29

Microbiology

Doctor 2017 | Medicine | JU

Sheet Slides

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Doctor

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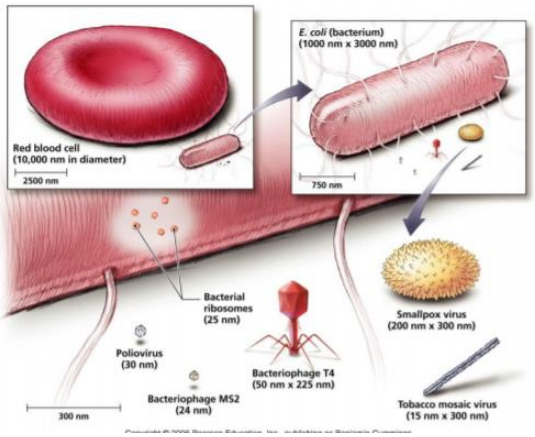
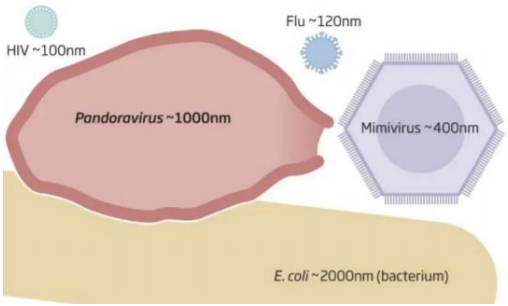
Throughout this sheet I didn't go into details about topics the doctor overlooked. There are a couple of images that we are not required to know in detail, just understand the concepts.

Introduction to Virology

- Viruses are **infectious** agents, obligate **intracellular** parasites compromising genetic material (DNA or RNA) surrounded by a **protein coat** and/or a **membrane**.
- They are **very small** (20-400 nm).
- Viruses can only be seen through the **electron microscope**. However, the discovery of the **Mimi virus** (400nm), the **Pandora virus** (1000nm) and other giant viruses followed, in which they are visible under the **Light microscope**.





Notes: ***Pandora virus*** *is bigger by far than any* ***other*** *known viruses, and* ***rivals' bacteria****.*

Why do we study viruses?

- Viruses are **everywhere**, in our bodies, around us and in the air we breathe in. We regularly eat and breathe **billions of viruses'** particles.
- Viruses infect **all** living things.
- Viruses cause human **diseases** and studying them helps to **study** and treat these diseases.
- Viruses can **cross species boundaries**; meaning that they can adapt to new host species infecting them *(e.g. Corona Virus).*
- Viruses are part of **our body**; viruses' genomes compromise part of the human genetic material.
- Viruses are valuable tools in **studying** and **manipulating** biology.

The number of viruses on earth:

Viruses make **huge** numbers of descendants, where 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** (viruses' that infect bacteria).

In the oceans of the world, about a **million** virus are present per **teaspoon**.

Viruses Classification

(the doctor didn't emphasize on the details through this)

- Viruses are **not** classified as members of **kingdoms**, they do **not obey** the classical hierarchical system taxonomy (Kingdom, phylum, class, order, family, genus and species).

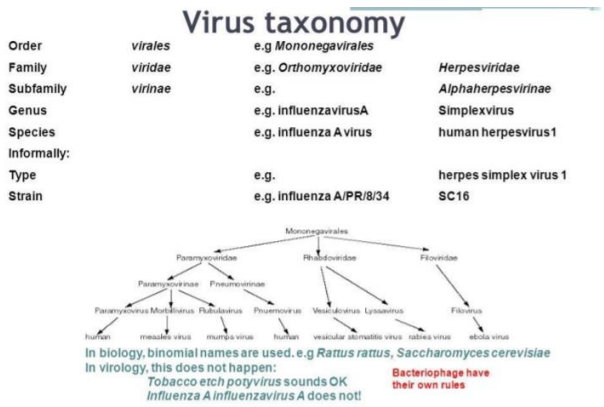
- The **international committee on taxonomy of viruses** (ICTV), stated that: "A specie is a monophyletic group of viruses whose properties can be distinguished from those of other species by multiple criteria".

- Viral Classification starts at the **level of Order** and continues as follow, with taxon suffixes given in *italics*:

1. **Order** *(-virales)*
2. **Family** *(-viridae)*
3. **Genus***(-virus)*
4. **Species**, species names generally take the form of *[Disease] virus.* Also. Species can show different **genotypes**.

