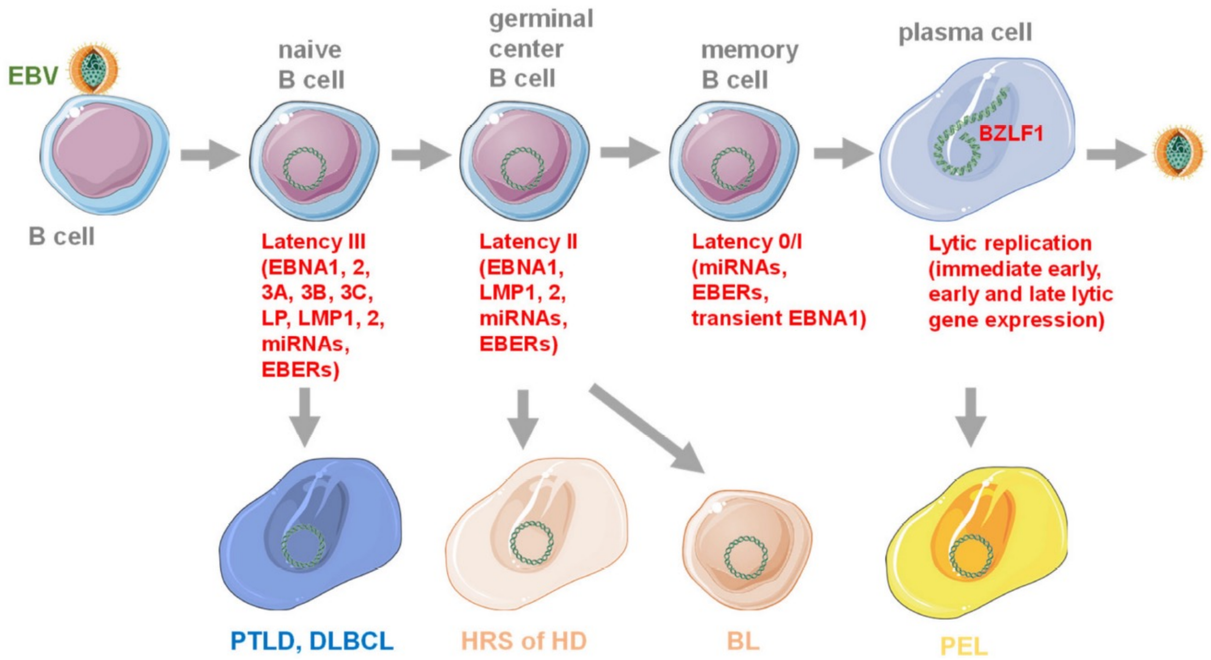
EBV-associated disease	Latency type	EBV viral gene expression
Healthy individuals (resting EBV-infected B cells)	0	EBERs, BARTs
Burkitt lymphoma (BL)	I	EBERs, BARTs, EBNA1
Gastric carcinoma	I or II	EBERs, BARTs, EBNA1
Hodgkin lymphoma (HL)	II	EBERs, BARTs, EBNA1, LMP1, LMP2
NK/T cell lymphoma (NKTL)	II	EBERs, BARTs, EBNA1, LMP1, LMP2
Nasopharyngeal carcinoma (NPC)	II	EBERs, BARTs, EBNA1, LMP1, LMP2
Diffused large B cell lymphoma (DLBCL)	II or III	EBERs, BARTs, EBNA1, EBNA2, EBNA3A,B,C, EBNA-LP, BHRF1 miRNAs
HIV-associated lymphomas	III	EBERs, BARTs, EBNA1, LMP1, LMP2, EBNA2, EBNA3A,B,C, EBNA-LP, BHRF1 miRNAs
Post-transplant lymphoproliferative disease (PTLD)	III	EBERs, BARTs, EBNA1, LMP1, LMP2, EBNA2, EBNA3A,B,C, EBNA-LP, BHRF1 miRNAs

Damania B., et al. Cell 2022

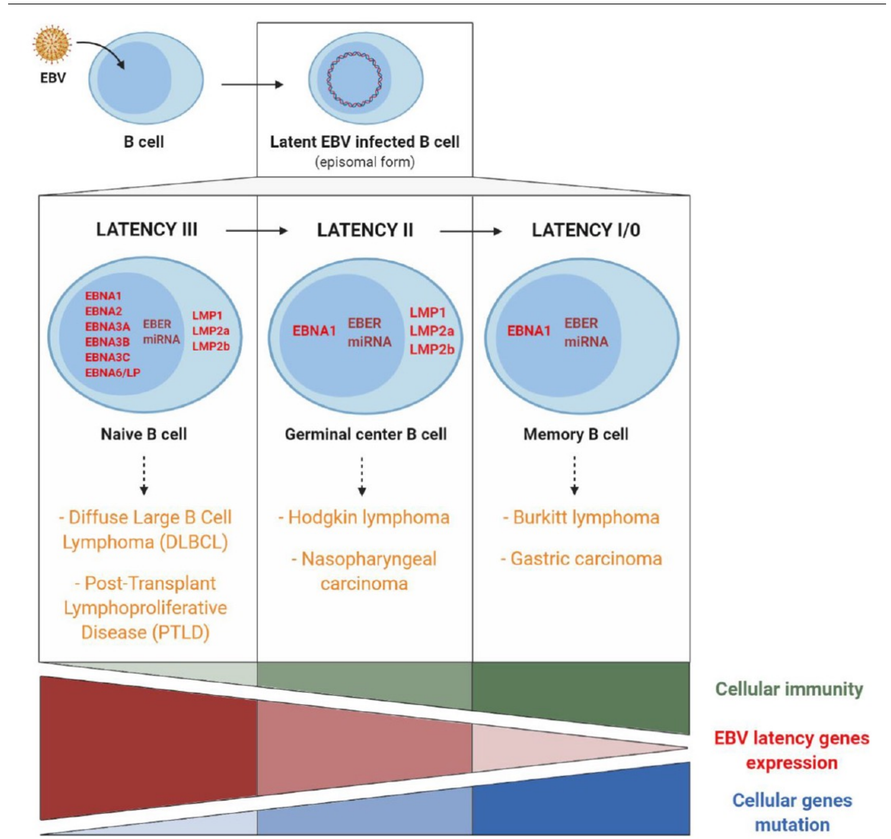


Sausen D., et al. Cancers 2023

Why so many associated lymphomas?

