# Virology

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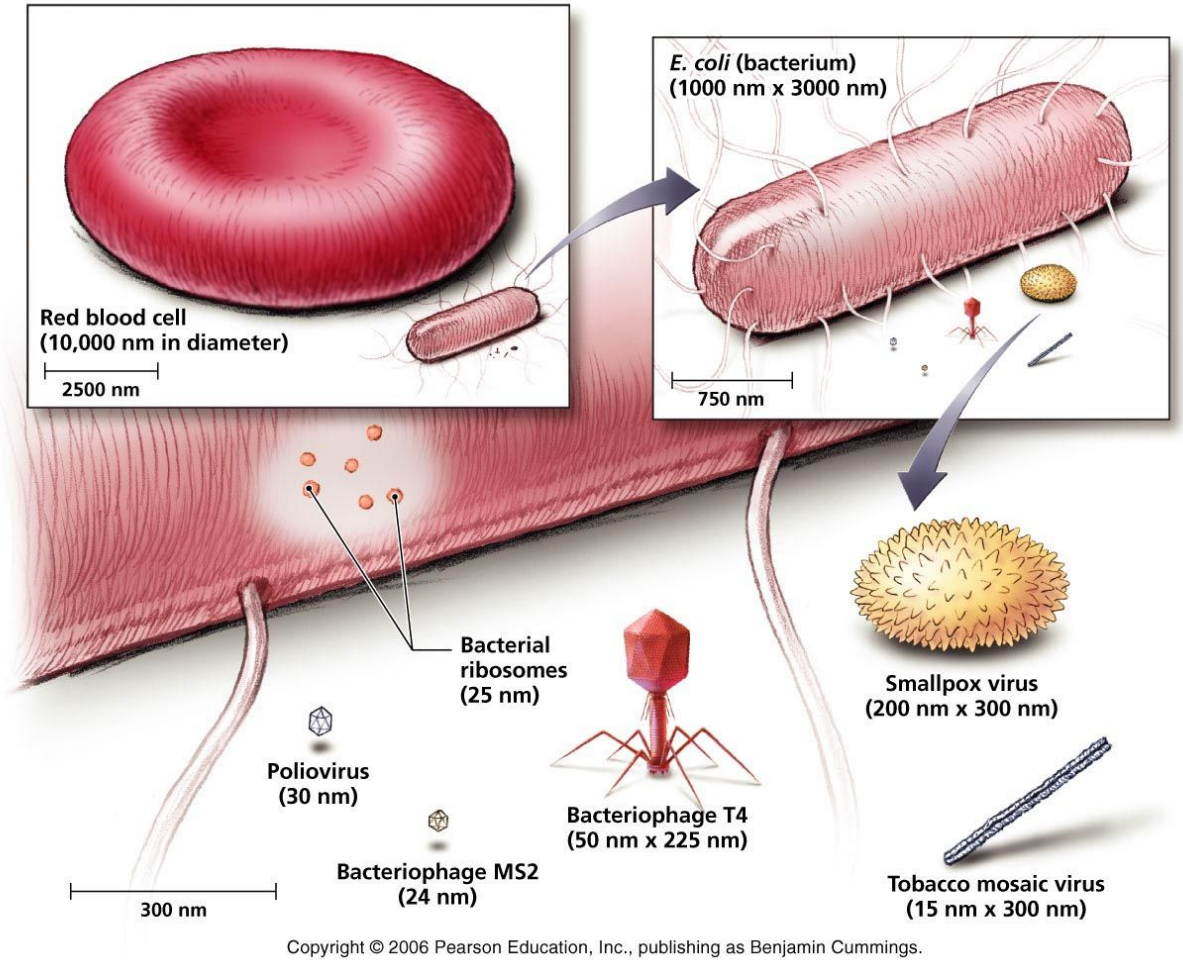
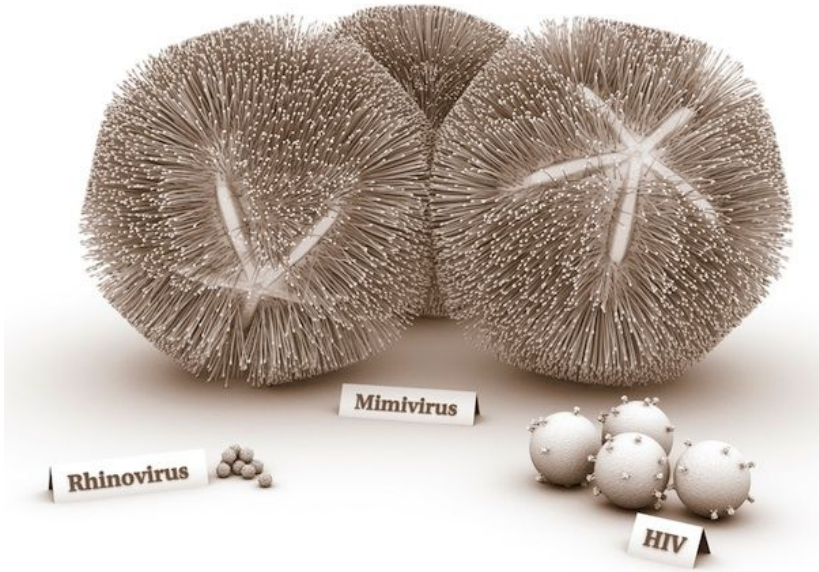
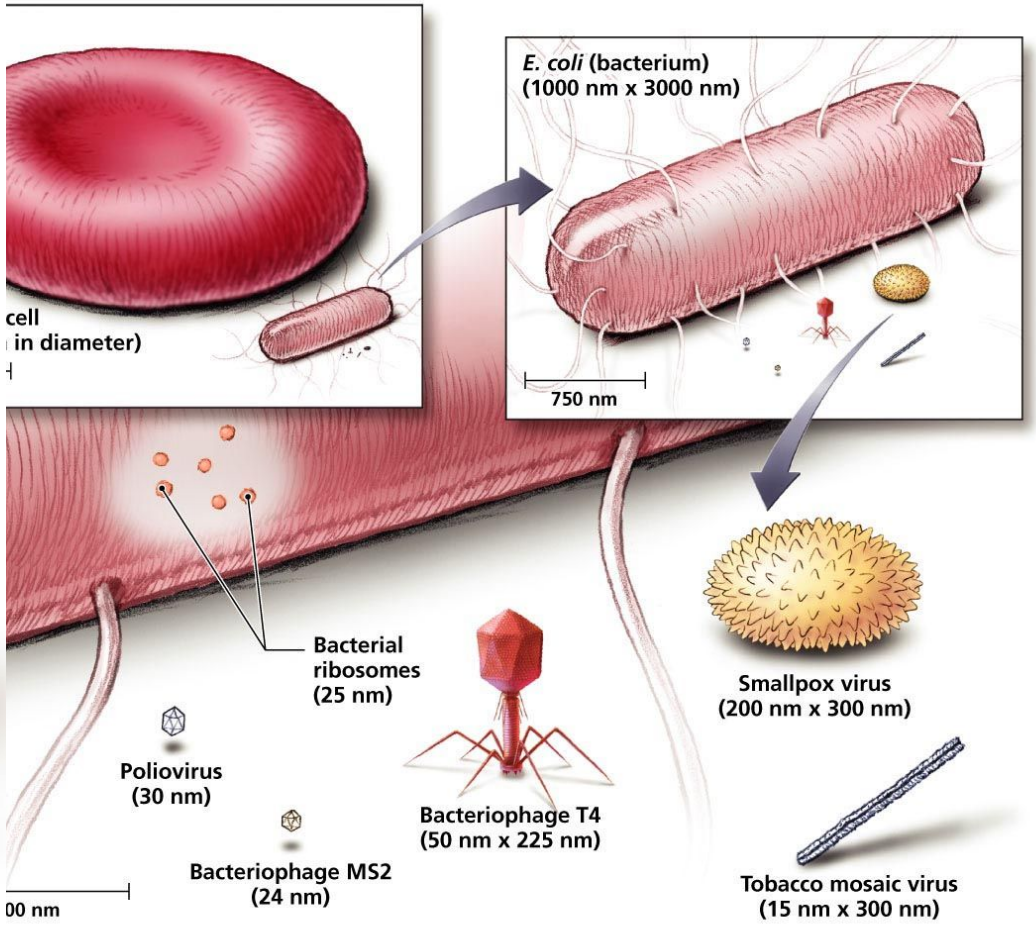
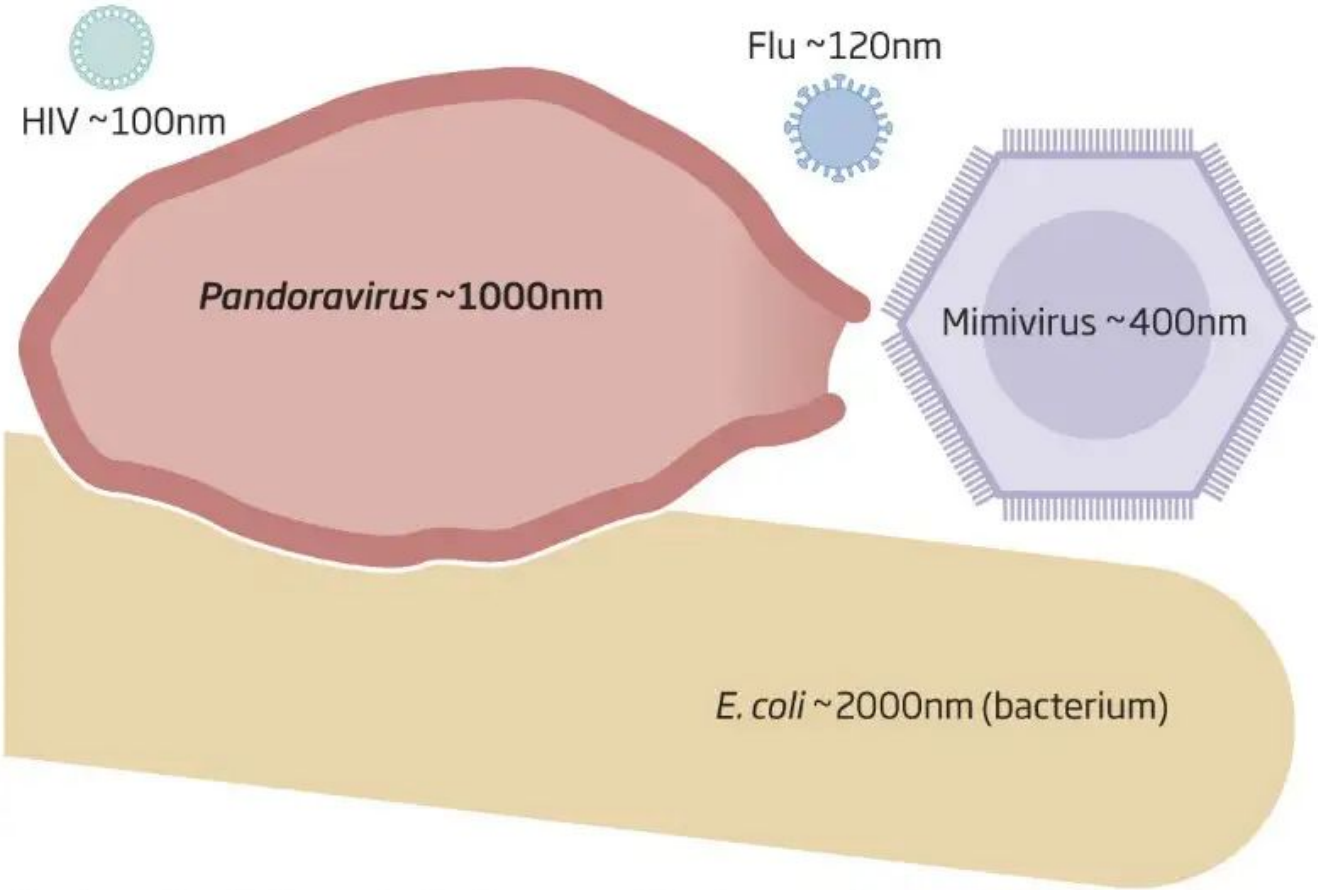


