Revised & Approved

Bassam Alasmari
Rania Almutiri

Immunology of HIV/AIDS

Color index

Important

Extra

Notes

IMMUNOLOGY
TEAM 439

Objectives

- To know the modes of transmission of HIV.
- To understand HIV interactions with CD4 positive helper lymphocytes.
- To understand the mechanisms involved in immunodeficiency associated with HIV.
- To know the course of immunological events from the time of infection with HIV until the development of AIDS.

Editing File

Click here!

Please check frequently

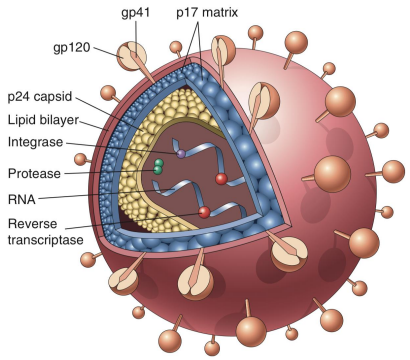
We recommend studying microbiology (HIV/AIDS lecture) before studying immunology

Good luck!

Structure of HIV

Introduction

- HIV is an **enveloped retrovirus** that infects **CD4 receptor-expressing cells**; this includes: CD4 T cells and APCs such as macrophages and dendrites (later in slides)



- **Target cells of HIV infection:**
  - **Lymphocytes** (Lymph nodes, thymus, bone marrow)
  - **Macrophages** (Brain, body fluids, Skin, GIT, Lung)

- **Transmission:**
  - **Sexually (most common),** mainly in homosexuals
    - Genital or colonic mucosa
  - **Parenterally:**
    - Blood transfusions with infected blood, sharing contaminated needles
  - **Perinatally**: mother to infant
    - Transplacentally (25%): treatment with reverse transcriptase inhibitors **(zidovudine)** during pregnancy can reduce the chance of transmission in most cases
    - During delivery (50%): treatment with transcriptase inhibitor **(nevirapine)** as single dose during delivery can reduce the transmission
    - Post delivery through breast feeding
  - Accidental occupational exposure: using contaminated or not adequately sterilized tools in surgical or cosmetical practice

HIV Structure

	Structure	Function
Genome	**2 molecules of ss-RNA**	-
Envelope Protein	**gp120**	Attaches to host CD4+ T-cells
	gp41	Assists in fusion and entry of the virus into the host cell
Matrix Protein	**p17**	-
Core Protein	**p24**	-
Enzymes	**Reverse Transcriptase**	Converts viral RNA into DNA
	Integrase	Integrates viral DNA with host DNA forming provirus, persisting infection.
	Protease	Cleaves viral polyprotein

Pathophysiology (How HIV Enters Cells?)

1. **Envelope protein gp120 (Main Protein) binds to host CD4 molecule (receptor)**
   - **a.** CD4 found on: T cells, monocytes, macrophages, and microglial cells
   - **b.** **Binding to CD4 is not sufficient for entry,** co-receptor binding is essential

2. **Envelope protein gp120 binds to co-receptor. Co-receptor = chemokine receptors which are: CXCR4 and CCR5 (imp for MCQ)**
   - T-cell tropic strains bind to the co-receptor CXCR4
   - Macrophage-tropic strains bind to the co-receptor CCR5
   - A **mutant CCR5 receptor gene** that prevents the virus from binding to the cell has been discovered. **Homozygosity** for this mutant gene is strongly protective against HIV infection. Heterozygous people are not protected from infection but the disease may take longer to develop.

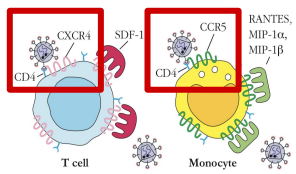
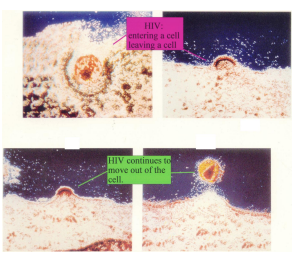


FIGURE 18-15 CXCR4 and CCR5 serve as coreceptors for HIV infection.

