2- Viral Replication and Pathogenesis

Mohammad Altamimi, MD, PhD
The Hashemite University, 2024

By : Sara Jaber

Objectives

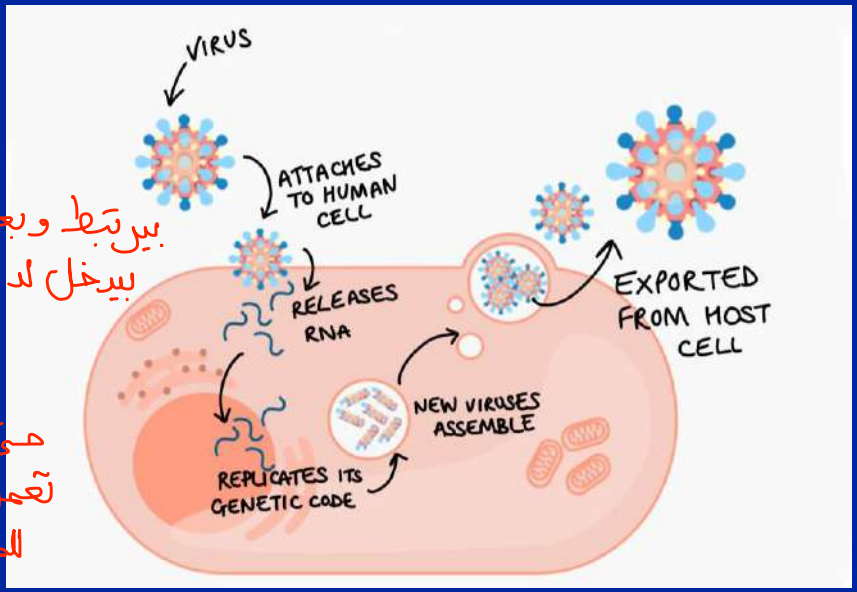
1. Understand the steps of viral replication
2. Differentiate DNA and RNA viral replication
3. Understand steps of viral pathogenesis
4. Factors affecting viral pathogenesis
5. Outcomes of viral infections
6. Host Responses to Viral Infections

immun

Viral Replication

- The host cell is absolutely necessary for viral multiplication

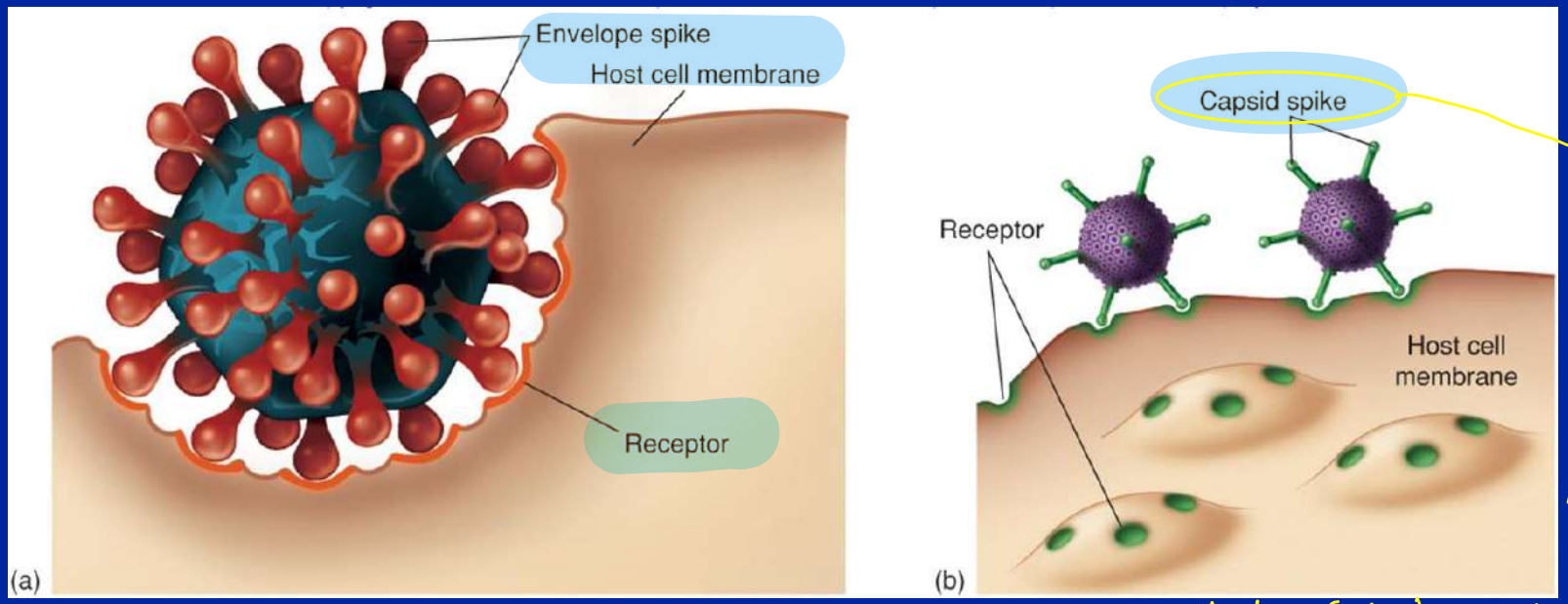
1. adsorption (attachment)
2. entry
3. uncoating
4. transcription
5. synthesis of virus components
6. assembly
7. release