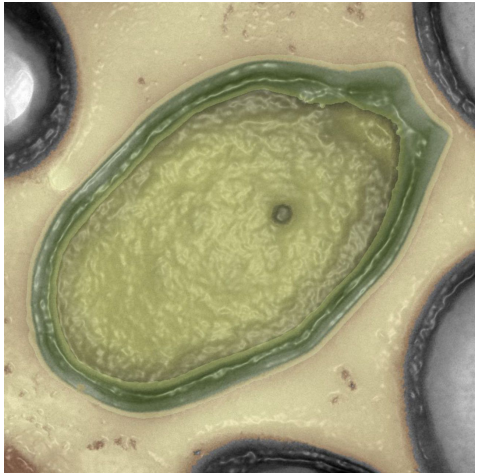
AMERICAN
Scientist
July–August 2011
www.americanscientist.org




SIGMA XI
THE SCIENTIFIC RESEARCH SOCIETY

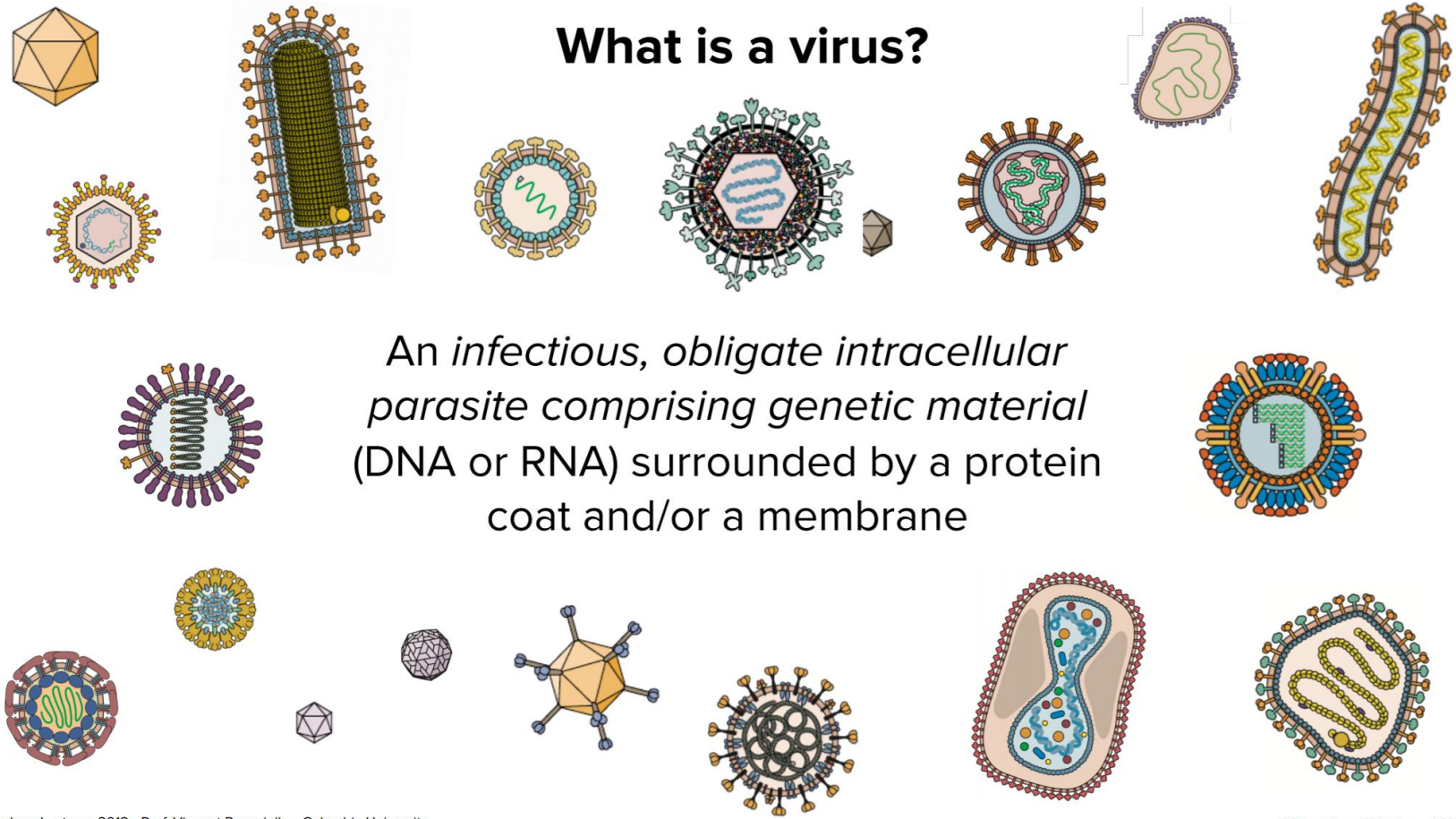




Pandora virus is bigger by far than any other known virus, and rivals bacteria

# What is a virus?



An *infectious, obligate intracellular parasite comprising genetic material* (DNA or RNA) surrounded by a protein coat and/or a membrane

# Why we study viruses?

- ✓Viruses Are Everywhere
- ✓Viruses Infect All Living Things
- ✓Viruses Cause Human Diseases
- ✓Viruses Can Cross Species Boundaries
- ✓Virus “R” Us
- ✓Viruses Are Uniquely Valuable Tools with Which to Study Biology
- ✓Viruses Can Be Used To Manipulate Biology

# We live and prosper in a cloud of viruses

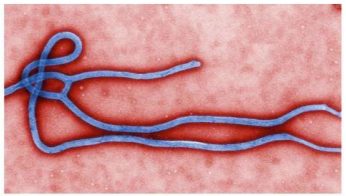
- Viruses are everywhere!! Inside our bodies or around us and even in the air we breathe in.
- We regularly eat and breath billions of virus particles.
- Viruses infect every living thing in the planet.
- We carry genomes as part of our own genetic material

# Virus classification

http://ictvonline.org/

Classical hierarchical system:

| | |
|---|---|
| Kingdom | |
| Phylum | |
| Class | |
| Order (*-virales*) | |
| Family (*-viridae*) | *Filoviridae* (filovirus family) |
| Genus (*-virus*) | *Ebolavirus* |
| Species | *Zaire ebolavirus* |



# International Committee on Taxonomy of Viruses (ICTV)

- In July 2013, the ICTV definition of species changed to state: "A species is a monophyletic group of viruses whose properties can be distinguished from those of other species by multiple criteria."

Viral classification starts at the level of order and continues as follows, with the taxon suffixes given in italics:

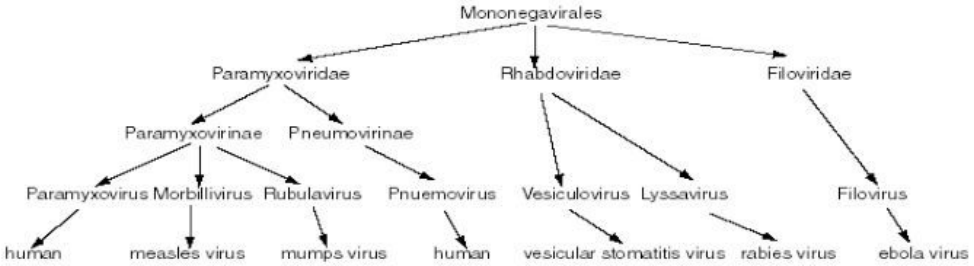
- Order (*-virales*)
- Family (*-viridae*)
- Subfamily (*-virinae*)
- Genus (*-virus*)
- Species

Species names generally take the form of *[Disease] virus*.

**Of, pertaining to, or affecting a single phylum (or other taxon) of organisms.

# Virus taxonomy

| | | | |
|---|---|---|---|
| Order | *virales* | e.g *Mononegavirales* | |
| Family | *viridae* | e.g. *Orthomyxoviridae* | *Herpesviridae* |
| Subfamily | *virinae* | e.g. | *Alphaherpesvirinae* |
| Genus | | e.g. influenzavirusA | Simplexvirus |
| Species | | e.g. influenza A virus | human herpesvirus1 |
| Informally: | | | |
| Type | | e.g. | herpes simplex virus 1 |
| Strain | | e.g. influenza A/PR/8/34 | SC16 |




In biology, binomial names are used. e.g *Rattus rattus, Saccharomyces cerevisiae*

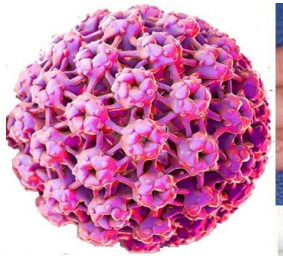
In virology, this does not happen:

*Tobacco etch potyvirus* sounds OK

*Influenza A influenzavirus A* does not!

Bacteriophage have their own rules

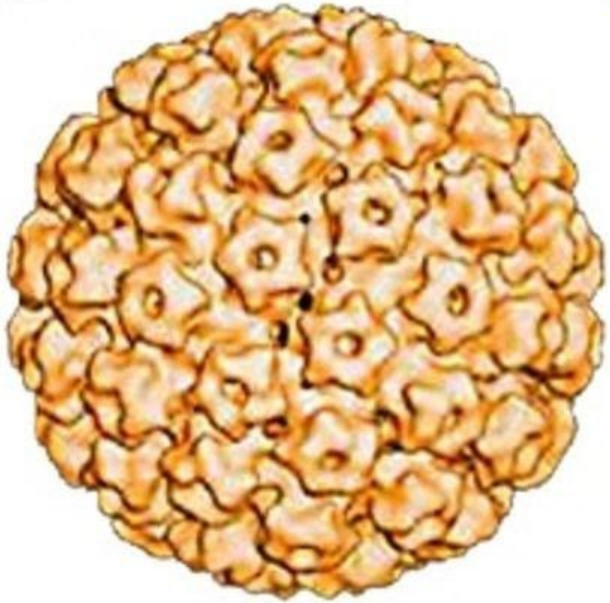
| Family | Genus | Species | Genotype |
|---|---|---|---|
| Papillomaviridae | High risk for Cancer | Alphapapillomavirus | Human papillomavirus-16 | Type 16, Type 31, Type 33, Type 35, Type 52, Type 58 |
| | | | Human papillomavirus-18 | Type 18, Type 39, Type 45, Type 59, Type 68 |
| | | | Human papillomavirus-26 | Type 26, Type 51, Type 82 |
| | | | Human papillomavirus-34 | Type 73 |
| | | | Human papillomavirus-53 | Type 53, Type 56, Type 66 |
| | Low risk for cancer | Alphapapillomavirus | Human papillomavirus-6 | Type 11, Type 44, Type 55 |
| | | | Human papillomavirus-7 | Type 40, Type 91 |
| | | | Human papillomavirus-32 | Type 32, Type 42 |
| | | | Human papillomavirus-54 | Type 54 |
| | | | Human papillomavirus-61 | Type 61, Type 72, Type 81, Type 83, Type 84, Type 62, Type '87, Type 89 |
| | | | Human papillomavirus-71 | Type 71 |
| | | Unclassified Papillomavirus | Human papillomavirus types | Type 64 |



Human Papillomavirus Infection

# HPV is a necessary cause of cervical cancer – 99.7%[4]

## HPV



### Cancer causing Types[1,2,4]

- HPV 16
- HPV 18

- >75% of Cervical Cancer[5,6]
- >50% of Vaginal & Vulvar Cancer[5]

### Non-cancer causing types[1,2]

- HPV 6
- HPV 11

90% of Anogenital warts[5]

# The number of viruses on earth staggering

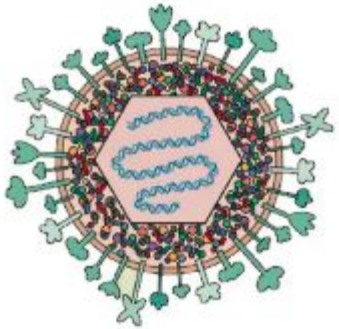
- The whole game with viruses is numbers, they make huge numbers of progeny and maybe a few of them end up infecting a cell and moving on; because life is hard out there for a virus.

- The number of viruses on earth is amazing, just in the oceans alone there are $10^{30}$ bacteriophages (the virus that infect bacteria).

- In the oceans of the world about a million virus per teaspoon.