3. Binding of virus to cell surface results **in fusion of viral envelope** with cell membrane. Viral core is released into cell cytoplasm - **HIV (Retrovirus) enters cell**

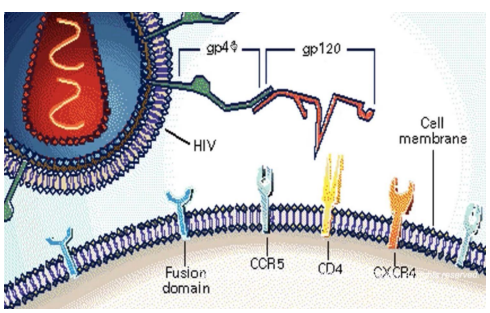
4. **Inside the cell:** Reverse transcriptase makes DNA copy of RNA. By action of integrase enzyme, viral DNA forms provirus with host DNA

5. **Forming new HIV:**
   - **a.** Viral DNA makes mRNA
   - **b.** mRNA makes HIV proteins
   - **c.** HIV proteins become HIV capsid
   - **d.** mRNA is collected inside of HIV capsid forming new HIV



6. New HIV leaves cell and wraps itself in host membrane forming its envelope **by budding**

Figure A



EXTRA

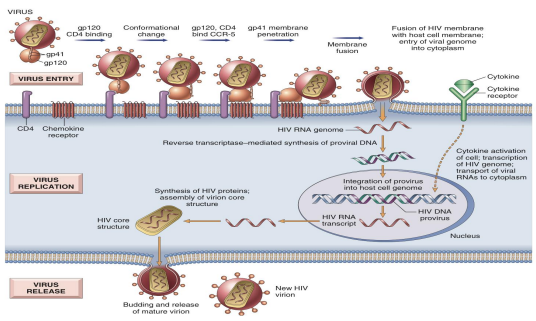


Figure A: shows HIV's attachment and entry into a host cell.
- **gp120** protein attaches to a CD4 receptor
- **gp41** is exposed for attachment to the host cell, and fusion of the cell membrane with the viral envelope starts

General Principles of Viral-Host Interaction

Viral-Host Dynamics

- About 10 billion virions are produced daily. Extremely high rates of viral replication results in every possible point mutation in the viral genome. In any given patient, the virus usually varies by 1-6% in the envelope gene.
- Average lifespan of an HIV virions in plasma is around 6 hours
- Average lifespan of infected CD4 cell is 1.6 days (live longer inside cells)
- Unlike other retroviruses, **HIV can lie dormant** within a cell for many years, especially in resting memory CD4 cells (patient is asymptomatic)

Viral-Host Interaction

Host	Host mounts HIV-specific immune responses: 1. Cellular (cell-mediated immunity) - **Most important** 2. Humoral (antibody-mediated)
Virus	HIV virus subverts the immune system. How? 1. It infects CD4 cells that control normal immune responses 2. Integrates into host DNA 3. High rates of mutation **(#micro: HIV-1 is HIGHLY susceptible to mutations)** 4. **Hides in tissue** not readily accessible to immune system **(lies dormant in cells like in: glial cells and lymphocytes)**

Cells infected by HIV

- Numerous organ systems are infected by HIV, all in which **their cells express CD4 receptor. Such as:**
  - **Brain:** macrophages and glial cells **(very imp site: virus will stay here for years)**
  - **Skin:** langerhans cells
  - **Lung:** alveolar macrophages
  - **Lymph nodes and thymus:** lymphocytes and dendritic cells (HIV can also stay here for years)
  - **Blood, semen, vaginal fluids:** macrophages
  - **Bone marrow:** lymphocytes (Hard to manage; difficult for drugs to reach this area)
  - **Colon, duodenum, rectum:** chromaffin cells

Immune Response to HIV

Cellular Immune Response to HIV

CD4 Helper T Lymphocyte (Th)	• Plays an important role in cell-mediated response
	• Recognizes viral antigens by an antigen presenting cell (APC)
	  ○ Utilizes major histocompatibility complex (MHC) class II
	• Differentiated according to the type of "help"
	  ○ Th1 - activate Tc (CD8) lymphocytes, promoting cell-mediated immunity by certain interleukins such IL-2, interferon-gamma (IFN-gamma), and tumor necrosis factor-beta (TNF-beta)
	  ○ Th2 - activate B lymphocytes, promoting antibody mediated immunity