1. Adsorption (attachment):

المقصود فيها: ارتباط الـ Virus بخلايا الـ Host بالمرحلة الأولى

- random collision ⇒ نادر ← تصادم عشوائي
- interaction between specific proteins on viral surface and specific receptors on target cell membrane (tropism) يكون متخصص أكثر
- some viruses may use more than one host cell receptor
- able to infect a limited spectrum of cell types



Spike الموجودة على السطح بتساعد في عملية الـ Attachment

Capsid او على بكون عليها Attachment Protien بتعابلها Receptor على سطح خلية الـ Host

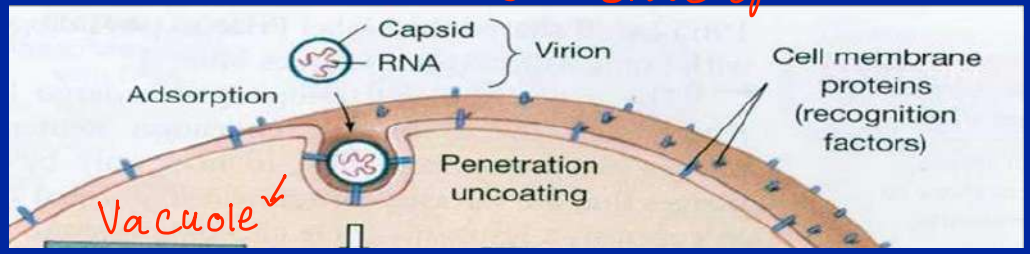
دخول الـ Virus لداخل الخلية

2. Entry (penetration):

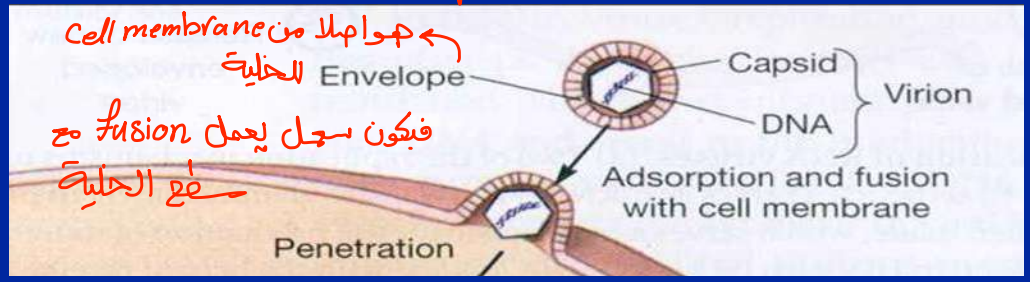
- Flexible cell membrane of the host is penetrated by the whole virus or its nucleic acid
- 2 mechanisms
- Endocytosis: entire virus engulfed by the cell and enclosed in a vacuole or vesicle
- The viral envelope can also directly fuse with the host cell membrane

في الحالتين يدخل الـ
Capsid + Genome
* only *

non-envelope



Envelope



الي وصل لجوا الخلية

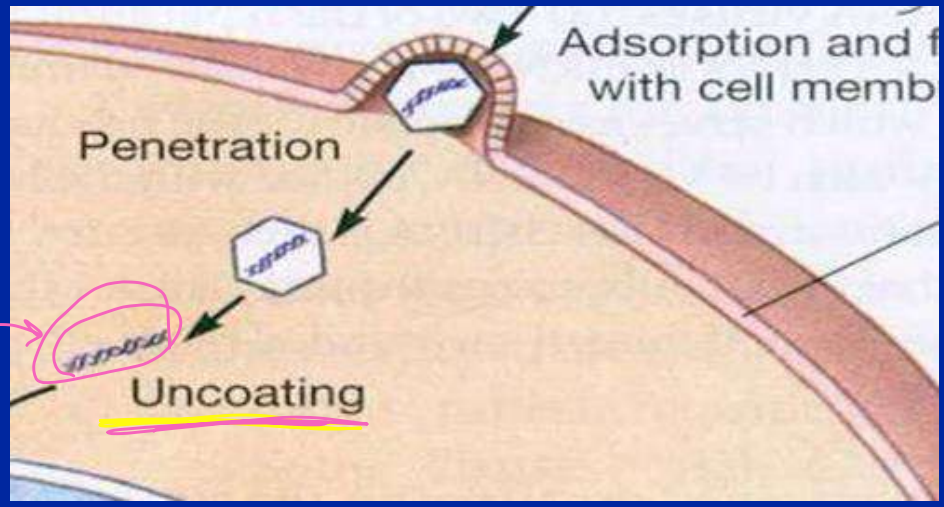
Capsid + Genome هو

بتتحلل By lysosomes

3. Uncoating

- release of viral genome
- cell enzymes (lysosomes) strip off the virus protein coat
- virion can no longer be detected; known as the "eclipse period"

معناها بالعربي مرحلة الكسوف يعني انه الفيروس اختفى "مؤقتاً"