# How infected we are?

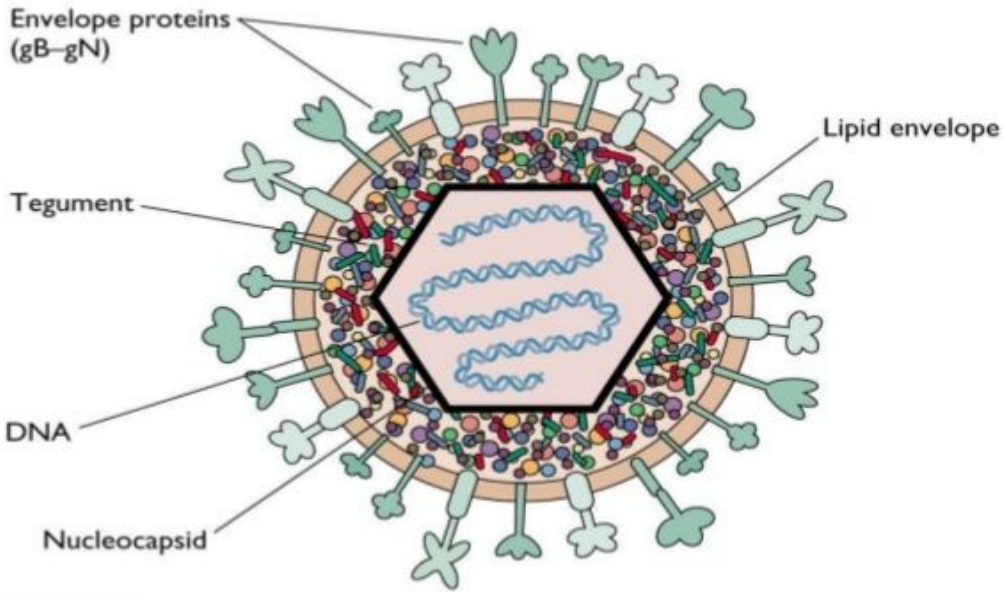
- We are all infected.
- We all are infected with some kind of herpes virus for sure.
- You probably got at least 2 of them up to now, as there is:
  - Herpes-simplex I (HSV-1)
  -Herpes-simplex II (HSV-2)
  -Varicella zoster virus (VZV)
  -Epstein-barr virus (EBV)
  -Cytomegalovirus (HCMV)
  -Human herpesvirus 6 (HHV-6)
  -Human herpesvirus 7 (HHV-7)
  -Human herpesvirus 8 (HHV-8)

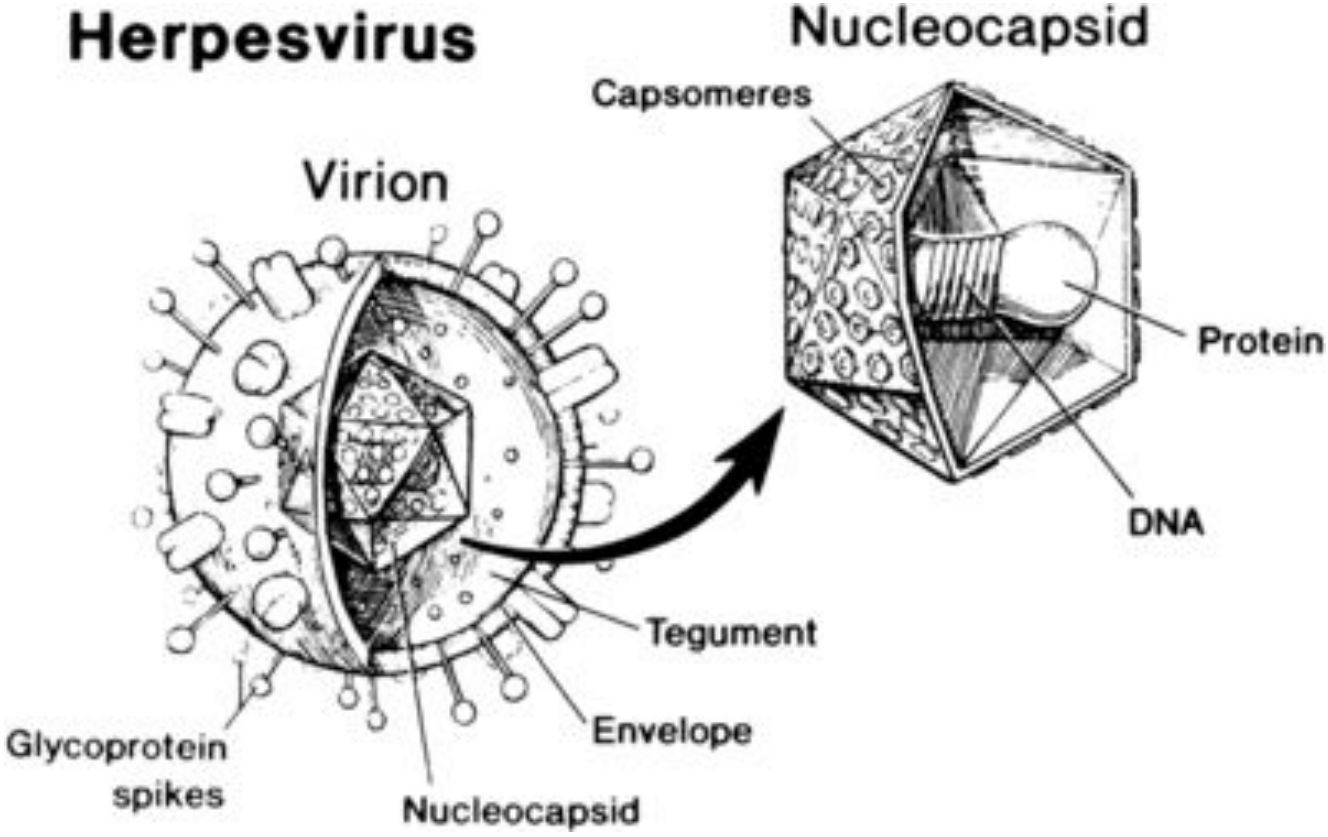


# Herpes Simplex Virus

- Herpes Simplex Virus Type (HSV) is a double stranded DNA virus that belongs to *Herpesviridae* family.
- It contains three main structural components.
- A central core holds the viral DNA, an inner core is surrounded by an envelope that is made of viral glycoproteins and a capsid.
- The tegument is located between the capsid and the envelope and various proteins that are delivered into the infected cell upon cell fusion.

## Structure




Herpesvirus
Virion
Nucleocapsid
Capsomeres
Protein
DNA
Tegument
Envelope
Glycoprotein
spikes
Nucleocapsid

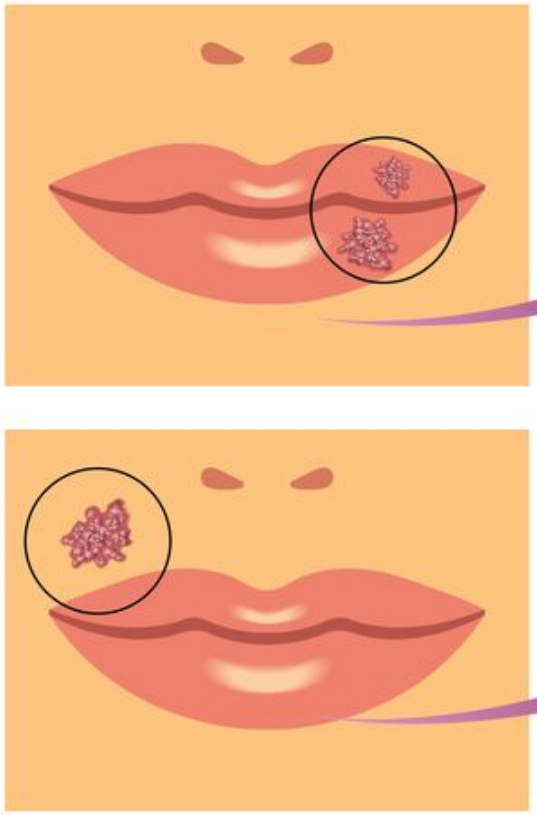
# Herpes Simplex 1

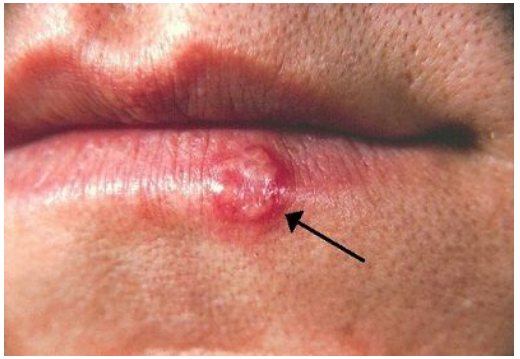
- Causes & Symptoms of HSV 1
- Treatment

# Herpes Simplex 2

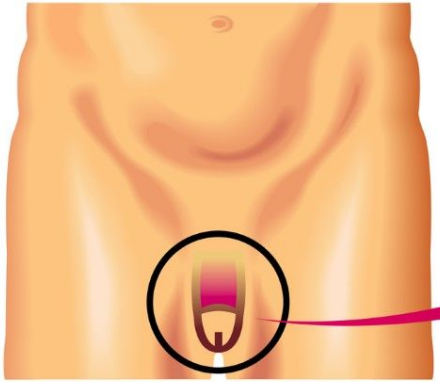
- Causes & Symptoms of HSV 2
- Treatment