Just an example*: *Family → *Filoviridae*, ***Genus*** → *Ebolavirus*, ***Specie*** → *Zaire Ebolavirus*

*Further example, just to understand the general idea of viruses' classification but we are **not** required to memorize the examples.*



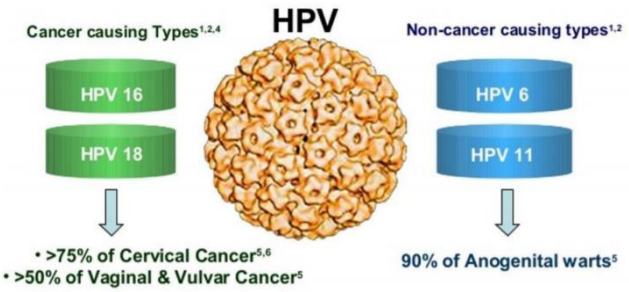
- Another way of classifying viruses is according to their **genetic material** which will be discussed later.

Human Papillomavirus (HPV)

- HPV is a necessary cause of **cervical cancer** (=99.7%) and **Anogenital warts**.

a- Cancer causing genotypes: HPV 16 and HPV 18

b- Non-cancer causing genotypes *(Anogenital warts):* HPV 6 and HPV 11



Are we infected with viruses?

We are **all** infected, even with a kind of **herpes virus** (HV) for sure. We probably have **at least 2** of them up to now, as there is: *(we will discuss what's in bold)*

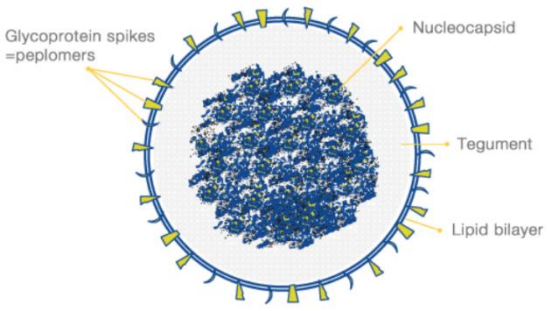
- **Herpes-simplex I (HSV-1)**
- **Herpes-simplex II (HSV-2)**
- **Varicella zoster virus (VZV)**
- **Epstein-Barr virus (EBV)**
- **Cytomegalovirus (CMV)**
- Human herpesvirus 6 (HHV-6)
- Human herpesvirus 7 (HHV-7)
- Human herpesvirus 8 (HHV-8)

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

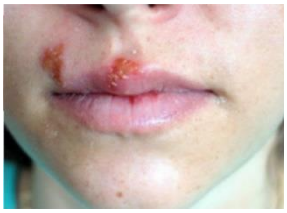
Herpes viruses (Herpesviridae family) that are of importance:

1- Herpes Simplex Virus (HSV)

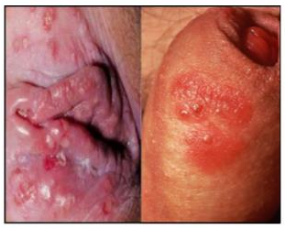
- HSV is a **double stranded** DNA virus that belongs to Herpesviridae family.
- It contains **3 main** structural components:
  - **a- Central core**: It holds the **viral DNA.**
  - **b- Inner core:** Surrounded by an **envelope** (a lipid bilayer; made of viral glycoproteins spikes) and a **capsid**.
  - **c- The tegument: Space** between the capsid and the envelope.



- Various proteins are delivered into the infected cell **upon fusion.**



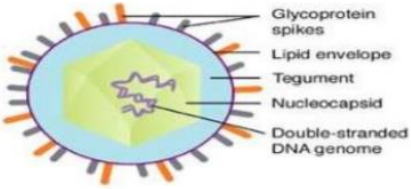
- **Herpes Simplex I** (Labial/oral herpes):
  Causes **sores** and fever **blisters** around the **mouth** and on **the face**.



- **Herpes Simplex II** (Genital herpes):
  Responsible for **genital herpes** outbreaks; Penis, vulva or anus.

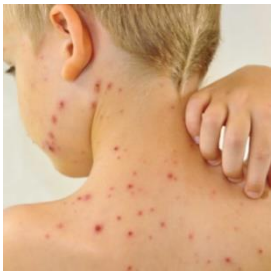
  HSV I, may also contribute to genitals herpes.