Pathogenic ما بكون الـ Virion بهاي المرحلة

لانه غير كافي وما وصل لمرحلة التطور

الي ممكن تسبب أمراض

4. Transcription/Translation

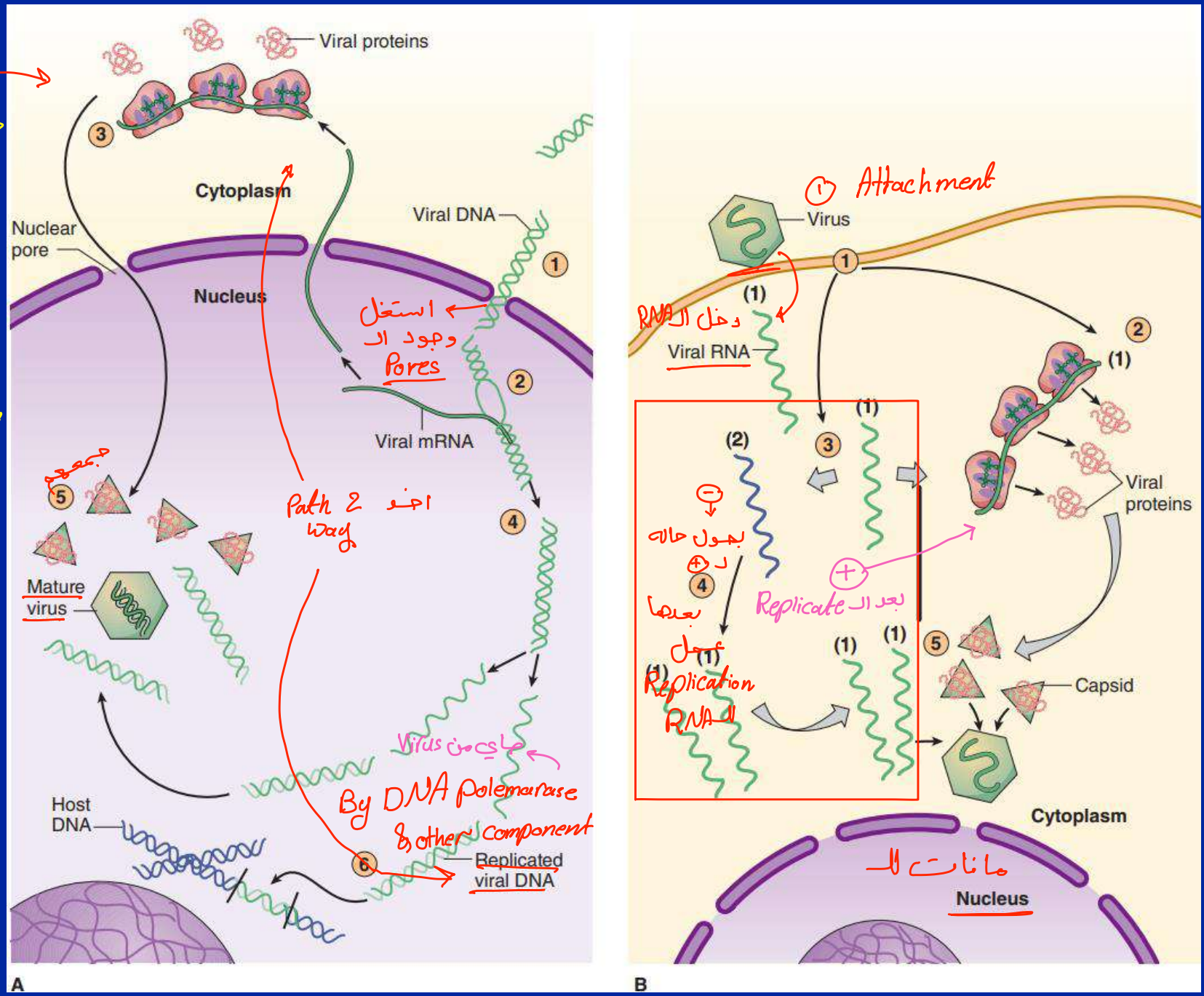
a) DNA viruses:

- replicate their DNA in host cell nucleus mediated by viral enzymes
- synthesize capsid and other proteins in cytoplasm using host cell enzymes
- new viral proteins move to nucleus where they combine with new DNA to form new viruses

b) RNA viruses:

- "+" sense RNA acts as mRNA - viral proteins are made immediately in cytoplasm mediated by viral enzymes
- "-" sense RNA - Ist makes a "+" sense RNA copy via viral enzyme

في DNA حالة بكون الـ Replication فيها استفاد من Nucluse واستفاد من Cytoplasm



5. Synthesis

هو مكون اهم اشي
Host انزيمات ال او يستخدم enzyme معه ممكن يكون Capsid & Genome من

