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Herpesviruses: overview of systematics, genomic complexity and life cycle

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Abstract

Herpesviruses are double-stranded DNA viruses with distinct morphological features and are among the largest and most complex viruses. According to the International Committee on Taxonomy of Viruses (ICTV), in 2022, there were 133 herpesviruses classified into three families: *Orthoherpesviridae*, infecting mammals and birds; *Malacoherpesviridae* infecting marine molluscs; and *Alloherpesviridae* infecting fish and amphibians. Herpesviruses have a complex genomic architecture, characterised by unique regions flanked by repeated and inverted sequences. Unique regions can undergo rearrangements leading to the formation of genomic isomers, which could have important implications for the life cycle of the virus. Herpesviruses life cycle consists of two main phases: the lytic phase, during which viral genes are expressed and translated into viral proteins that regulate DNA replication, capsid formation and the production of new particles; and the persistence phase, in which the virus persists in the host without being eliminated by the immune system. This review offers an updated and comprehensive overview of the *Herpesvirales* order, detailing their morphological characteristics, providing an in-depth taxonomic classification, examining their genomic architecture and isomers, and describing their life cycle.

Keywords Herpesvirus, Life cycle, Genomic architecture, Phylogeny

Background

Viruses play a major role in shaping life and driving evolution. They are the smallest and most abundant form of life, with an estimated 10^{31} particles in the biosphere, and occupy almost every ecosystem infecting all types of life forms [1–6]. Currently, there are four types of viral genome: double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), double-stranded DNA (dsDNA), single-stranded DNA (ssDNA) (https://ictv.global/virus-properties, consulted on 28/01/25). Herpesviruses are dsDNA viruses belonging to the order *Herpesvirales* within the realm *Duplodnaviria* (Fig. 1) [7].

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Herpesviruses are ubiquitous throughout the world and have co-existed with mankind for as long as there have been written records. Interestingly, ancient Egyptian hieroglyphics document the presence of herpetic lesions, suggesting that these viruses have been a concern issue for millennia [8]. The origin of herpesviruses has been studied since the 1990s, with several estimates suggesting that their most recent common ancestor existed between 150.1 and 209.9 million years ago, dating back to the Jurassic/Triassic periods [9–12]. It has long been thought that herpesviruses evolve with their hosts primarily through co-speciation [10, 13–15]. However, as the amount of genomic sequence available has increased and bioinformatic tools have evolved, the explanation for herpesviruses evolution has shifted. Current evidence suggest that host-switching events and intra-host speciation play a more important role in their evolutionary history [9, 13, 16].

Historically, the classification of herpesviruses has been defined on the basis of virion architecture and host

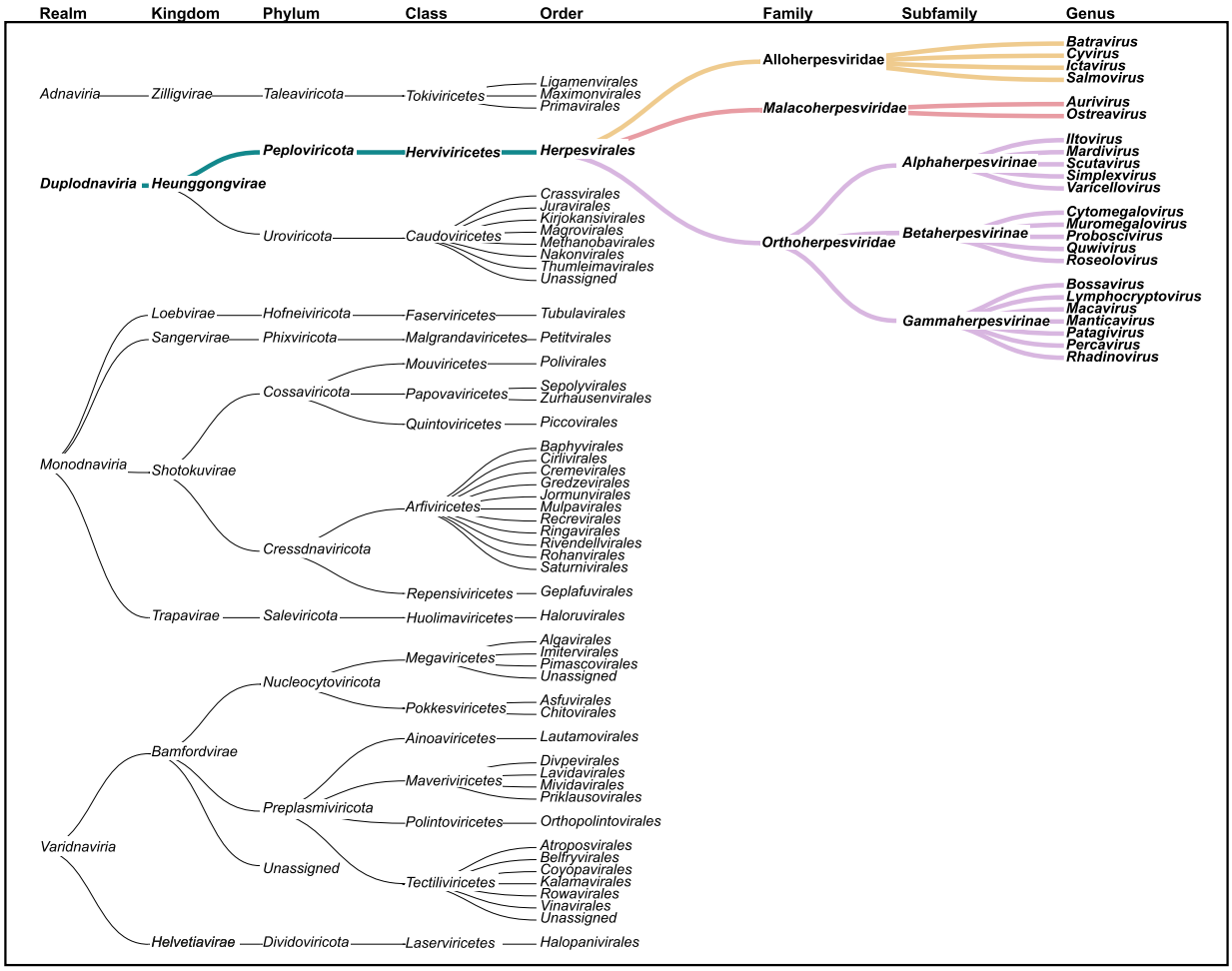

Fig. 1 Overall representation of DNA viruses. Realms, kingdoms, phyla, classes and orders are shown for all viruses whereas families, subfamilies are shown for herpesviruses (adapted from https://ictv.global/taxonomy/visual-browser)

species [17]. In recent decades, herpesvirus genetic data have accumulated and become extensive, with more than 1000 complete genome sequences now available in public databases (https://www.ncbi.nlm.nih.gov/datasets/genome/?taxon=548681, consulted on 28/01/2025). Currently, and based on genetic content, 133 distinct herpesvirus species have been identified and grouped into three families: *Orthoherpesviridae*, *Malacoherpesviridae* and *Alloherpesviridae* [7, 18] (https://ictv.global/taxonomy, consulted on 28/01/25). In addition, four new species (*Babylonia areolata* herpesvirus [19], Bufonid herpesvirus 1 [20], Lake sturgeon herpesvirus 1 [21] and Silurid herpesvirus 1 [22] have not yet been classified.

Herpesviruses are capable of infecting a wide range of animals including mammals, birds, fish, and invertebrates (marine molluscs) [13, 23]. Despite some differences in host specificity, tissue tropism, replication kinetics and pathogenic potential, herpesviruses share a common virion morphology and life cycle.

Most available reviews focus on the family *Orthoherpesviridae*, and more specifically the eight human herpesviruses species [8, 24–26]. The last comprehensive review providing a global overview of herpesvirus systematics, genomic architectures and lifecycles was published in 2013, when the order *Herpesvirales* comprised 90 herpesvirus species [27, 28]. Since then, 43 additional herpesviruses have been characterised and included in the ICTV classification while 4 new species need to be included.

Therefore, this review seeks to provide an updated and comprehensive overview of the order *Herpesvirales* with the aims to detail their morphological features, offer a complete and up to date taxonomic classification, and present an in-depth analysis of their genomic architecture. Additionally, the review includes a general description of their life cycle. This synthesis is intended to serve as a valuable reference for researchers,

facilitating a deeper understanding of the biology, evolution, and significance of these viruses.

Herpesviruses virion structure

Herpesviruses, members of the order *Herpesvirales* are double-stranded DNA (dsDNA) viruses with morphological characteristics that distinguish them from other viruses. The mature herpesvirus virion structure has been described for 27 of the 49 alphaherpesviruses, 17 of the 27 betaherpesviruses, 18 of the 42 gammaherpesviruses, 2 of the 3 malacoherpesviruses and 12 of the 16 alloherpesviruses and is composed of an envelope surrounding a tegument, a protein-rich matrix between the envelope and the capsid. The capsid encloses the core consisting in tightly packed dsDNA genome (Fig. 2). The size of herpesvirus mature virion varies between 120 to 260 nm in diameter, depending on the thickness of the tegument and the state of the envelope [8].

Envelope

The envelope is a lipid bilayer that maintains the quasi-spherical shape of the virion. Its trilaminar appearance has been demonstrated by electron microscopy [29]. The envelope consists mainly of virally encoded glycoproteins (Fig. 2). The number and relative amounts of viral glycoproteins vary among herpesviruses. For example, in *Simplexvirus humanalpha 1*, also known as Human Simplex Virus 1 (HSV-1), the envelope contains at least 11 different virion-associated glycoproteins and the copy number of individual glycoproteins can exceed 1,000 per virion [8]. The glycoproteins form numerous protrusions on the virion envelope that are more numerous and shorter than those found on the surface of many other enveloped viruses [8].

Tegument

The tegument is sometimes asymmetrically distributed and its thickness can vary depending on the location of the virion with the infected cell and is determined by the virus rather than the host [30]. The tegument contains more than 20 different virally encoded proteins, some of which are present in hundreds of copies per virion [8].

Capsid

The structural features of the capsid are characteristic of all herpesviruses. It measures 100 nm in diameter, contains 161 capsomers (150 hexons and 11 pentons) and has a capsid triangulation number of T = 16 [31–33]. Non-enveloped capsids are present in infected cells in three main forms: A-, B- and C-capsids, where A-capsids have no core structure and B-capsids contain the assembly scaffold but no genome. Only the C-capsids contain the complete dsDNA herpesvirus genome [8].