CD8 Cytotoxic T Lymphocyte (CTL)	• Derived from naïve T8 cells, which recognize viral antigens in context of MHC class I presentation • Directly destroy infected cell • Activity augmented by Th1 response

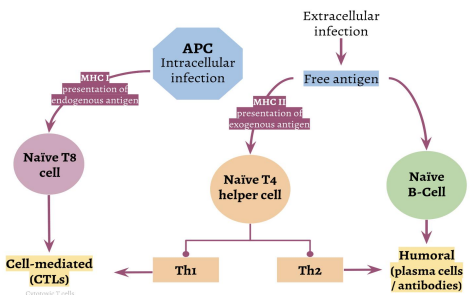
Humoral Immune Response to HIV

(Less effective in controlling HIV infection compared to cellular immunity)

Neutralization	• Antibodies against viral proteins bind to surface of virus to prevent attachment to target cell
Antibody-dependant cell-mediated cytotoxicity (ADCC)	• Fc portion of antibody binds to NK cell • Stimulates natural killer cell to indirectly destroy infected cell

General Principles of Immune Dysfunction due to HIV

- All elements of immune system are affected
- Advanced stages of HIV are associated with substantial disruption of lymphoid tissue
  - Impaired ability to mount immune response to **new antigen**
  - Impaired ability to maintain **memory responses** □
  - Susceptibility to **opportunistic infections**



Adaptive Immune Response

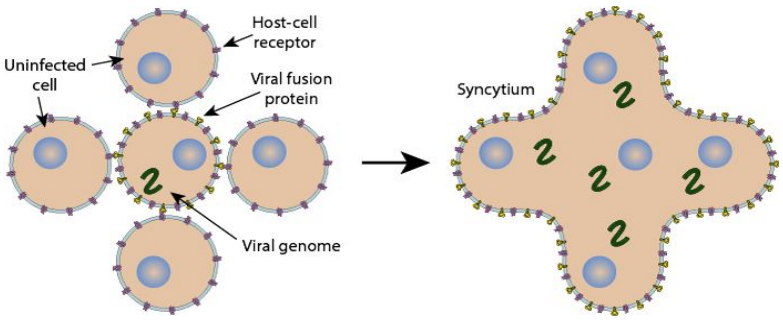
Figure (previous knowledge):

- This is an important slide representing the **adaptive immune response, which is the main response to HIV** (as opposed to the innate immune response).
- The adaptive immune response is divided into 2 types: cell-mediated (cytotoxic t-cell) type and humoral (antibody-mediated) type. In general, location of the infection (intracellular or extracellular) determines the type of adaptive immune response.
- **Intracellular** infections stimulate a cell-mediated response that will ultimately kill the infected cell. This is **mediated by T8 cells, and utilizes the MHC I system.**
- In **extracellular** infection, humoral response will be stimulated helping in containing free antigens which will be picked up by APCs, **presented by MHC II to the Th 1 or 2 cells**

Immune Dysfunction in HIV

CD4 Depletion and Dysfunction

Direct	• Elimination of HIV-infected cells by virus-specific immune responses • Loss of plasma membrane integrity because of viral budding

Indirect	• Apoptosis
	• **Autoimmunity** (HIV increases autoantibodies which increases incidence of autoimmune diseases)
	• **Syncytium formation**
	  ○ Observed in HIV infection, **most commonly in the brain** (Neuronal tissue is seen, but nonfunctional)
	  ○ Uninfected cells may then bind to infected cells due to viral gp120. This results in **fusion** of the cell membranes and subsequent **syncytium formation**
	  ○ These syncytia are highly unstable and **die** quickly
	 

Role of Cellular Activation in Pathogenesis of HIV

- **HIV induces immune activation:** Which may seem paradoxical because HIV ultimately results in severe immunosuppression
- **Activated T-cells support HIV replication:**
  - Intercurrent infections are associated with **transient increases in viremia**
  - Accounts for why **TB** worsens underlying HIV disease