2- Varicella Zoster Virus (VZV)

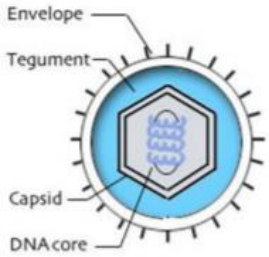


Structure of the varicella-zoster virus particle

- VSV also known as Human herpes virus 3 (**HHV3**), it belongs to the herpesvirus family.
- The **envelope** is interspersed by **spikes** made up of **viral glycoproteins**.
- The VZV genomes is **double stranded DNA** coiled upon a protein axis.
- It causes chickenpox (جدري الماء)

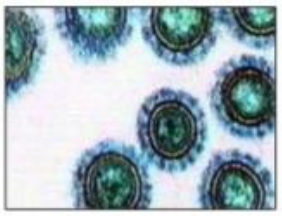


3- Epstein-Barr Virus (EBV)



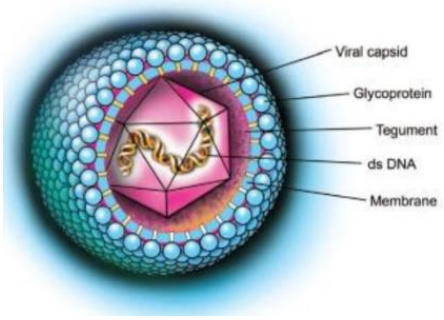
- **Family:** Herpesviridae
- **Host:** Humans
- It is **enveloped**, **Icosahedral** (20 triangular faces) and 120-200nm in diameter.
- **Genome**: Double stranded DNA, linear and made up of 125-240 Kbp.

  (Just know that the genetic material is small)



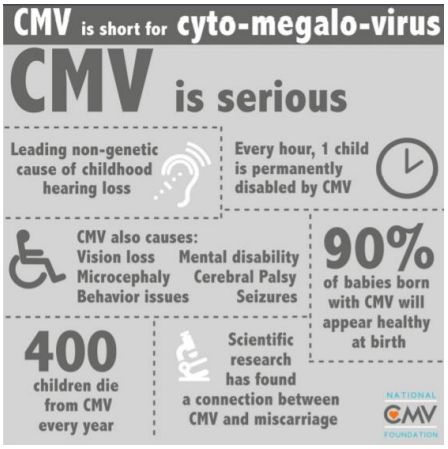
- EBV causes **infectious Mononucleosis**, known as the **kissing disease** because one way of spreading this disease to someone else is through kissing. This disease affects **different systems**.

4- Cytomegalovirus



- CMV (from Greek cyto- "cell", and -megalo "large") is a **viral genus** from the family Herpesviridae (or Herpes viruses).

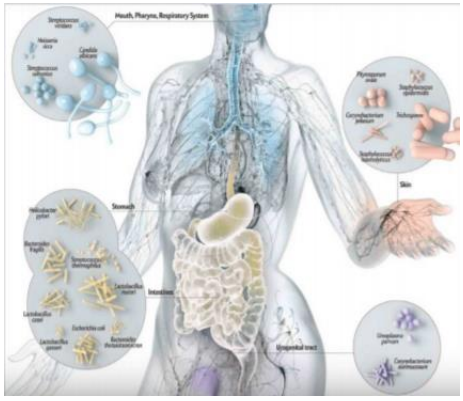
- The species that that **infect humans** is commonly known as human CMV (**HCMV**) or human herpesvirus-5 (HHV5) and it is the **most** studies of all cytomegaloviruses.
- CMV is **serious**, in which every hour 1 child is permanently disabled by CMV. It is a leading **non-genetic** cause of childhood **hearing loss**.
- **CMV can also cause**: Vision loss, mental disability, microcephaly, etc.
- The **highest** causative agent of US children born with or developing **long-term medical** conditions each year is CMV. However, the women's awareness of CMV is the **lowest**.



As we took before, in healthy individuals, the **bacteria** that colonizes every organ in the body makes up the **Microbiome**.

*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.*

Just as the human body has Microbiome, it has **Virome**.