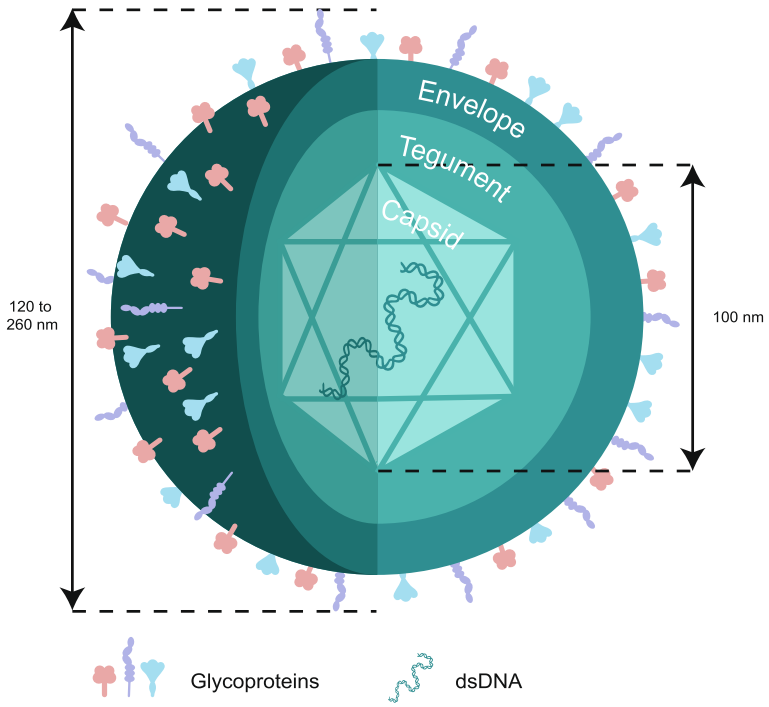

Fig. 2 Schematic representation of herpesvirus virion

Core

The core of the mature virion contains the viral genome as a single molecule in the form of dsDNA packed in an ordered manner in the form of a torus [33–36]. The exact arrangement of the DNA in the torus is not known but the DNA is tightly packed so that the internal volume of the capsid is approximately equal to the cylindrical volume of the genome [8, 37].

Towards a better characterization of herpesvirus particle structure

In total there is less than 60% of the described herpesvirus species for which the virion structure has been characterised. Furthermore, the number of proteins contained in the virions is not precisely known and may vary from one virus to another. Proteomics analyses have identified up to 71 structure-related proteins in virions of human, mice and monkey herpesviruses. These proteins are distributed as follows: 4 to 7 in the nucleocapsid, 9 to 20 in the tegument and 4 to 19 in the envelope plus a number of proteins whose location within virions is unknown [8, 38–42]. Recent advances including high-resolution cryo-electron microscopy and integrative structural approaches provide powerful tools to better characterize herpesvirus particles. For example, cryo-electron-microscopy has revealed significant differences between A- and B-capsids and mature C-capsids, providing new opportunities to understand why only the C-capsids contain the complete dsDNA herpesvirus genome [43]. Moreover, native mass spectrometry could be used to accurately determine the mass of viral capsids and identify the proteins they contain [44]. Advancing the structural characterisation of herpesvirus virions would greatly improve our understanding of how these viruses infect their hosts and could be helpful to design not only new diagnostic tools but also new strategies to block infection.

Herpesvirales clade

Herpesviruses are host-specific pathogens classified into three families on the basis of the DNA polymerase sequences: *Orthoherpesviridae* infecting mammals, birds, and reptiles (118 species); *Alloherpesviridae* infecting fish and amphibians (16 species); and *Malacoherpesviridae* infecting marine molluscs (3 species) (Fig. 3A).

Orthoherpesviridae

The family *Orthoherpesviridae* contains 118 described herpesviruses species and is divided into three subfamilies: *Alphaherpesvirinae* with 49 species; *Betaherpesvirinae* with 27 species; and *Gammaherpesvirinae* with 42 species (https://ictv.global/taxonomy, consulted on 28/01/25).

Alphaherpesvirinae

Viruses in this subfamily include the *Simplexvirus* genus infecting humans, primates, rabbits, marsupials and bats the *Varicellovirus* genus infecting humans, cattle, dogs, primates, bovids, deer, horses, donkeys, giraffes, felines, whales, seals and swine the *Scutavirus* genus infecting marine and terrestrial turtle, *Mardivirus* and *Iltovirus* genera both infecting birds (Fig. 3A) (Table 1).

Betaherpesvirinae

Viruses in this subfamily include the *Cytomegalovirus* genus infecting primates and humans, the *Muromegalovirus* genus infecting mice and rats, the *Proboscivirus* genus infecting elephants, the *Quwivirus* genus infecting rodents, and bats, and the *Roseolovirus* genus infecting humans, primates, swine and mice (Fig. 3A) (Table 2).

Gammaherpesvirinae

Viruses in this subfamily include the *Lymphocryptovirus* genus infecting humans and primates, the *Bossavirus* genus infecting dolphins, the *Macavirus* infecting bovids, cattle, swine and hipparion, the *Manticavirus* genus infecting marsupials, the *Patagivirus* genus infecting bats, the *Percavirus* genus infecting horses, felines, badgers, seals and bats and the *Rhadinovirus* genus infecting primates, cattle, rodents, mice and humans (Fig. 3A) (Table 3).

Malacoherpesviridae

Only few species have been characterized in the *Malacoherpesviridae* family. This family encompasses viruses infecting marine molluscs such as oysters, abalones and

(See figure on next page.)

Fig. 3 *Herpesvirales* phylogeny based on DNA polymerase sequences. DNA polymerase protein sequences from all available herpesviruses were extracted from public databases and aligned using Mafft v.7.520.A phylogenetic tree was constructed from the alignment file using phyml v.3.3.2 and the LG model with gamma distribution, invariant sites and amino acid frequencies. The resulting tree was then manually improved using Illustrator to add the names abbreviations, genomic architecture, size, isomers and latency characterization of the herpesviruses and the host they infect. **A** DNA polymerase tree, ICTV names, abbreviations and hosts. **B** Size and genomic architecture, grey colored sizes correspond to partial genome and black colored sizes correspond to complete genome. U: Unique region, TR: Terminal Repeat, IR: Internal Repeat, UL: Unique Long, US: Unique Short, TRL/IRL: Terminal/Inverted Repeat Long, TRS/IRS: Terminal/Internal Repeat Short, X: X region, a: a region, n: number of the repeat. **C** Genomic isomers. **D** Ability to establish persistence described in literature. L: latency demonstrated, P: Persistence described.

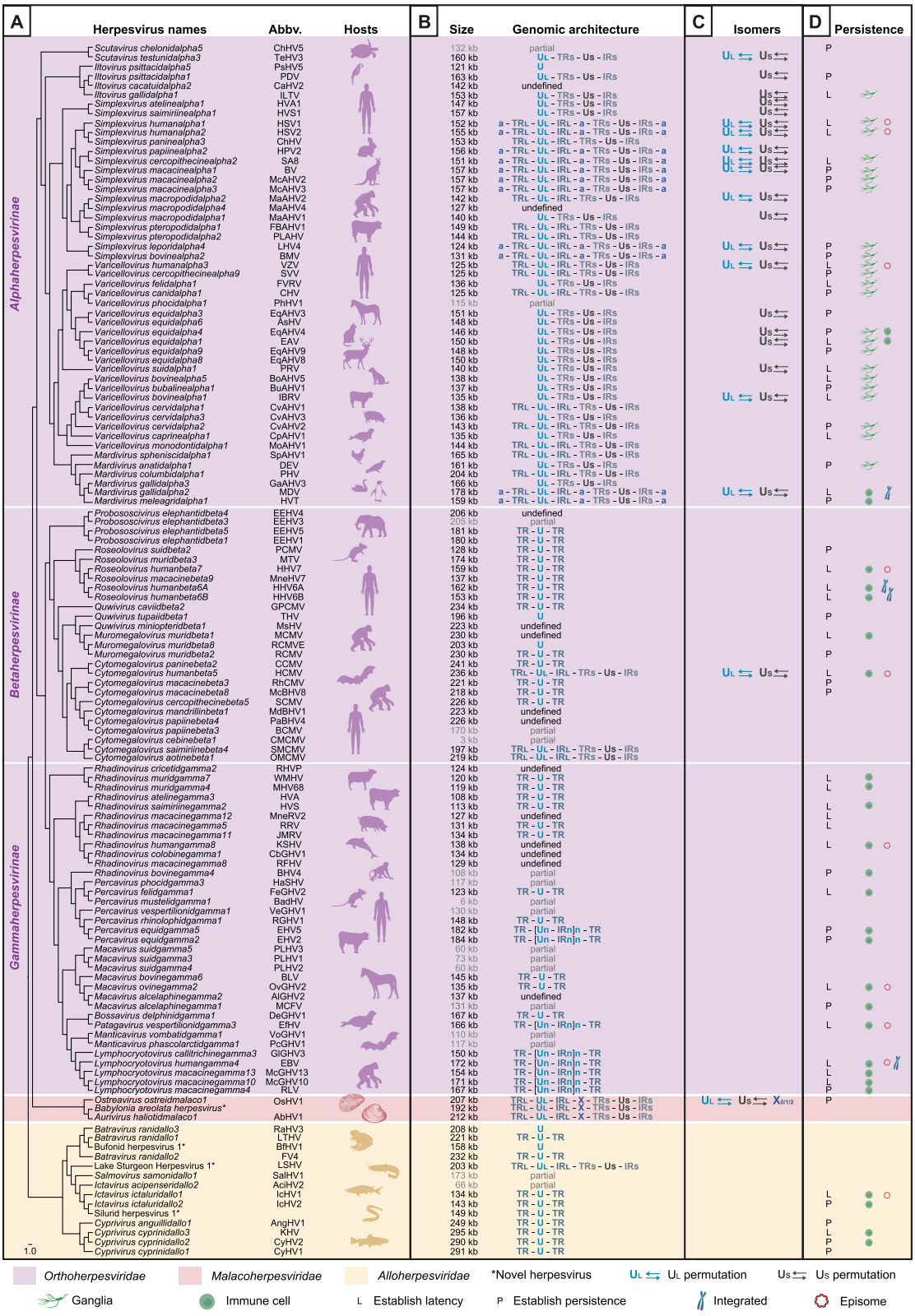

Fig. 3 (See legend on previous page.)