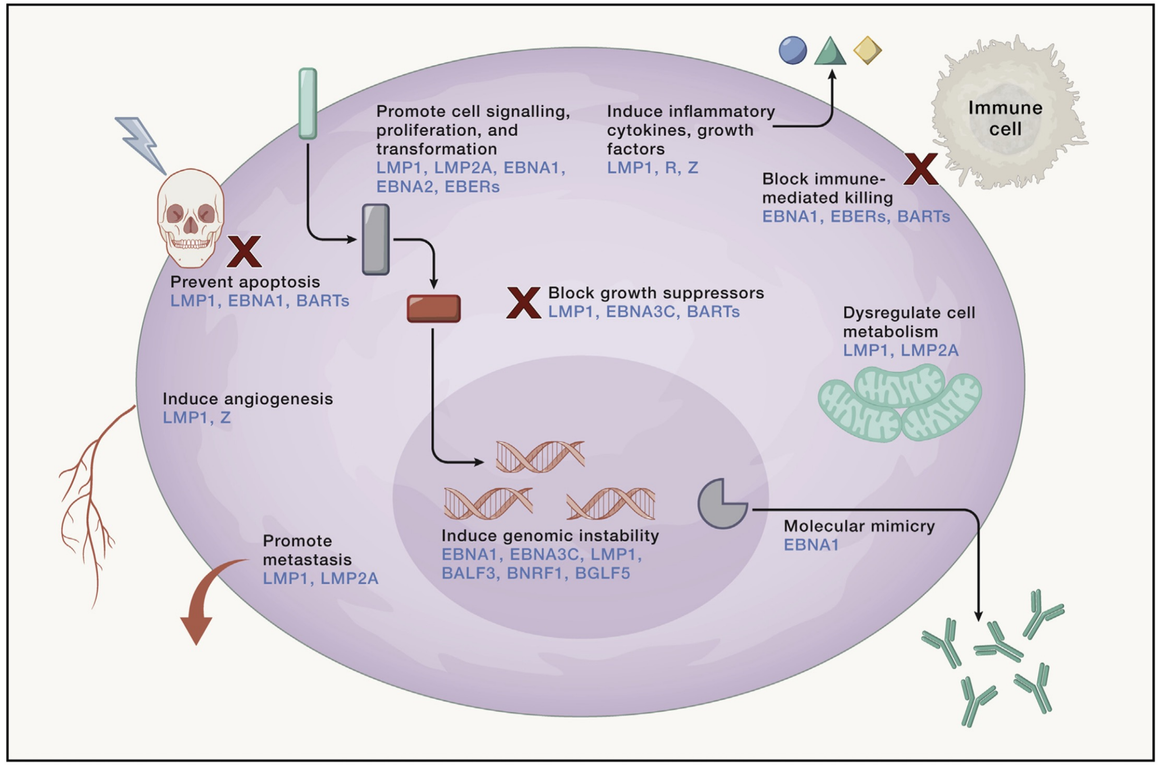


Munz C. Cells 2020

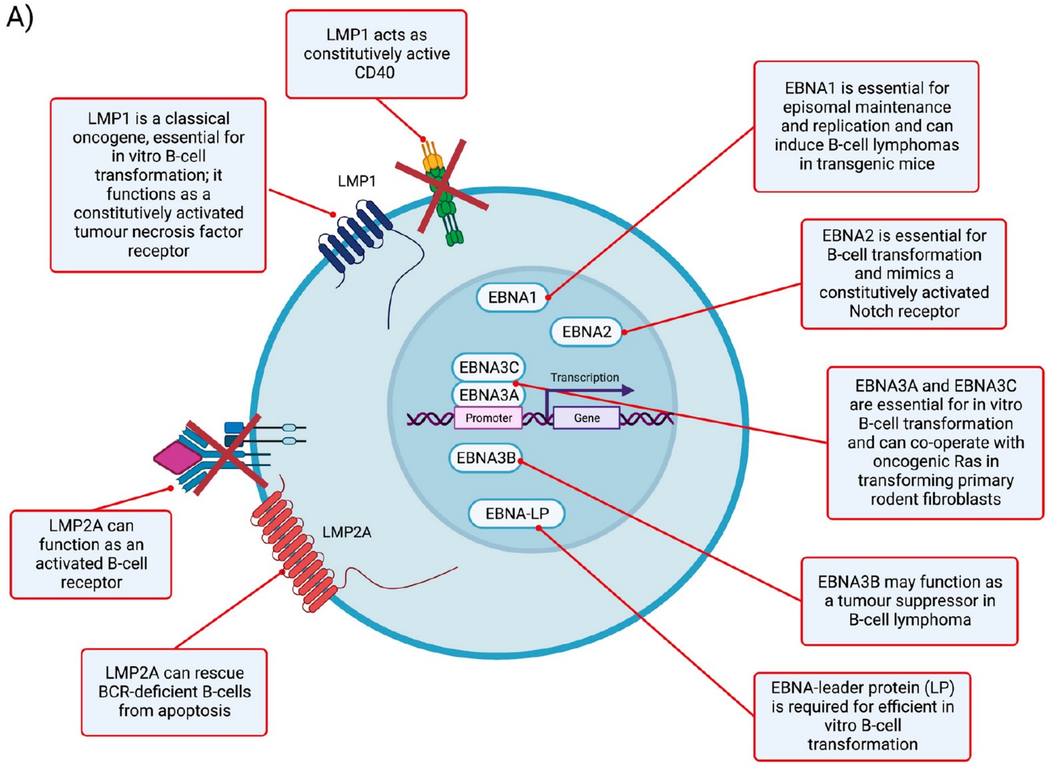


Jean-Pierre V,. et al. Frontiers in Immunology 2021

EBV mechanisms of lymphomagenesis

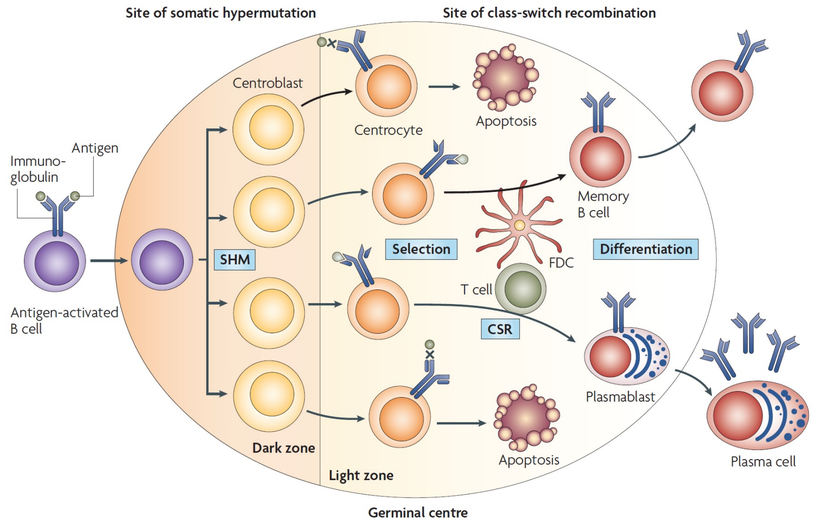


Damania B., et al. Cell 2022



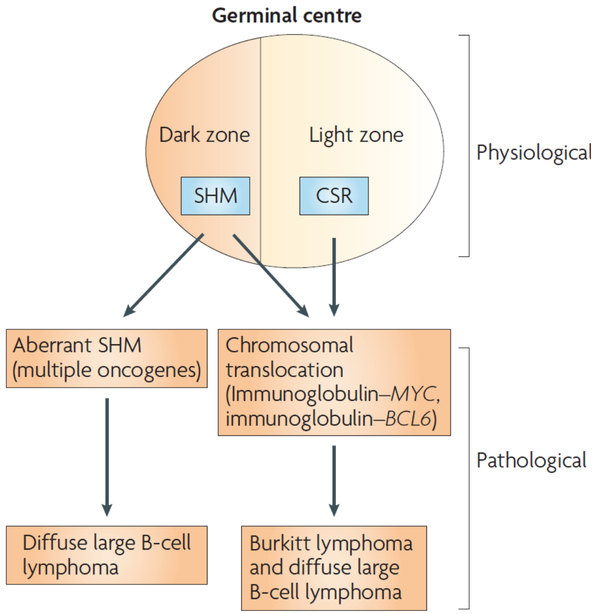
Ross A., et al. Life 2023

AID

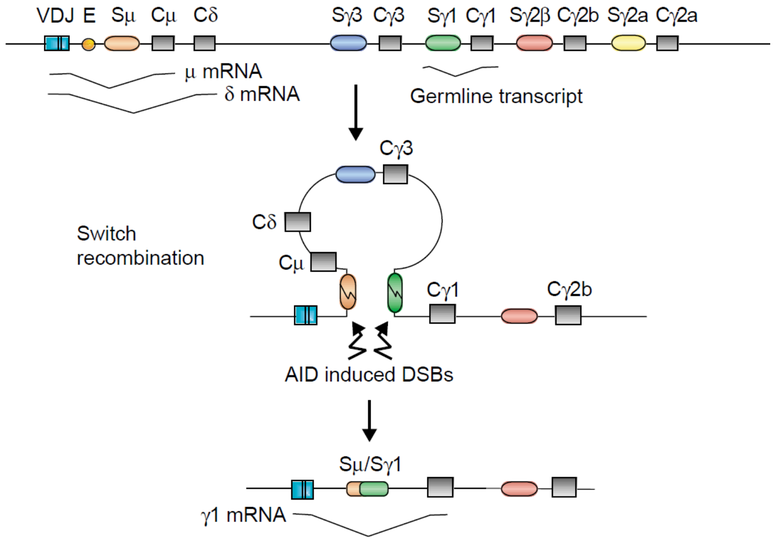


Klein U., et al. Nature Reviews 2008

CSR → Activation Induced Cytidine Deaminase

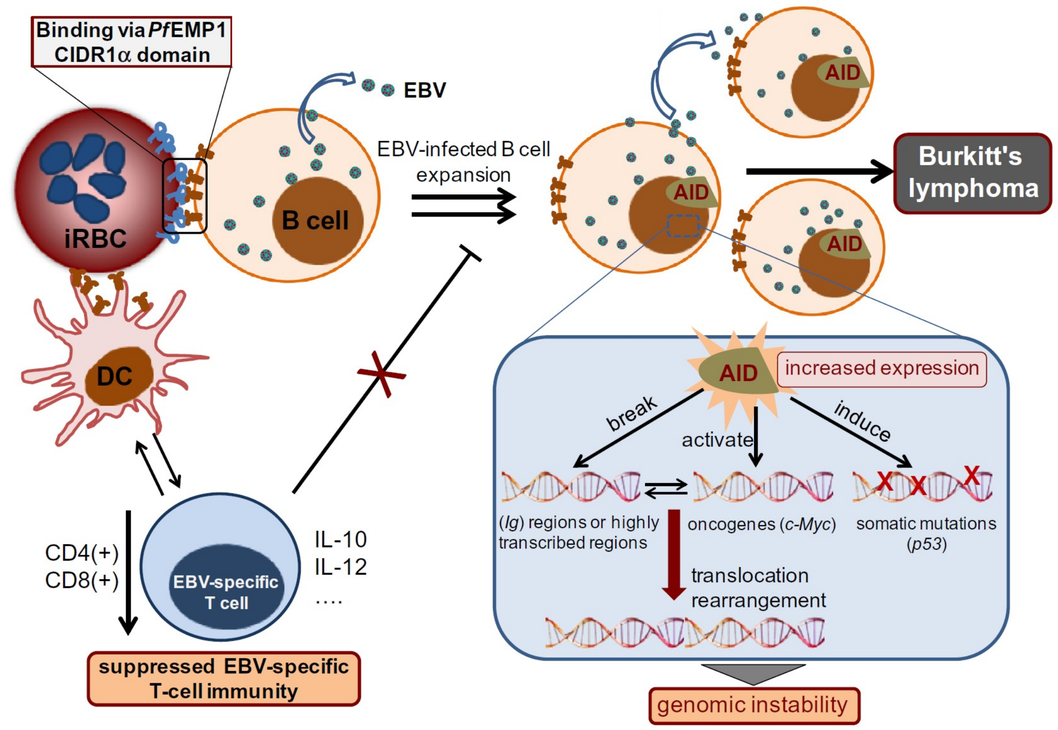


Klein U., et al. Nature Reviews 2008

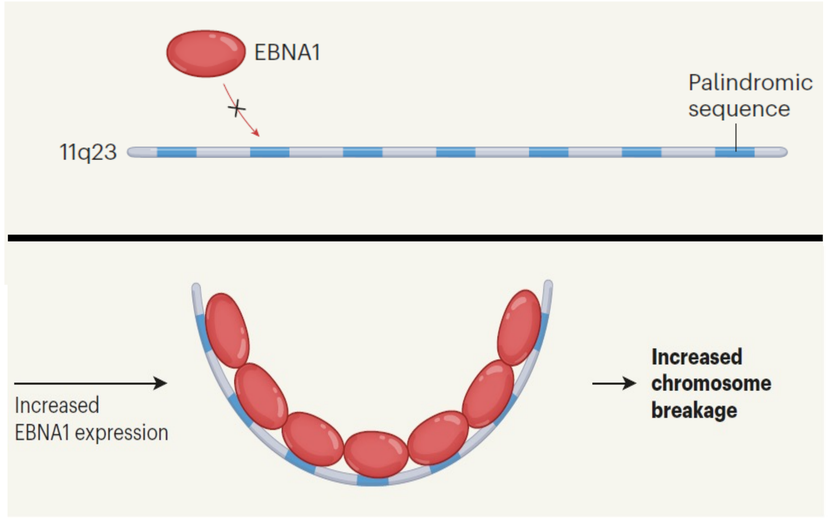


Kenter A., Current Opinion 2003

Burkitt lymphoma and c-Myc translocation



van Tong H., et al. EBioMedicine 2016



Frappier L., et al. Cancer 2023

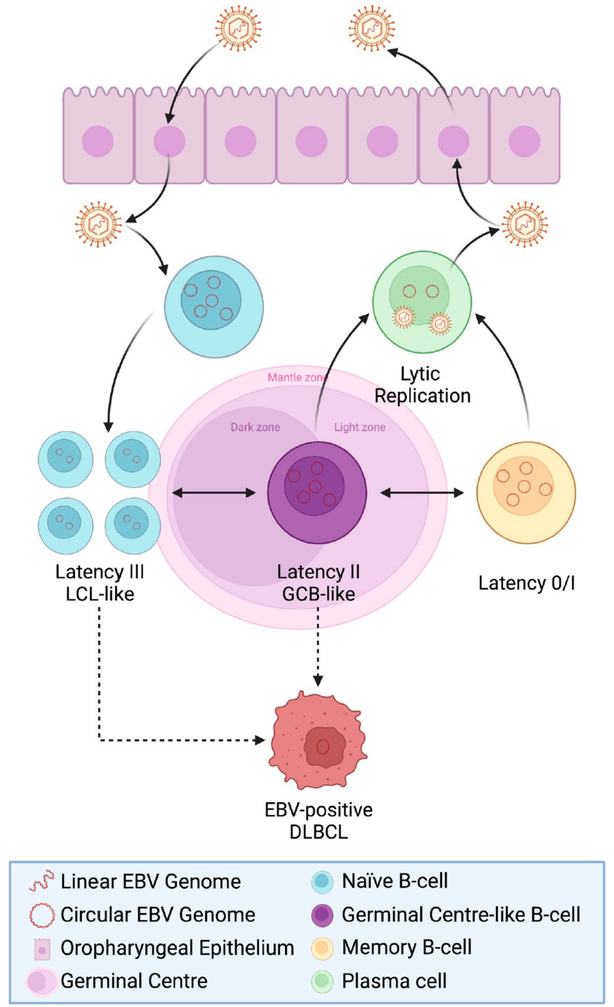
AID ↑ ↓ Apoptosis

- EBV-positive BLs most frequently occur in sub-Sahara Africa;
- Greater than 90% of BLs in this region (‘‘endemic’’ BLs) are EBV-infected;
- BLs in other parts of the world (‘‘sporadic’’ BLs) are usually EBV-negative;
- In BL endemic Plasmodium falciparum malaria infection is very common;
- P. falciparum infection contribute to the development of EBV positive BLs by inducing polyclonal B cell activation;
- enhancing AID expression in GC B cells;
- greatly increasing the number of EBV-infected B cells.

Damania B., et al. Cell 2022

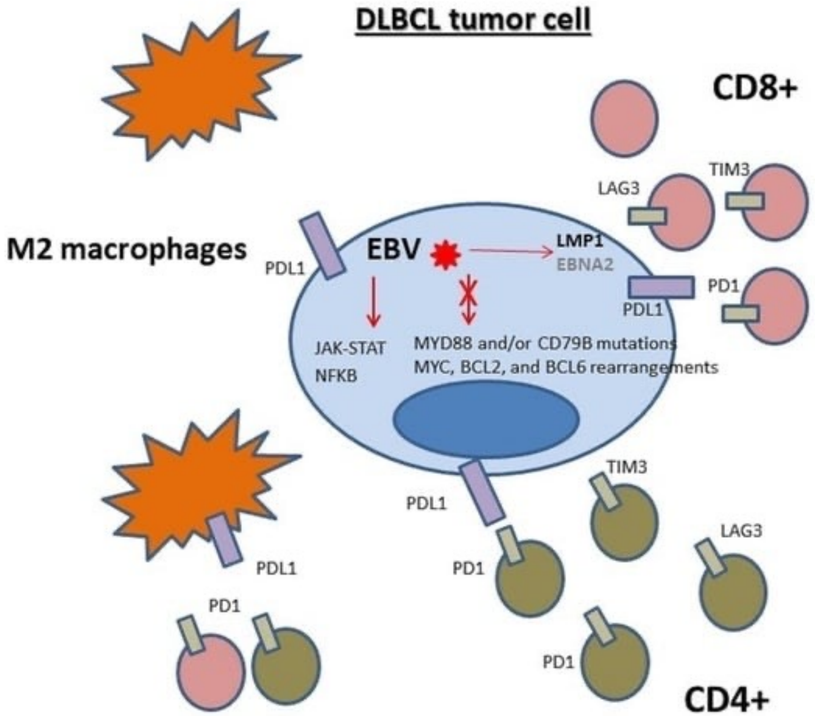
Diffuse Large B-Cell Lymphoma

- The presence of EBV in DLBCL is relatively rare (approx. 5–15% of DLBCL tumours are diagnosed as EBV+);
- EBV+DLBCL associated with poorer outcomes even after adjusting for confounding factors;
- Higher presence in ABC DLBCL substype;
- (Usually) The pathogenic mechanisms in EBV-positive DLBCL is enhanced NFκB activity.

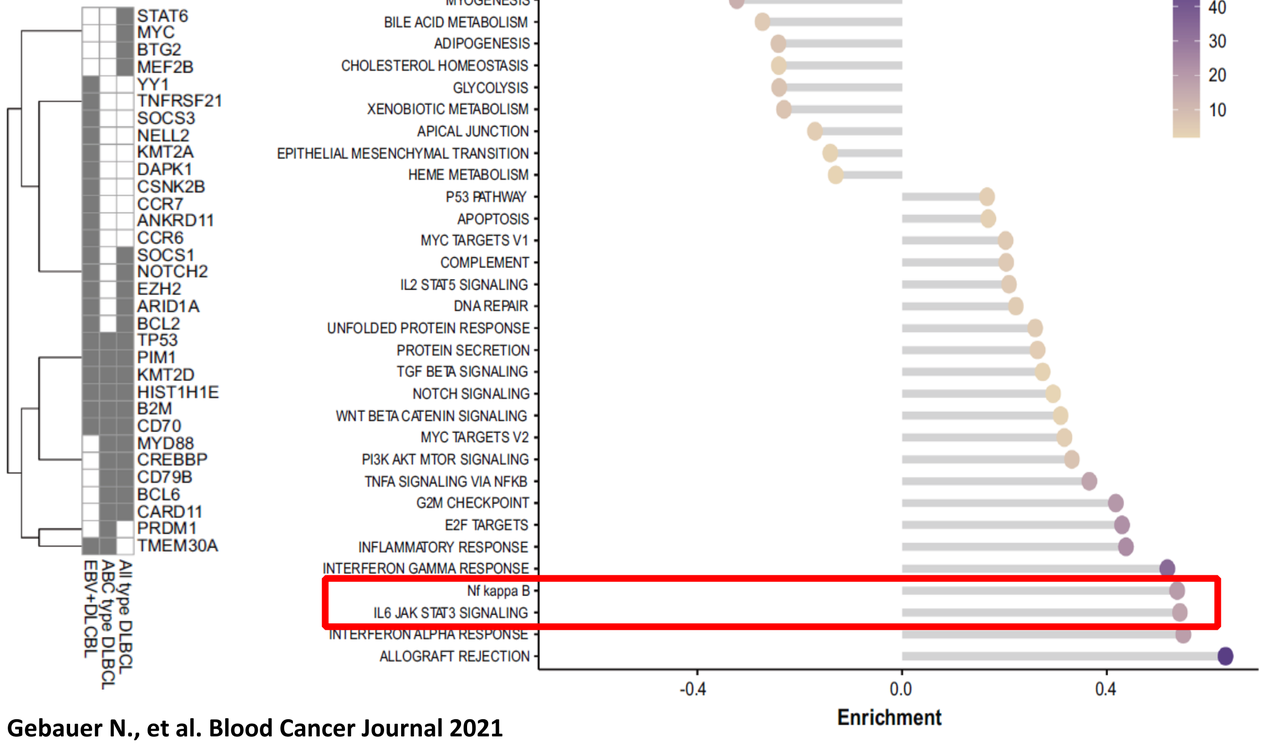


Ross A., et al. Life 2023

Diffuse Large B-Cell Lymphoma



Chabay P., Cancers 2021



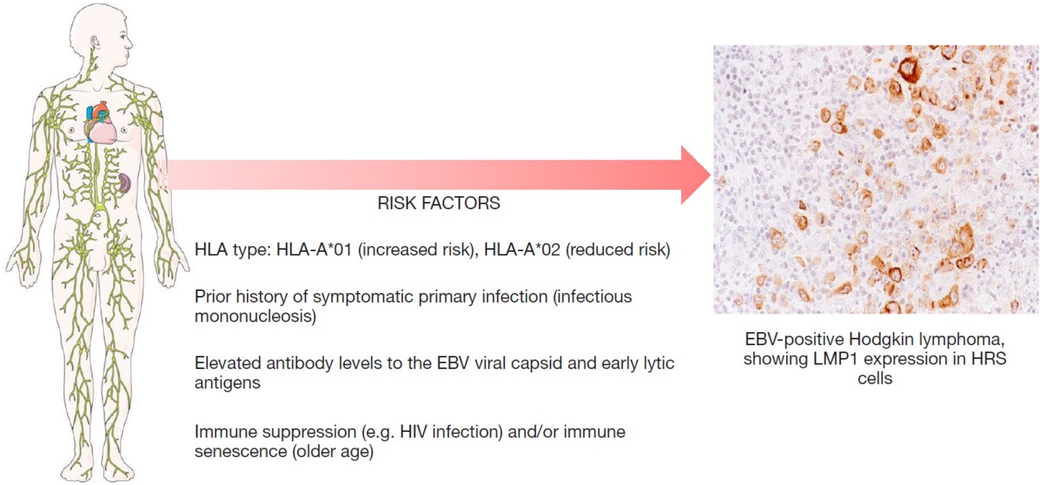
Gebauer N., et al. Blood Cancer Journal 2021

EBV+DLBCL TET2, DNMT3A ↑ MYD88, CD79B ↓ — Mutations

MYC, BCL2, BCL6 ↓ — CNA

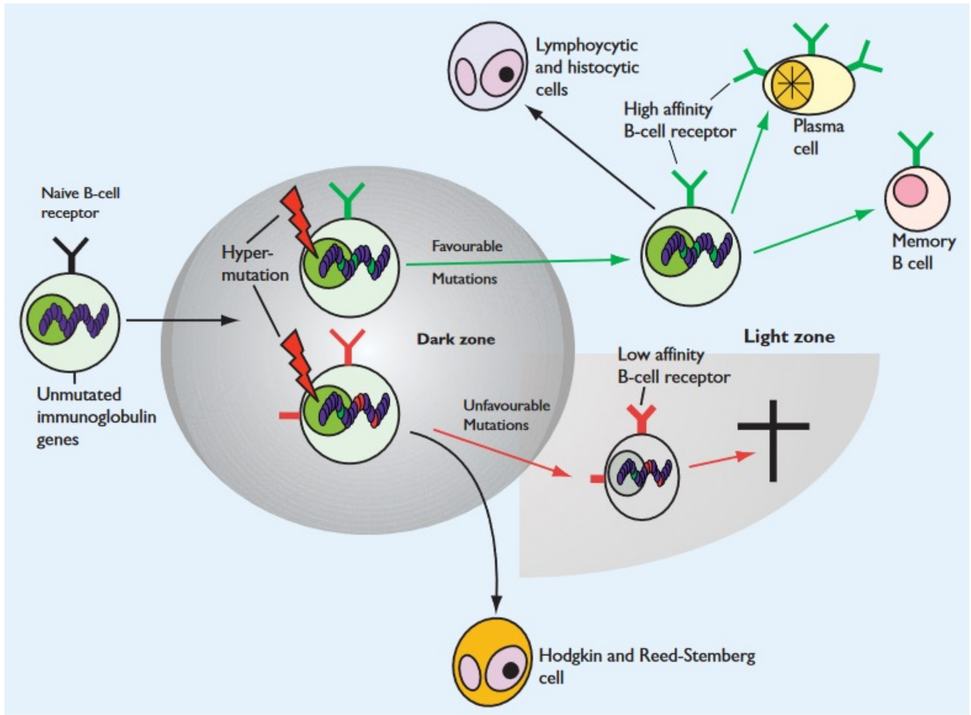
Hodgkin Lymphoma

- In 30%-40% of cHLs HRS cells have evidence of latent EBV infection and associated expression of LMP1 and LMP2;
- constitutes the best-established etiological factor in cHL.