Virome

- Even as though Virome is as important as Microbiome, it doesn't get the same attention. Maybe because it is **harder** to count the Virome.
- In studying the **microbiome** all you need to do is to **extract** some **nucleic acid** from the sample (for example from skin swap or stool sample) and after extracting the nucleic acid, you **sequence** the **rRNA**, then you will have an idea about **what bacteria** inhabit the sample.
- However, 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.

- The whole genome of the body must be known to identify the viruses in the sample.

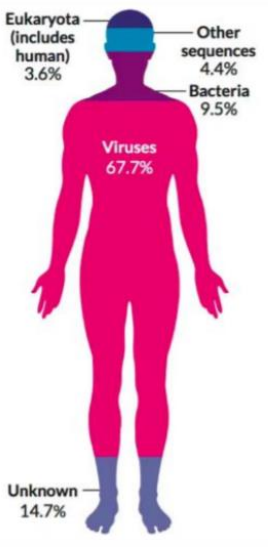
  The human blood is **taken**, nucleic acid is **extracted** from it and a **very high throughput sequencing** (NGS) is done. The sequencing gave a good idea about the present nucleic acid, and the figure here to the right represent the **results** from that sequencing.

  The way we identify the sequences is by comparing it to a **database**.

  67.7% of the sequences in the blood are **viral**.

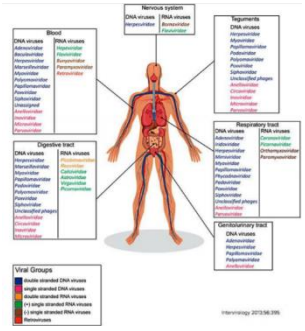
  9.5% of the sequences are **bacteria**.

  Only **3.6 %** of the sequences are for **eukaryote** including human.



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

  (the viruses in the picture are not for memorization)



- There is a **huge** Virome in the human body and it is **continuously changing**.

> ***Notes:*** *We can get rid of **bacteria** using **antimicrobials**. However, this can't be done with **viruses**.*

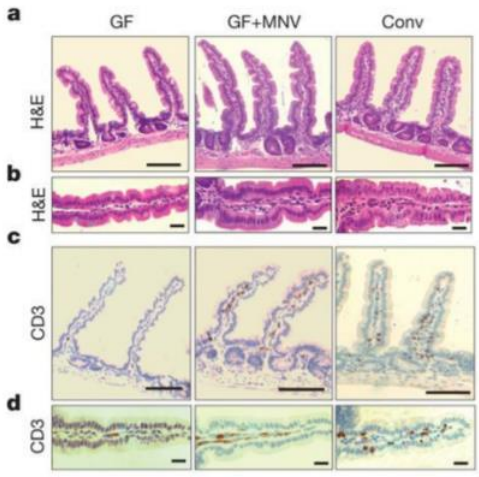
Is the Virome beneficial or not?

Intestinal microbial communities are known to have **profound effects** on healthy host physiology. Whereas the role of **viruses** that are present in the gastrointestinal tract is **undefined**.

Here it is demonstrated that a common **Murine Norovirus** (enteric RNA virus) can replace the beneficial function of commensal bacteria in the **intestine**.

Murine norovirus (**MNV**) infection of **germ-free (GF)** or antibiotic-treated mice restored intestinal microvilli normal morphology and lymphocyte function **without** causing inflammation and **disease**.

This indicates that eukaryotic **viruses** have the capacity to **support** intestinal homeostasis and **shape** mucosal immunity, similarly to **commensal bacteria**.



Human endogenous retroviruses (HERVs) & LTR-Transposons

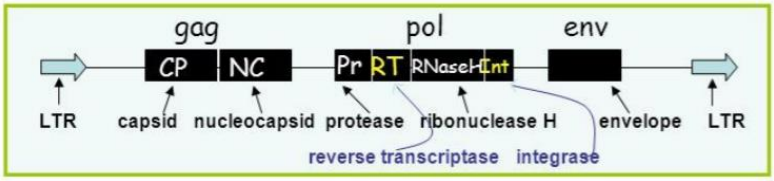
For anybody having difficulties through this topic, do not hesitate and contact me.

Terms to understand:

1- ***Reverse Transcriptase****: It is an enzyme used to generate complementary DNA from an RNA template and vice versa, this process is termed as reverse transcription.*

2- ***Transposons****: DNA sequence that can change its position within a genome, sometimes creating or reversing mutations and altering the cell's genetic identity.*

3- ***Long terminal repeat (LTR) transposons:*** *Retroviral RNA, forms DNA by reverse transcription. At the ends of the proviral DNA, LTR- transposons are found.*
LTR- transposons are used by viruses to integrate their genetic material into the host's genomes.