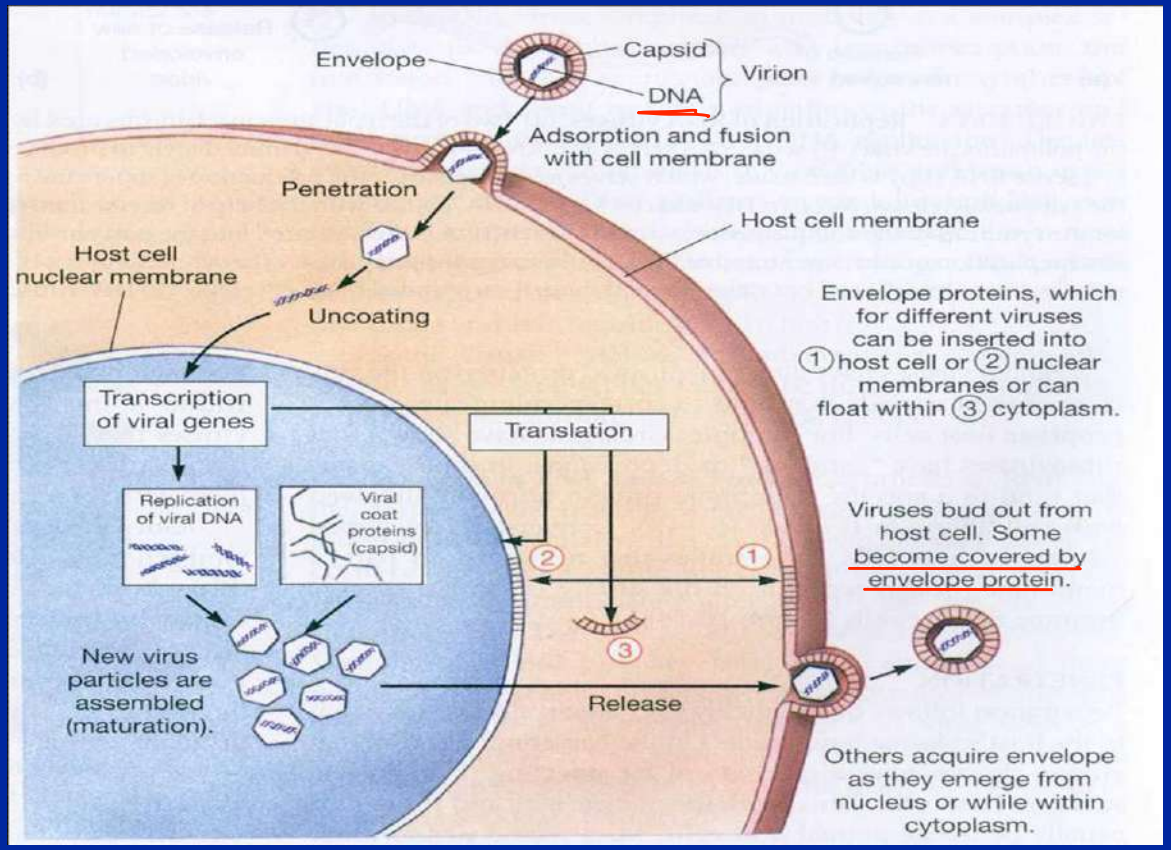
- Protein synthesis - 2 types
  - structural → Capsid
  - non-structural (enzymes for replication)
- Nucleic acid synthesis
  - new virus genome
  - most often by a virus - coded polymerase or replicase; with some DNA viruses a cell enzyme carries this out

Protien
Nucleic acid

التجميع

6. Assembly

- Mature virus particles are constructed from the growing pool of parts
- may take place in cell nucleus, cytoplasm or (with most enveloped viruses) at the plasma membrane



7. Release

- Nonenveloped and complex viruses are released when the cell lyses or ruptures
- Enveloped viruses are liberated by budding or exocytosis
- Anywhere from 3,000 to 100,000 virions may be released, depending on the virus
- Entire length of cycle- anywhere from 8 to 36 hours

Viral Pathogenesis

- The process by which a viral infection leads to disease
- The majority of viral infections are subclinical
- The consequences of viral infections depend on the interplay between a number of viral and host factors

غالبًا لا يوجد أعراض واضحة

* بعض الأمراض الفيروسية قاتلة وبعضها مزمن وجزء منها بتختفي بعد فترة قصيرة ، ليش؟

← لأنها بتعتمد على الـ interaction Between Host و viral infection

Factors in Viral Pathogenesis

- Entry into the Host
- Course of Infection (Primary Replication, Systemic Spread, Secondary Replication)
- Cell/Tissue Tropism
- Effects of viral infection on cells (Cellular Pathogenesis)
- Cell/Tissue Damage
- Host Immune Response
- Virus Clearance or Persistence
- Viral shedding

Steps in Viral pathogenesis

1. Viral Entry & Primary Replication طريقة الدخول والتكاثر الأولية
2. Viral Spread & Cell tropism
3. Cellular injury & Clinical illness ⇒ كمية Cell injury ومعدلها راح تأثر على شدة المرض
4. Recovery from infection → Repair cells
5. Viral clearance or persistence
6. Viral shedding

إذا ما قدرنا نعالجه ↓ Chronic

Viral Entry

الأعراض الأولية مرتبطة بمكان دخول الفايروس

- Skin - through cuts or abrasions, animal bites e.g. Rabies virus
  - جرح خشط وخدش عضات الحيوانات
  - الأعراض الأولية بتظهر على الجلد مثل الالتهاب
  - Respiratory tract e.g. Influenza, Parainfluenza virus Common
  - Gastrointestinal tract e.g. Rotavirus, Poliovirus
  - ملتحمة العين Conjunctiva and other mucous membranes
  - Genitourinary tract e.g. HIV
  - Directly into Bloodstream by
    - Needles : HBV, HIV
    - Blood transfusions : HIV, HCV, HBV
    - Insect vectors : Arboviruses

Routes of Transmission

من شخص لشخص اخر

- Horizontal transmission:
  - Direct contract (secretions, blood etc.)
  - Respiratory (aerosol)
  - Contaminated inanimate objects
  - Insect vector (mosquitoes, ticks, etc.)
  - Zoonoses

من الأم للطفل

- Vertical transmission:
  - Mother to fetus [Transplacental (Congenital), Perinatally]

Course of Viral Infection

- **Primary Replication** → Cell Damage الفايروس يتكاثر بالمكان الذي دخل منه و يعمل
  - Viruses usually replicate at the site of initial entry into the host.
  - The infection remains localized at the site of entry
- **Systemic Spread**
  - Many viruses produce disease at sites distant from point of entry
  - After primary replication, they spread via blood, neurons or lymphatics to other organs. (1) (2) (3)
  - Presence of virus in blood is called VIREMIA
  - Viral spread is determined by its organ & cell specificity – CELL TROPISM
- **Secondary Replication**
  - Secondary replication takes place at susceptible organs/tissues following systemic spread.