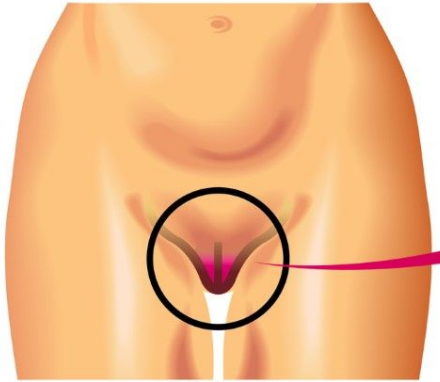
# HSV-1
# Labial Herpes

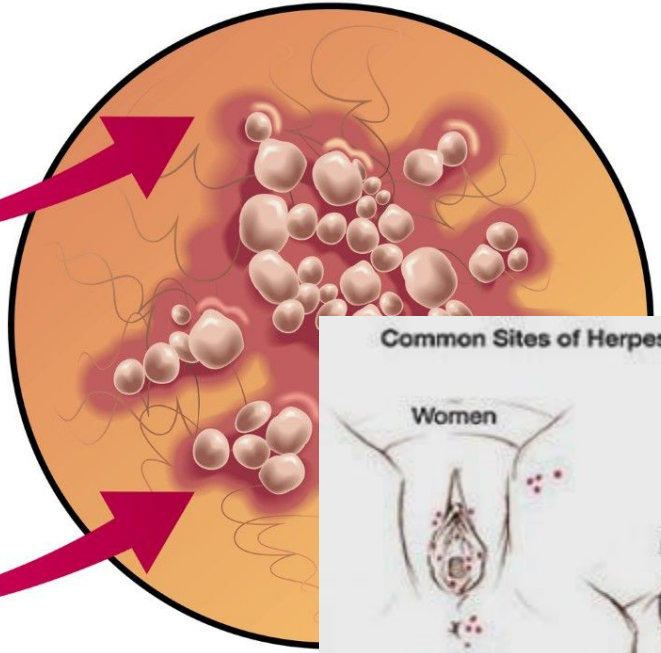


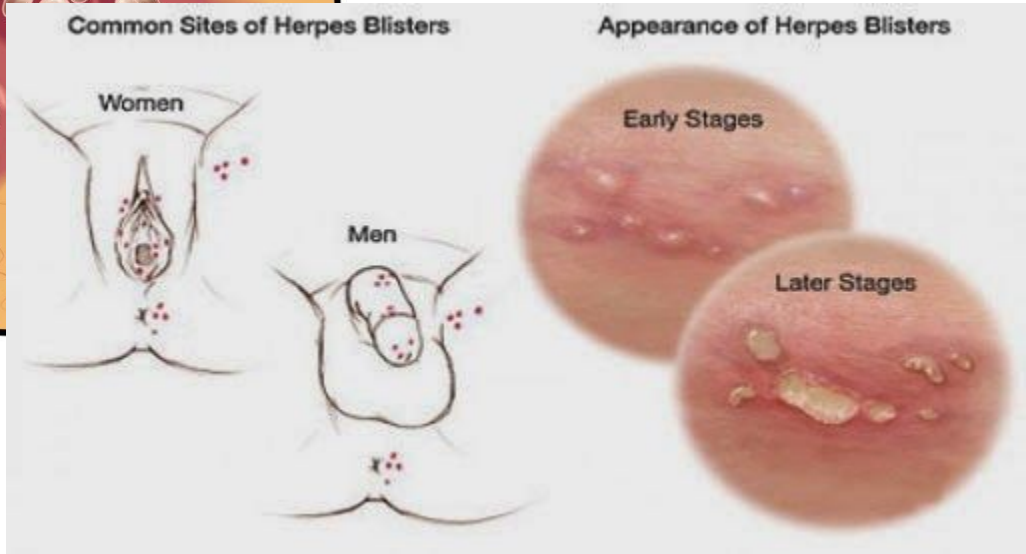


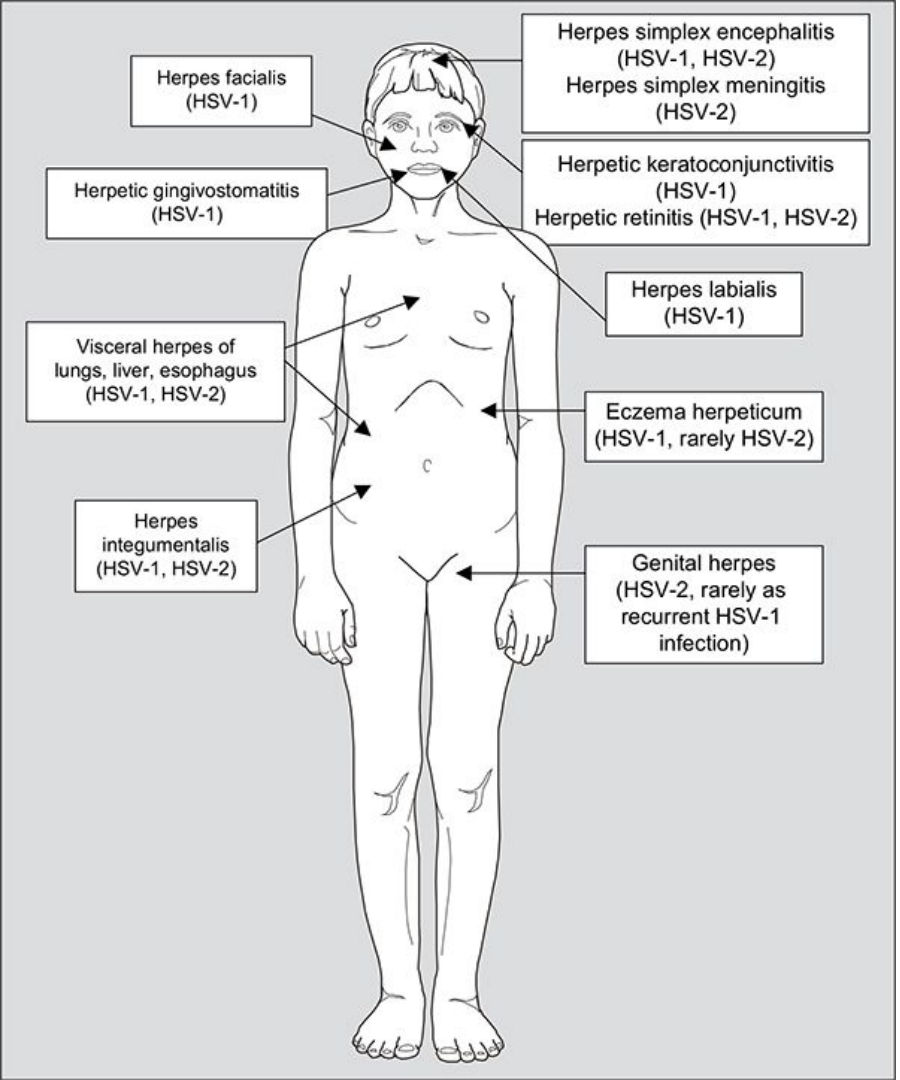
# HSV-2
# Genital Herpes





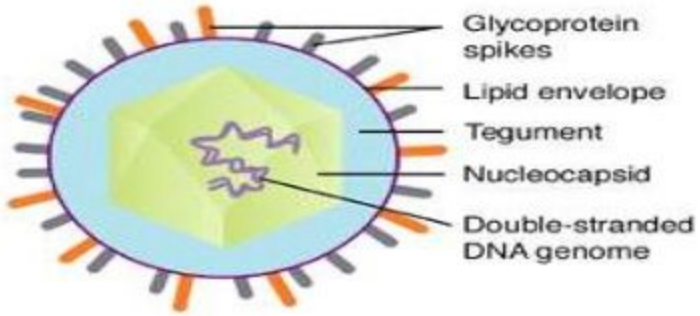





Herpes facialis (HSV-1)
Herpes simplex encephalitis (HSV-1, HSV-2)
Herpes simplex meningitis (HSV-2)
Herpetic gingivostomatitis (HSV-1)
Herpetic keratoconjunctivitis (HSV-1)
Herpetic retinitis (HSV-1, HSV-2)
Herpes labialis (HSV-1)
Visceral herpes of lungs, liver, esophagus (HSV-1, HSV-2)
Eczema herpeticum (HSV-1, rarely HSV-2)
Herpes integumentalis (HSV-1, HSV-2)
Genital herpes (HSV-2, rarely as recurrent HSV-1 infection)

# VARICELLA ZOSTER VIRUS

- VZV also known as human herpesvirus 3 (HHV3) belongs to the herpesvirus family.
- The envelope is interspersed by spikes made up of viral glycoproteins.
- The VZV genome is double stranded DNA coiled upon a protein axis.

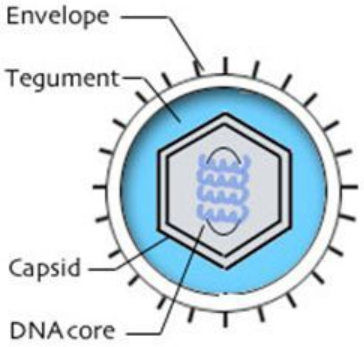



Structure of the varicella-zoster virus particle

# Epstein-Barr Virus

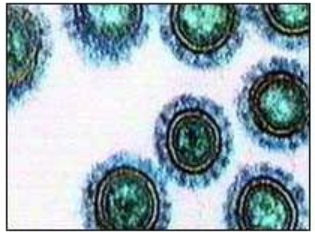
## At a glance

- Family: *Herpesviridae*
- Host: Humans
- Enveloped
- Icosahedral
- 120-200 nm diameter
- Genome: dsDNA
  125-240 kbp (kilobase pairs)
  linear

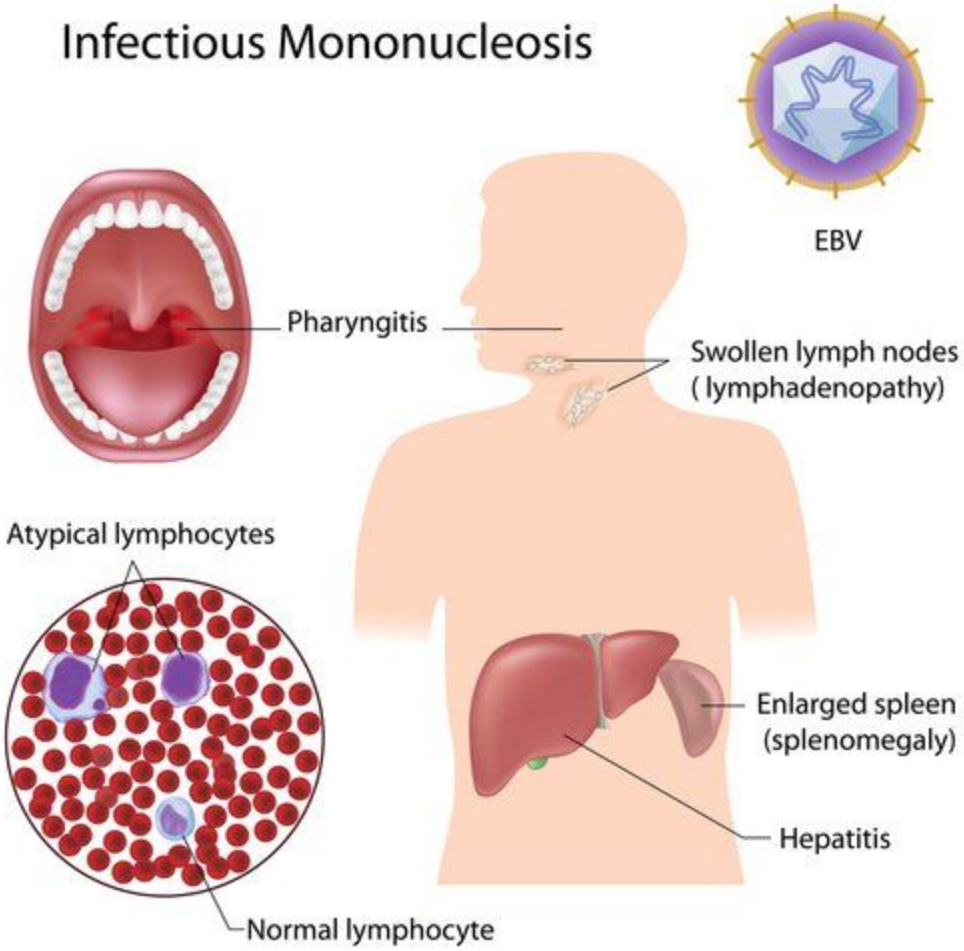


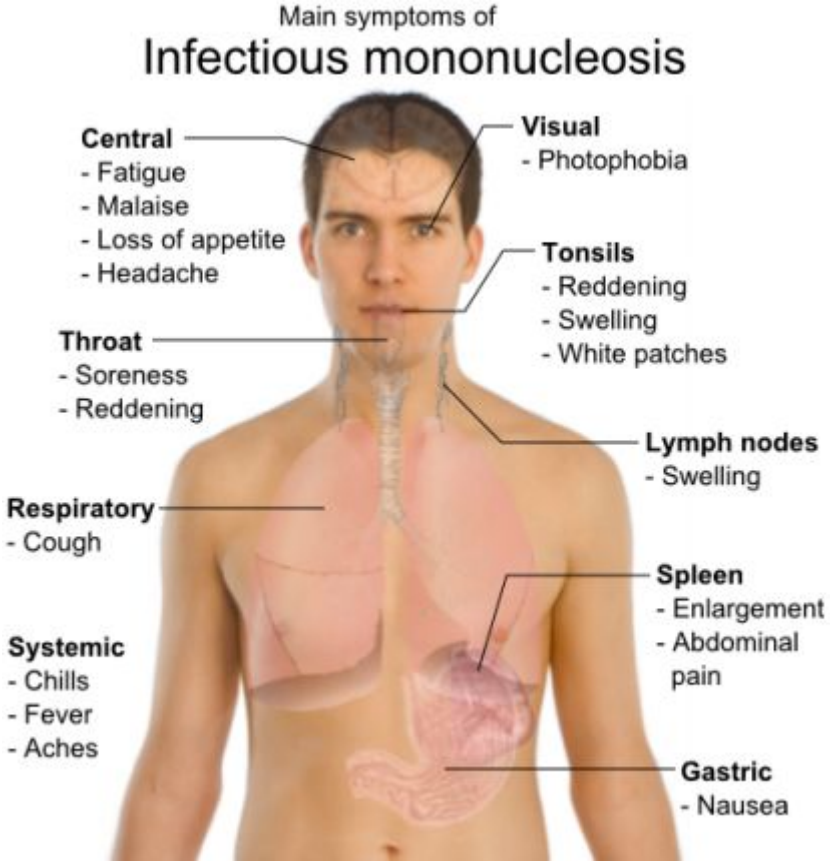

dsDNA ——— transcription ——— (+) mRNA

genome replication ——— dsDNA



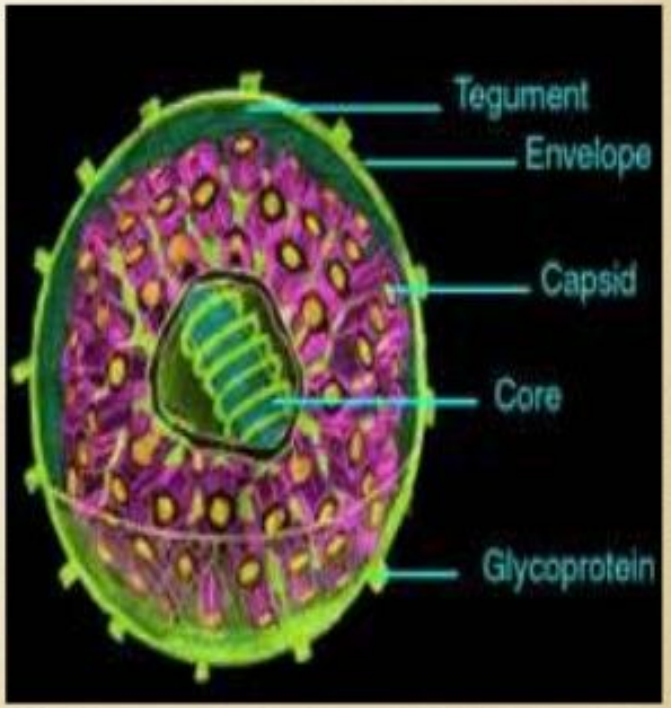
EBV causes mononucleosis aka "mono."
aka "kissing disease" because of one way you can spread it to someone else