Table 1 Summary table of viruses of the subfamily *Alphaherpervirinae*

	Scientific name	Common name	Abbv	Acc. Number (ICTV)	Reference Acc. Number	Host	Complete genomes	Sequencing technology for ref. genome
Simplexvirus	*atelinealpha1*	Ateline alphaherpesvirus 1	HVA1	KY385637	[45]	Primate	1	Sanger, Illumina
	bovinealpha2	Bovine alphaherpesvirus 2	BMV	MT862163	[46]	Cattle	2	Sanger, Illumina, ONT
	cercopithecinealpha2	Cercopithecine alphaherpesvirus 2	SA8	AY714813	[47]	Primate	1	Sanger
	humanalpha1	Herpes simplex virus type 1	HSV1	JN555585	[48]	Human	71	Illumina
	humanalpha2	Herpes simplex virus type 2	HSV2	JN561323	[48]	Human	14	Illumina
	leporidalpha4	Leporid herpesvirus 4	LHV4	JQ596859	[49]	Lepus	1	454
	macacinealpha1	Macacine alphaherpesvirus 1	BV	AF533768	[50]	Primate	18	Sanger
	macacinealpha2	Macacine alphaherpesvirus 2	McAHV2	KY628968	[45]	Primate	1	Sanger, Illumina
	macacinealpha3	Macacine alphaherpesvirus 3	McAHV3	KY628970	[45]	Primate	1	Sanger, Illumina
	macropodidalpha1	Macropodid alphaherpesvirus 1	MaAHV1	KT594769	[51]	Marsupial	1	Illumina
	macropodidalpha2	Macropodid alphaherpesvirus 2	MaAHV2	MT900475	[52]	Marsupial	1	Illumina
	macropodidalpha4	Macropodid alphaherpesvirus 4	MaAHV4	MT900474	[52]	Marsupial	1	Illumina
	paninealpha3	Panine alphaherpesvirus 3	ChHV	JQ360576	[53]	Primate	1	454
	papiinealpha2	Herpesvirus papio 2	HPV2	DQ149153	[54]	Primate	6	Sanger
	pteropodidalpha1	Fruit bat alphaherpesvirus 1	FBAHV1	AB825953	[55]	Bat	1	454
	pteropodidalpha2	Bat alphaherpesvirus	PLAHV	LC492974	[56]	Bat	1	Sanger, ONT
	saimiriinealpha1	Herpesvirus saimiri 1	HVS1	HM625781	[57]	Primate	1	Sanger, 454
Mardivirus	*anatidalpha1*	Duck enteritis virus	DEV	JF999965	[58]	Bird	10	454
	columbidalpha1	Pigeon herpesvirus	PHV	KX589235	[59]	Bird	2	Sanger
	gallidalpha2	Marek's disease virus	MDV	AF243438	[60]	Bird	65	Sanger
	gallidalpha3	Gallid herpesvirus 3	GaAHV3	HQ840738	[61]	Bird	2	454
	meleagridalpha1	Turkey herpesvirus	HVT	AF291866	[62]	Bird	1	Sanger
	spheniscidalpha1	Spheniscid alphaherpesvirus 1	SpAHV1	LT608135	[63]	Bird	2	454
Varicellovirus	*bovinealpha1*	Infectious bovine rhinotracheitis virus	IBRV	JX898220	[64]	Cattle	50	Sanger, Illumina
	bovinealpha5	Bovine encephalitis herpesvirus	BoAHV5	AY261359	[65]	Cattle	4	Sanger
	bubalinealpha1	Water buffalo herpesvirus	BuAHV1	KU936049	[66]	Cattle	1	Illumina
	canidalpha1	Canine herpesvirus	CHV	KT819633	[67]	Dog	11	Illumina
	caprinealpha1	Goat herpesvirus	CpAHV1	MG989243	[68]	Bovid	1	Illumina
	cercopithecinealpha9	Simian varicella virus	SVV	AF275348	[69]	Primate	1	Sanger
	cervidalpha1	Cervid alphaherpesvirus 1	CvAHV1	MH036942	*Unpublished*	Deer	1	Illumina
	cervidalpha2	Cervid alphaherpesvirus 2	CvAHV2	MH036943	*Unpublished*	Deer	1	Illumina
	cervidalpha3	Cervid alphaherpesvirus 3	CvAHV3	MH036941	*Unpublished*	Deer	1	Illumina

Table 1 (continued)

	Scientific name	Common name	Abbv	Acc. Number (ICTV)	Reference Acc. Number	Host	Complete genomes	Sequencing technology for ref. genome
	equidalpha1	Equine abortion virus	EAV	AY665713	[70]	Horse	28	Sanger
	equidalpha3	Equine coital exanthema virus	EqAHV3	KM051845	[71]	Horse	1	454, Illumina
	equidalpha4	Equine rhinopneumonitis virus	EqAHV4	AF030027	[72]	Horse	10	Sanger
	equidalpha6	Ulcerative stomatitis in donkeys	AsHV	MT012704	[73]	Donkey	1	Illumina
	equidalpha8	Asinine herpesvirus 3	EqAHV8	MF431611	[74]	Horse	6	Illumina
	equidalpha9	Equid alphaherpesvirus 9	EqAHV9	AP010838	[75]	Giraffe	1	Sanger
	felidalpha1	Feline viral rhinotracheitis virus	FVRV	FJ478159	[76]	Feline	37	454
	humanalpha3	Varicella-zoster virus	VZV	X04370	[77]	Human	21	Sanger
	monodontidalpha1	Beluga whale alphaherpesvirus 1	MoAHV1	MF678601	[78]	Whale	1	Illumina
	phocidalpha1	Phocid herpesvirus 1	PhHV1	MH509440	[79]	Seal	0	-
	suidalpha1	Pseudorabies virus	PRV	JF797218	[80]	Swine	51	Illumina
Iltovirus	*cacatuidalpha2*	Cacatuid herpesvirus 2	CaHV-2	MK360902	[81]	Bird	1	Illumina
	gallidalpha1	Infectious laryngotracheitis virus	ILTV	JN596962	[82]	Bird	65	454
	psittacidalpha1	Pacheco's disease virus	PDV	AY372243	[83]	Bird	1	Sanger
	psittacidalpha5	Psittacid alphaherpesvirus 5	PsHV-5	MK955929	[84]	Bird	2	Illumina
Scutavirus	*chelonidalpha5*	Chelonid alphaherpesvirus 5	ChHV5	HQ878327	[85]	Turtle	0	-
	testudinidalpha3	Testudinid herpesvirus 3	TeHV3	KM924292	[86]	Turtle	5	Illumna

This table contains the scientific and common names, abbreviations, accession numbers from ICTV, related articles, hosts, number of complete genomes available on NCBI and the sequencing technology used for the reference genome (according to the accession number and related articles) of viruses of the *Alphaherpesvirinae* subfamily

sea snails. To date three viruses species are characterized in this family: the abalone herpesvirus *Aurivirus haliotidmalaco1*, also known as Abalone Herpesvirus (AbHV-1), the gastropod herpesvirus *Babylonia areolata* herpesvirus (BaHV) (not classified by ICTV yet) and the oyster herpesvirus *Ostreavirus ostreidmalaco1*, better known as Ostreid Herpesvirus Type 1 (OsHV-1) (Fig. 3A) (Table 4) (https://ictv.global/taxonomy, consulted on 28/01/2025).

Alloherpesviridae

The viruses of the *Alloherpesviridae* family contains 13 characterised species, including 3 herpesviruses not classified yet by ICTV (Table 5, herpesviruses with an asterisk), clustered into four genera: the genus *Batravirus* infecting frogs, the genus *Cyvirus* infecting eels and carps, the genus *Ictavirus* infecting sturgeons and catfishes, and the genus *Salmovirus* infecting salmons (Fig. 3A) (Table 5) (https://ictv.global/taxonomy, consulted on 28/01/25).

Perspective on Herpesvirus classification

While the *Orthoherpesviridae* is the largest and most extensively described family, some studies suggest that the *Alloherpesviridae* and *Malacoherpesviridae* families may contain a greater number of as yet uncharacterised herpesviruses [154, 155]. Indeed, interrogation of publicly available sequencing data has recently led to the identification and characterisation of additional herpesviruses, as demonstrated by the detection of ancient HSV-1 and *Simplexvirus* humanalpha2 (HSV-2), strains in Neanderthal genome data [156], and the discovery of four novel malacoherpes-like viruses in SRA database samples [155]. In addition, environmental DNA sequencing-based approaches could facilitate detecting herpesviruses infecting hosts that are difficult to sample, such as terrestrial or marine wildlife species [157, 158]. Finally, methods such as the use of degenerated primers, loop-mediated isothermal amplification, microparticles, or tangential flow filtration, could further

Table 2 Summary table of viruses of the subfamily *Betaherpervirinae*

	Scientific name	Common name	Abbv	Acc. Number (ICTV)	Reference Acc. Number	Host	Complete genomes	Sequencing technology for ref. genome
Cytomegalovirus	*aotinebeta1*	Aotine betaherpesvirus 1	MCMV	FJ483970	*Unpublished*	Primate	1	not published
	cebinebeta1	Cebine herpesvirus 1	CMCMV	JQ264772	*Unpublished*	Primate	0	-
	cercopithecinebeta5	Cercopithecine betaherpesvirus 5	SCMV	FJ483968	*Unpublished*	Primate	3	not published
	humanbeta5	Human cytomegalovirus	HCMV	AY446894	[87]	Human	345	Sanger
	macacinebeta3	Rhesus cytomegalovirus	RhCMV	AY186194	[88]	Primate	30	Sanger
	macacinebeta8	Macaque cytomegalovirus	McBHV8	JN227533	[89]	Primate	7	Illumina
	mandrillinbeta1	Mandrillus leucophaeus cytomegalovirus	MdBHV1	KR297253	[90]	Primate	1	454
	paninebeta2	Panine betaherpesvirus 2	CCMV	AF480884	[91]	Primate	1	Sanger
	papiinebeta3	Olive baboon cytomegalovirus	BCMV	AC090446	*Unpublished*	Primate	0	-
	papiinebeta4	Chacma baboon cytomegalovirus	PaBHV4	KR351281	[90]	Primate	1	454
	saimiriinebeta4	Saimiriine betaherpesvirus 4	SMCMV	FJ483967	*Unpublished*	Primate	1	not published
Muromegalovirus	*muridbeta1*	Murine cytomegalovirus	MCMV	GU305914	[92]	Mice	15	Sanger
	muridbeta2	Rat cytomegalovirus strain Maastricht	RCMV	AF232689	[93]	Rat	1	Sanger
	muridbeta8	Rat cytomegalovirus strain England	RCMVE	JX867617	[94]	Rat	3	454, Sanger
Quwivirus	*caviidbeta2*	Guinea pig cytomegalovirus	GPCMV	KC503762	[95]	Rodent	2	Illumina
	miniopteridbeta1	Miniopterus schreibersii herpesvirus	MsHV	JQ805139	[96]	Bat	1	454
	tupaiidbeta1	Tupaiid betaherpesvirus 1	THV	AF281817	[97]	Shrew	1	Sanger
Roseolovirus	*humanbeta7*	Human herpesvirus 7	HHV7	AF037218	[98]	Human	2	Sanger
	humanbeta6a	Human herpesvirus 6A	HHV6A	X83413	[99]	Human	4	Sanger
	humanbeta6b	Human herpesvirus 6B	HHV6B	AF157706	[100]	Human	3	Sanger
	macacinebeta9	Macaca nemestrina herpesvirus 7	MneHV7	KU351741	[101]	Primate	1	Illumina
	muridbeta3	Mouse thymic virus	MTV	KY355735	[102]	Mice	2	Illumina, PacBio, Sanger
	suidbeta2	Porcine cytomegalovirus	PCMV	KF017583	*Unpublished*	Swine	1	Illumina

Table 2 (continued)

	Scientific name	Common name	Abbv	Acc. Number (ICTV)	Reference Acc. Number	Host	Complete genomes	Sequencing technology for ref. genome
Proboscivirus	*elephantidbeta1*	Elephantid endotheliotropic herpesvirus 1	EEHV1	KC462165	[103]	Elephant	5	Illumina
	elephantidbeta3	Elephantid endotheliotropic herpesvirus 3	EEHV3	MN373268	[104]	Elephant	0	-
	elephantidbeta4	Elephantid endotheliotropic herpesvirus 4	EEHV4	KT832477	[105]	Elephant	1	Sanger, Illumina
	elephantidbeta5	Elephantid endotheliotropic herpesvirus 5	EEHV5	KF921519	[103]	Elephant	2	Illumina

This table contains the scientific and common names, abbreviations, accession numbers from ICTV, related articles, hosts, number of complete genomes available on NCBI and the sequencing technology used for the reference genome (according to the accession number and related articles) of viruses of the *Betaherpesvirinae* subfamily

improve the detection and characterization of previously unknown herpesviruses [159–163]. While many herpesviruses remain uncharacterized, the 137 currently known herpesvirus species share a highly conserved virion structure,

consisting of a large, linear, double-stranded DNA genome, but exhibit considerable diversity in genetic content and genomic architecture.