لو وصل للدم راح يتوزع لكل اجهزة الجسم ولكن يختلف استجابة الخلايا حسب اختلاف الـ Virus

لو الخلايا استجابت

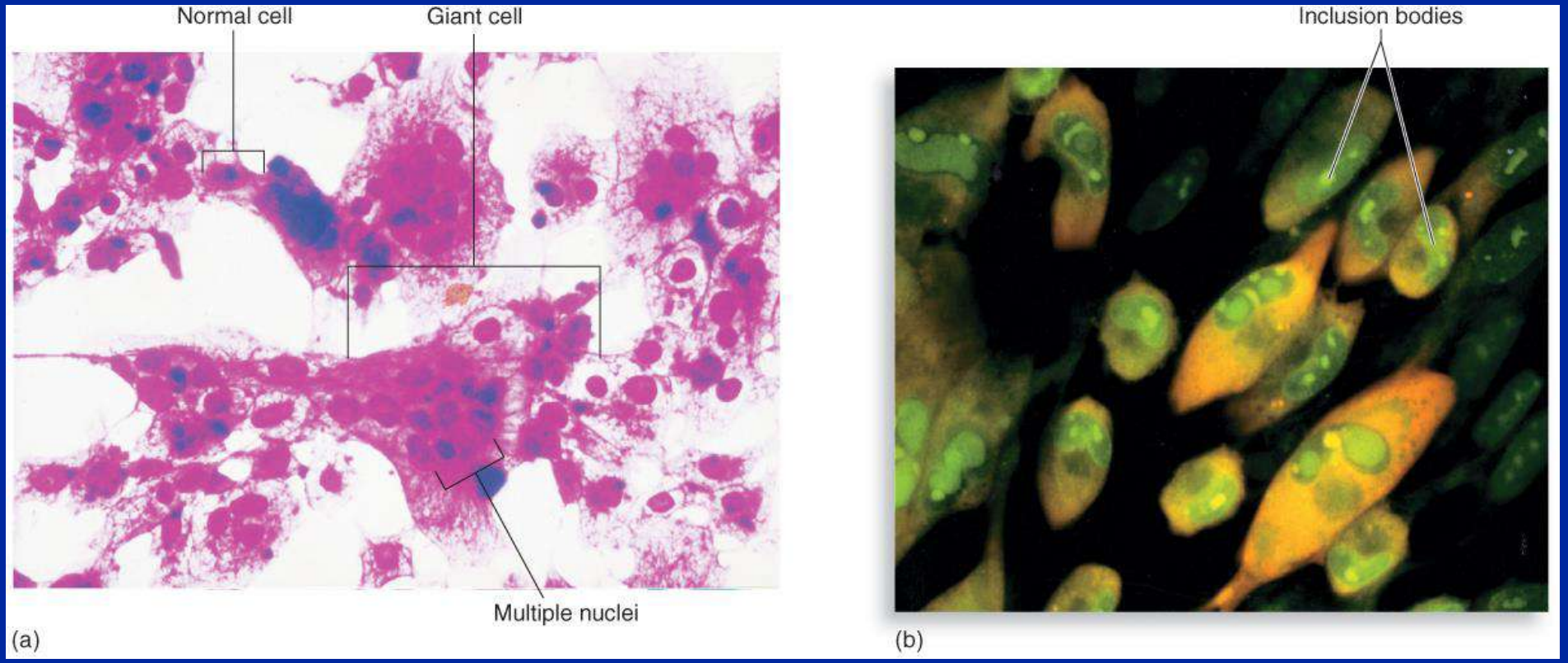
Effects of Viral Infection on Cells

- Cells can respond to viral infections in following ways:
  - No apparent change
  - Cell death or lysis e.g. poliovirus
  - Cellular proliferation e.g. Molluscum
  - Malignant transformation e.g. Oncogenic viruses
  - Cytopathic effects as in tissue cultures
    - Cytopathic effects- virus-induced damage to the cell that alters its microscopic appearance
    - Inclusion bodies- compacted masses of viruses or damaged cell organelles

Non enveloped viruses → Complete cell lysis
Tissue على حسب قدرة ال Death
Repair على بيعتمد ال effect

تكاثر

Cancer cells تحول لها


Normal cell
Giant cell
Multiple nuclei
(a)
Inclusion bodies
(b)

Outcome of Viral Infection

- Clinical outcome – subclinical (Inapparent) or clinical (apparent) infections. Clinical infections can be:

1. Acute Infection
   - Complete recovery يشفى في آخر
   - Recovery with residual effects
   - Proceed to chronic infection (latency)
2. Chronic Infection
   - Silent subclinical infection for life لمدى الحياة بدون أعراض
   - A long silent period before disease يشفى بدون effect لفترة ولكن المناعة تضعف بيرجع Active
   - Reactivation to cause acute disease ⇒ Virus دخل → Chronic بيات → Silent → رجع بعضها Acute وبيات أظهر أعراض Acute
   - Chronic disease with relapses and excerbations
   - Cancers