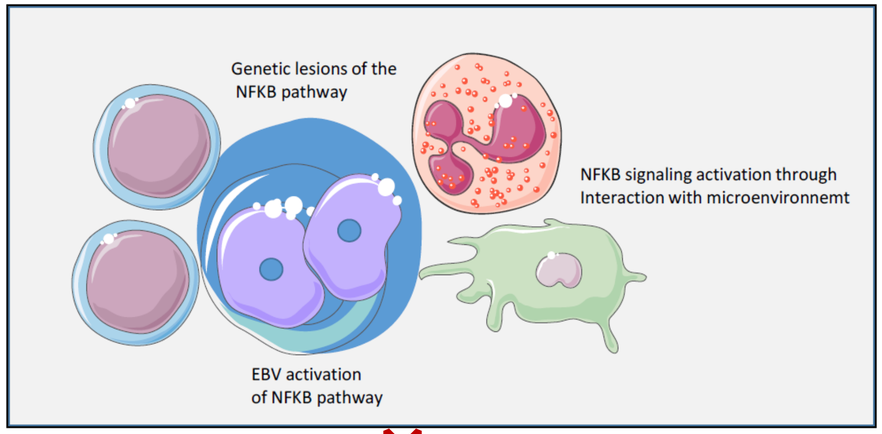
EBV-positive Hodgkin lymphoma, showing LMP1 expression in HRS cells

Vrzalikova K., et al. Annals of Lymphoma 2021



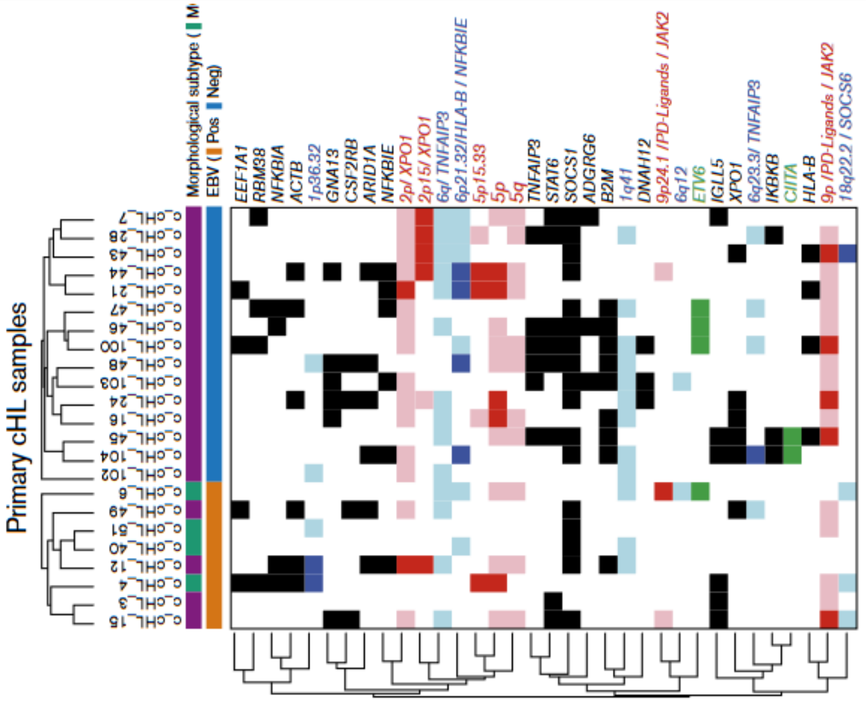
Thomas R., et al. The Lancet Oncology 2004

Hodgkin Lymphoma: mutations and NFkB pathway



Apoptosis / cell proliferation
JAK/STAT pathway activation
B-cell markers expression loss
Microenvironment cross-talk
Immune escape
Positive NFKB feed back loop

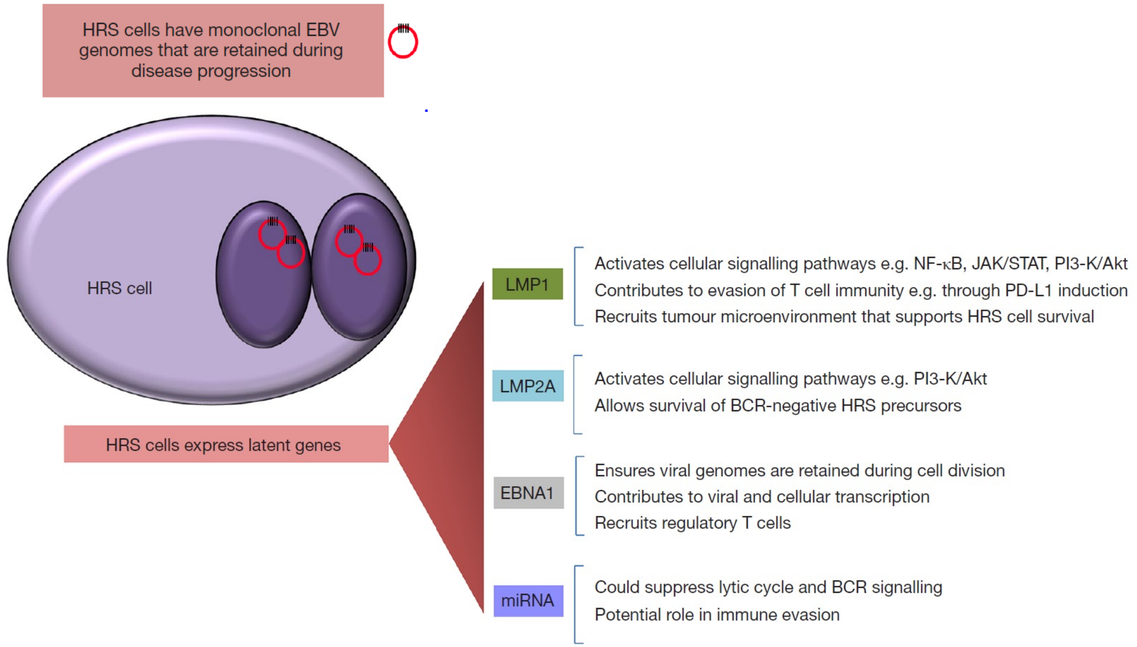
Jardin F. Biomedicines 2022



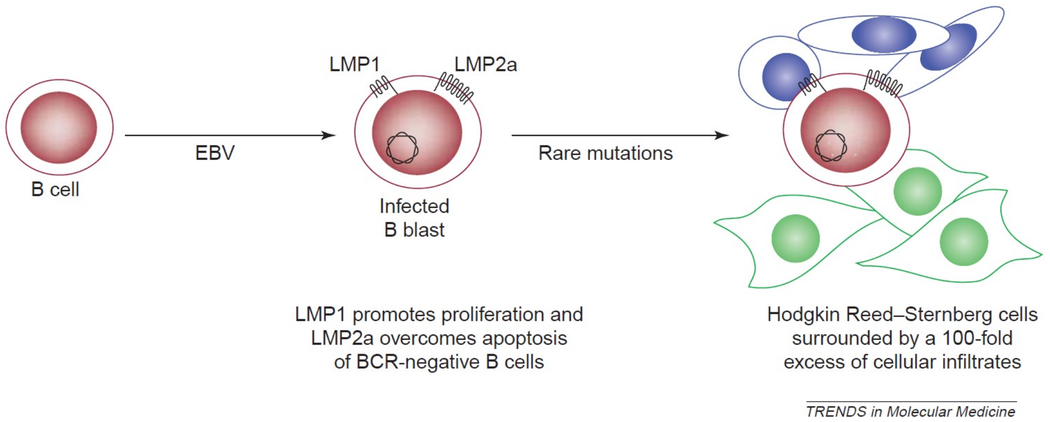
- EBV-positive cHLs exibites less mutational burden than EBV-negative;
- EBV– negative cHLs have more exhibit genetic alterations of specific NF-kB signaling and MHC class I antigen presentation;
- EBV-positive HRS cells express LMP1, which activates NFkB.

Wienand K., et al. Blood Advances 2019

Hodgkin Lymphoma

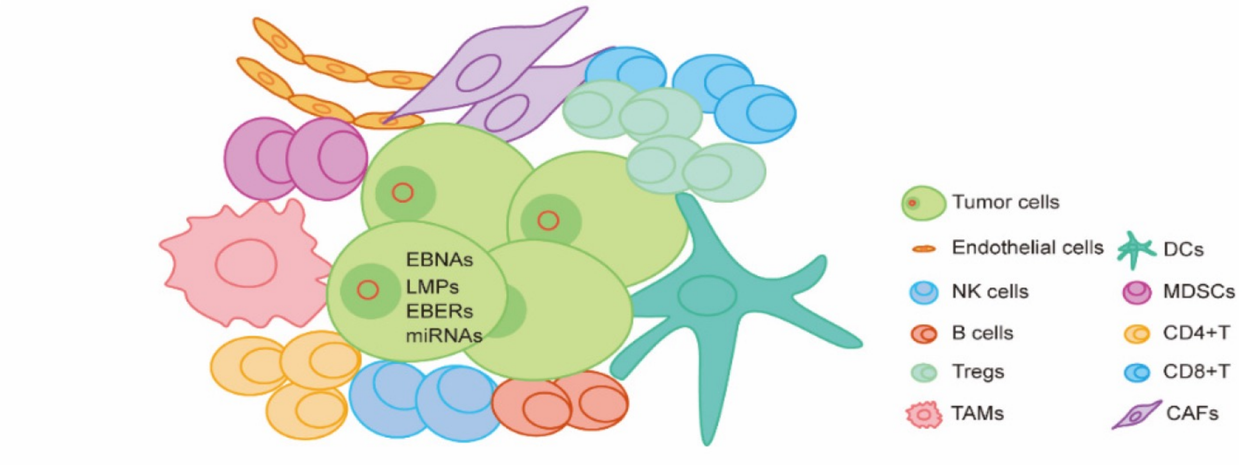


Vrzalikova K., et al. Annals of Lymphoma 2021



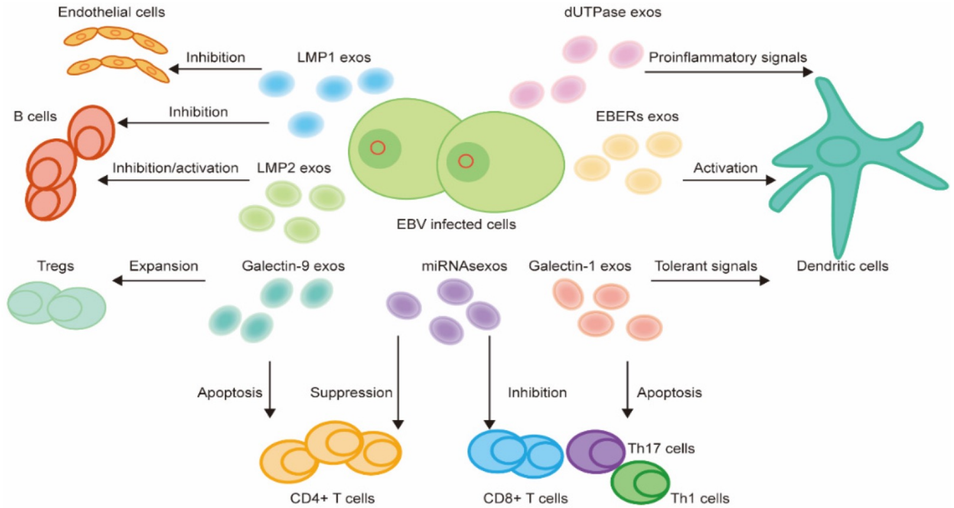
- LMP1 is a constitutively active CD40 receptor homolog;
- LMP2A is a BCR mimic that allows B-cell development in the absence of normal BCR signaling.

EBV and Microenvironmental interactions.

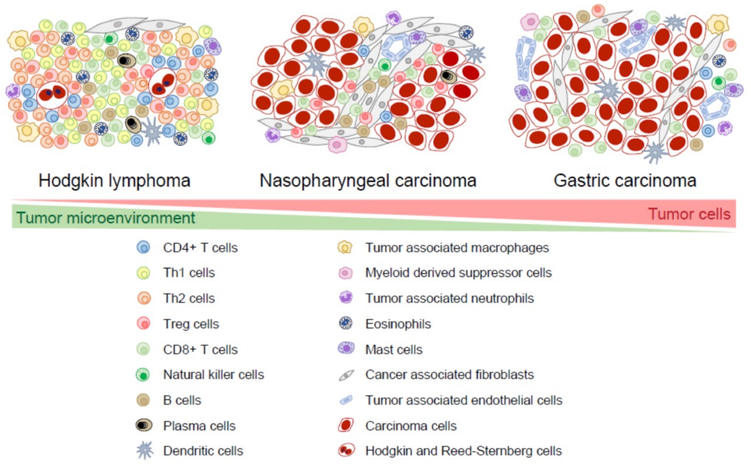


Cellular components	Molecular componets	Extracellular vesicles
Effective CD8+T cells ↓ Exhausted CD8+T cells ↑ Tregs ↑ M2 TAMs ↑ CAFs ↑ MDSCs ↑ LAMP3+ DCs ↑ NK cells ↓ Endothelial cells ↑	Pro-inflammatory factors: IFN-γ, IP10, IL-1β, TNF-α ↑ Immunosuppressive factors: IL-4, IL-6, IL-8, IL-10, IL-13 ↑ Galectin-1 ↑ Immune checkpoints: PD-1, PD-L1, PD-L2, CTLA-4 ↑	LMP1 LMP2 EBERs miRNAs dUTPase Galectin-1 Galectin-9