Genomic architecture of *Herpesvirales*

Herpesvirus DNA genomes are linear, double stranded and their length varies from 119 kb for the *Rhadinovirus muridgamma4* (MHV68) [132] to 295 kb for *Cyvirus cyprinidallo3* (CyHV3) [151] (Fig. 3B).

An interesting feature of herpesviruses is their distinctive genomic organization [28]. In this section, the different genomic architectures of herpesviruses complete genome are described. To this end, genomic data were collected from the literature and from the genomic public database. For genome without known genomic structure, characterisation was performed manually by visualising genome via the self-alignment dotplot tool implemented in Geneious Prime (https://www.geneious.com/features/prime).

Seven distinct genomic architecture have been described:

- Arch-1: consisting of two unique regions named Unique Long (U_L) and Unique Short (U_S) with the U_S region flanked by inverted repeat regions (IR_S: Internal Repeat Short and TR_S: Terminal Repeat Short), (i.e. U_L—IR_S—U_S—TR_S) (Table 6).
- Arch-2: consisting of two unique regions (U_L and U_S) both flanked by inverted repeat sequences (IR_L: Internal Repeat Long, and TR_L: Terminal Repeat Long for the U_L and IR_S/TR_S for the U_S region), (i.e., TR_L—U_L—IR_L—IR_S—U_S—TR_S) (Table 6).
- Arch-3: similar to Arch-2 with three copies of "a" region, located at both ends of the genome and between the IR_L and IR_S regions (i.e., a-TR_L—U_L—IR_L—a—IR_S—U_S—TR_S-a) (Table 6).
- Arch-4: consisting of a unique DNA sequence (i.e. U) without any repeat sequences.
- Arch-5: consisting in a unique long region (U) flanked by direct repeat regions (i.e. TR—U—TR) (Table 6).
- Arch-6: consisting of terminal repeats (TR) located at either end of the genome, together with internal repeats (IR) interspersed throughout. Unlike the linked repeat arrangement seen in previous genomic architectures, these repeats are not directly linked in pairs. (i.e. TR—$[U_{(n)}$—$IR_{(n)}]_n$—TR) (Table 6).
- Arch7: consisting of two unique regions, U_L and U_S, flanked by the TR_L/IR_L and TR_S/IR_S regions and another region named X located between the IR_L and the IR_S region (i.e. TR_L—U_L—IR_L—X—IR_S—U_S—TR_S) (Table 6).

Orthoherpesviridae

The genomic architecture of *Orthoherpesviridae* viruses varies between families and different genera, as well as within the same genus.

Table 3 Summary table of viruses of the subfamily *Gammaherpervirinae*

	Scientific name	Common name	Abbv	Acc. Number (ICTV)	Reference Acc. Number	Host	Complete genomes	Sequencing technology for ref. genome
Bossavirus	*delphinidgamma1*	Common bottlenose dolphin gammaherpesvirus 1	DeGHV1	KY965444	[106]	Dolphin	1	Illumina
Macavirus	*alcelaphingamma1*	Wildebeest-associated malignant catarrhal fever virus	MCFV	AF005370	[107]	Bovid	0	-
	alcelaphingamma2	Hartebeest-associated malignant catarrhal fever virus	AlGHV2	KF274499	[108]	Bovid	1	Sanger
	bovinegamma6	Bovine lymphotropic herpesvirus	BLV	KJ705001	[109]	Cattle	1	Illumina
	caprinegamma2	Caprine herpesvirus 2	CpHV2	AF283477	[110]	Bovid	0	-
	hippotragine-gamma1	Roan antelope herpesvirus	HiGHV1	DQ083950	[111]	Hipparion	0	-
	ovinegamma2	Sheep-associated malignant catarrhal fever virus	OvGHV2	AY839756	[112]	Bovid	2	Sanger
	suidgamma3	Porcine lymphotropic herpesvirus 1	PLVH1	AF478169	[113]	Swine	0	-
	suidgamma4	Porcine lymphotropic herpesvirus 2	PLHV2	AY170317	[114]	Swine	0	-
	suidgamma5	Porcine lymphotropic herpesvirus 3	PLHV3	AY170316	[114]	Swine	0	-
Percavirus	*equidgamma2*	Equine herpesvirus 2	EHV2	U20824	[115]	Horse	20	Sanger
	equidgamma5	Equine herpesvirus 5	EHV5	KM924295	[116]	Horse	2	Illumina
	felidgamma1	Felis catus gammaherpesvirus 1	FcaGHV1	KT595939	[117]	Feline	1	Sanger, Illumina
	mustelidgamma1	Badger herpesvirus	BadHV	AF376034	[118]	Badger	0	-
	phocidgamma3	Harp seal herpesvirus	HaSHV	KP136799	[119]	Seal	0	-
	rhinolophid-gamma1	Rhinolophus gammaherpesvirus 1	RGHV-1	LC333428	[120]	Bat	1	Ion Torrent
	vespertilionid-gamma1	Bat gammaherpesvirus 8	VeGHV1	KU220026	[121]	Bat	0	-
Rhadinovirus	*atelinegamma2*	Herpesvirus ateles strain 810	AtGHV2	M22036	[122]	Primate	0	-
	atelinegamma3	Herpesvirus ateles	HVA	AF083424	[123]	Primate	1	Sanger
	bovinegamma4	Bovine herpesvirus 4	BHV4	AF318573	[124]	Cattle	0	-
	colobinegamma1	Colobine gammaherpesvirus 1	CbGHV1	MH932584	[125]	Primate	1	Illumina
	cricetidgamma2	Rodent herpesvirus Peru	RHVP	HQ221963	[126]	Rodent	1	454

Table 3 (continued)

	Scientific name	Common name	Abbv	Acc. Number (ICTV)	Reference Acc. Number	Host	Complete genomes	Sequencing technology for ref. genome
	humangamma8	Kaposi's sarcoma-associated herpesvirus	KSHV	AF148805	[127]	Human	37	Sanger
	macacin-egamma11	Japanese macaque rhadinovirus	JMRV	AY528864	[128]	Primate	3	Sanger
	macacin-egamma12	Pig-tailed macaque rhadino-virus 2	MneRV2	KP265674	[129]	Primate	1	Sanger
	macacinegamma5	Rhesus rhadino-virus	RRV	AF083501	[130]	Primate	5	Sanger
	macacinegamma8	Retroperitoneal fibromatosis-asso-ciated herpesvirus	RFHV	KF703446	[131]	Primate	1	Sanger, Illumina
	muridgamma4	Murine gamma-herpesvirus 68	MHV68	U97553	[132]	Mice	3	Sanger
	muridgamma7	Wood mouse herpesvirus	WMHV	GQ169129	[133]	Mice	1	Sanger
	saimiriinegamma2	Herpesvirus saimiri	HVS	X64346	[134]	Primate	1	Sanger
Patagivirus	*vespertilionid-gamma3*	Eptesicus fuscus gammaherpes-virus	EfHV	MF385016	[135]	Bat	1	Illumina, ONT
Manticavirus	*phascolarctid-gamma1*	Koala gammaher-pesvirus 1	PcGHV1	MG452722	[136]	Marsupial	0	-
	vombatidgamma1	Wombat gamma-herpesvirus 1	VoGHV1	MG452721	[136]	Marsupial	0	-
Lymphocryp-tovirus	*callitrichin-egamma3*	Marmoset lym-phosarcoma virus	ClGHV3	AF319782	[137]	Primate	1	Sanger
	gorillinegamma1	Pongine herpes-virus 3	GoGHV1	AJ581752	[138]	Primate	0	-
	humangamma4	Epstein-Barr virus	EBV	AJ507799	[139]	Human	311	Sanger
	macacin-egamma10	cynomolgus macaque lym-phocryptovirus	McGHV10	KP676001	[140]	Primate	1	Illumina
	macacin-egamma13	Macaca arctoides gammaherpesvi-rus 1	McGHV13	NC_076963	[141]	Primate	1	Sanger, Illumina
	macacinegamma4	rhesus lym-phocryptovirus	RLV	AY037858	[142]	Primate	1	Sanger
	paninegamma1	Pongine herpes-virus 1	PnGHV1	AJ581751	[138]	Primate	0	-
	papiinegamma1	Cercopithecine herpesvirus 12	PaGHV1	AJ581750	[138]	Primate	0	-
	ponginegamma2	Pongine herpes-virus 2	PoGHV2	AJ581753	[138]	Primate	0	-

This table contains the scientific and common names, abbreviations, accession numbers from ICTV, related articles, hosts, number of complete genomes available on NCBI and the sequencing technology used for the reference genome (according to the accession number and related articles) of viruses of the *Gammaherpesvirinae* subfamily

Alphaherpesvirinae

Among the 49 herpesviruses species in the subfamily *Alphaherpesvirinae*, 45 genomes have been well characterized, two have only partial genomes and two have no nucleotide sequences in public databases (https://ictv.global/report/chapter/orthoherpesviridae/orthoherpesviridae/alphaherpesvirinae, consulted on 28/01/2025). Their genome size ranges from 120 kb for the bird

Table 4 Summary table of viruses of the family *Malacoherpesviridae*

Scientific name	Common name	Abbv	Acc. Number (ITCV)	Reference Acc. Number	Host	Complete genomes	Sequencing technology for ref. genome
Aurivirus haliotidmalaco1	Abalone herpesvirus	AbHV1	JX453331	[143]	Abalone	3	Sanger, 454, Illumina
Babylonia areolata herpesvirus	Gastropod herpesvirus	-	BK064993	[19]	Sea Snail	1	Illumina, ONT
Ostreavirus ostreidmalaco1	Ostreid herpesvirus type 1	OsHV1	AY509253	[32]	Oyster	28	Sanger