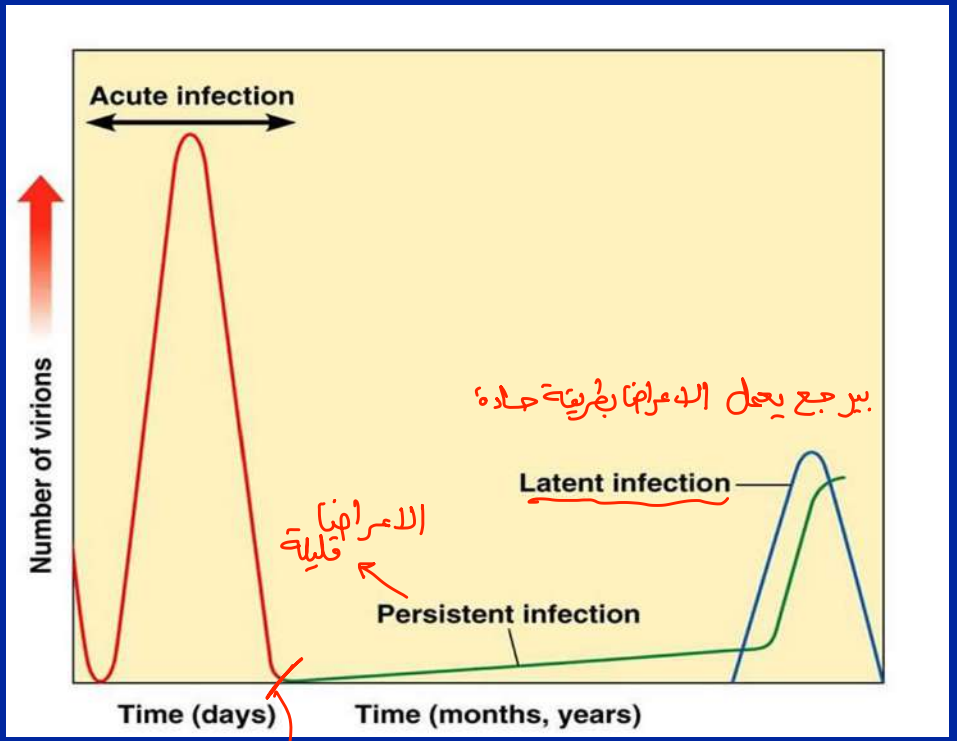
Virus Shedding

- Last stage in pathogenesis
- Necessary step to maintain a viral infection in a population of hosts
- Usually occurs from the site of entry
- Occurs at different stages of disease depending on the agent
- Represents the time at which an infected individual is infectious to contacts
- In certain cases, shedding does not occur e.g. Rabies

Viral Persistence

Majority of viral infections are cleared but certain viruses may cause persistent infections. There are 2 types of persistent infections:

1. Chronic infections – virus is continuously detected but at low levels
2. Latent infections - virus remains completely latent following primary infection. Intermittent flare ups of disease