# Cytomegalovirus

- **Cytomegalovirus** (from the Greek cyto-, "cell", and -megalo-, "large") is a viral genus of the viral family known as Herpesviridae or herpes viruses. The species that infects humans is commonly known as human CMV (HCMV) or human herpesvirus-5 (HHV-5), and is the most studied of all cytomegaloviruses



# CMV is short for cyto-megalo-virus

# CMV is serious

Leading non-genetic cause of childhood hearing loss

Every hour, 1 child is permanently disabled by CMV

CMV also causes:

Vision loss
Microcephaly
Behavior issues
Mental disability
Cerebral Palsy
Seizures

**90%**
of babies born with CMV will appear healthy at birth

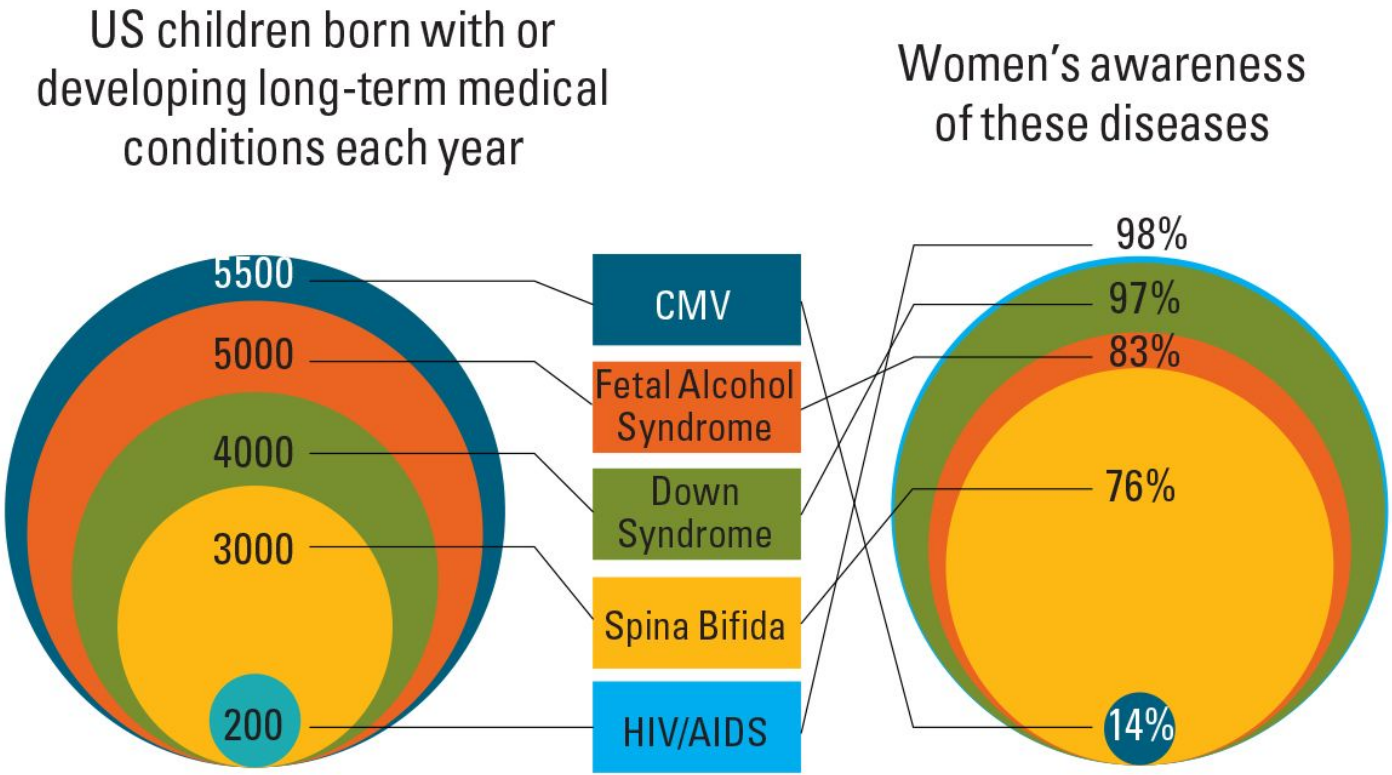
**400**
children die from CMV every year



Scientific research has found a connection between CMV and miscarriage

NATIONAL CMV FOUNDATION

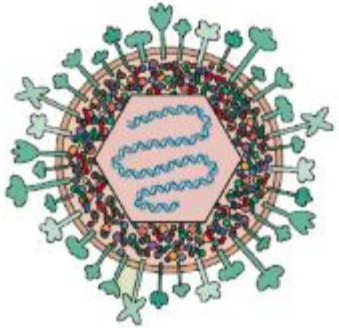
# CYTOMEGALOVIRUS (CMV)




From National CMV Foundation (www.nationalCMV.org

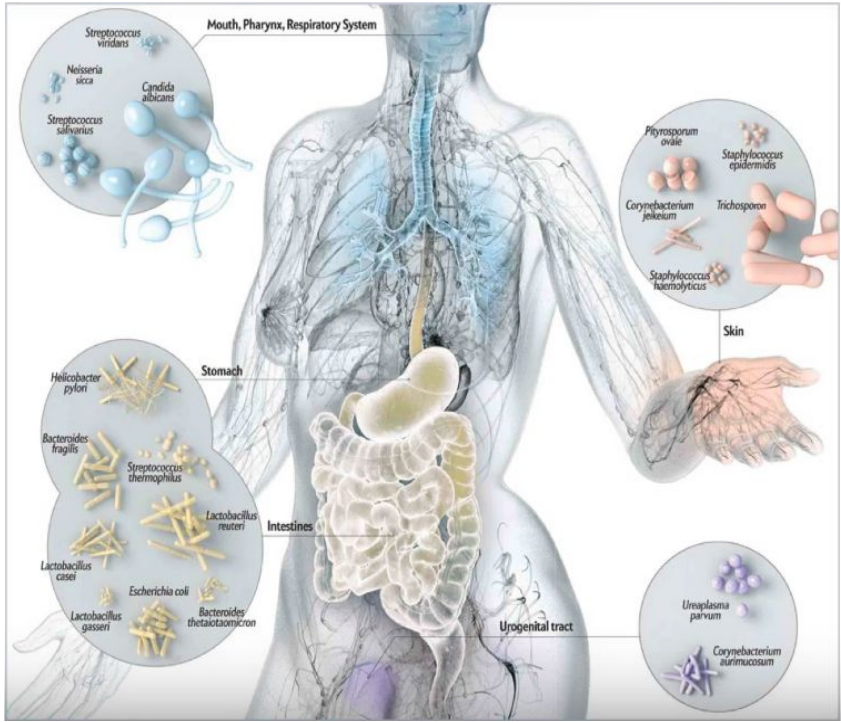
# How infected we are?

- You get Herpes virus quite young in age, most of them from your parents.
- Through their saliva, and they already have HV.
- Once infected it is for life.
- We have no way to cure anyone from herpes.



# Microbiome

- Microbiome: bacteria that colonize every organ system of the body.
- The figure shows some of the bacteria that inhibits some parts of the body, we have for example skin microbiome that differ greatly from one person to another, and even from the right to left hand.
- Now like we have microbiome we have virome



# Virome

- Even though it is as important as microbiome it doesn't get the same attention. Maybe because it is harder to enumerate the virome.

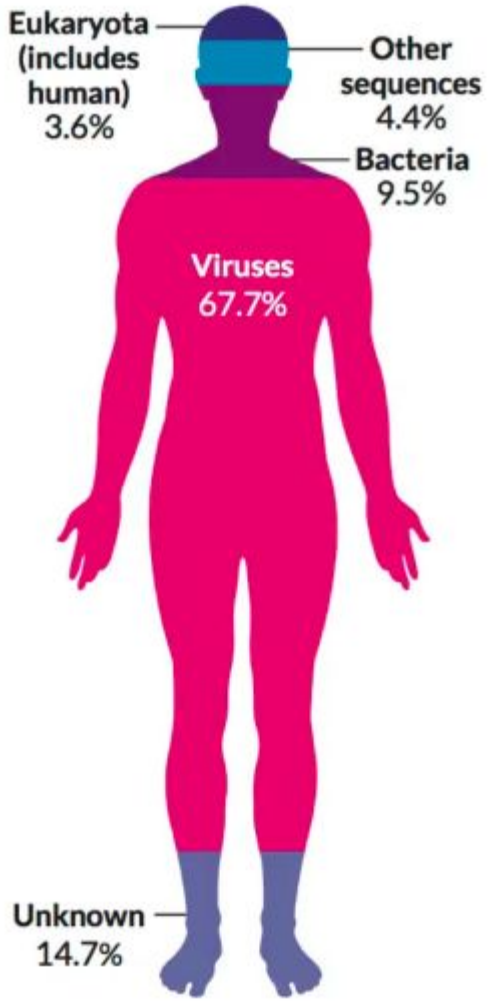
- To study microbiome all you need to do is to extract some nucleic acid from the sample (for example from skin swap or stool sample) after extracting the nucleic acid, you sequence the rRNA, then you will have an idea about what bacteria inhabit the sample.

- The case with the virome is different, because viruses don't have a common sequence (like the bacteria have rRNA) to identify the viruses in the sample.

# Virome

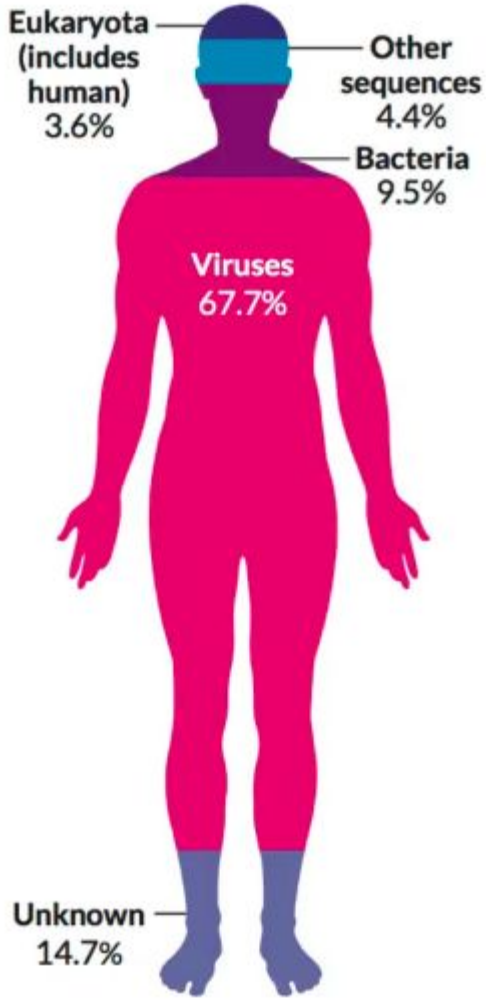
- Whole genome must be done to identify the viruses in the sample.

- They took human blood and extracted nucleic acid from it and did very high throughput sequencing (NGS).
- The sequencing gave a good idea about the present nucleic acid, and the figure here to the right represent the results from that sequencing.