This table contains the scientific and common names, abbreviations, accession numbers from ICTV, related articles, hosts, number of complete genomes available on NCBI and the sequencing technology used for the reference genome (according to the accession number and related articles) of viruses of the *Malacoherpesviridae* family

Table 5 Summary table of viruses of the family *Alloherpesviridae*

	Scientific name	Common name	Abbreviations	Acc. Number (ICTV)	Reference acc. Number	Host	Complete genomes	Sequencing technology for ref. genome
Batravirus	*ranidallo1*	Lucké tumor herpesvirus	LTHV	DQ665917	[144]	Frog	1	Sanger
	ranidallo2	Frog virus 4	FV4	DQ665652	[144]	Frog	1	Sanger
	ranidallo3	Ranid herpesvirus 3	RaHV3	KX832224	[145]	Frog	1	Illumina
	Bufonid herpesvirus 1		BfHV1	NC_040681	[20]	Frog	1	Illumina
Ictavirus	Lake sturgeon herpesvirus 1		LSHV	OK485036	[21]	Sturgeon	1	Illumina
	Silurid herpesvirus 1			MH048901	[22]	Catfish	1	Illumina
	acipenseridallo2	White sturgeon herpesvirus 2	AciHV2	FJ815289	[146]	Sturgeon	0	-
	ictaluridallo1	Channel catfish virus	IcHV1	M75136	[147]	Catfish	2	Sanger
	ictaluridallo2	Black bullhead herpesvirus	IcHV2	MG271984	[148]	Catfish	1	Sanger, Illumina
Cyvirus	*anguillidallo1*	Japanese eel herpesvirus	AngHV1	FJ940765	[149]	Eel	3	Sanger
	cyprinidallo1	Carp pox herpesvirus	CyHV1	JQ815363	[150]	Carp	1	Sanger
	cyprinidallo2	Goldfish hematopoietic necrosis virus	CyHV2	JQ815364	[150]	Carp	6	Illumina
	cyprinidallo3	Koi herpesvirus	KHV	DQ657948	[151]	Carp	21	Sanger
Salmovirus	salmonidallo1	Herpesvirus salmonis	SalHV1	AF023673	[152]	Salmon	0	-
	salmonidallo2	Oncorhyncus masou herpesvirus	SalHV2	EU349274	[153]	Salmon	0	-
	salmonidallo3	Epizootic epitheliotropic disease virus	SalHV3	EU349277	[153]	Salmon	0	-

This table contains the scientific and common names, abbreviations, accession numbers from ICTV, related articles, hosts, number of complete genomes available on NCBI and the sequencing technology used for the reference genome (according to the accession number and related articles) of viruses of the *Alloherpesviridae* family

herpesvirus *Iltovirus psittacidalpha5*, more commonly known as Psittacid alpaherpesvirus 5 (PsHV-5) [84], to 204 kb for the bird herpesvirus *Mardivirus columbidalpha1*, or Columbid Alphaherpesvirus 1 (CoAHV-1, PHV) [59] (Fig. 3B).

Four different genomic architectures have been described in the subfamily *Alphaherpesvirinae*: 22 alphaherpesviruses of the genera *Scatuvirus*, *Iltovirus*, *Mardivirus*, *Simplexvirus* and *Varicellovirus* share the genomic architecture Arch-1 (Table 6), 11 alphaherpesviruses of the genera *Mardivirus*, *Simplexvirus* and *Varicellovirus* share the genomic architecture Arch-2 (Table 6), 11 alphaherpesviruses of the genera *Mardivirus* and *Simplexvirus* share the genomic architecture Arch-3 (Table 6) and the *Iltovirus*

Table 6 Representation of the six canonical genomic architectures found in herpesviruses

Name	Genomic structure	Isomers identified	Family
Arch-1	U_L—IR_S—U_S—TR_S	U_S permutation	*Alphaherpesvirinae*
Arch-2	TR_L—U_L—IR_L—IR_S—U_S—TR_S	U_L and U_S permutations	*Alphaherpesvirinae, Betaherpesvirinae*
Arch-3	a—TR_L—U_L—IR_L—a—IR_S—U_S—TR_S—a	U_L and U_S permutations	*Alphaherpesvirinae*
Arch-4	U	-	*Betaherpesvirinae, Alloherpesvirinae*
Arch-5	TR—U—TR	-	*Gammaherpesvirinae, Betaherpesvirinae, Alloherpesvirinae*
Arch-6	TR—$[U_{(n)}$—$IR_{(n)}]_n$—TR	-	*Gammaherpesvirinae*
Arch-7	TR_L—U_L—IR_L—X—IR_S—U_S—TR_S	U_L and U_S permutations	*Malacoherpesvirinae*

psittacidalpha5 (PsHV-5) [84] have the genomic architecture Arch-4 (Table 6) (Fig. 3B).

Betaherpesvirinae

Among the 27 herpesviruses species of the subfamily *Betaherpesvirinae*, 24 have a complete genome, while three possess only partial genome. Of the 24 herpesviruses with a complete genome, the genomic arrangement of 19 has been characterized. Their size ranges from 128 kb for the swine herpesvirus *Roseolovirus suidbeta2*, more commonly known as porcine cytomegalovirus (SuBHV2; PCMV) [164], to 241 kb for the primate herpesvirus *Cytomegalovirus paninebeta2*, more commonly known as chimpanzee cytomegalovirus (PnBHV2, CCMV) [91] (https://ictv.global/report/chapter/orthoherpesviridae/orthoherpesviridae/betaherpesvirinae, consulted on 28/01/2025).

Three distinct genomic architecture have been described in the subfamily *Betaherpesvirinae*: three betaherpesviruses of the genus *Cytomegalovirus* share the genomic architecture Arch-2 (Table 6), one herpesvirus of the genus *Quwivirus* and one herpesvirus of the genus *Muromegalovirus* share the genomic architecture Arch-4 (Table 6), and 14 viruses of the genera *Cytomegalovirus*, *Muromegalovirus*, *Proboscivirus*, *Quwivirus* and *Roseolovirus* share the genomic architecture Arch-5 (Table 6) (Fig. 3B).

Gammaherpesvirinae

Among the 42 herpesvirus species of the subfamily *Gammaherpesvirinae*, 26 have a complete genome, whereas 16 possess only a partial genome. Of the 26 herpesviruses species with a complete genome, the genomic architecture of 18 viruses has been characterized. The genome size of these viruses ranges from 119 kb for the *Rhadinovirus muridgamma4*, better known as Murine gammaherpesvirus 68 (MHV68) [132], to 184 kb for the equine herpesvirus *Percavirus equidgamma2*, better known as equine herpesvirus 2 (EqGHV2, EVH2) [115] (https://ictv.global/report/chapter/orthoherpesviridae/orthoherpesviridae/gammaherpesvirinae, consulted on 28/01/2025).

Two distinct genomic architectures have been described in *Gammaherpesvirinae*: 10 viruses of the genera *Bossavirus*, *Macavirus*, *Percavirus* and *Rhadinovirus* share the genomic architecture Arch-5 (Table 6) whereas 8 gammaherpesviruses of the genus *Lymphcryptovirus* and *Patagavirus* share the genomic architecture Arch-6 (Table 6) (Fig. 3B).

Malacoherpesviridae

The complete genomes of the three viruses of the family *Malacoherpesviridae* have been characterized. With sizes ranging from 192 kb for the Babylonia areolate herpesvirus [19] to 212 kb for the Aurivirus haliotidmalaco 1; better known as Abalone herpesvirus 1 [143] (https://ictv.global/report/chapter/malacoherpesviridae/malacoherpesviridae, consulted on 28/01/2025).

These three malacoherpesviruses share the genomic architecture Arch-7 (Table 6) (Fig. 3B).

Alloherpesviridae

The family *Alloherpesviridae* contains 13 viruses of which 9 have a complete genome available in genomic public database. Among these 9 herpesviruses, the genomic architecture of 8 viruses have been characterized. The genome sizes of these viruses range from 134 kb for the catfish herpesvirus *Ictavirus ictaluridallo1*, more commonly known as ictalurid herpesvirus 1 (CCV) [147], to 295 kb for the koi herpesvirus *Cyvirus cyprinidallo3*, or Cyprinid herpesvirus 3 (CyHV3) [151] (https://ictv.global/report/chapter/alloherpesviridae/alloherpesviridae, consuled on 28/01/2025).

Two distinct genomic architecture have been described in the family *Alloherpesviridae*: the *Batravirus ranidallo3*, also known as Ranid herpesvirus 3 (RaHV3) [145] and the bufonid herpesvirus 1 (not classified by ICTV yet) [20] share the genomic architecture Arch-4

(Table 6), and the Lake sturgeon herpesvirus 1 (not classified by ICTV yet) [21] has the genomic architecture Arch-2 (Table 6) whereas all viruses with a complete genome of the genera *Cyvirus* and *Ictavirus*, the Silurid herpesvirus 1 (not classified by ICTV yet) [22] and two viruses of the genus *Batravirus* share the genomic architecture Arch-5 (Table 6) (Fig. 3B).

Insights into the role of herpesvirus genomic architecture

Herpesvirus genomes are among the most complex viral genomes [6]. The genomic architecture of these genomes varies between families and genera. However, the majority of herpesviruses have inverted repeat regions making their genomes difficult to characterise. While the genome architecture of known *Malacoherpesviridae* viruses has been fully characterized, it is still lacking for some viruses of the *Alloherpesviridae*, *Betaherpesvirinae* and *Gammaherpesvirinae* families. Recent advances in long-read sequencing technologies have provided powerful tools for the sequencing and assembly of complex viral genomes, enabling more accurate and comprehensive analyses of genomic structures. For instance, long-read sequencing has allowed resolving the inverted repeat regions of OsHV-1 [165], HSV-2 [166], and EfHV [135], and detecting genomic isomerization events through sequencing [160, 165–167]. Inverted repeat regions are thought to contribute to the formation of genomic isomers within individual viruses, with potential implications for the regulation of the herpesvirus life cycle [168, 169]. Therefore, a better understanding of these genomic architectures is crucial to characterise and understand their impact on the viral life cycle, viral infectivity and adaptation to their host.

Genomic isomerization of *Herpesvirales* and its phenotypic implications

The genomic architectures described above represent the canonical genomic organisation of the various herpesviruses characterized to date (Tables 1, 2, 3, 4 and 5). However, several large structural variations termed isomers, resulting from the permutation of the unique regions surrounded by repeated and inverted regions (IR_L/TR_L and IR_S/TR_S) have been described [32, 49, 86, 165–174]. Several approaches have been used to characterise these viral isomerisations, including restriction endonuclease digestion and southern blot hybridisation [32, 49, 86, 167–173], DNA denaturation and electron microscopy [166], long-range PCR [174] and more recently long-read sequencing [160, 165].