Zheng X., et al. Viruses 2022



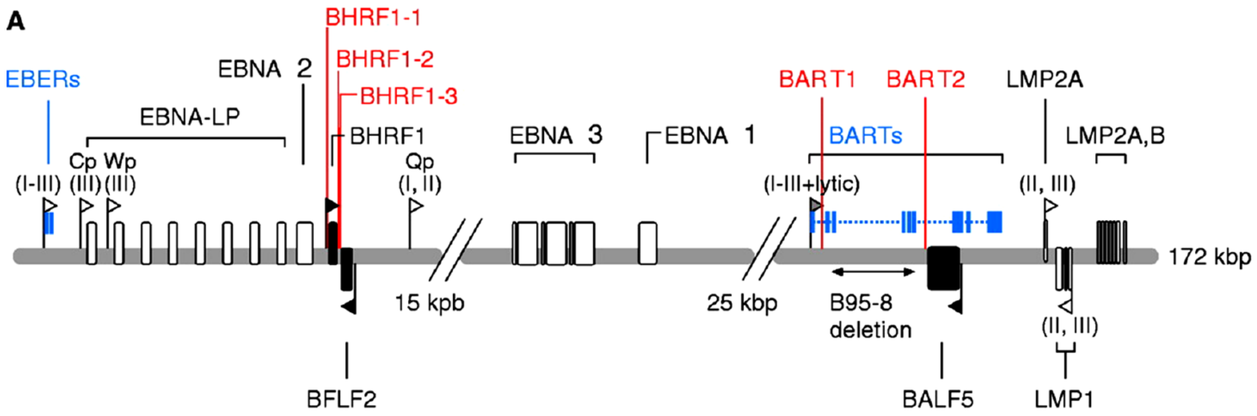
Zheng X., et al. Viruses 2022



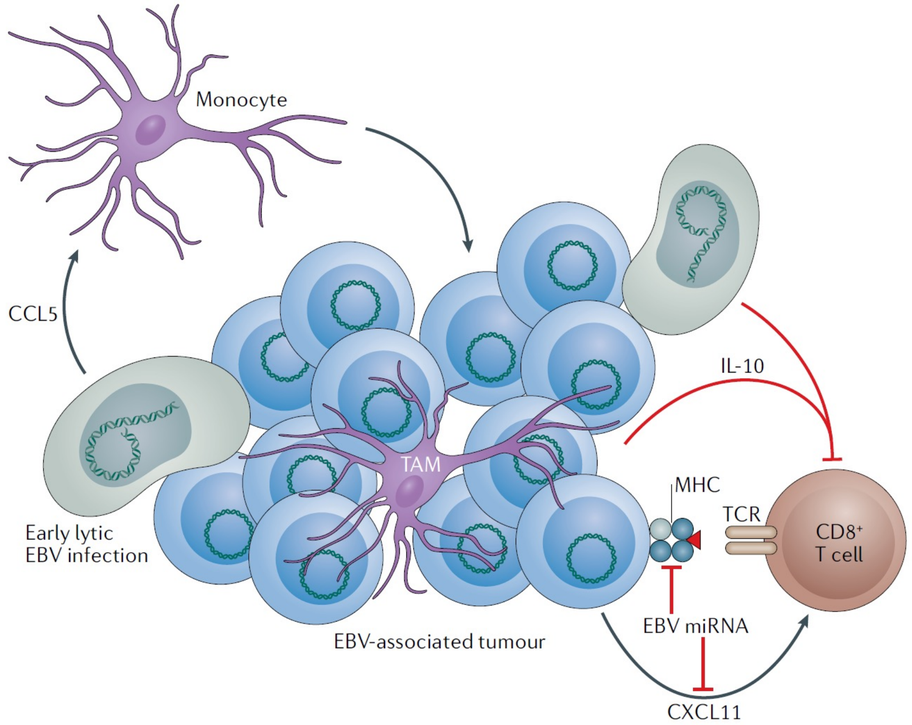
Wee Tan G., et al. Pathogens 2022

Potential functions of EBV non-coding RNAs

EBV can encode approximately 23 precursors and 44 mature miRNAs from 2 cluster



Yin H., et al. Medical Microbiology and Immunology 2019



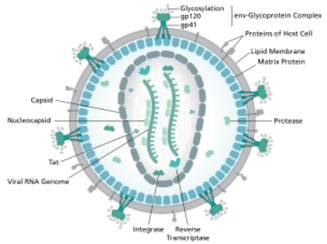
Munz C., Nature Reviews 2019

- EBV
- HIV
- HCV

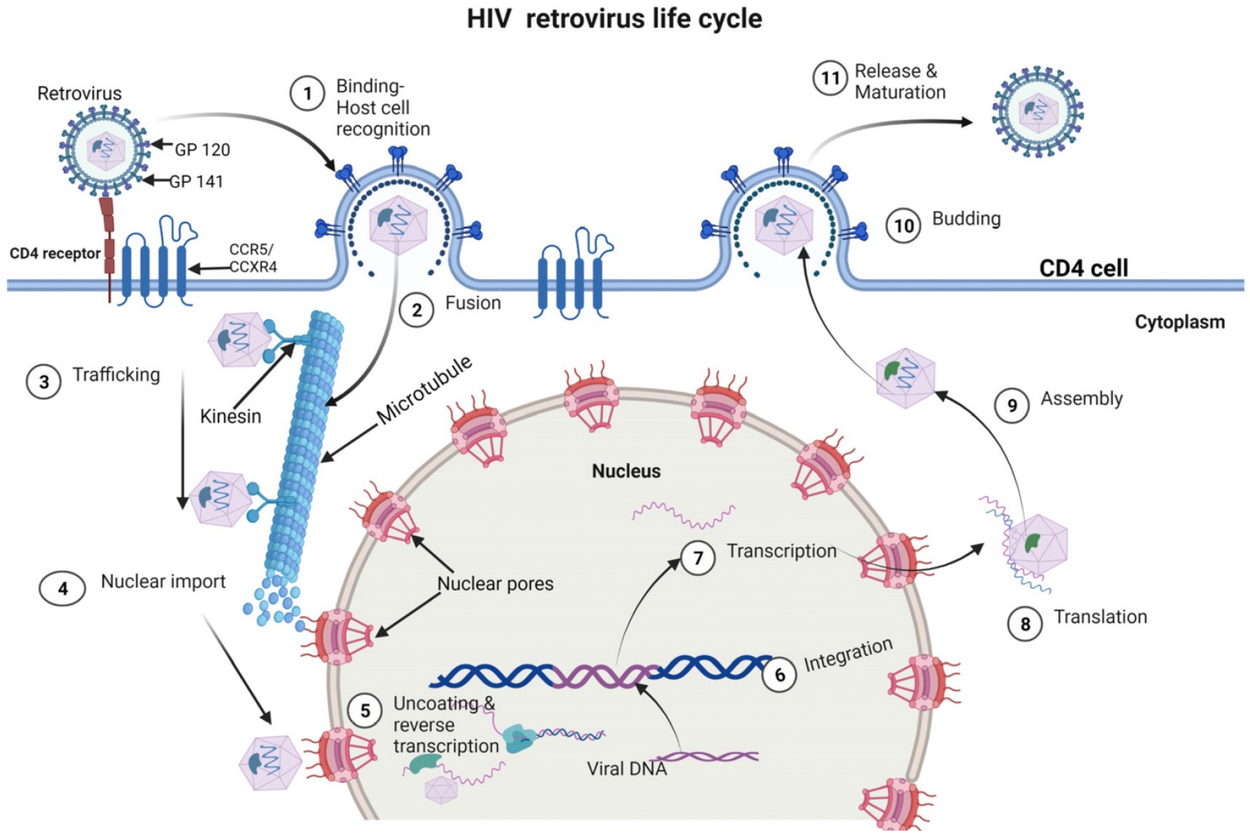
Human immunodeficiency virus (HIV)

- Lentivirus belonging to the retroviridae;
- responsible for the HIV/AIDS pandemic;
- existed as far 1920s;
- two copies of positive-sense single-stranded RNA, only 9 genes for 19 protein;
- persists in human cells for a lifetime;
- divided into two types: HIV-1 and HIV-2. HIV-1 is the most virulent and widespread;
- X4 HIV-1 affinity for the CXCR4, R5 HIV-1 affinity for the CCR5.

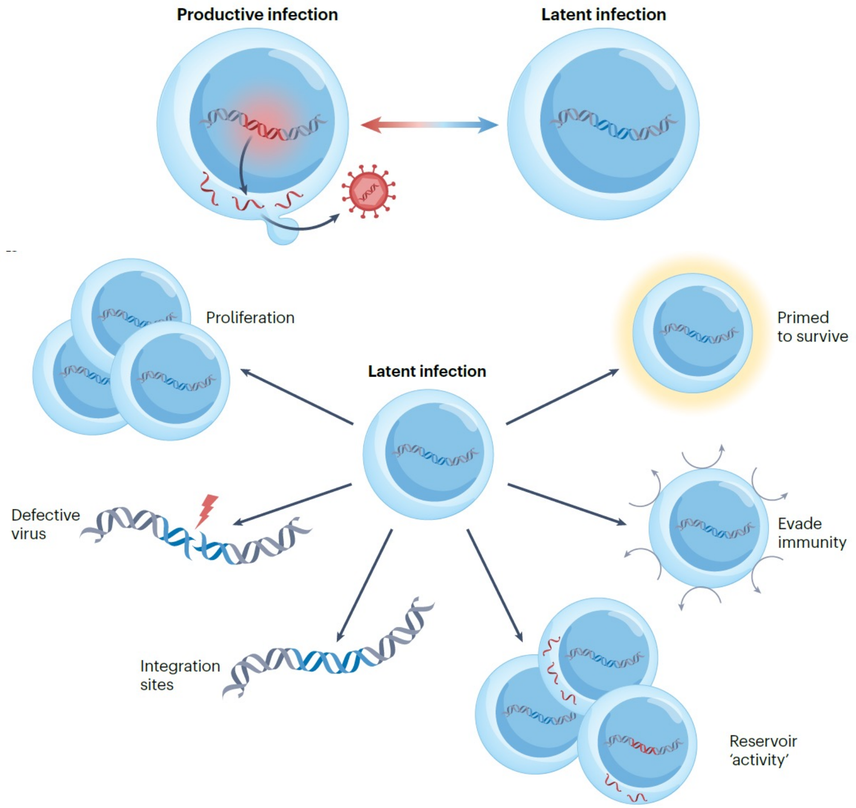
Species	Virulence	Infectivity	Prevalence	Inferred origin
HIV-1	High	High	Global	Common chimpanzee
HIV-2	Lower	Low	West Africa	Sooty mangabey



The life cycle of HIV-1

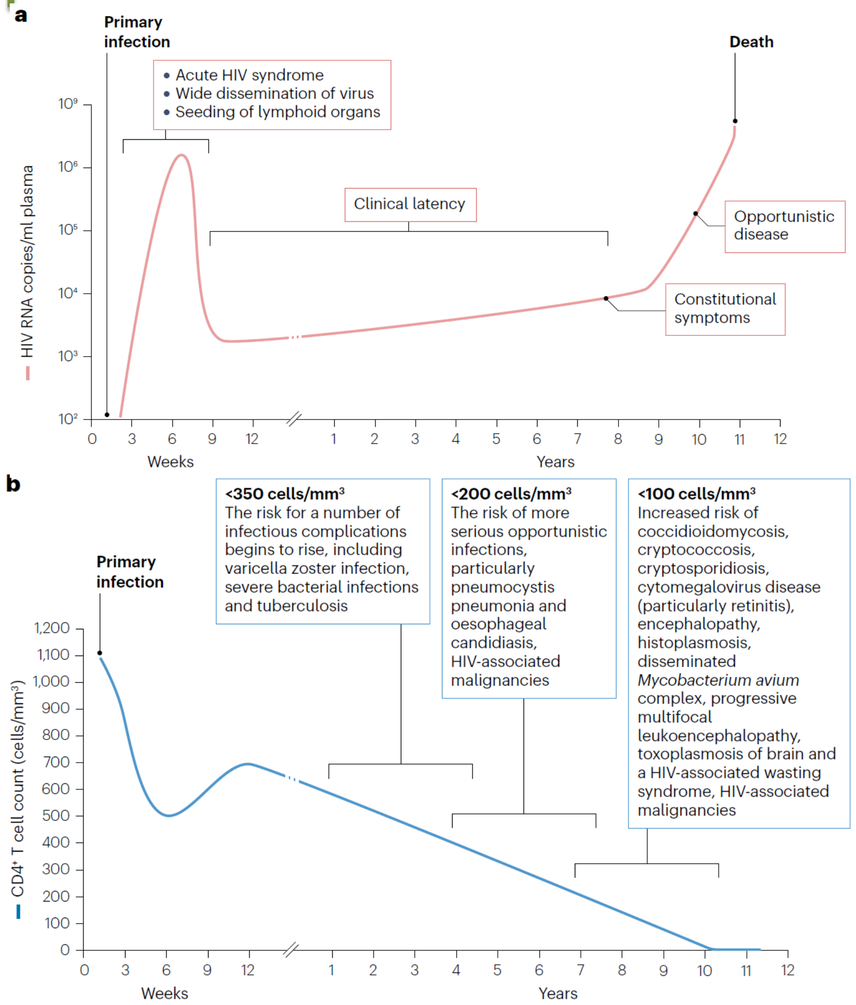


Masenga S., et al. Cell 2023



Bekker L., et al. Nature Reviews 2023

HIV infection and disease progression



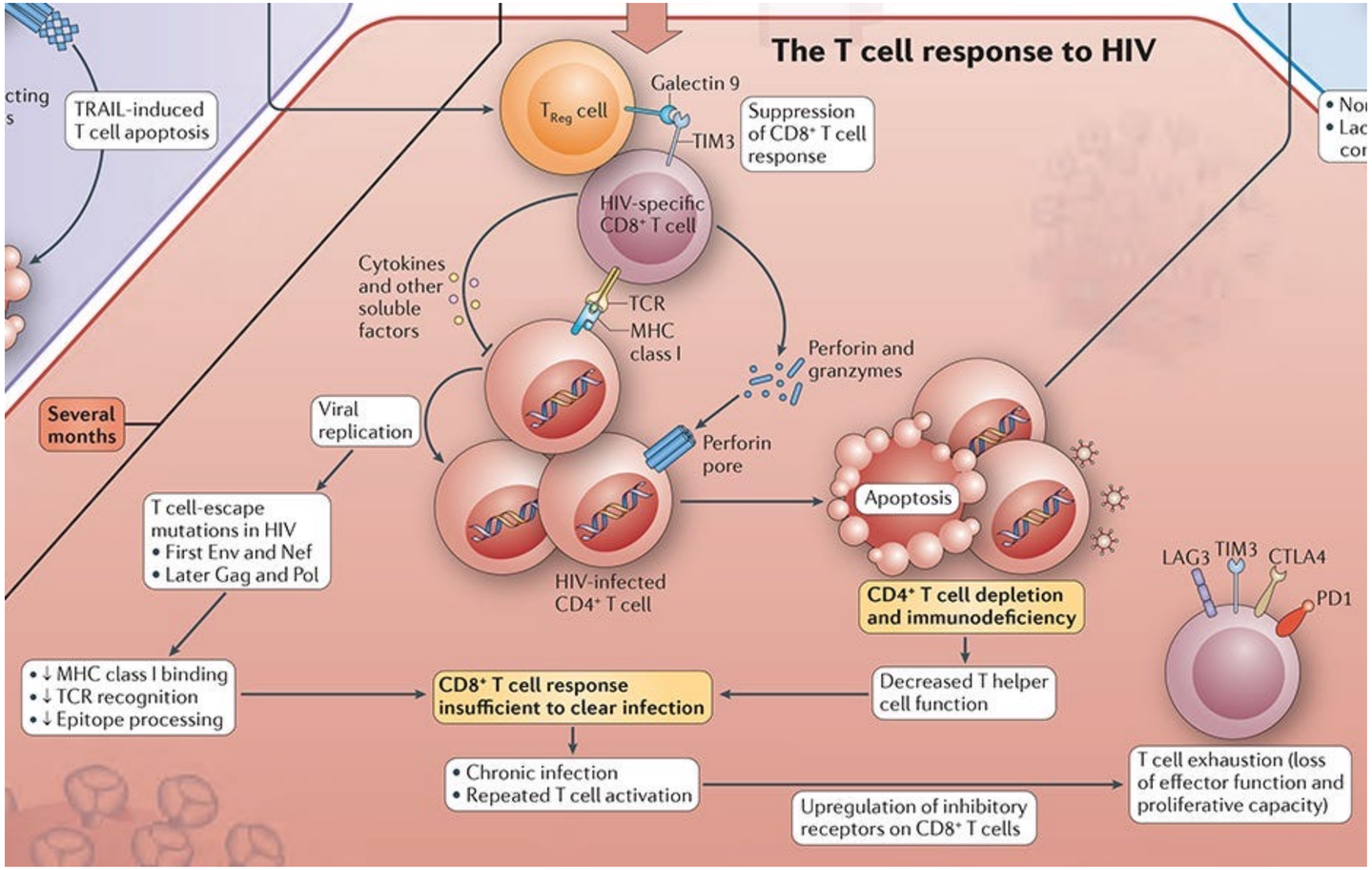
Bekker L., et al. Nature Reviews 2023

Factors associated with immune dysfunction other than destruction of CD4+ T cells

Cell type	Immunopathological effects
$CD8^+$ cytotoxic T lymphocytes	Above the normal range during acute phase (normal $CD8^+$ T cell range: 150–1,000 cells/mm^3)
	Decline at later stages
Natural killer cells	Impaired numbers
	Impaired function
Monocytes and macrophages	Defects in chemotaxis
	Inability to promote T cell proliferation (normal $CD4^+$ T cell range: 460–1,600 cells/mm^3)
	Defects in Fc receptor function, which is an important requirement for monocytes and macrophages to recognize and eliminate antibody bound to a foreign antigen
B cells	Increased production of IgG and IgA
	Antibody responses to multiple pathogens, after either prior infection or vaccination, are low compared with people without HIV infection