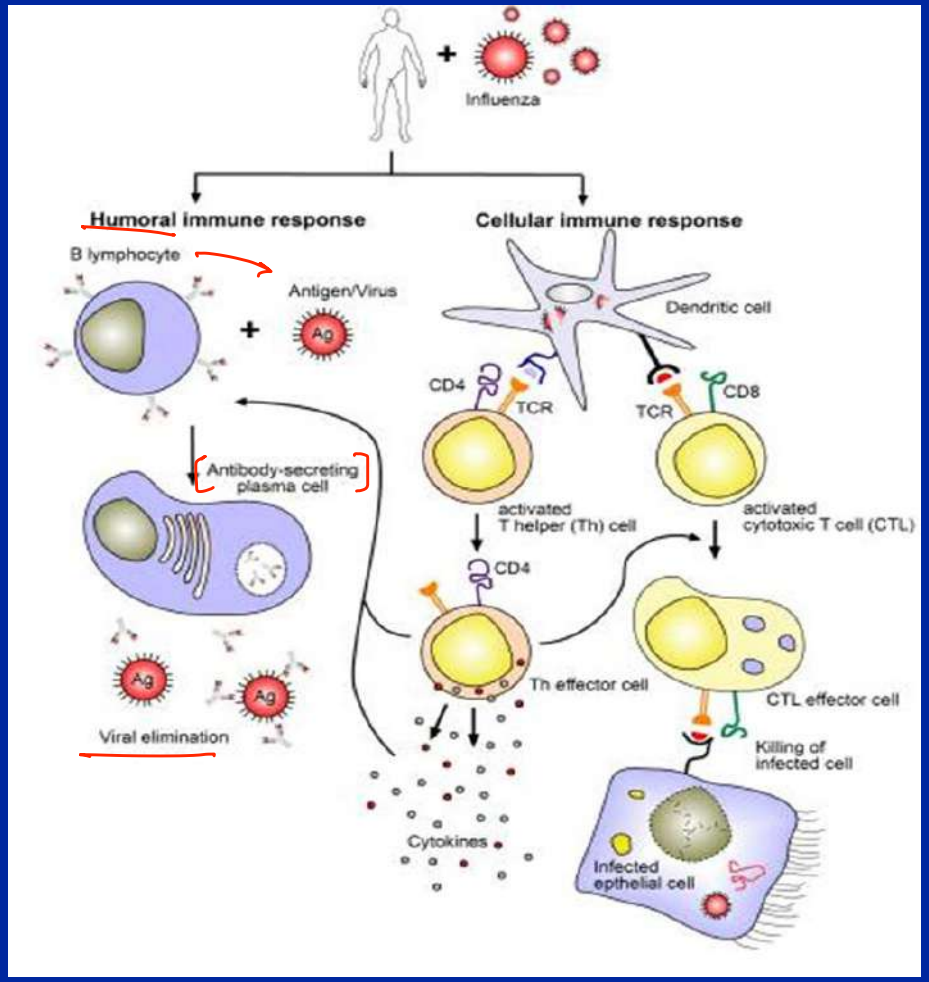


Host Responses to Viral Infections

- Innate immunity – Interferons مضاد للفيروسات
- Humoral response – protects the host against reinfection by same virus
  - IgG & IgM : Blood & tissue
  - IgA : mucosal surfaces of respiratory & gastrointestinal tract
  - Neutralising Abs prevents initiation of infection
- Cellular response – recovery from viral infection, destroy viral infected cells
- Mostly gives lifelong protection

By Anti-Body

By T cells

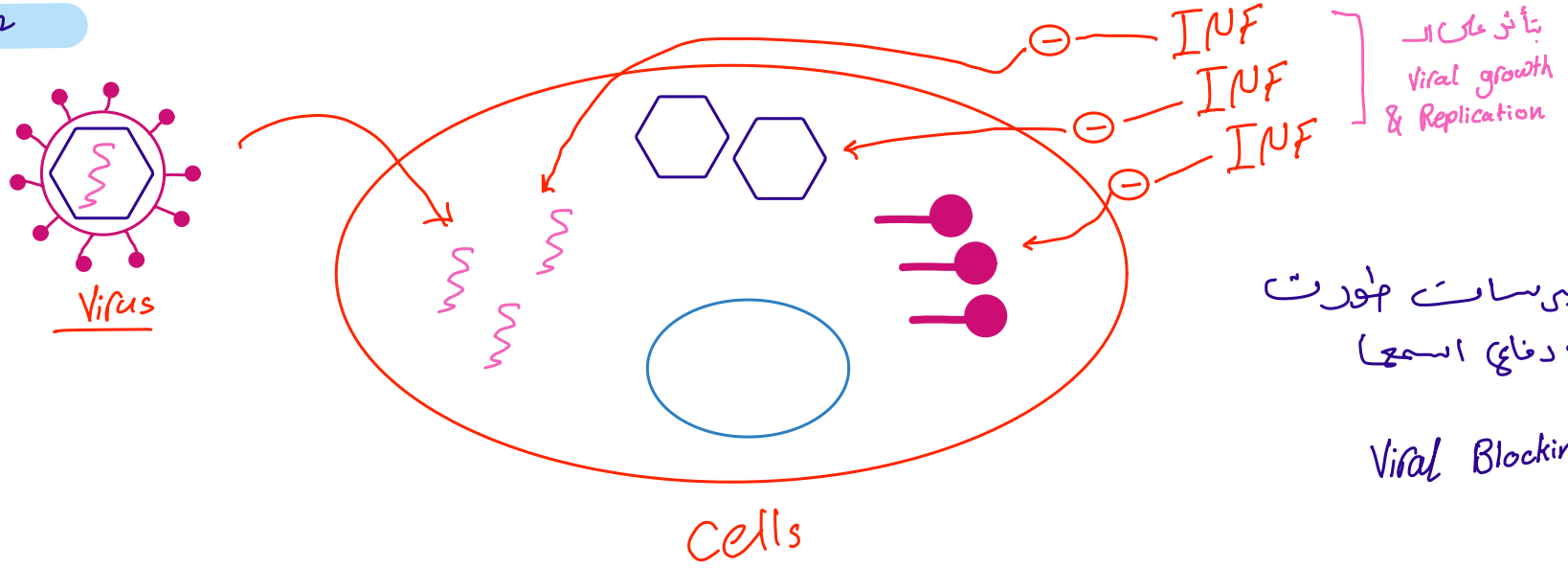


① Innate - interferons → non specific

البروتينات [INF]

- Cytokines (protien) → INF α, INF β, INF γ → Type I ⇒ Anti-Viral effect (RNA) → تأثيرهم على RNA > DNA
- Secreation : Body cells + immune cells (macrophages)
- Effect : Rapid (hours) + Non-spesific → ما بجمع نوع الفايروس عنده عامة mechanism
  Killing diffirent viruses