Three genomic architectures (Arch-2, Arch-3, and Arch-7) can lead to four viral isomerisation by the permutation of U_L and U_S in the *Alphaherpesvirinae*, *Betaherpesvirinae* and *Malacoherpesviridae* families (Table 6) [32, 47, 49, 50, 50, 51, 54, 86, 165, 172–176]. In addition, the genomic architecture Arch-1 can lead to two viral isomerisations resulting from the permutation of the U_S region, specifically in the *Alphaherpesvirinae* subfamily [45, 51, 57, 83, 168, 170, 171, 177].

Cause and consequence of genome isomerisation of herpesviruses are still not fully understood. However, for HSV-1, one of the herpesviruses whose isomers have been well studied, isomerisation appears to result from homologous recombination between inverted repeat regions during DNA replication [178, 179]. DNA denaturation and electron microscopy allowed characterizing four HSV-1 genome isomers [166]: (i) the P isomer (for prototype), where U_L and U_S are in sense direction; (ii) the I_L where U_L is inverted; (iii) the I_S where U_S is inverted; and finally (iv) the I_{LS}, involving inversions of both the U_L and U_S regions. These isomers are typically found in equimolar proportions in HSV-1 [180, 181]. Similar isomer proportion patterns have been observed for HSV-2 [165] and for OsHV-1 [32, 160].

Interestingly, for HSV-1, isomer proportions seem to depend on the type of cells infected and the virus strain. Indeed, in HSV-1 KOS strain isolated from the mouse cornea, the proportions of the four isomers are equivalent. In contrast, when the virus is isolated from the trigeminal ganglia of infected mice, a site where HSV-1 establishes latency, the I_{LS} isomer is overrepresented [175].

Although, isomers have been identified and characterised for several herpesvirus families, many other herpesviruses including repeated and inverted genomic regions could also show signs of isomerisations. New long read sequencing methods should facilitate the characterisation of herpesvirus isomerisation. Interestingly, analysis of gene annotations across all complete herpesvirus genomes shows that viral genes do not span isomerization boundaries suggesting that gene integrity is preserved during genomic isomerization events. However, the functional consequences of isomerization remain unclear. Further investigation is needed to determine whether different genomic isomers influence viral replication dynamics or infectivity, and whether the coexistence of multiple isomeric forms within the same host cell is required for productive infection. To date, the biological role of genomic isomers remains largely unknown, particularly with respect to their potential impact on replication fidelity and viral fitness.

Herpesviruses life cycle

The viral cycle of herpesviruses is divided into two main phases: a lytic phase and a persistence phase. During the lytic phase, viral genes are expressed and translated

into viral proteins that regulate viral DNA replication, the formation of new capsids and the production of new viral particles shed from infected host cells, allowing the virus to replicate and spread to new hosts [182]. During the persistence phase, the virus remains in the host without being damaged by the host's immune system. In general, two scenarios can occur during this phase: the virus can either establish a balance between its replication rate and the host's immune response, or it can enter a latent state in which viral replication ceases [183–185]. Although all herpesviruses studied for persistence characterisation enter latency, the persistence phase has not been described for all herpesviruses. In the following sections, we will use the term "persistence" (Fig. 3D) to refer to herpesviruses known to establish persistence but for which latency has not been demonstrated or studied at the molecular level, and "latency" (Fig. 3D) to refer to those with demonstrated latency.

Lytic phase

The lytic phase described in this section provides a general overview of the herpesvirus lytic cycle, primarily based on key steps elucidated in extensively studied human herpesviruses. In contrast, the replication cycles of herpesviruses infecting non-human hosts remain largely uncharacterized. To date, among the 137 herpesvirus species, replication has been studied in only 19 of 49 alphaherpesviruses, 9 of 27 betaherpesviruses, 9 of 42 gammaherpesviruses, 2 of 3 malacoherpesviruses, and 3 of 16 alloherpesviruses. This limited knowledge is largely attributable to the difficulty of working with unculturable viruses, as suitable cell lines are unavailable for most host species.

The lytic phase of herpesviruses generally involves several key steps (Fig. 4). First, viral particles bind to receptors on the surface of host cells, a process mediated by glycoproteins located on the surface of the viral envelope (Fig. 4, step 1). Once receptor binding is complete, herpesviruses enter in the cells via two primary mechanisms: direct fusion of the viral envelope with the cell membrane, or membrane fusion following uptake by endocytosis (Fig. 4, step 2) [8, 186, 187]. Once within the host cell, the capsid along with the viral proteins carried by the envelope are released into the cytoplasm. These envelop proteins facilitate the transport of the capsid to the host cell nucleus. In fact, due to the dense and highly organised structure of the cytoplasm, diffusion alone is not sufficient for capsid movement from the cell surface to the nucleus. Instead, capsids actively use microtubules as a transport pathway by binding to microtubule motors through a series of interactions (Fig. 4, step 4). Finally, capsids dock with the nuclear pore complex and release their DNA which is then translocated into the nucleus [8, 25, 188].

Once the viral genome is released into the nucleus, transcription of viral genes begins with the expression of specific viral genes (Fig. 4, step 4). These genes have been classified in three categories depending on the chronology of their expression: (1) immediate-early (IE) or α genes, (2) early (E) or β genes, and (3) late (L) or γ genes [8, 191, 193]. The first genes to be transcribed are the IE genes and code for protein involved in the activation of the transcription of other viral genes [193, 194], RNA splicing [195], and inhibit transcription of host genes [196]. Polypeptides and proteins encoded by E genes are mainly involved in the activation of DNA replication [8, 193], but also in the inhibition of the expression of some IE genes and host cell genes. Finally, late genes are expressed once the genome replication starts [8, 187]. Many of these L genes code for structural proteins involved in virus assembly [8, 25]. At this stage of the infection, the three categories of genes may be expressed simultaneously [25, 26].

DNA replication occurs in the nucleus of infected cells and usually begins when E genes are expressed (Fig. 4, step 5). DNA replication is a two-step process involving initiation by the binding of the origin binding protein to the origin of replication leading to the formation of the replication complex, which replicates the molecule through an intermediate such a theta molecule (Fig. 4, step 5.a) in a process that produces circular progeny DNA molecules. A rolling circle mechanism has been proposed for the second step of DNA synthesis (Fig. 4, step 5b) [8]. This mechanism produces long concatemers of viral genomes (i.e. long DNA molecules consisting of repeated genomes forming a linear multimer), which are cut into genomic units during packaging of the DNA into newly formed capsids [192, 197].

Newly synthesized capsid proteins accumulate in the nucleus to form three types of capsids: C capsids, in which DNA is packaged (Fig. 4, step 6); B capsids, in which viral proteins accumulate; and A capsids which remain empty of DNA or viral proteins and are likely the result of aborted packaging step [25, 26].

The DNA-filled capsids (nucleocapsids) exit the nucleus through a process of envelopment at the inner nuclear membrane forming a primary enveloped particle within the perinuclear space (Fig. 4, step 7.a.). This step is followed by fusion of the primary enveloped particle with the outer nuclear membrane releasing the nucleocapsid without the primary envelop into the cytoplasm with the help of the nuclear egress complex (NEC) (Fig. 4, Step 7.b) [198–201]. The released nucleocapsid then acquires its tegument and mature envelope through different cytoplasmic organelles depending on the herpesvirus species. For example, HCMV tegumentation takes place in the cytoplasmic virion assembly complex

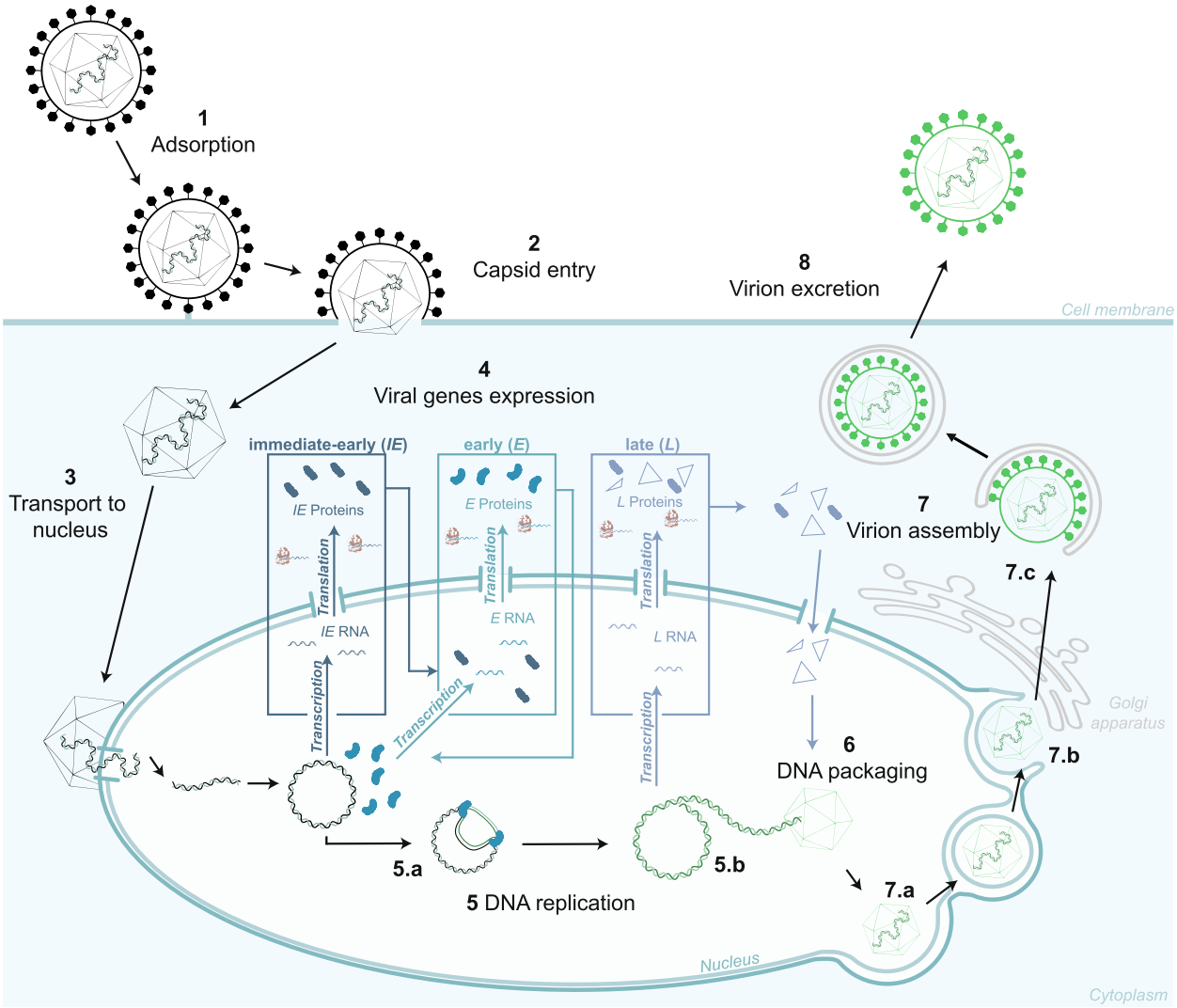

Fig. 4 Herpesviruses proposed lytic phase. Adapted from [25, 26, 154, 182, 189–194]

(cVAC) [202–204] whereas HSV-1 acquires its tegument from the Golgi apparatus [8]. Tegumented nucleocapsids acquire their mature (secondary) envelope either in the trans-Golgi network for HSV-1, recycling endosomes for HCMV or multivesicular bodies for HHV-6A (Fig. 4, step 7.c) [8, 198, 199]. Vesicles containing enveloped virions are transported to the plasma membrane, where vesicle membrane fuses with the plasma membrane. Mature virions are then released into the extracellular space where they can infect other cells from the same or from different individuals (Fig. 4, step 8) [8, 25, 198, 199].