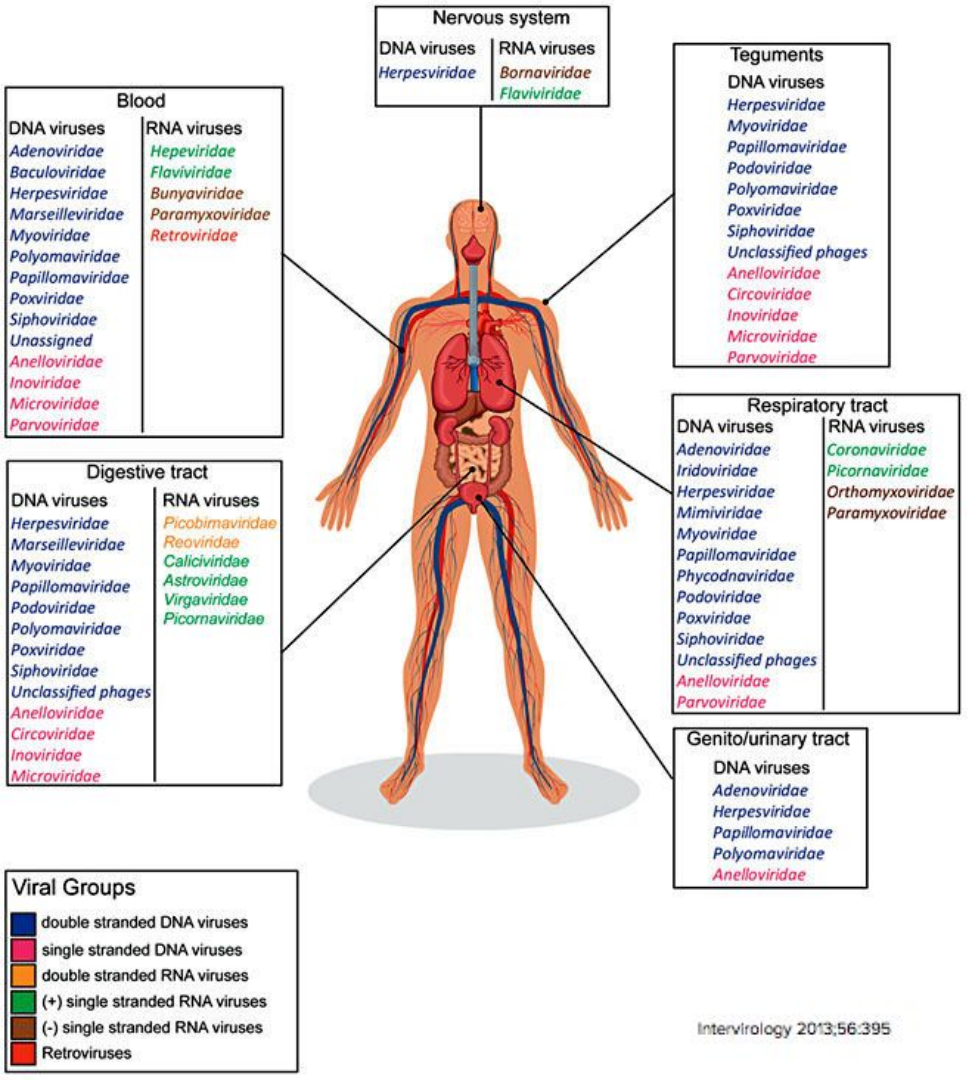
# Virome

- 67.7% of the sequences in the blood are viral.
- 9.5%  of the sequences are bacteria.
- Only 3.6 % of the sequences are for eukaryota including human.
- The way we identify the sequences is by comparing it to a database.
-



# Virome

- This figure is more detailed study of the human virome in every part of the body.
- There's a unique set of viruses that are listed here.
- DNA and RNA viruses at each of these locations.
- These viruses can be found in healthy humans.
- There is a huge virom in the human body and it is always changing.



# Virome

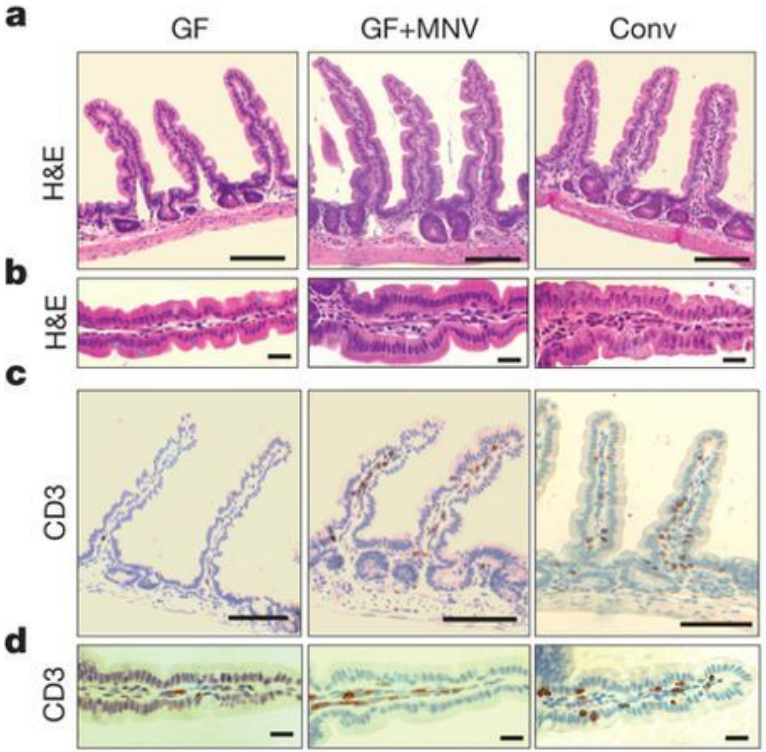
- What are we trying to understand now is, if the virom is beneficial or not, and how can we manipulate it.

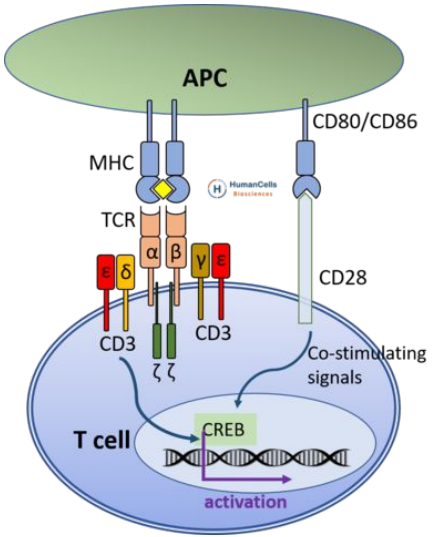
- We can get rid of bacteria by treatment with antimicrobials.

- We can't do this with viruses; we don't have that many antiviral that will simply wipe out your virome and then we can see what happens.

# An enteric virus can replace the beneficial function of commensal bacteria

## MNV reverses intestinal abnormalities in GF mice



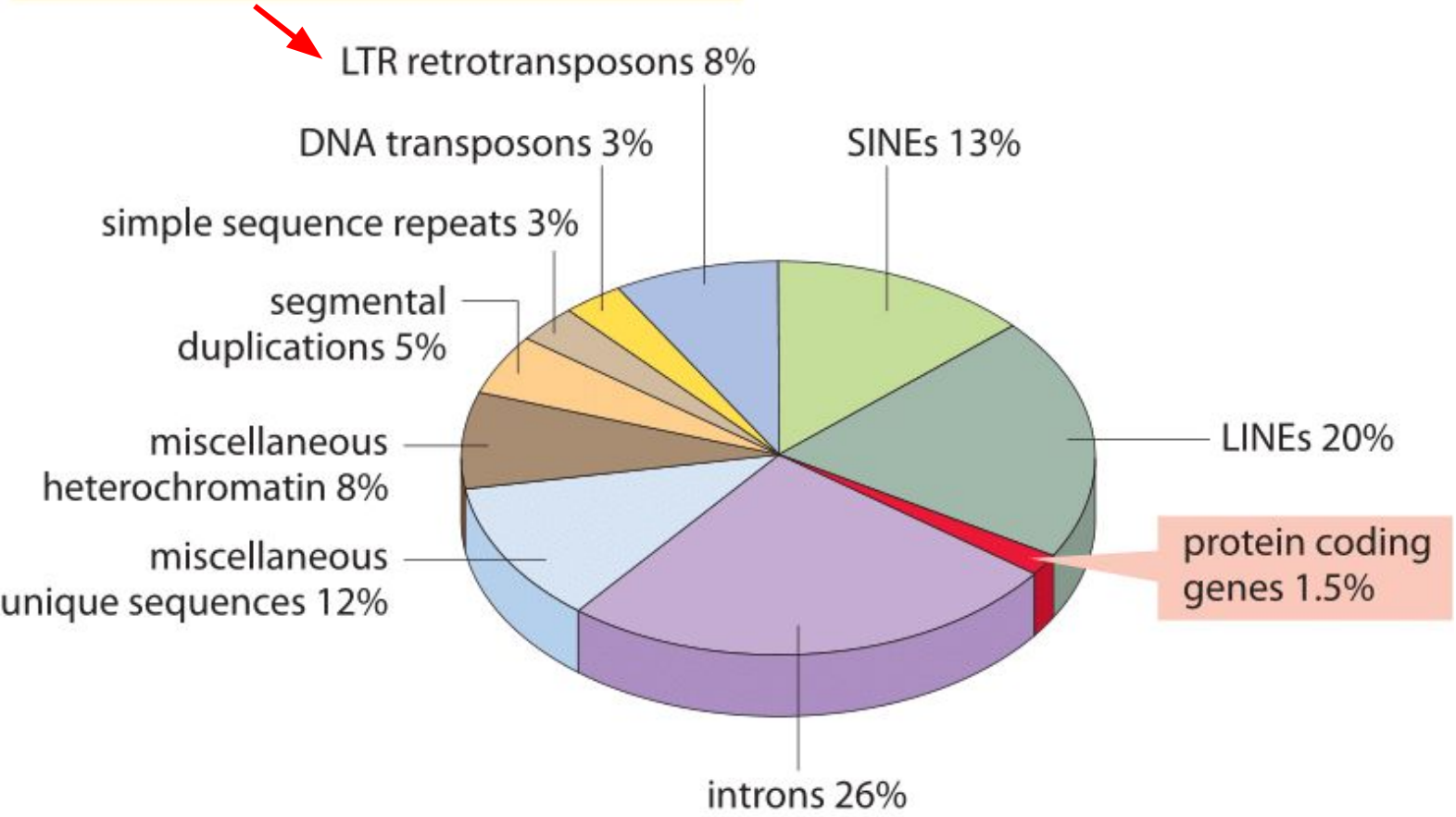




Murine norovirus (MNV) infection of germ-free or antibiotic-treated mice restored intestinal morphology and lymphocyte function without inducing overt inflammation and disease.

Nature. 2014 Dec 4;516(7529):94-8. doi: 10.1038/nature13960. Epub 2014 Nov 19.

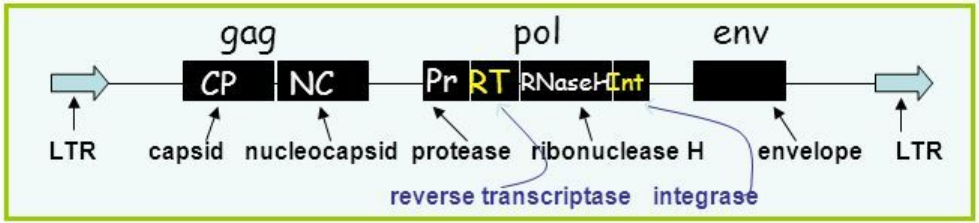
main components of the human genome

3.2 billion bases




- It was mentioned earlier that we have viral genetic sequence as part of the human DNA.

# Human endogenous retroviruses (HERVs) & LTR-transposons



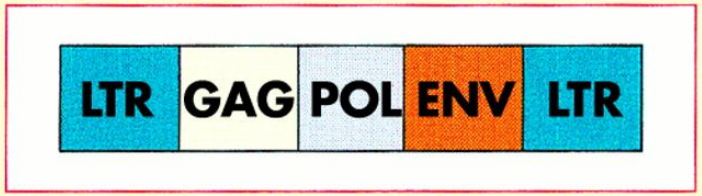

LTR retrotransposons are compose of **8%** of the genome, but only **1%** of them has a structure similar to those of retroviruses, the others are degenerated. All of them are mutant: they are not able to form infective virions but, de some of them can move by the enzymes of other elements.

The genome of chimp and other monkeys contains infective retroviruses.