*8% of the genome is composed of **LTR retrotransposons**, but only **1%** of them are similar to **retroviruses** degenerating the rest. They are all **mutant**; unable to form infective virions.*

> ***Note:*** *The genome of **Chimp** and other **monkeys** contain **infective retroviruses**.*

- **Endogenous retroviruses** (ERVs) descend from **ancient** infectious **RNA viruses** containing a **reverse transcriptase** gene (found in all retroviruses), which converts **RNA into DNA**. Then, it is **integrated** into the chromosomal DNA of the host animal.
- The integrated viral genomes, termed **proviruses**, were subsequently fixed, and have been **vertically** inherited for tens of millions of years through generations, having varying degrees of **mutations** and deletions.
- Human endogenous retroviruses (HERVs) are **footprints** indicating **previous** exposure to **retroviruses**, thus they are coined as **Fossil Viruses**. HERVs constitute approx. 1% of the human genome.
- They have **similar** genomic organization to **exogenous** retroviruses (e.g. HIV-1, HLTV-1).
- 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, since it turns out that many of the proteins have been **exapted** "pre-adapted".

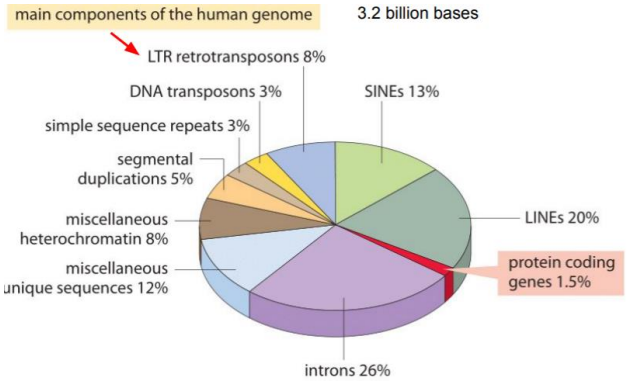
  Exapted protein means that a virus protein is **acquired** and then used it to **our own purposes**. We have exapted **several** retroviruses genes for our **own use** over the years.

- The human genome is made up of **3.2 billion bases**, and it is divided up into the different parts as shown in the pie chart:

Protein coding genes are **1.5%** of the DNA; the minority of the DNA codes for proteins.

While**, 8%** of the DNA are **LTR retrotransposons.** Many of these are retroviral DNAs.

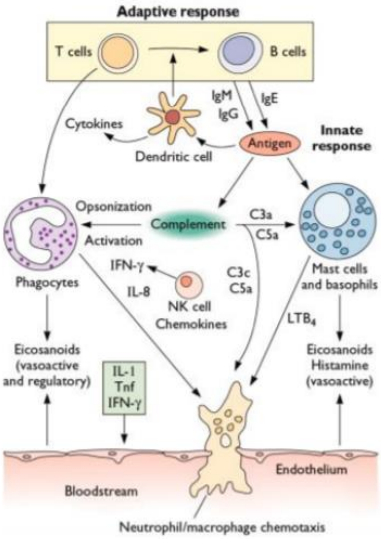
The rest of the genome is all sort of stuff, such as: Introns, heterochromatin, duplicated sequences, etc.



Amazingly, the **vast majority** of viruses that infect us **have little or no impact** on our health or wellbeing. Why?

1- Most viruses that pass through us "ingest" regularly with food, are **non-animal viruses**. Metagenomic analysis in human feces revealed that most viral sequences are like **plant viruses**; 91% of the obtained sequences are for plant viruses.

2- We have an amazing immune system.
The figure on the right shows the work of the immune system (just understand).
The immune system takes care of any viral infection **protecting us**.



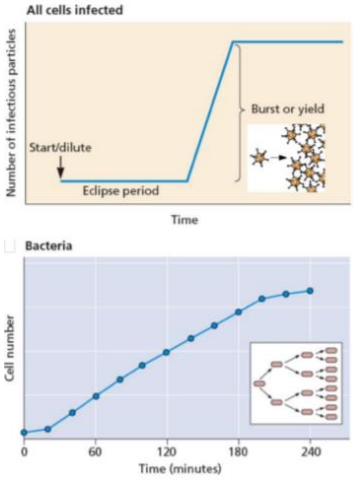
Viruses Replication

Viruses replicate by **assembly** of **pre-formed parts** into many **particles**. *(Parts formed → Assembled into final product)*

As the graph shows, viruses go through **two** phases:

1- Eclipse phase, Viruses parts are built.
2- Burst or yield phase, Viruses are assembled.