Persistent phase

The second phase of the herpesvirus life cycle is the persistence phase. Among the 137 recognized herpesvirus species, persistence has been investigated in 28 of 49 alphaherpesviruses, 10 of 27 betaherpesviruses, 17 of 42 gammaherpesviruses, 1 of 3 malacoherpesviruses, and 6 of 13 alloherpesviruses. However, molecular evidence of latency has been demonstrated for only 31 of these 62 species (Fig. 3D) [49, 133, 140, 141, 205–234].

Herpesviruses that have been characterized for persistence primarily persist in two specific tissues within their hosts. Herpesviruses of the family *Alphaherpesvirinae* establish persistence primarily in the trigeminal ganglion of their hosts (23 herpesviruses species, Fig. 3D) [47, 67, 80, 211, 214, 223, 230, 235–245] (Fig. 3D). However, Galliformes herpesviruses and herpesviruses of the subfamilies *Betaherpesvirinae, Gammaherpesvirinae,* and of the families *Malacoherpesviridae* and *Alloherpesviridae* establish their persistence in the immune system cells of their hosts (28 herpesviruses species, Fig. 3D) [24, 140, 216, 224, 225, 228, 246–248] (in green in Fig. 3D).

Based on a comprehensive literature review of 31 herpesviruses with documented latency at the molecular level, the following sections describe the mechanisms that maintain viral genome and gene expression during latency and the processes that trigger herpesvirus reactivation.

Maintenance of the viral genome during latency

Depending on the host, different mechanisms are required to maintain latency. For herpesviruses that establish latency in dividing cells, these mechanisms must ensure stable retention of the viral genome in the nucleus of infected cells and its transmission to daughter cells during cell division. There is relatively little information in the literature about these mechanisms. To date, two main mechanisms have been described to maintain viral herpes genome in infected cells: the circularisation of the viral genome as episome (10 herpesviruses species, Fig. 3D) or the integration of the viral genome into host DNA (4 herpesviruses species, Fig. 3D).

Episomes formation has been demonstrated for several herpesviruses including human herpesviruses (i.e. HSV-1, HSV-2, *Cytomegalovirus humanbeta5* (HCMV), *Varicellovirus humanalpha3* (VZV), *Lymphocryptovirus humangamma4* (EBV), HHV-6, and *Roseolovirus humanbeta7* HHV-7) [24], bovines herpesvirus (*Macavirus ovinegamma2*, OvGHV-2) [228, 249], bat herpesvirus (*Patagivirus vespertilionidgamma3*, EfHV) [250], mouse herpesvirus (*Rhadinovirus muridgamma4*, MHV68) [251] and fish herpesvirus (i.e. *Ictavirus ictaluridallo1*, IcHV1) [227] (Fig. 3D). After initial infection and virus entry into the trigeminal ganglion or host immune cells, the linear herpesvirus genome becomes circularised by fusion of terminal repeats located at both ends of the genome and is rapidly chromatinised in the nucleus [24, 252–254, 254, 255]. Herpesviruses that establish latency in immune cells capable of division must ensure their persistence during cell replication (Fig. 3D). To achieve this, they synthesize viral proteins that facilitate the attachment of the viral episome to the host chromosome, enabling the transmission of the viral genome to daughter cells. [256] (Fig. 5A).

Integration into host DNA has been described for MDV, HHV-6 and EBV (Fig. 5B). The process of integration involves the terminal regions of MDV and HHV-6 genomes that contain perfect repeats of the telomeric sequence of their host chromosomes [257–259]. While the precise mechanisms underlying this integration remain unclear, certain viral proteins such as 5'-3' exonuclease, single-strand DNA binding protein or adeno-associated virus 2 integrase, may facilitate MDV and HHV-6 integration, respectively [260]. In contrast, EBV does not integrate at a single site like MDV and HHV-6; instead, its integration is non-random, occurring predominantly in heterochromatic regions of the host genome, which are rich in repetitive sequences and lack functional genes [261]. By integrating into the host DNA, these herpesviruses ensure the stable maintenance of their genome during cell division.

Regulation of viral genes expression during latency

To evade detection by the host immune system, herpesviruses must tightly regulate the expression of their lytic genes and modulate host genes activity to prevent elimination of the infected cell. This is achieved by three different mechanisms including expression of viral long non-coding RNAs (lncRNA), microRNAs (miRNA) and non-lytic protein-coding genes.

Many herpesviruses express lncRNAs that contribute to the establishment of latency. These transcripts are transcribed antisense to immediate-early genes and induce the regulation of their transcription [24, 231, 262, 263]. lncRNAs are also involved in epigenetic modifications of histones, such as trimethylation and demethylation, leading to the formation of repressive heterochromatin around viral DNA, thereby preventing lytic gene transcription. In addition, these lncRNAs contribute to the inhibition of apoptosis, ensuring the long-term persistence of the viral genome (Fig. 6) [24, 262].

Viral and host miRNAs play an important role in modulating latency [24, 264, 265]. They can contribute to the degradation of lytic mRNA or to the inhibition of lytic protein translation, and to the regulation of host cell genes expression. All these mechanisms lead to the evasion of recognition of latently infected cells by the host immune system, to reduce the expression of immediate-early genes and are also involved in the inhibition of apoptosis [24, 264, 266, 267] (Fig. 6).

Finally, some herpesviruses express protein-coding genes that play also essential roles in maintaining latency. Similar to lncRNAs and miRNAs, these non-lytic proteins are involved in epigenetic modifications of histone, tethering the viral episome to the host chromosome, promoting cell cycle progression, and inhibiting apoptosis. Together, all these processes contribute to the stable persistence of the viral genome inside host cells (Fig. 6) [24, 209, 268].

While these mechanisms ensure the long-term viral latency, herpesviruses have also developed strategies to emerge from this dormant state upon stress activation and when conditions are favourable for viral replication.

Reactivation

The success of herpesviruses is primarily due to their ability to reactivate from a latent state. Viral

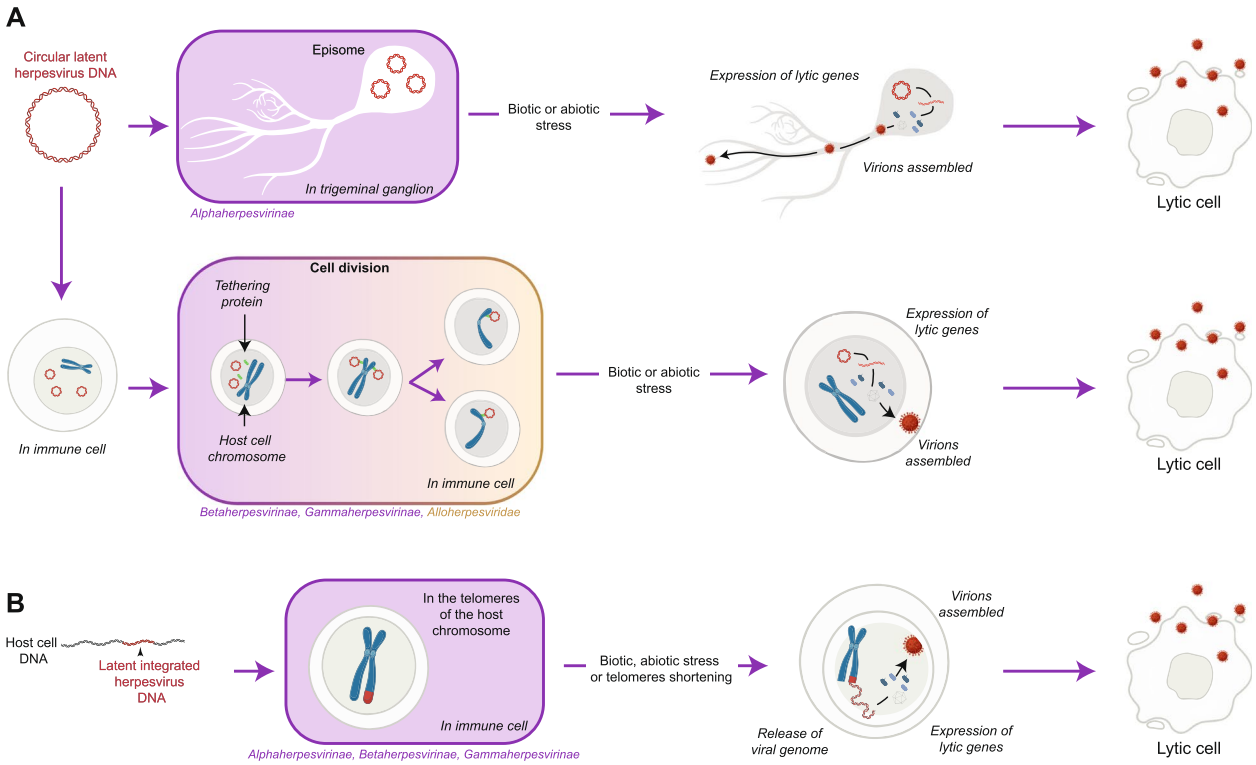

Fig. 5 Mechanisms of herpesvirus latency maintenance and reactivation. **A** Herpesvirus DNA can be maintained in a circular episomal form within hosts cells. In ganglia cells, episome stay free in the cell while in immune cell, the viral episome is tethered to the host chromosome by specific proteins ensuring that viral DNA is passed on during cell division. Stress can lead to reactivation of herpesvirus. **B** Some herpesviruses can integrate their latent DNA directly into the host cell genome. This integration often occurs in the telomeric regions of the host chromosome, allowing the virus to persist and evade immune detection. A stress or the natural shortening telomeres can lead to reactivation of the herpesvirus genome

reactivation can occur spontaneously, but is more likely to occur in response to biotic or abiotic stress of their host. In the case of HSV-1, several stimuli that induce neuronal stress have been shown to trigger viral reactivation in cell culture, including removal or inhibition of neurotrophic factors and exposure to UV light. In humans, triggers include exposure to sunlight, hormonal fluctuations or surgical resection [193, 269–273]. For *Varicellovirus felidalpha1* (FVRV) which infects cats, stressors such as environmental changes can lead to viral reactivation [220], while for MDV: *Mardivirus gallidalpha2,* also known as Marek's disease virus (MDV), factors such as hypoxia, apoptosis or a decrease of temperature can induce viral reactivation in cell culture [24, 251, 274] (Fig. 5A). For herpesviruses that integrate inside telomeres of their host chromosome, viral reactivation could also be induced by the natural shortening of the telomeres that could either relieve suppression of viral gene transcription or inducing telomere-telomere recombination, resulting in release of the virus genome from the integration site (Fig. 5B) [260].