Bekker L., et al. Nature Reviews 2023

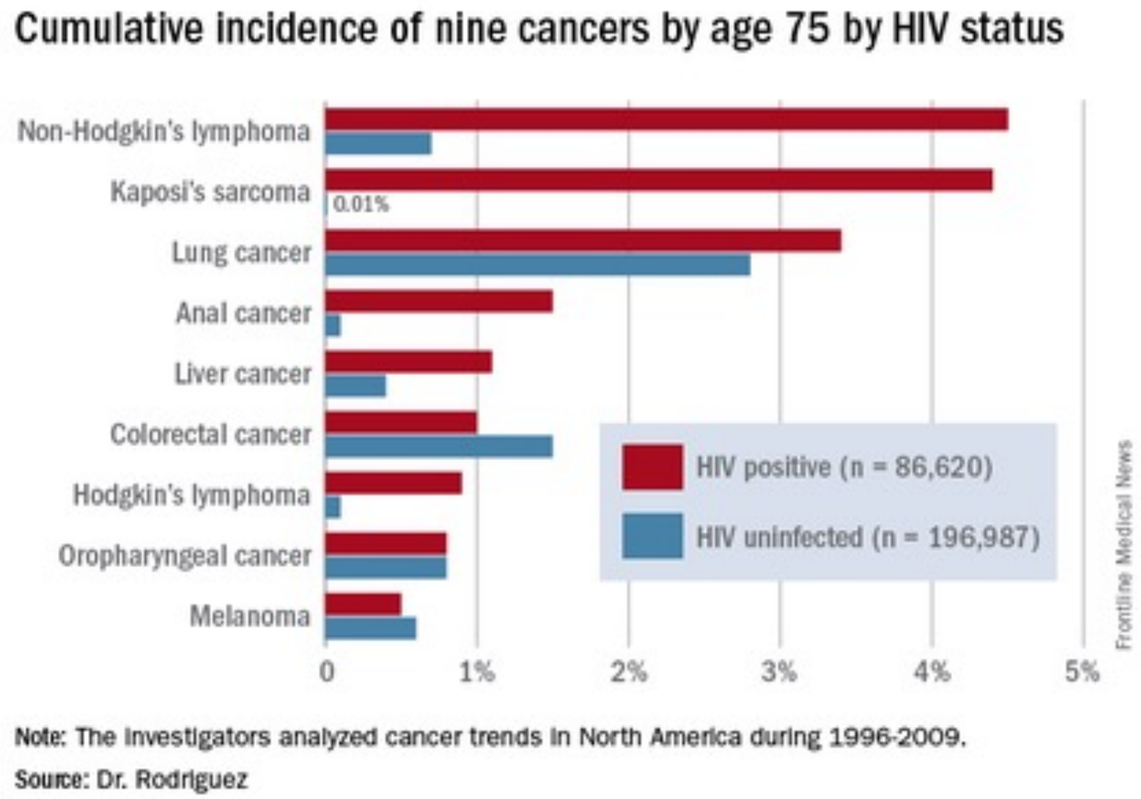
The life cycle of HIV-1



https://www.stemcell.com/immunology-features/immune-response-to-hiv

HIV-1 associated cancers

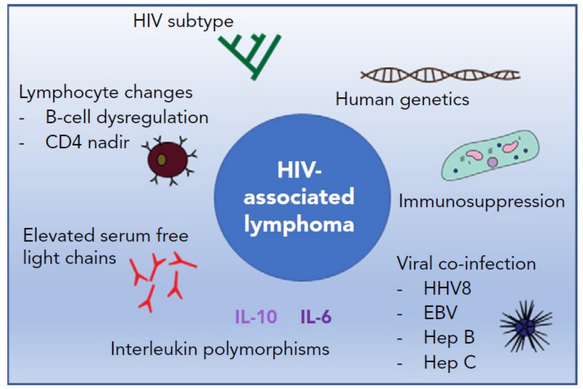
Cancer	Male (aged ≥ 15 years; *n* = 10,911) Person-years: 60,115.89 case	ID*	SIR	95% CI
Total	406	675.36	1.84	(1.66, 2.03)**
ADCs	116	192.96	23.48	(19.40, 28.16)**
Kaposi's sarcoma	25	41.59	415.80	(269.01, 613.84)**
NHL	91	151.37	18.65	(15.01, 22.89)**
Cervix				
NADCs	290	482.40	1.37	(1.22, 1.54)**
HPV-related head and neck cancer	9	14.97	1.62	(0.74, 3.08)
Stomach	26	43.25	0.63	(0.41, 0.92)**
Colorectal	27	44.91	0.83	(0.55, 1.21)
Anus	19	31.61	85.92	(51.71, 134.18)**
Liver	57	94.82	2.16	(1.63, 2.79)**
Pancreas	9	14.97	1.63	(0.74, 3.09)
Lung	35	58.22	1.37	(0.96, 1.91)
Non-melanoma skin	4	6.65	1.21	(0.33, 3.10)
Breast	1	1.66	6.63	(0.09, 36.88)
Prostate	25	41.59	1.79	(1.16, 2.64)**
Kidney and renal pelvis	5	8.32	0.64	(0.21, 1.50)
Bladder	5	8.32	0.99	(0.32, 2.30)
Thyroid	9	14.97	0.46	(0.21, 0.86)**
Hodgkin's lymphoma	6	9.98	15.03	(5.49, 32.71)**
Multiple myeloma	5	8.32	3.81	(1.23, 8.89)**
Leukemia	5	8.32	1.41	(0.45, 3.29)



Ok Lee., et al. Scientific Report 2022

Diffuse Large B-Cell Lymphoma

- 60-70% of all NHLs in HIV-1 infections are DLBCL;
- Specific mechanisms of HIV-1 in inducing DLBCL are still under investigations;
- DLBCL in HIV-positive is more often associated with high-risk factors as MYC or BCL6 translocations or proliferation indices;



Noy A. Blood 2019

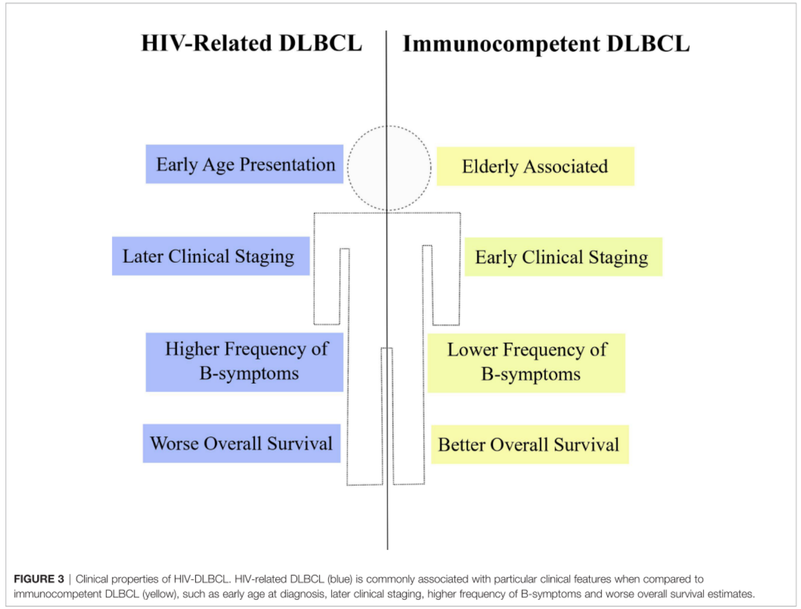


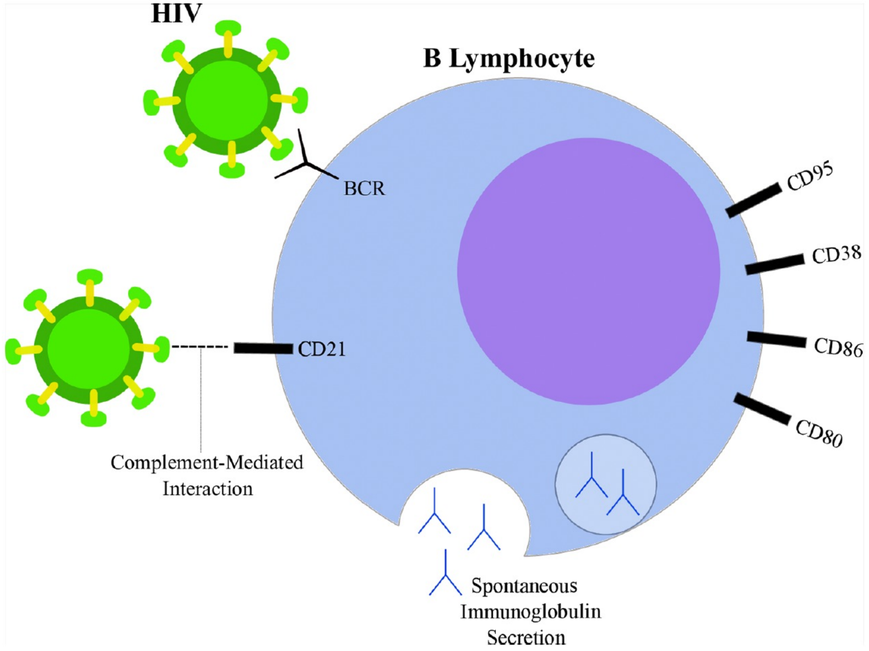
FIGURE 3 | Clinical properties of HIV-DLBCL. HIV-related DLBCL (blue) is commonly associated with particular clinical features when compared to immunocompetent DLBCL (yellow), such as early age at diagnosis, later clinical staging, higher frequency of B-symptoms and worse overall survival estimates.

de Carvalho P., et al. Frontiers in oncology 2021

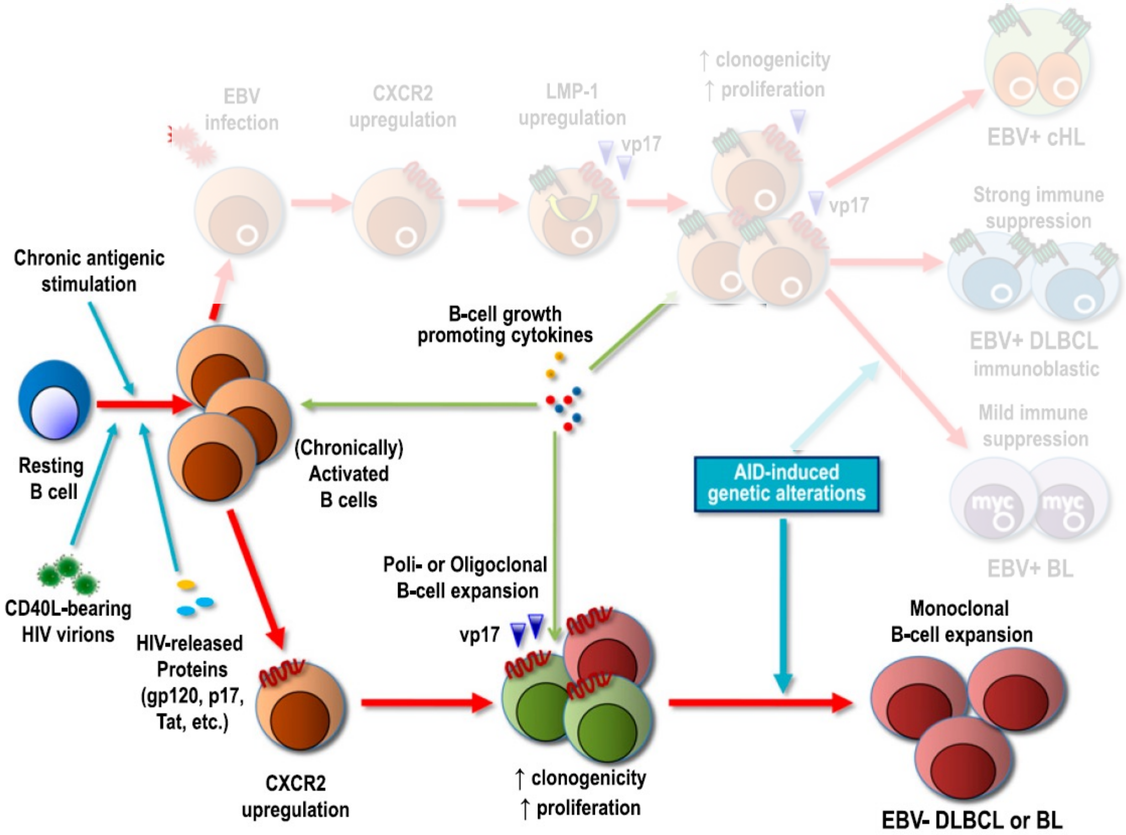
Lymphoma subtype	EBV$^+$	KSHV$^+$	EBV Latency pattern	CD4$^+$ T cell count
ABC-DLBCL	90%	-	II/III	Low
GCB-DLBL	30%	-	-	Preserved
BL	30-60%	-	I	Preserved
PBL	70-80%	-	0/I	Low
PEL	80-90%	100%	I	Low
KSHV-LCL	-	100%	-	Low
PCNSL	100%	-	II/III	Very low
HL	100%	-	II	Preserved

Lurain K., et al. Seminars in Hematology 2022

Diffuse Large B-Cell Lymphoma



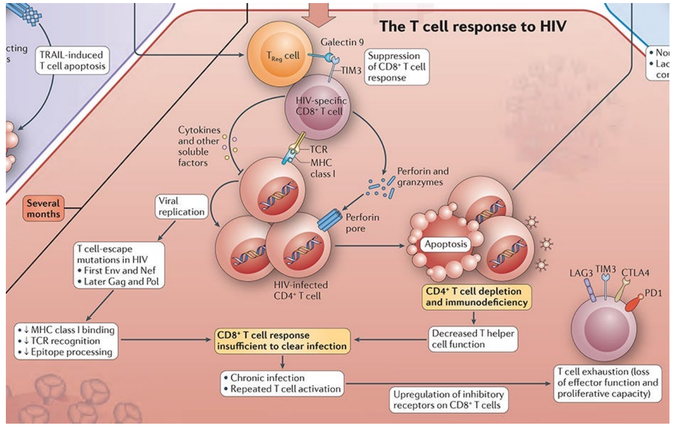
de Carvalho P., et al. Frontiers in Oncology 2021