> ***Note:*** *They do **not** replicate through **binary fission** as in **bacteria**.*



How old are viruses?

Estimates of molecular evolution suggest **marine origin** of some **retroviruses** (>450 Myr) known as the **Ordovician period**. This means that they most likely originated even **before cells**, which can be true since they are **simpler** in structure.

The Baltimore Classification

A question in the final exam will surely come from this topic as the doctor stated

As it was mentioned before, another way of classifying viruses is based upon their **genetic material**, into the following groups:

Group I: Double stranded DNA viruses (dsDNA).

Group II: Single stranded DNA viruses (ssDNA).

Group III: Double stranded RNA viruses (dsRNA).

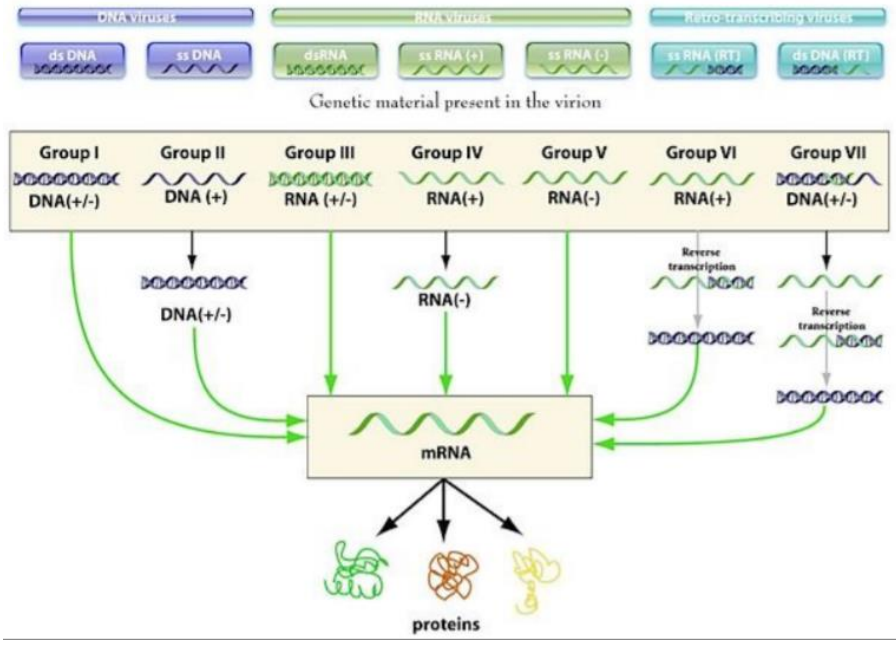
Group IV: Single stranded RNA viruses (+ ssRNA). +/- signs will be discussed later.

Group V: Single stranded RNA viruses (- ssRNA).

Group VI: Single stranded RNA viruses, but with a **reverse transcriptase** gene.

Group VII: Double stranded DNA viruses (dsDNA), but with a **reverse transcriptase** gene.

> ***Note:*** ***Reverse transcriptase****, generate* ***DNA*** *from* ***RNA*** *and vice versa.*



Please memorize this table.

Class	Nucleic Acid	Examples
I	dsDNA	Herpes virus Poxvirus Adenovirus Papillomavirus
II	ssDNA	Adeno-associated virus
III	dsRNA	Reovirus
IV	(+) ssRNA	Togavirus Poliovirus Foot-and-mouth disease virus Hepatitis A virus Hepatitis C virus
V	(-) ssRNA	Influenza virus
VI	(reverse) RNA	HIV
VII	(reverse) DNA	Hepatitis B virus

Note: *An example on **Class VI,** is the **HIV** having a **reverse transcriptase**. When HIV enters the cell, it converts the **RNA** template into **DNA**. Then, DNA of HIV **integrates** into the genome of the **host's cell**.*

*An example on **Class II**, is **AAV**. It is used in **gene therapy** (Retinal gene therapy).*

Good Luck