Mechanism

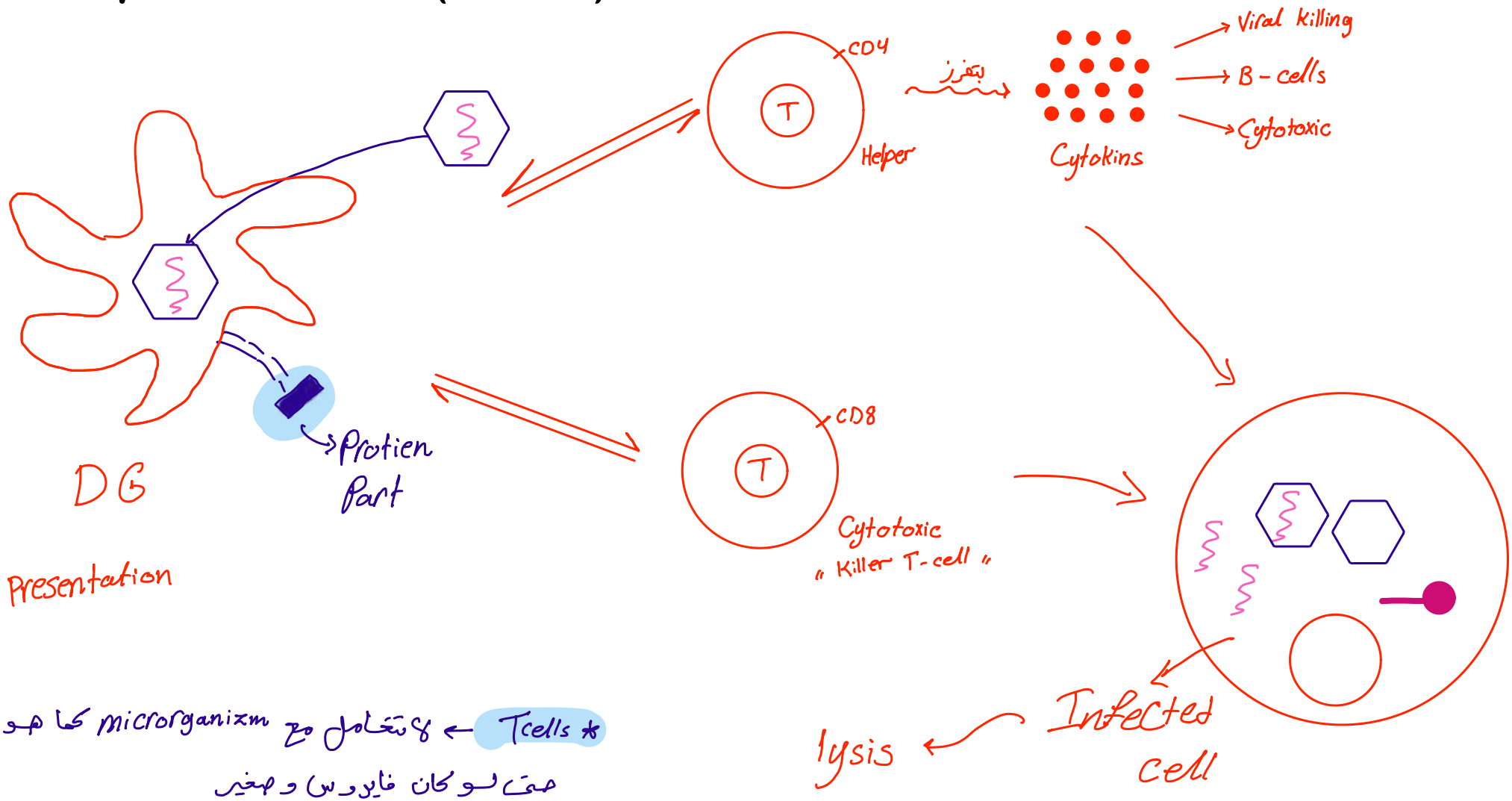


بعض الفيروسات طورت
وسيلة دفاع اسمها

Viral Blocking INF

Virus presentation ← كانها تشمل أكثر تعقيدًا

② Adaptive- cellular (T cells)

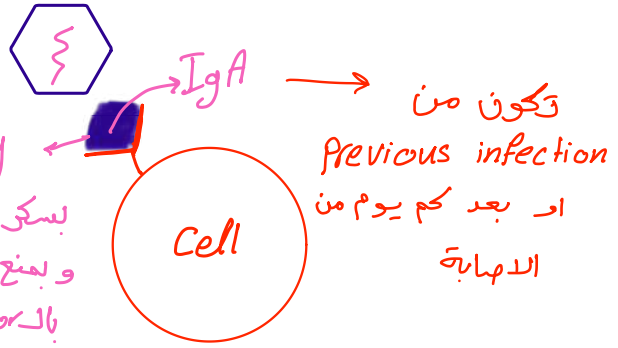


* Tcells ← بتتعامل مع microorganizm كما هو
حتى لو كان فايروس و صغير
بتتعامل مع peptied بحجم محدود
فلازم يكون في خلية تحضن الـ Virus وبتكسره و بتجهزه
حتى تقدر تربطه فيه T-cells

③ Adaptive-humoral (B-cells)

بتفرز Anti-Body

Ⓐ Attachment (IgA)
Neutralization

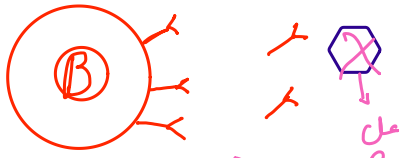


تكون من
Previous infection
او بعد كم يوم من
الاصابة

العملية اسمها Nuetralization
Very effective
لانها بتمنع الخطوة الاولى
Attachment

Ⓑ Antibody mediated killing

لما يكون الـ Virus داخل الخلية
الـ B-cells ما بتقدر تشوفه لكن بعرف
ما بيطلع من الخلية و بيجيب لخلية ثانية



مع البروتينات ضعيف و الـ Capsid بروتين

Ⓒ T - Helper B-cells activation
بتتعرف على Virus
وبتعمل Activation
لـ B-cells
بتنتج Antibody

HIV بيستهدف T cells وبيدمرها
والجهاز المناعي بيضعف بالتدريج