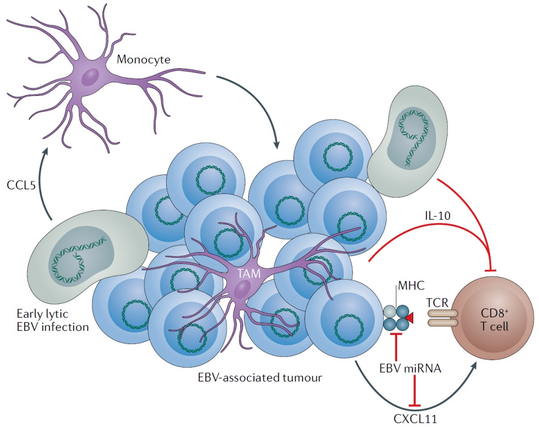
Dolcetti R., et al. Blood 2016

HIV-1+DLBCL IL6, Il10 ↑ B-cell activation, proliferation ↑ Ig-Switch ↑

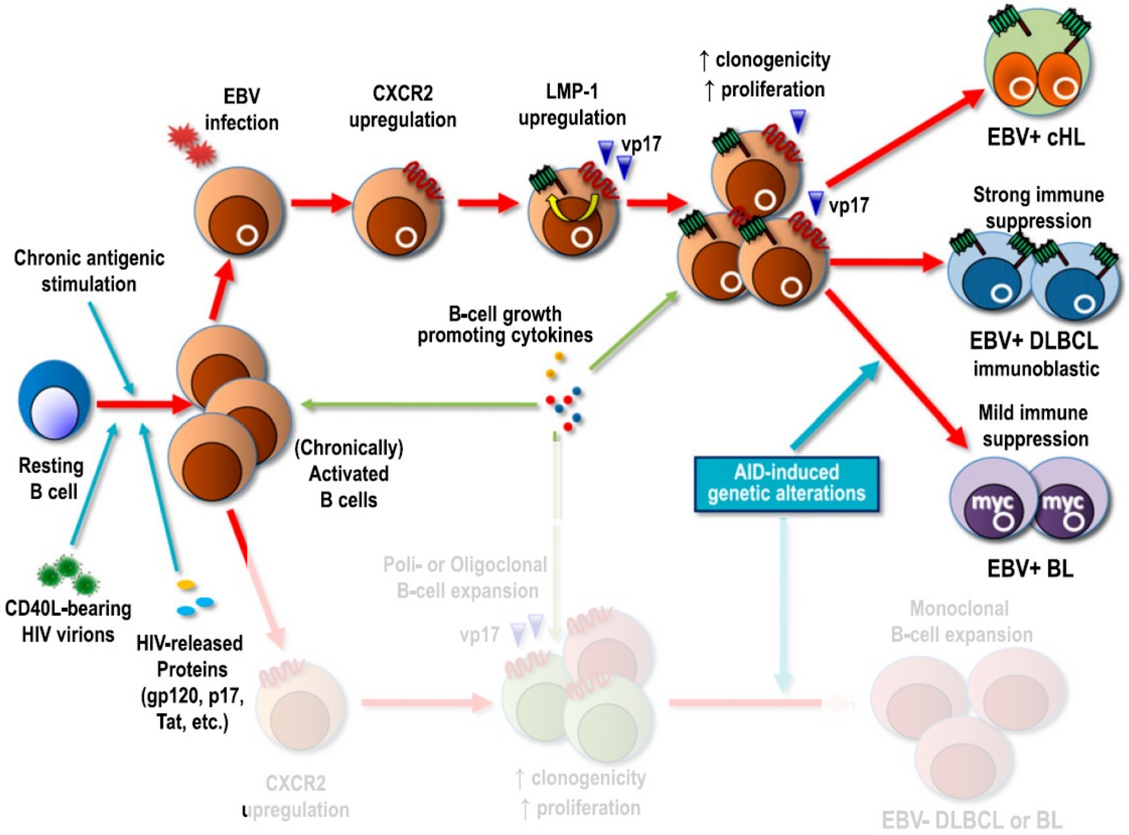
DLBCL HIV-1+EBV



https://www.stemcell.com/immunology-features/immune-response-to-hiv

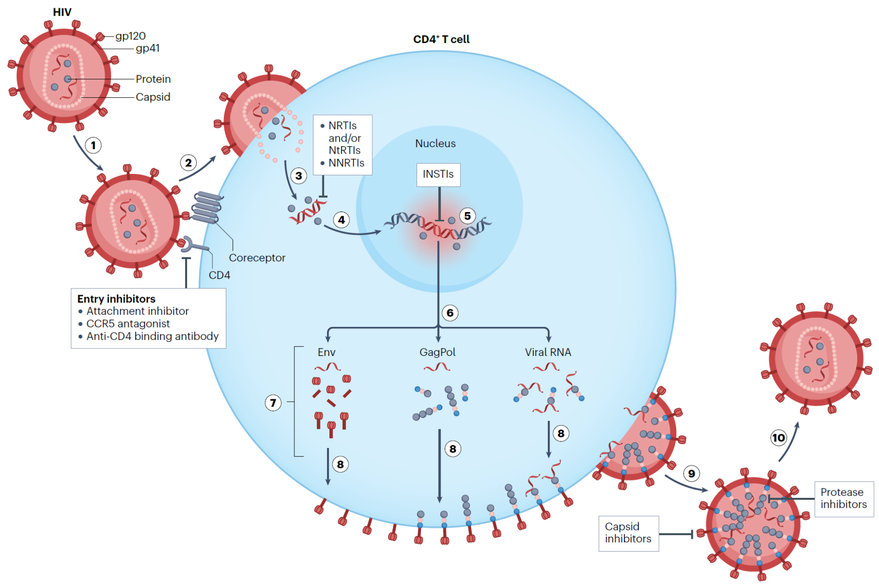


Munz C., Nature Reviews 2019

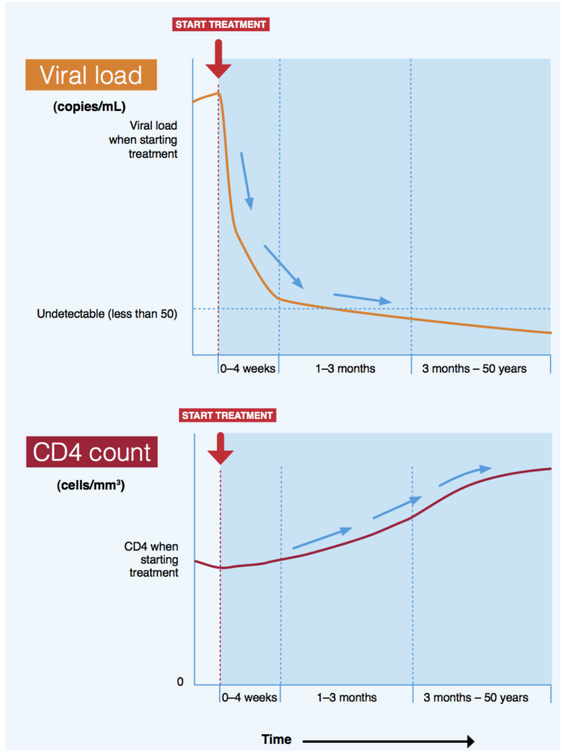


Dolcetti R., et al. Blood 2016

Antiretroviral therapy (ART)



Bekker L., et al. Nature Reviews 2023



https://i-base.info/guides/art-in-pictures/hiv-after-starting-art

- ART wipes out most actively infected CD4 cells,
- immune system can recover naturally;
- HIV drugs do not directly increase the CD4 count, they help make an environment where this can happen;
- ART enables the CD4 count to increase to higher and safer levels;
- the risk of HIV-related complications is reduced.
- CD4 counts can also continue to increase each year, even after ten years.

ART and cancers

Cancer	SIR (95% CI)		SIR Ratio (95% CI)
	Optimal ART adherence	Non-optimal ART adherence	
Total	1.32 (1.15, 1.51)	2.41 (2.11, 2.75)	0.55 (0.45, 0.66)*
ADCs	8.61 (6.49, 11.21)	19.22 (15.12, 24.09)	0.45 (0.31, 0.64)*
Kaposi's sarcoma	346.11 (157.93, 657.06)	1,121.90 (640.85, 1822.02)	0.30 (0.12, 0.73)*
NHL	13.98 (9.99, 19.04)	35.18 (26.71, 45.48)	0.40 (0.26, 0.61)*
Cervix	1.71 (0.63, 3.73)	0.45 (0.01, 2.48)	3.84 (0.47, 176.60)
NADCs	0.99 (0.84, 1.16)	1.63 (1.38, 1.92)	0.61 (0.48, 0.77)*
HPV-related head and neck cancer	2.10 (0.68, 4.89)	4.55 (1.66, 9.91)	0.46 (0.11, 1.81)
Stomach	0.71 (0.40, 1.18)	0.91 (0.45, 1.63)	0.78 (0.34, 1.89)
Colorectal	0.88 (0.50, 1.43)	1.17 (0.60, 2.04)	0.75 (0.33, 1.74)
Anus	39.90 (15.98, 82.21)	122.64 (63.30, 214.25)	0.33 (0.11, 0.90)*
Liver	2.35 (1.55, 3.43)	4.97 (3.42, 6.98)	0.47 (0.44, 0.81)*
Pancreas	0.91 (0.18, 2.66)	3.42 (1.25, 7.44)	0.27 (0.04, 1.25)
Lung	1.54 (0.94, 2.38)	2.61 (1.54, 4.12)	0.59 (0.30, 1.19)
Non-melanoma skin	1.79 (0.48, 4.59)	0.83 (0.01, 4.63)	2.16 (0.21, 106.22)
Breast	0.11 (0.01, 0.38)	0.36 (0.10, 0.91)	0.30 (0.03, 2.09)
Prostate	3.18 (1.82, 5.16)	3.63 (1.65, 6.88)	0.88 (0.37, 2.25)
Kidney and renal pelvis	1.31 (0.42, 3.06)	NA (NA)	NA (NA)
Bladder	1.88 (0.51, 4.82)	0.87 (0.01, 4.83)	2.17 (0.22, 106.84)
Thyroid	0.24 (0.10, 0.47)	0.23 (0.07, 0.54)	1.03 (0.30, 4.02)
Hodgkin's lymphoma	14.36 (2.89, 41.94)	30.78 (8.28, 78.79)	0.47 (0.07, 2.76)
Multiple myeloma	1.19 (0.02, 6.64)	8.95 (2.41, 22.91)	0.13 (0.00, 1.35)
Leukemia	NA (NA)	3.97 (1.28, 9.28)	0.00 (0.00, 0.66)*

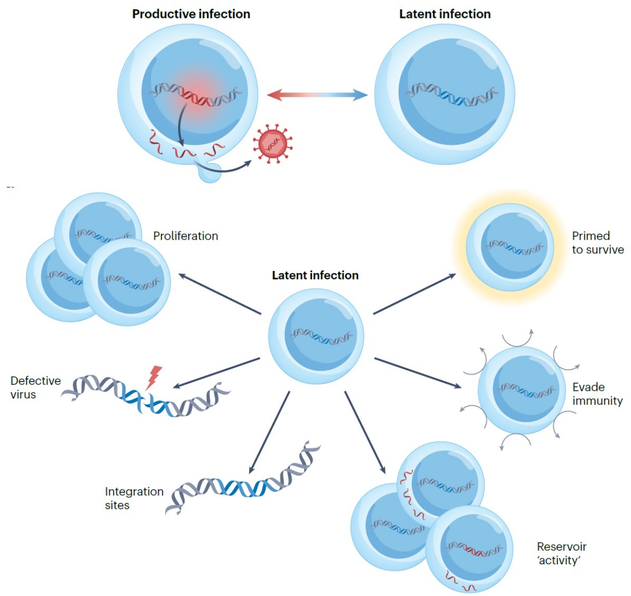
Ok Lee., et al. Scientific Report 2022

Table 1. OS of HIV lymphoma subtypes both pre- and post-ART

	Pre-ART, %	Current ART era, %
Burkitt lymphoma	10-40[36,57,58,119]	70-80[61,62]
DLBCL	40[119]	70-80[36,37]
HL	55[87]	80-90[86,87]
PBL	6[64]	75[68]
Primary CNS lymphoma	20[69]	60[73,74]
PEL	33[82]	40[82]

Noy A. Blood 2019

ART and latent infection



Bekker L., et al. Nature Reviews 2023

- Lifelong treatment is required and there is no cure;
- although most HIV-infected achieve viral suppression;
- some still display viral persistence;
- residual inflammation;
- metabolic disturbances;
- incomplete immunological response;

- HIV can integrate in the host genome and persist for the life span of the infected cell;
- Latently infected cells are not recognized as foreign because they are largely transcriptionally silent, but contain replication-competent virus that drives resurgence of the infection once ART is stopped.

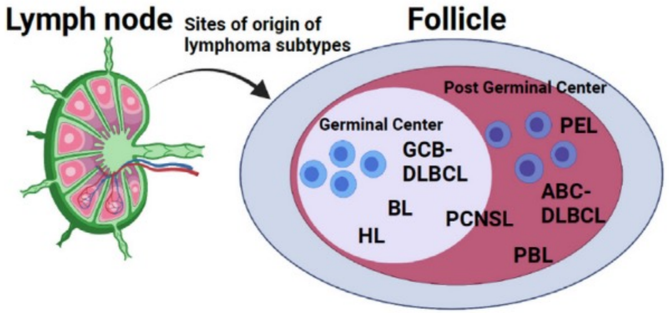
ART and cancers

Table 1. Distribution of lymphoma subtypes in people with HIV through 3 decades. Data from Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) USA cohort of 476 patients [5].

	1996–2000 CNICS (n = 132)	2001–2005 CNICS (n = 201)	2006–2010 CNICS (n = 143)	Trend
DLBCL * (%)	43.9	45.8	35.7	↓
BL * (%)	7.6	10.9	16.8	↑
PCNSL * (%)	14.4	10.4	9.8	↓
HL * (%)	15.2	15.4	19.6	↑
Others (%)	18.9	17.4	18.2	=

* DLBCL: diffuse large B-cell lymphoma; BL: Burkitt lymphoma; PCNSL: primary central nervous system lymphoma; HL: Hodgkin lymphoma.

Huguet, M. et al. Cancers 2023

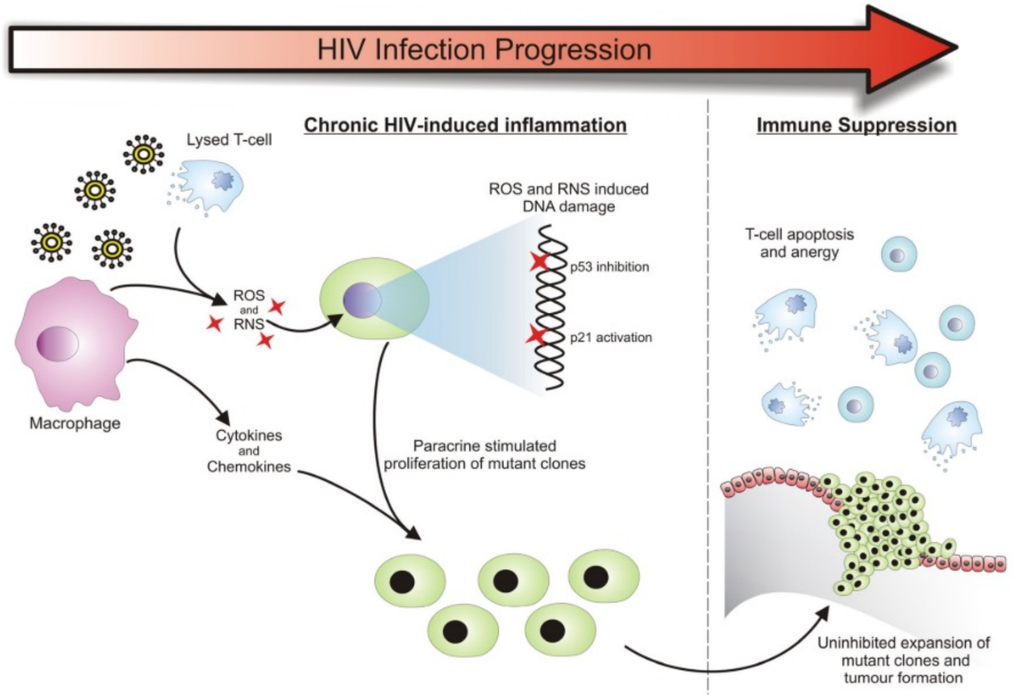


NON-HODGKIN LYMPHOMA

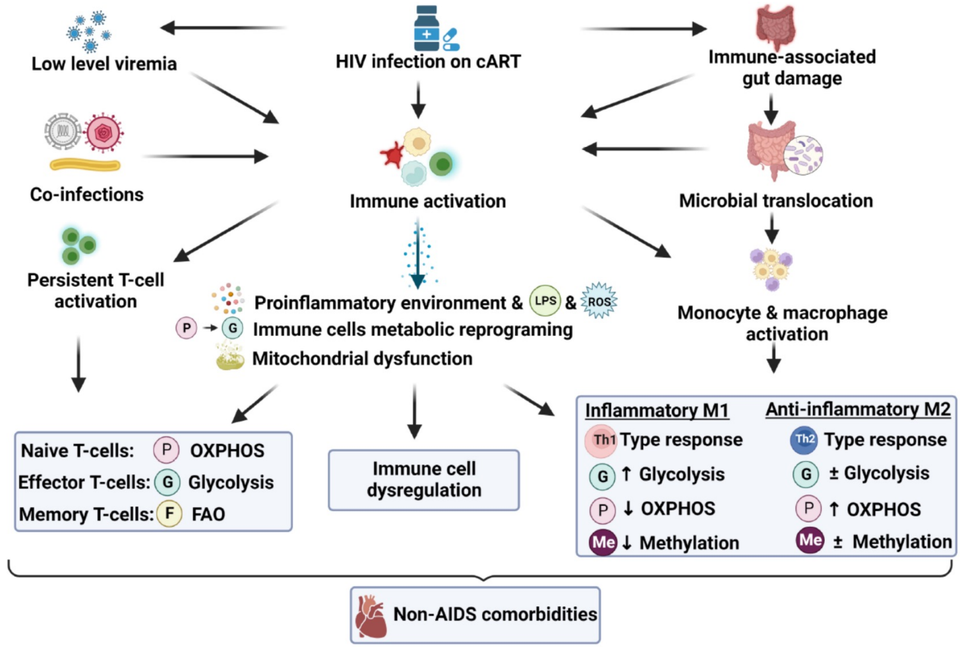
HL	BL	GCB-DLBCL	PCNSL	ABC-DLBCL	PBL	PEL
CD20- CD30+ CD15+ MUM1/IRF4⁺	CD20⁺ CD10⁺ BCL6⁺ MUM1/IRF4⁻	CD20⁺ CD10⁺ BCL6⁺ MUM1/IRF4⁻	CD20⁺ Variable phenotype resembling ABC-DLBCL	CD20⁺ CD10⁻ BCL6⁻ MUM1/IRF4⁺	CD20⁻ CD138⁺ CD30⁺/⁻ MYC* 60% MUM1/IRF4⁺	CD20⁻ CD138⁺ CD38⁺ CD30⁺/⁻ MUM1/IRF4⁺
EBV⁺ 100% EBV LP II	EBV⁺ 30-60% EBV LP I	EBV⁺ 30% EBV LP unknown	EBV⁺ 100% EBV LP II-III	EBV⁺ 90% EBV LP II-III	EBV⁺ 70-80% EBV LP 0-I	KSHV⁺ 100% EBV⁺ 80% EBV LP I
HIV characteristics (CD4⁺ T cell count preserved vs. low)						
Preserved⁺⁺	Preserved⁺⁺	Preserved⁺	Low⁺⁺⁺	Low⁺	Low⁺⁺	Low⁺⁺
Prevalence in post ART era (Increased vs. Decreased)						
Increased	Increased	Decreased	Decreased	Decreased	Increased	Increased
Prognosis (Better vs. Worse)						
Better	Better	Better	Worse	Worse	Worse	Worse