**gag:** capsid (structural element)
**pol:** polymerase: reverse transcriptase, integrase, protease, RNase H
**env:** envelope (structural element)
**LTR (long terminal repeat):** promoter

# Human endogenous retroviruses

- HERVs: footprints of previous exposure to retroviruses; coined "fossil viruses"
- Constitute approximately 1% of the human genome
- Similar genomic organisation to exogenous retroviruses e.g. HIV-1, HTLV-I




- Transmitted vertically in the germline through successive generations
- Possess a reverse transcriptase gene region found in all retroviruses

# The human genome

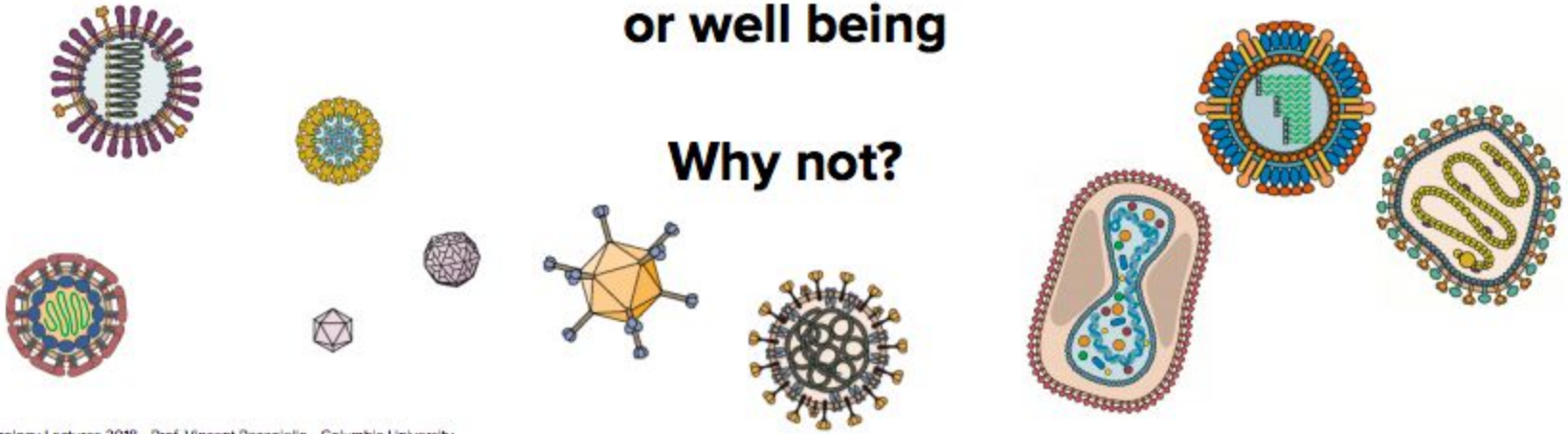
- 3.2 billion bases and it is divided up into the different parts that is shown in the pie chart.
- Protein coding genes are 1.5% of the DNA. (the minority of the DNA actually encodes proteins)
- The rest of the genome is all sort of stuff, we are just in the beginning to understand, like introns, heterochromatin, duplicated sequences, interspersed elements like lines and signs.
- 8.3% LTR **retrotransposons**, many of these are retroviral DNAs; a virus called retroviruses that is an RNA virus that inverts its genome into DNA and then integrates it into the infected cell.

# The human genome

- Many animals on earth have experienced retroviral infection.
- Those DNAs integrated into chromosomes of the animals, are passed on to their children and so forth.
- Most of these sequences don't make infectious viruses.
- But turns out that many of the proteins have been exapted.
- Exapted protein means you take a virus protein and use it to your own purposes.
- We have exapted a number of retroviruses genes for our own use over the years.

**Amazingly, the vast majority of the viruses that infect us have little or no impact on our health or well being**

**Why not?**



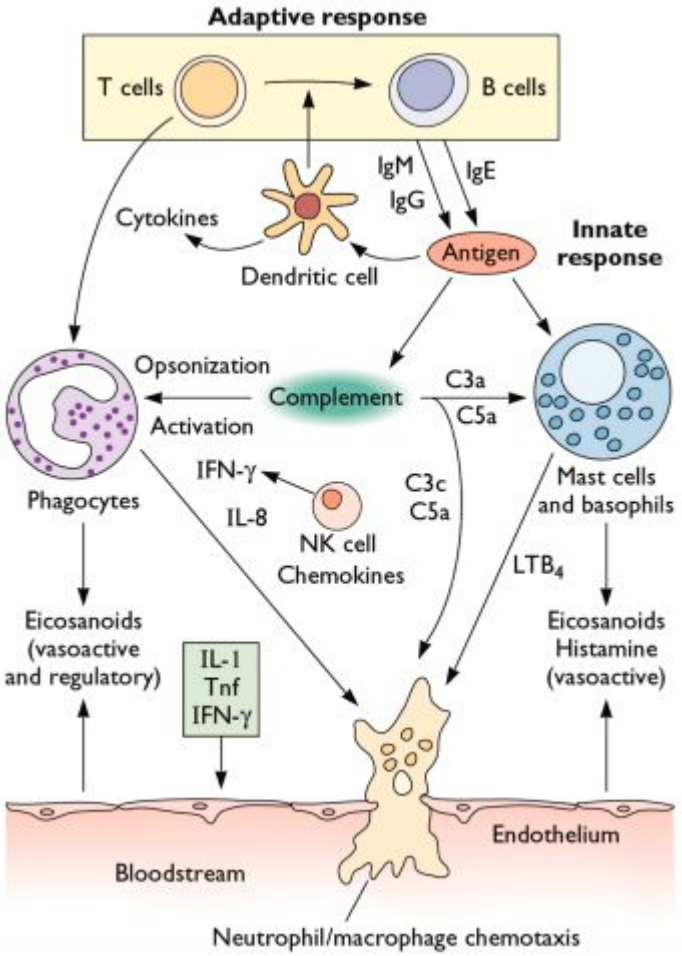
# Why not?

- Most viruses pass through us, we ingest many non-animal viruses regularly with food.
  - Metagenomic analysis in human feces reveal that most viral sequences are similar to plant viruses.
  - 91% of the obtained sequences are for plant viruses.

- We have an amazing immune system.

# Our immune system

- The figure on the right diagram the work of the immune system.
- The immune system takes care of any viral infection.

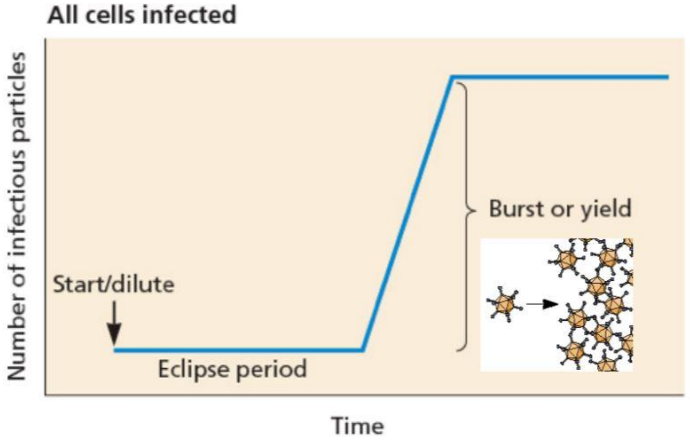


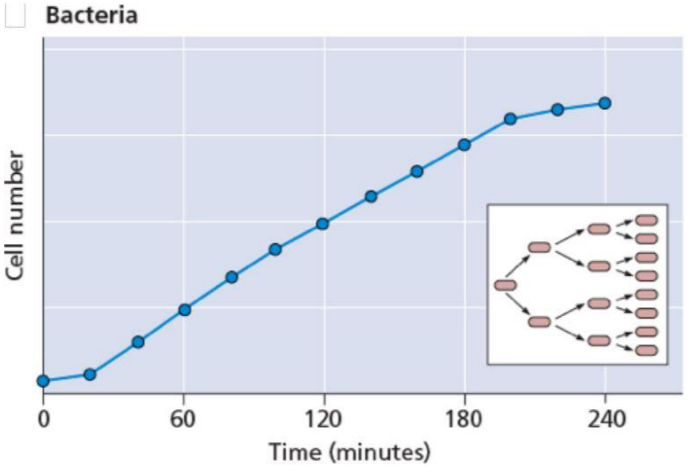
# Viruses replicate by assembly of pre-formed components into many particles

## Make the parts, assemble the final product

Eclipse: viruses parts are built
Burst: Viruses are assembled

*Not binary fission like cells*

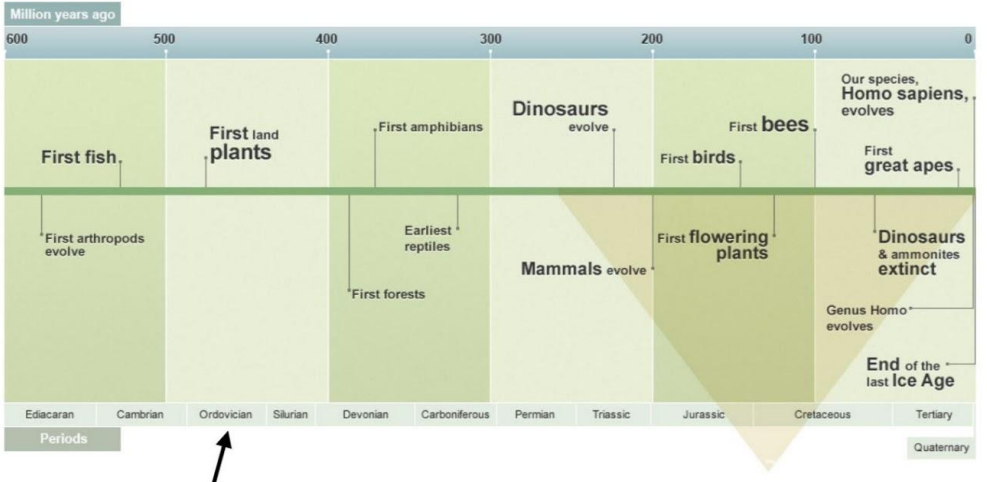


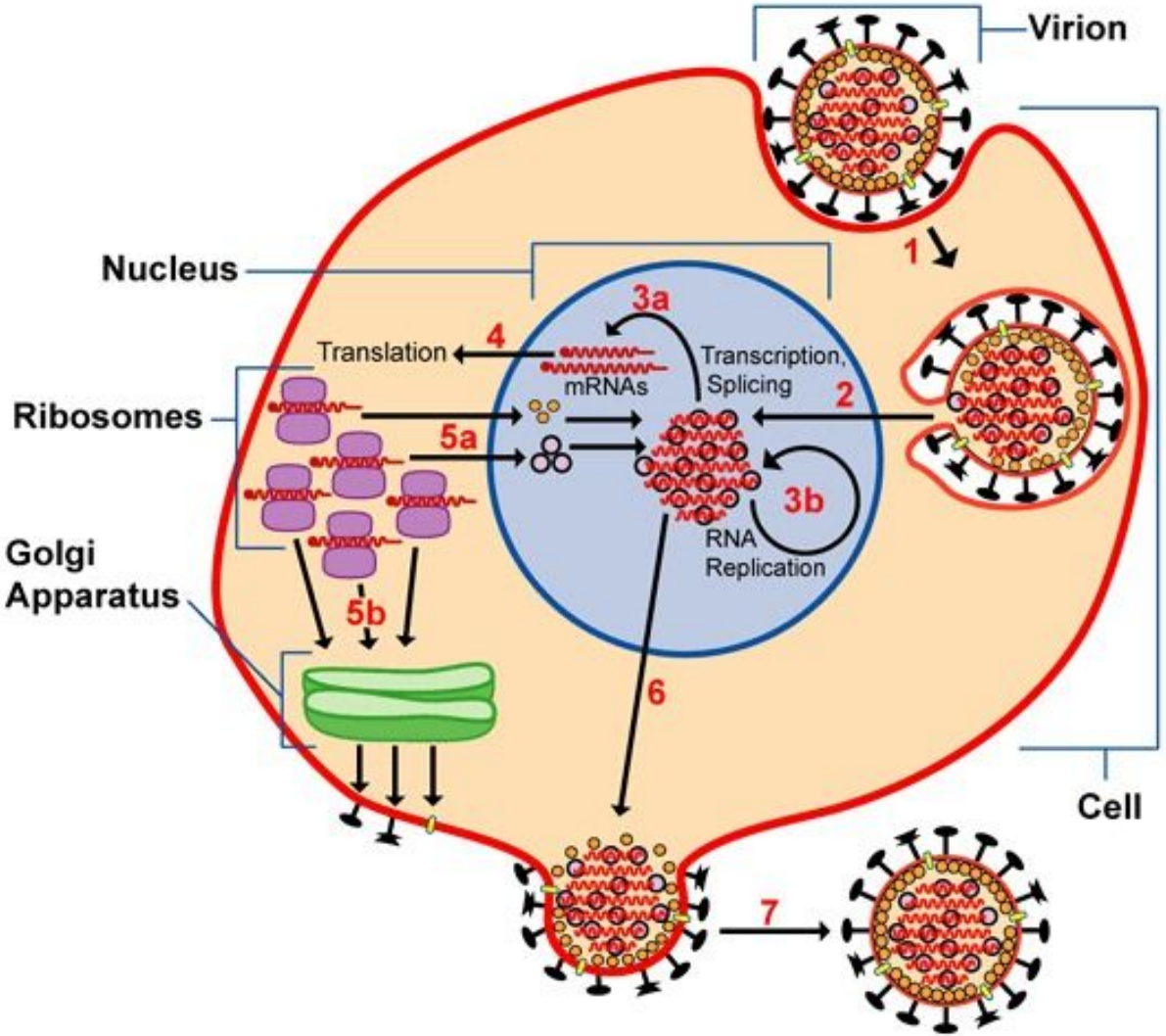
# How old are viruses?