The mechanisms of herpesviruses reactivation are not fully understood. Based on the work done on HSV-1 and murine neurons, the reactivation can be divided in two phases. The first one, called "animation", involves decrease of lncRNAs and miRNAs expression, transcription from the silenced DNA that does not follow the same well-ordered process of gene transcription that occurs during the lytic phase [193, 253, 263, 275, 276]. Once some viral proteins are translated, the second reactivation phase starts, classical cascade of virus gene expression occurs (see Lytic Phase), progeny virions are assembled and transported to axon termini to be released in epithelial cells in the mucosa or skin resulting in disease [24, 193, 276].

Perspectives and insights into herpesvirus life cycle comprehension

For most herpesvirus species (95 out of 137), the lytic phase has not yet been described at the transcriptomic level. This is likely due to the high transcriptional complexity of herpesviruses [277], as well as challenges in developing suitable models to study them and/or

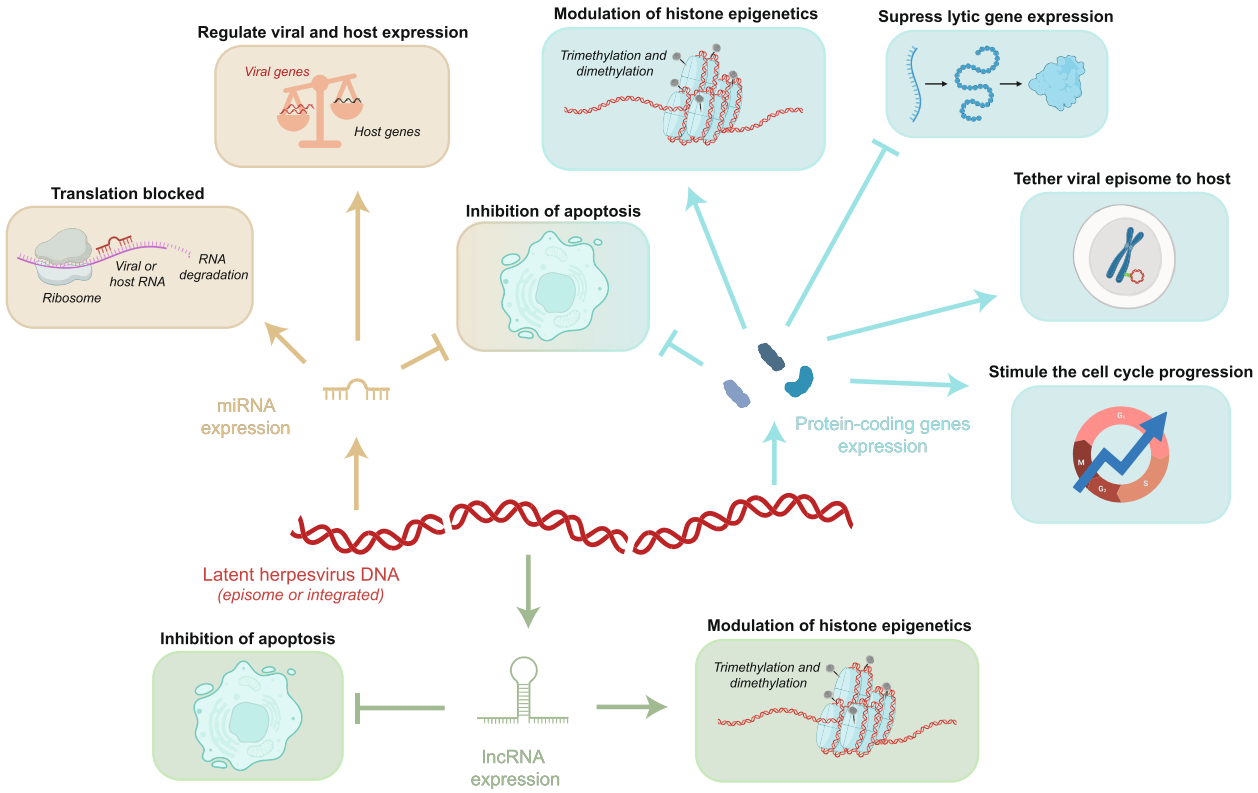

Fig. 6 Mechanisms of regulation of viral genes expression during latency.LncRNAs, protein-coding genes and miRNAs are expressed during the latency phase and play a role in the maintenance of the latency by modulating histone epigenetics, inhibiting apoptosis of the infected cells, stimulating the cell cycle progression, blocking translation of lytic proteins, regulating viral and host expression and suppressing lytic gene expression

difficulties in inducing the lytic phase in some species [278]. Latency has been demonstrated in 31 of the 137 known herpesvirus species but it is likely that other herpesviruses also have the ability to establish latency in their hosts. With the exception of the *Malacoherpesviridae* family, all herpesvirus families contain at least one species for which latency has been demonstrated at the molecular level, supporting the hypothesis that latency is a common feature of the persistent phase. Indeed, aquatic herpesviruses become undetectable at low water temperatures in winter and reactivate in summer when temperatures rise, suggesting the presence of a latency phase [279].

Recent advances in sequencing and imagery technologies, such as single-cell genomics and transcriptomics, spatial transcriptomic and multi-omics approaches, allow studying viral gene expression alongside the host cell immune response, providing a more comprehensive view of the viral development in different tissues or even in different cell types [280, 281]. Long-read sequencing technologies enable the characterization of full-length viral transcripts and the identification of polycistronic RNAs [282, 283]. Moreover, the study of epigenetic modifications [284–287] could also provide new insights into the life cycle of herpesvirus. This may not only help to characterize the production of new virions at the transcriptomic level, but also to identify non-coding viral transcripts that may support latency.

In addition, many viral genes have not yet been fully functionally annotated, and their true coding potential is still poorly understood. Transcriptomics coupled with proteomics analyses could overcome these limits [283, 288]. Furthermore, machine learning tools such as AlphaFold [289] and DeepLoc (https://services.healthtech.dtu.dk/services/DeepLoc-2.1/) could be used to investigate virus-host protein interactions as well as to predict the localization of the protein in the host cell.

These recent advances in sequencing technologies and bioinformatics tools should significantly improve our knowledge of herpesvirus biology in the coming years.

Conclusion

This review offers an overview on the available information on systematics, genomic architecture and life cycle of herpesviruses. Herpesviruses are large and complex double-stranded DNA viruses, characterized by a capsid that encloses tightly packed DNA, surrounded by a

protein-rich tegument and an outer envelope. They have a complex, family-specific genomic architecture that can be divided into seven groups. For almost all herpesviruses, the genomic architecture includes inverted repeat regions, that lead to the formation of isomers that coexist in equimolar proportions within host cells. The function of these isomers remains poorly understood, probably due to the challenges of their characterization.

To date, 137 herpesviruses species have been described, but many more, particularly within the *Malacoherpesviridae* and *Alloherpesviridae* families, are likely to remain undiscovered. Advances in database analysis, long-read sequencing and purification methods may help facilitate their characterization.

The life cycle of human-infecting herpesviruses is well documented, showing a sequential expression of three categories of genes required for the assembly of new viral particles. In contrast, the replication cycles of non-human herpesviruses remain poorly understood largely due to the lack of suitable cell lines for many non-human species, making in vitro studies difficult. Similar limitations apply to the study of latency at the molecular level. Although several long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) involved in maintaining the viral genome during latency, either integrated or circularized as an episome, have been identified in human herpesviruses, much less is known about these processes in other hosts. This knowledge gap is particularly evident for members of the families *Gammaherpesviridae*, *Malacoherpesviridae*, and *Alloherpesviridae*.

Improving our understanding of the genomic architecture, isomeric configurations and life cycles of herpesviruses, especially those that infect non-human hosts, will be crucial to fill current knowledge gaps. Recent breakthroughs in genomics, transcriptomics, proteomics and imaging now provide the tools to explore these aspects in greater depth and unravel the complex biology and evolutionary dynamics of these viruses, ultimately helping to develop strategies to prevent reactivation and associated disease.

Abbreviations

AbHV-1	*Aurivirus haliotidmalaco1*
BaHV	*Babylonia areolate* Herpesvirus
CCV	*Ictavirus ictaluridallo1*
CoAHV-1, PHV	*Mardivirus columbidalpha1*
cVAC	Cytoplasmic Virion Assembly complex
CyHV3	*Cyvirus cyprinidallo3*
dsDNA	Double-stranded DNA
dsRNA	Double-stranded RNA
E	Early
EBV	*Lymphocryptovirus humangamma4*
EfHV	*Patagivirus vespertilionidgamma3*
EqGHV2, EHV2	*Percavirus equidgamma2*
FRV	*Varicellovirus felidalpha1*
HCMV	*Cytomegalovirus humanbeta5*
HHV-6A	*Roseolovirus humanbeta6*
HHV-7	*Roseolovirus humanbeta7*
HSV-1	*Simplexvirus humanalpha1*
HSV-2	*Simplexvirus humanalpha2*
IcHV1	*Ictavirus ictaluridallo1*
ICTV	International Committee on Taxonomy of Viruses
IE	Immediate-early
IR	Internal Repeat
IR_L	Internal Repeat Long
IR_S	Internal Repeat Short
L	Late
lncRNA	Long non-coding RNA
MDV	*Mardivirus gallidalpha2*
MHV68	*Rhadinovirus muridgamma4*
miRNA	Micro RNA
NEC	Nuclear Egress Complex
NGS	Next Generation Sequencing
OcGHV2	*Macavirus ovinegamma2*
OsHV-1	*Ostreavirus ostreidmalaco1*
PnBHV2, CCMV	*Cytomegalovirus paninebeta2*
PsHV-5	*Iltovirus psittacidalpha5*
RaHV3	*Batravirus ranidallo3*
ssDNA	Single-stranded DNA
ssRNA	Single-stranded RNA
SuBHV2, PMCV	*Roseolovirus suidbeta2*
TR	Terminal Repeat
TR_L	Terminal Repeat Long
TR_S	Terminal Repeat Short
U_L	Unique Long
U_S	Unique Short
VZV	*Varicellovirus humanalpha3*

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