Lurain, K. et al. Seminars in Hematology 2022

HIV Chronic Inflammation in the Development of Cancers



Omar, A. et al. Cancers 2024



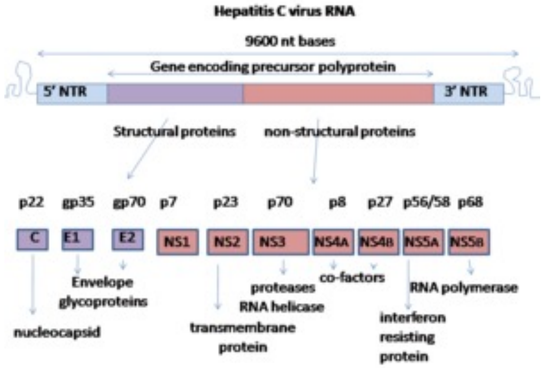
Teer E., et al. Viruses 2022

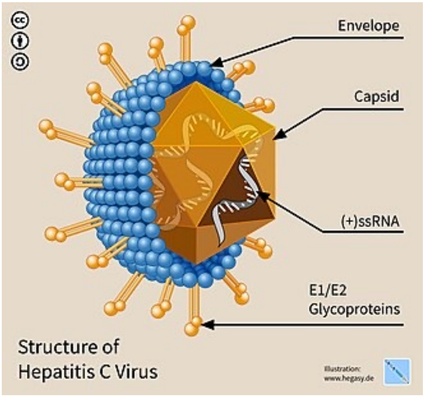
- Despite HIV controlled by ART, the virus itself does activate the host's immune system;
- immune activation creates a chronic inflammation strongly associated with neoplasia;
- example are reactive oxygen and nitrogen species (ROS and RNS).

- EBV
- HIV
- HCV

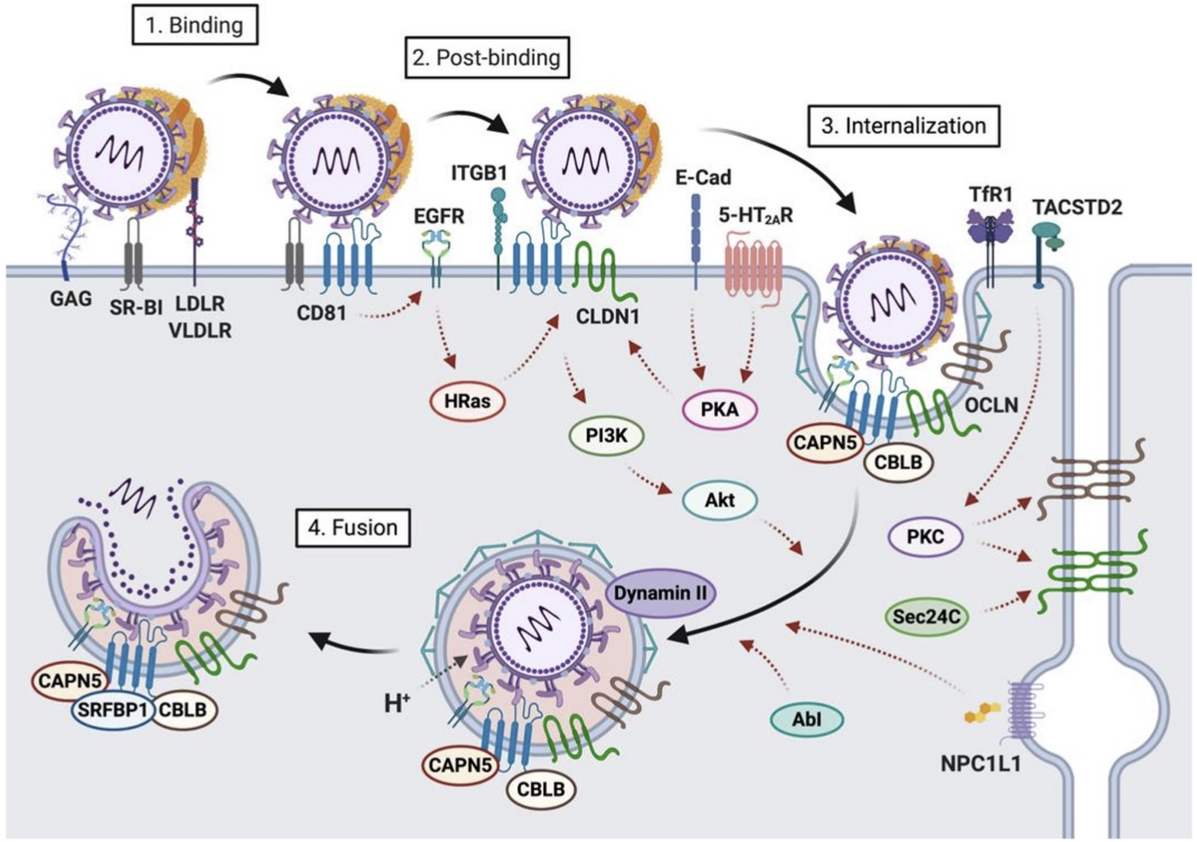
Hepatitis C virus (HCV)

- Belonging to Hepacivirus in the family Flaviviridae;
- discovered in 1989;
- seven different genotypes;
- single copy of positive-sense single-stranded RNA, 11 proteins;
- HCV does not code for oncogenes and is unable to integrate into the host genome
- It can replicate both in the liver and in lymphocytes;
- More than 95% of people with chronic infection can be cured when treated with direct-antiviral agents (DAA);
- average relative risk of NHL ranging from 1.7 to 3.0.

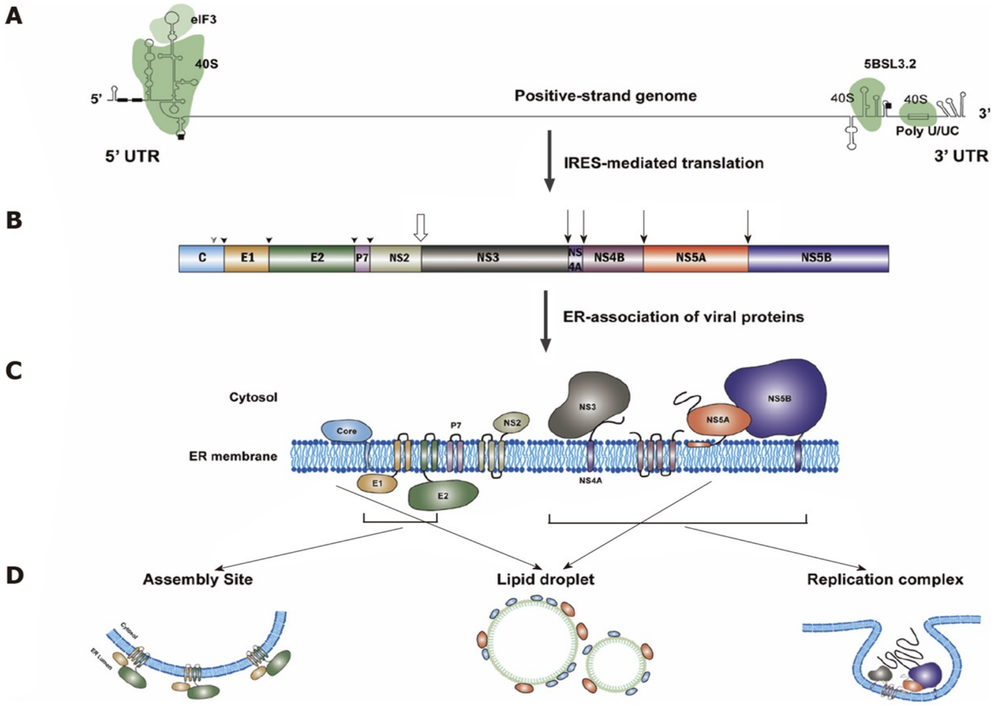




The life cycle of HCV

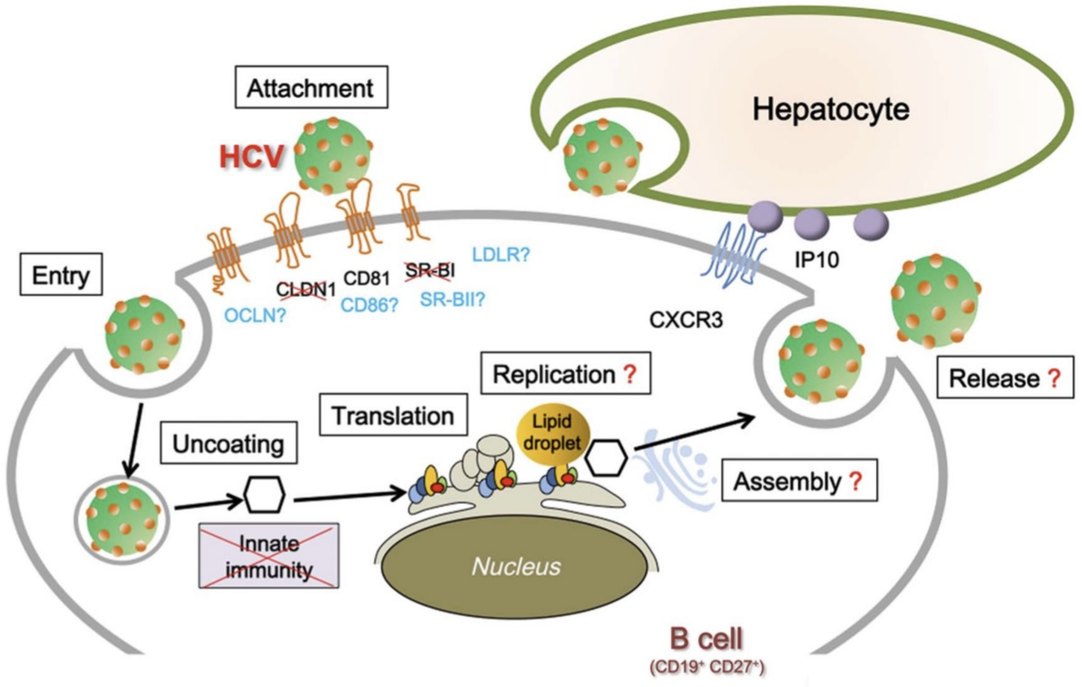


Colpitts C., et al. Molecular Science 2020

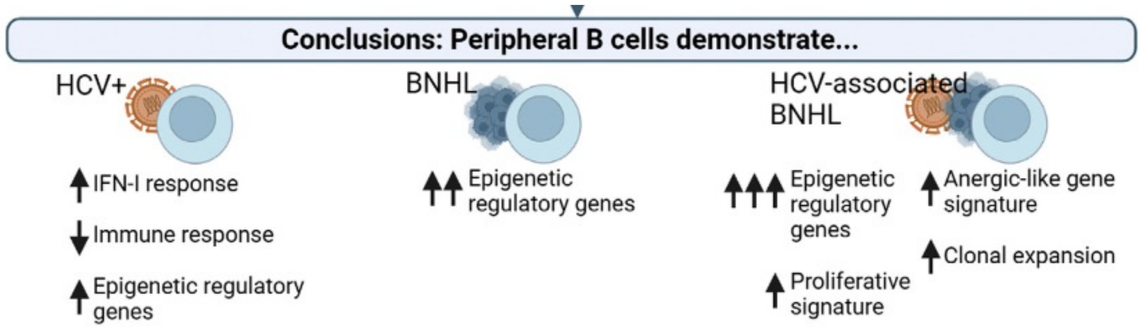


Li H., et al. World Journal of Gastroenterology 2021

The life cycle of HCV in B-lymphocytes



Ito M., et al. Frontiers in microbiology 2011



Amanda M., et al. iScience 2022

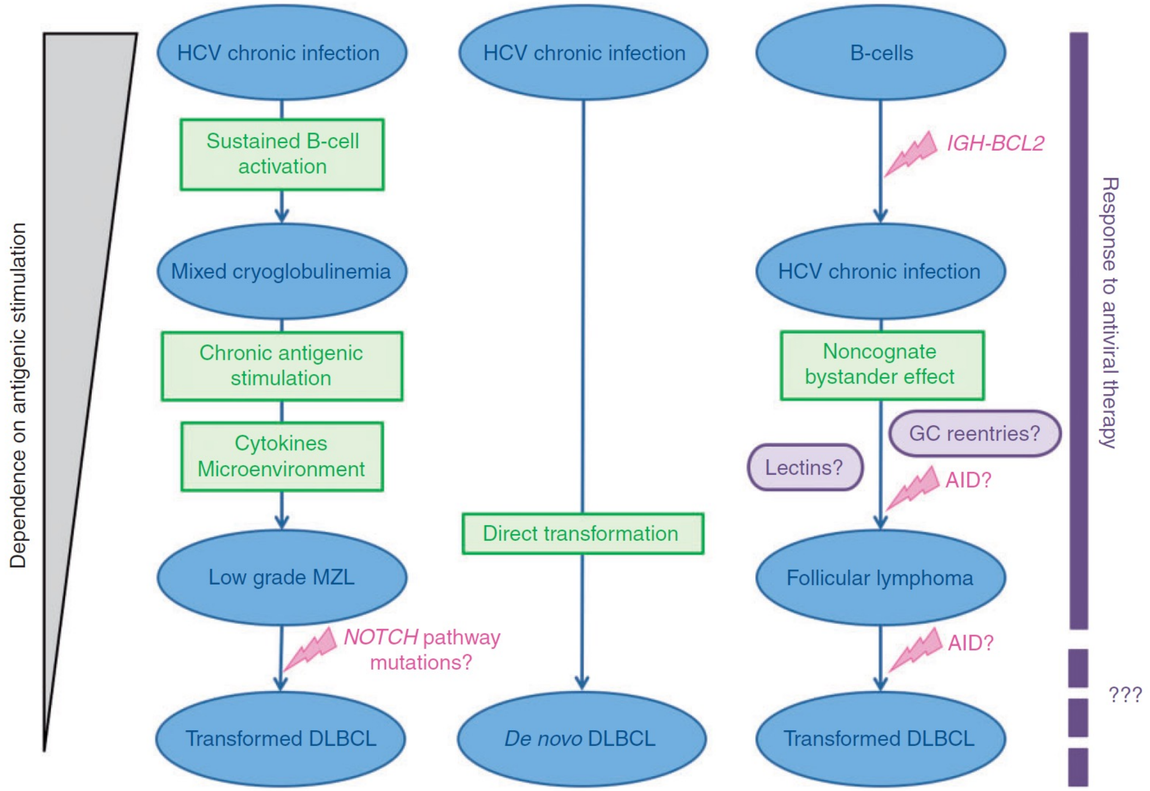
HCV associated NHL

Table 1 Risk of Various Non-Hodgkin's Lymphoma Subtypes in HCV Infected Patients Compared to Noninfected Population