*Orthoceras*, a nautiloid cephalopod, 488 Ma

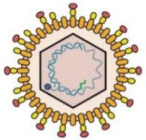
Nobu Tamura (http://spinops.blogspot.com)

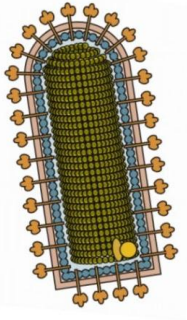
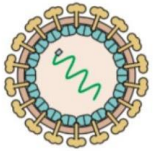
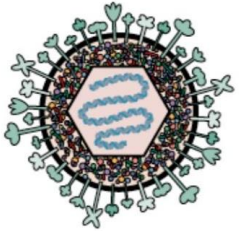
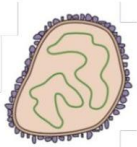
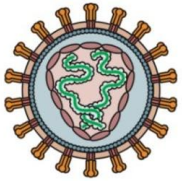
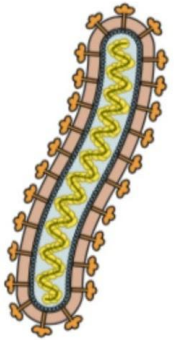



- Estimates of molecular evolution suggest marine origin of some retroviruses >450 Ma, Ordovician period
- Likely originated billions of years ago - before cells?

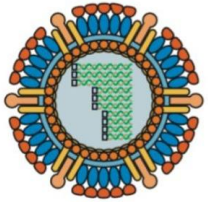
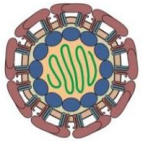
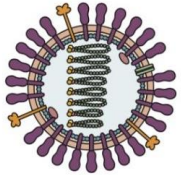
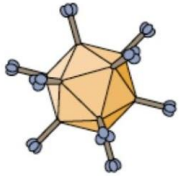
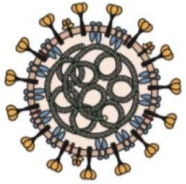
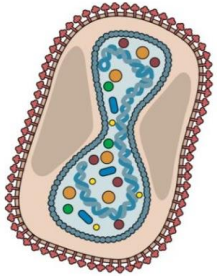

Virion
Nucleus
1
3a
4
Translation
mRNAs
Transcription,
Splicing
2
Ribosomes
5a
3b
RNA
Replication
Golgi
Apparatus
5b
6
Cell
7

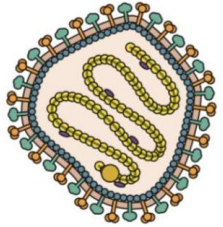
# Virus classification

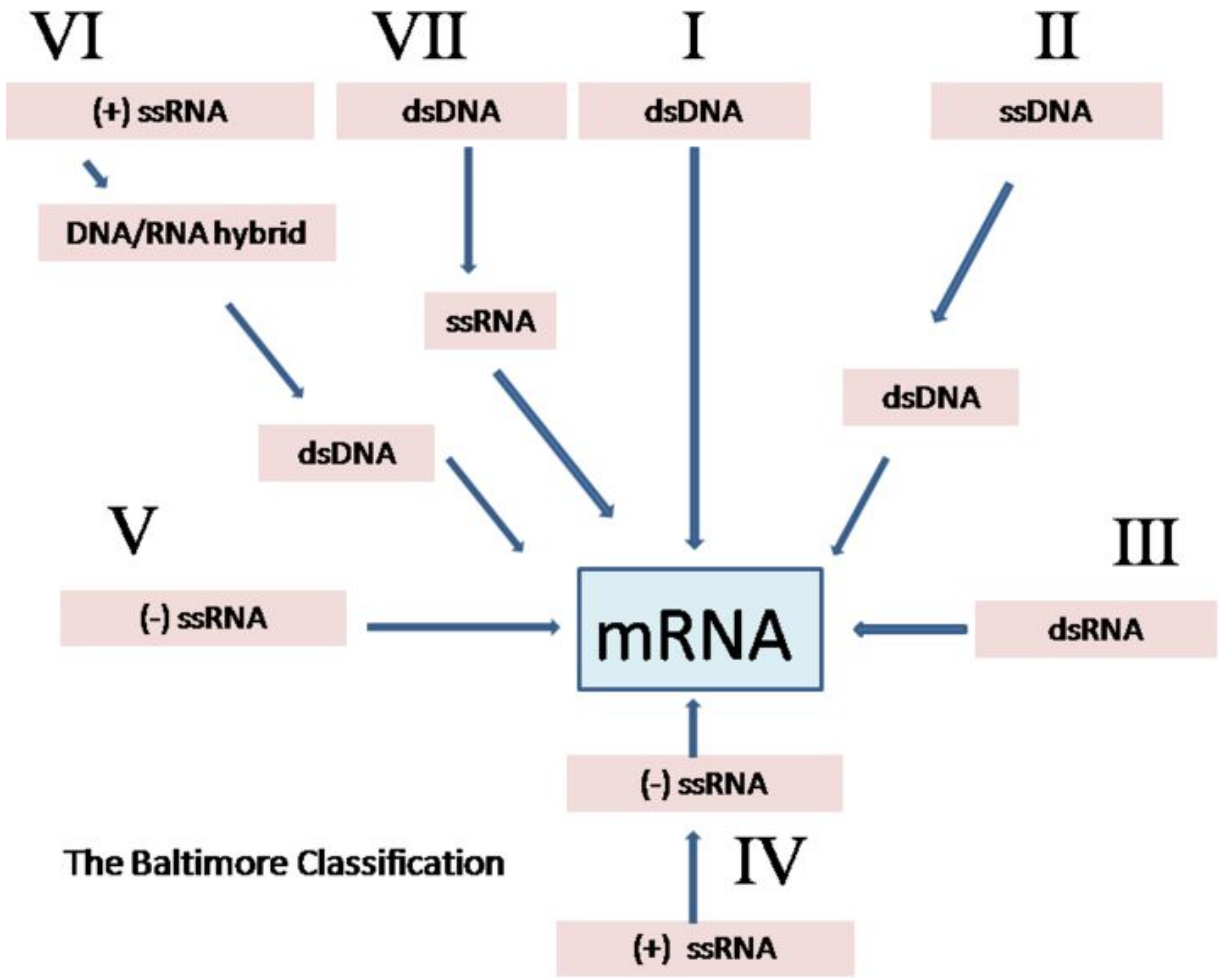



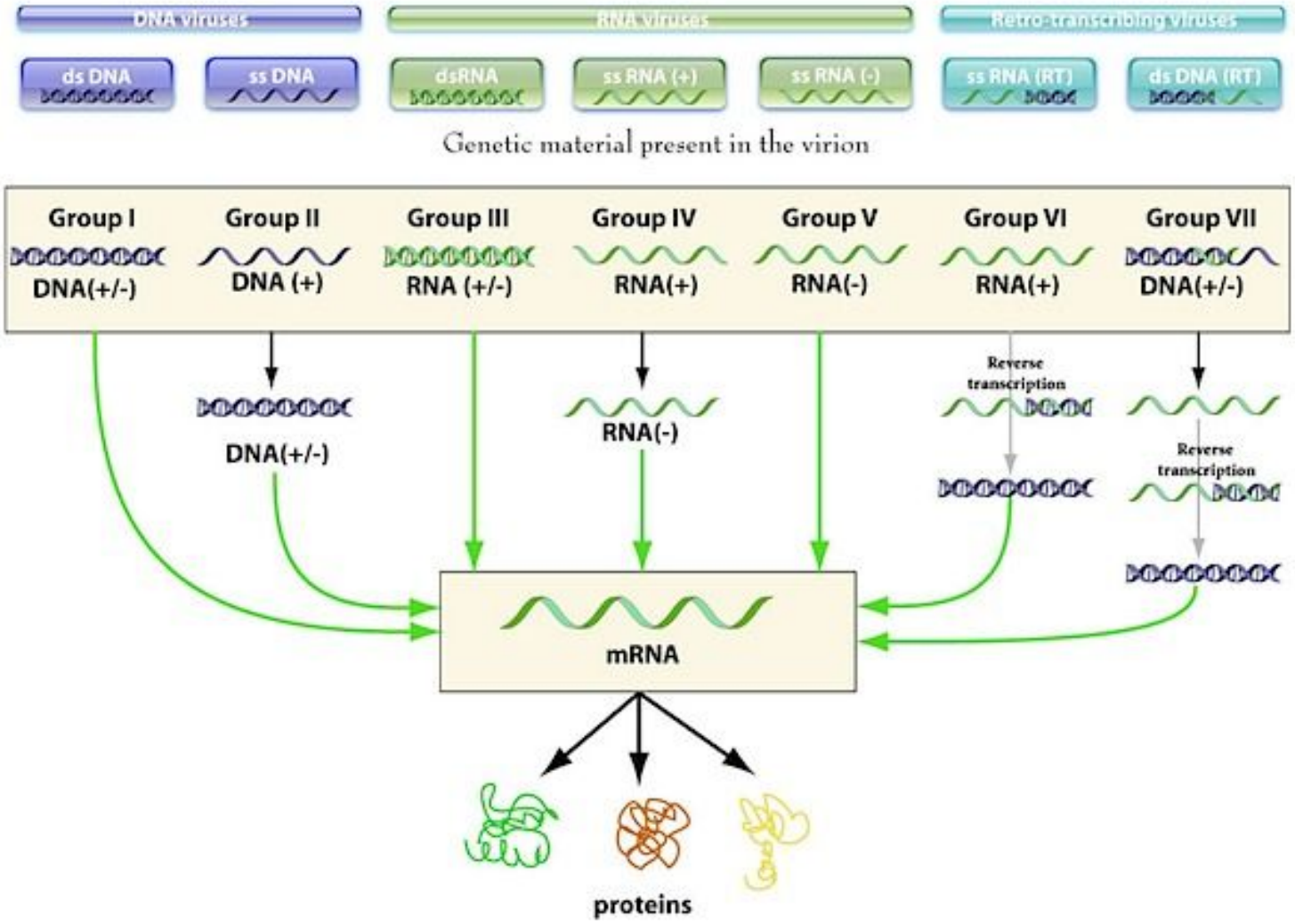







- Nature and sequence of nucleic acid in virion
- Symmetry of protein shell (capsid)
- Presence or absence of lipid membrane (envelope)
- Dimensions of virion & capsid




VI
(+) ssRNA
DNA/RNA hybrid
VII
dsDNA
ssRNA
I
dsDNA
II
ssDNA
dsDNA
dsDNA
V
(-) ssRNA
mRNA
III
dsRNA
(-) ssRNA
IV
(+) ssRNA
The Baltimore Classification


DNA viruses
RNA viruses
Retro-transcribing viruses
ds DNA
ss DNA
dsRNA
ss RNA (+)
ss RNA (-)
ss RNA (RT)
ds DNA (RT)
Genetic material present in the virion
Group I
DNA(+/-)
Group II
DNA (+)
Group III
RNA (+/-)
Group IV
RNA(+)
Group V
RNA(-)
Group VI
RNA(+)
Group VII
DNA(+/-)
DNA(+/-)
RNA(-)
Reverse transcription
Reverse transcription
mRNA
proteins

| Class | Nucleic Acid | Examples | Envelope | Genome size (kb) |
|---|---|---|---|---|
| I | dsDNA | Herpes virus | Yes | 120 - 220 |
| | | Poxvirus | Yes | 130 - 375 |
| | | Adenovirus | No | 3.0 - 4.2 |
| | | Papillomavirus | No | 5.3 - 8.0 |
| II | ssDNA | Adeno-associated virus | No | 5.0 |
| III | dsRNA | Reovirus | No | 18 - 31‡ |
| IV | (+) ssRNA | Togavirus | Yes | 9.7 - 11.8 |
| | | Poliovirus | No | 7.4 |
| | | Foot-and-mouth disease virus | No | 7.5 |
| | | Hepatitis A virus | No | 7.5 |
| | | Hepatitis C virus | Yes | 10.5 |
| V | (-) ssRNA | Influenza virus | Yes | 12 - 15‡ |
| VI | (reverse) RNA | HIV | Yes | 9.7 |
| VII | (reverse) DNA | Hepatitis B virus | Yes | 3.1 |

# Classification des virus