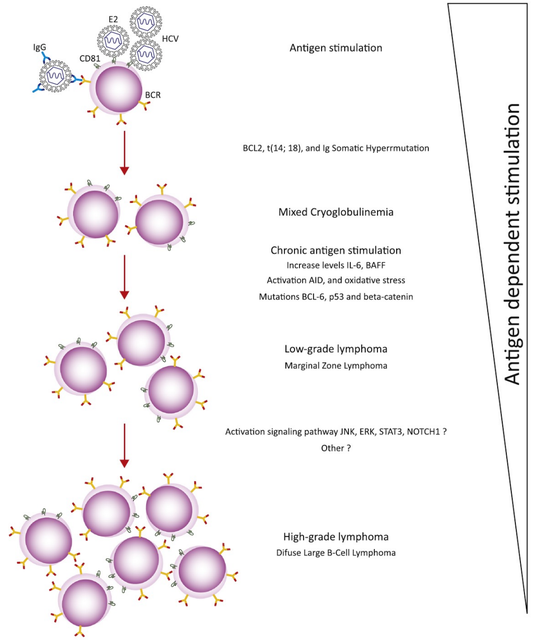
	HCV Population	Control Population	Odds Ratios (Confidence Interval 95%),
	N = 129,970	*N* = 37,961,970	*P* Value
Chronic lymphocytic leukemia	220	45,370	1.4 (1.2-1.6), $P < .001$
Follicular lymphoma	80	8620	2.7 (2.2-3.4), $P < .001$
Marginal zone lymphoma	40	2240	5.2 (3.8-7.1), $P < .001$
Lymphoplasmacystic lymphoma	30	3330	2.6 (1.8-3.8), $P < .001$
Diffuse large B-cell lymphoma	60	4010	4.4 (3.4-5.6), $P < .001$
Burkitt's lymphoma	30	2100	4.2 (2.9-6.0), $P < .001$
Mantle cell lymphoma	10	2240	1.3 (0.7-2.4), $P = .402$
Non-Hodgkin's T-cell lymphoma	120	14,100	2.5 (2.1-3.0), $P < .001$
Primary cutaneous T-cell lymphoma	50	5930	2.5 (1.9-3.3), $P < .001$
Non-Hodgkin's lymphoma[a]	940	107,480	2.6 (2.4-2.7), $P < .001$

Alkrekshi A., et al. Clinical Lymphoma Myeloma e Leukemia 2021

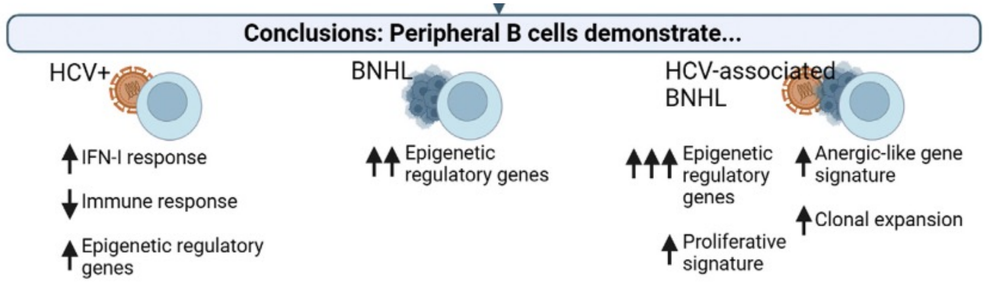
Models of HCV-related lymphomagenesis



Couronnè L., et al. Annals of Oncology 2017



Mazzaro C., et al. Seminars in Heamatology 2022



Amanda M., et al. iScience 2022

DAA therapy

Author, Year [Ref], Country, Study Identifier	No.	Male; HIV; PWID, n (%)	Duration of Infection: Screening Protocol Defined, mo	Duration of Infection: Baseline Weeks, Median (Range)	HCV Genotype, %	Baseline HCV RNA, Median (Range), log_{10} IU/mL	Symptomatic Infection; Jaundice, n (%)	DAA Regimen Duration	SVR12 ITT; SVR12 PP, % (n/N)
Pan-genotypic regimens									
Matthews et al, 2021 [13], international, NCT02625909	95	91 (96); 65 (68); 49 (52)	≤12	25 (17, 35)[a]	1a: 60%, 1b: 2%, 2: 4%, 3: 18%, 4: 16%	5.4 (4.4, 6.3)	14 (15); NR	Sofosbuvir-velpatasvir 12 wk	91% (86/95); 100% (77/77)
	93	91 (98); 65 (70); 50 (54)	≤12	26 (17, 34)[a]	1a: 62%, 1b: 4%, 1: 1%, 2: 0%, 3: 16%, 4: 16%	5.6 (4.8, 6.5)[a]	16 (17); NR	Sofosbuvir-velpatasvir 6 wk	82% (76/93); 93% (69/74)
Maasoumy et al, 2022 [14], Germany, NCT03818308	20	19 (95); 0; NR	≤4	NR	1a: 60%, 1b: 5%, 2: 5%, 3: 15%, 4: 15%	5.0 (3.9, 6.2)[a]	NR; 4 (20)	Sofosbuvir-velpatasvir 8 wk	90% (18/20); 100% (20/20)
Martinello et al, 2020 [15]; Australia, UK, New Zealand, NCT02634008	30	30 (100); 23 (77); 14 (47)	≤12	29 (13, 52)	1a: 73%, 1b: 3%, 1: 7%, 3: 7%, 4: 10%	6.2 (0.9, 7.7)	6 (20); 5 (17)	Glecaprevir-pibrentasvir 6 wk	90% (27/30); 96% (27/28)
Martinello et al, 2023 [16]; Australia, UK, New Zealand, NCT02634008	23	22 (96); 16 (70); 13 (57)	≤12	17 (9, 52)	1: 74%, 2: 4%, 3: 9%, 4: 9%	5.8 (4.2, 7.5)	3 (13); 0	Glecaprevir-pibrentasvir 4 wk	78% (18/23); 82% (18/22)
Genotype-specific regimens									
Boerekamps et al, 2019 [17]; Netherlands, Belgium, NCT02600325	80	80 (100); 73 (91); NR	≤6	18[b]	1a: 64%, 4: 36%	5.5 (4.5, 6.1)[a]	NR; 2 (3)	Grazoprevir-elbasvir 8 wk	94% (75/80); 99% (75/76)
Boyd et al, 2020 [18], France, NCT02886624	30	30 (100); 28 (93); 5 (17)	≤6	NR	1a: 50%, 1b: 3% 4: 47%	5.7 (5.1, 6.4)[a]	NR; NR	Grazoprevir-elbasvir 8 wk	93% (28/30); 96% (28/29)
Ji et al, 2022 [19], China, ChiCTR2000034389	68	50 (74); 0; NR	≤6	NR	1b: 100%	5.6[b]	NR; NR	Grazoprevir-elbasvir 8 wk	100% (68/68); 100% (68/68)
Deterding et al, 2017 [20], Germany NCT02309918	20	12 (60); 0; 0	≤4	NR	1a: 55%, 1b: 45%	4.0 (1.2, 7.2)	19 (95%); 8 (40%)	Sofosbuvir-ledipasvir 6 wk	100% (20/20); 100% (20/20)
Rockstroh et al, 2017 [21]; Germany, UK, NCT02457611	26	26 (100); 26 (100); NR	≤6	NR	1a: 73%, 4: 27%	5.4[b] (1.1, 7.3)	NR; 2 (8%)	Sofosbuvir-ledipasvir 6 wk	77% (20/26); 87% (20/23)
Naggie et al, 2019 [22], USA, NCT02128217	27	27 (100); 27 (100); 5 (19)	≤6	17[c] (13, 24)	1a: 85%, 1b: 11%, 4: 4%	6.2 (4.5, 6.6)[a]	NR; NR	Sofosbuvir-ledipasvir 8 wk	100% (27/27); 100% (27/27)
Palaniswami et al, 2018 [23], USA, NR	25	25 (100); 25 (100); NR	≤6	18[d] (6, 44)	1a: 92%, 1b: 98%	5.1 (4.2, 5.9)[a]	NR; 3 (12%)	Sofosbuvir-ledipasvir 8 wk	100% (25/25); 100% (25/25)

Martinello M., et al. Clinical Infectious diseases 2023

Lymphoma after DAA therapy?

original reports

Direct-Acting Antivirals as Primary Treatment for Hepatitis C Virus–Associated Indolent Non-Hodgkin Lymphomas: The BArT Study of the Fondazione Italiana Linfomi

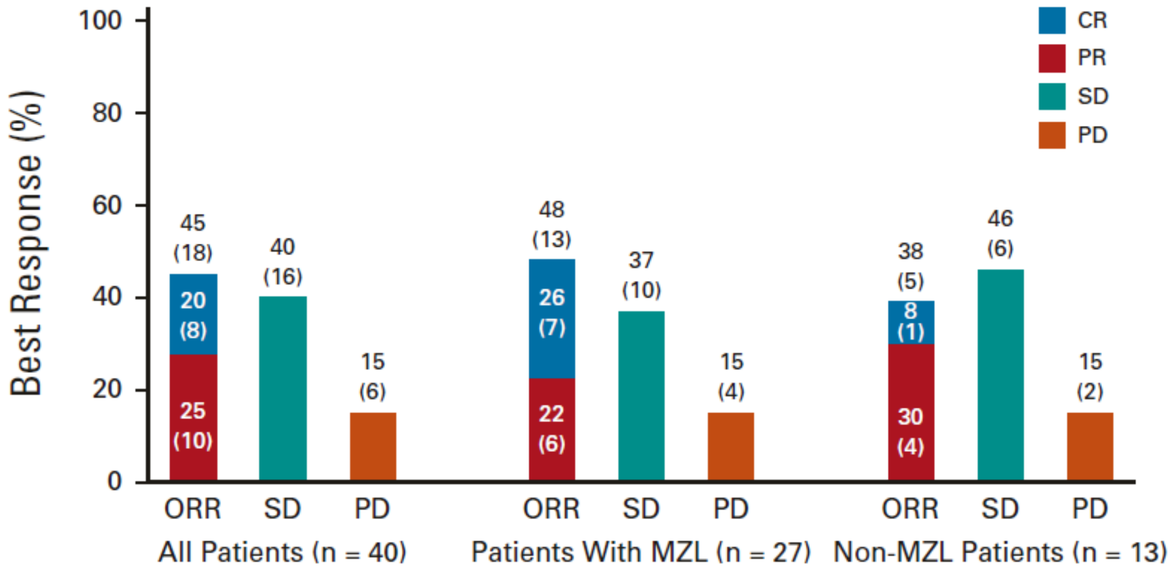
Michele Merli, MD[1]; Sara Rattotti, MD[2]; Michele Spina, MD[3]; Francesca Re, MD[4]; Marina Motta, MD[5]; Francesco Piazza, MD[6]; Lorella Orsucci, MD[7]; Andrés J.M. Ferreri, MD[8]; Omar Perbellini, MD[9]; Anna Dodero, MD[10]; Daniele Vallisa, MD[11]; Alessandro Pulsoni, MD[12]; Armando Santoro, MD[13]; Paolo Sacchi, MD[14]; Valentina Zuccaro, MD[14]; Emanuela Chimienti, MD[3]; Filomena Russo, MD[4]; Carlo Visco, MD[15]; Anna Linda Zignego, MD[16]; Luigi Marcheselli, MSc[17]; Francesco Passamonti, MD[1,18]; Stefano Luminari, MD[19,20]; Marco Paulli, MD[21,22]; Raffaele Bruno, MD[14,23]; and Luca Arcaini, MD[2,22]; on behalf of Fondazione Italiana Linfomi

METHODS FIL_BArT is a prospective, multicenter, phase II trial that evaluated genotype-appropriate DAAs in untreated HCV-positive patients with indolent lymphomas without criteria for immediate conventional anti-lymphoma treatment. The primary objective was sustained virologic response, whereas the main secondary objectives were overall response rate of lymphoma and progression-free survival.

Relevance (*J.W. Friedberg*)
The results of BArT study suggest eradication of HCV with DAAs may result in durable lymphoma regression in a subset of patients. Further studies in patients with HCV-related indolent lymphomas not requiring immediate conventional treatment from other geographic areas are warranted.*

HCV eradication with DAAs in HCV-positive patients with B-cell indolent lymphomas strongly supports the direct etiological role of HCV in lymphomagenesis.

Lymphoma after DAA therapy?



Merli F., et al. JCO 2022

TABLE 2. Lymphoma Responses After Direct-Acting Antivirals in 40 Patients With Hepatitis C Virus–Positive Indolent Lymphomas

	Response, No. (%)				
Histology	**CR**	**PR**	**SD**	**PD**	**ORR**
All (n = 40)	8 (20)	10 (25)	16 (40)	6 (15)	18 (45)
MZL (n = 27)	7 (26)	6 (22)	10 (37)	4 (15)	13 (48)
Splenic (n = 6)	0	0	4	2	0 (0)
Nodal (n = 7)	3	0	3	1	3 (43)
MALT (n = 14)	4	6	3	1	10 (71)
Non-MZL (n = 13)	1 (8)	4 (30)	6 (46)	2 (16)	5 (38)
CD5-NOS (n = 4)	1	1	1	1	2 (50)
SLL (n = 2)	—	1	—	1	1 (50)
LPL (n = 6)	—	1	5	—	1 (17)
FL (n = 1)	—	1	—	—	1 (100)

Lymphoma after DAA therapy?

Table 1
Response to DAAs according to histological subtypes in patients with B-cell lymphoproliferative disorders associated with HCV infection

	Total	CR	PR	SD	PD
Low grade					
MZL all	46	20	19	6	1
Splenic	19	5	9	5	0
Nodal	1	1	0	0	0
Extranodal	13	6	7	0	0
Leukemic	5	2	2	1	0
MZL origin non-specified*	8	6	1	0	1
low-grade NOS	1	1	0	0	0
FL	2	0	2	0	0
LPL	2	0	1	1	0
CLL/SLL	4	0	0	4	0
High grade					
DLBCL	72	70	2	0	0
other	1	1	0	0	0
Concomitant chemo therapy†	79	77	2	0	0

Data according to Carrier et al [14], Alrich et al [53], Peveling et al [54], Arcaini et al [15], Merli et al [17], and Persico et al [18];
MZL = marginal zone lymphoma; FL; = follicular lymphoma; LPL = lymphoplasmacytic lymphoma; CLL =: chronic lymphocytic leukemia; SLL = small lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma;
CR: complete remission; PR: partial response; SD: stable disease; PD: progressive disease.

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- higher rate of complete remission after DAAs therapy was obtained in the DLBCL context;
- in all DLBCL patients DAAs therapies were concomitantly administrated with chemo-immuno-therapy;
- 43% of MZL achieved CR after DAAs;
- 6/20 MZL patients who reached CR were treated with chemo-immuno-therapy, accordingly 14/46 (30%) MZL patients were able to obtain a CR with the use of DAAs alone;
- no major complications were reported with the concomitant use of chemo-immuno and DAAs therapy.

Conclusions

- How do viruses cause lymphomagenesis?
- **Both directly (modifying cells) and indirectly (modifying microenvironment)**
- Do viruses interact with each other for lymphomagenesis?
- **Yes they can (accidentally not on purpose)**
- Does lymphoma still need viruses after lymphomagenesis?
- **Depending on the lymphoma**

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