Role of Cytokine Dysregulation in Pathogenesis of HIV

Increased expression	HIV is associated with increased expression of **pro-inflammatory cytokines:** • **TNF-alpha, IFN-gamma, IL-1,IL-6, IL-10**
Disruption and loss	HIV results in disruption and **loss of immunoregulatory cytokines:** • **IL-2, IL-12** • Necessary for modulating effective cell-mediated immune responses (CTLs and natural killer cells)

Stages of HIV Infection

Primary Infection (Acute)	
Clinical features	• **70- 80% are symptomatic** (#micro & #path: at least 50% of cases are asymptomatic), **3 - 12 weeks** after exposure (incubation period) • **Symptoms include:** ○ **Fever, rash, cervical lymphadenopathy,** aseptic meningitis, encephalitis, myelitis, polyneuritis
Lab markers	• **Surge (great increase)** in **viral RNA,** copies to >1 million. **(high viral load)** • **Fall** in CD4 T cell count to 300-400 cells/mm^3 (normal: 500-1500 cells/mm^3) • **Recovery** in 7-14 days (2 weeks)
Latent/Asymptomatic Infection (Chronic)	
Clinical features	• Remain well with no evidence of HIV disease except for generalized lymphadenopathy. **(#micro: usually totally asymptomatic but the patients is still contagious)** • **#Micro & #Path: Lasts 8 - 10 years**
Lab markers	• **Fall** of CD4 T cell count by about 50-150 cells per year **(#micro: CD4 count decreases BUT still higher than 200 cells/mm^3)**
End-stage: Progression to Acquired Immunodeficiency Syndrome (AIDS)	

Clinical features	• Depletion of CD4 cells causes defects in cellular immunity and therefore makes the body highly susceptible to:
	  ○ **Tumors: such as kaposi sarcoma, B-cell lymphoma** (mainly in the brain, mostly associated with EBV) **(imp for MCQ)**
	  ○ **Opportunistic infections:**
	  ▪ Viruses: cytomegalovirus, **Epstein-Barr Virus,** Herpes Simplex Virus
	  ▪ Fungi: candida albicans, **pneumocystis jirovecii**

Lab markers	• Gradual reduction in number of circulating CD4 cells is **inversely (very imp)** correlated with the viral load.
	  ○ **High levels:** Viral load - viral RNA
	  ○ **Low levels:** CD4+ T cell count **less than** 200 cells/mm^3

Clinical Course of HIV Infection

Seroconversion

- Definition: it is the time period during which **a specific antibody develops and becomes detectable in the blood.**
- **In HIV, seroconversion occurs 8 weeks after infection** (within primary stage)
- **Levels of viral load post seroconversion correlate with risk of progression of disease.**

Infection Course

Figure A:
Shows infection course in relation to antibody formation and diagnostic approach

#438: Untreated Clinical Course

Note that ELISA is positive only after the 4th week

- In HIV, it takes **4-**8 weeks after infection for seroconversion (according to drs notes and slides, but figure shows 4w). The time it takes for seroconversion to occur is called the **window period**
  - **Window period: The time between infection and detectability of HIV antibodies (very imp), begins at the time of infection and can last 4 to 8 weeks.**
  - **In other words:** During this period, a person is infected, with a high viral load and a **negative** HIV antibody test (from week 0-4), the point when the HIV antibody test becomes positive is called the point of **seroconversion**
- The level of viral load post seroconversion correlates with risk of progression of disease (hence why PCR is used for follow up)

Figure B:
Shows infection course in relation to symptoms, viral load (HIV RNA), and CD4 T cell count

- Acute (primary) retroviral syndrome is the initial event after infection, which is **characterized by a rapid decline in CD4 cell count and high plasma viremia**
- Development of cytotoxic T-cell (CTL) response results in clinical recovery of acute infection and a reduction in plasma viremia. The virus reaches "set point" as a result of this immune response. The viral load at this "set point" correlates with the rate of CD4 decline and disease progression. Overtime, HIV RNA levels gradually increase.
- **When the CD4 count falls below 200, patients develop opportunistic infections, tumors, and neurological complications.** The median survival after the CD4 count has fallen to <200 is 3.7 years, if untreated.

Figure A

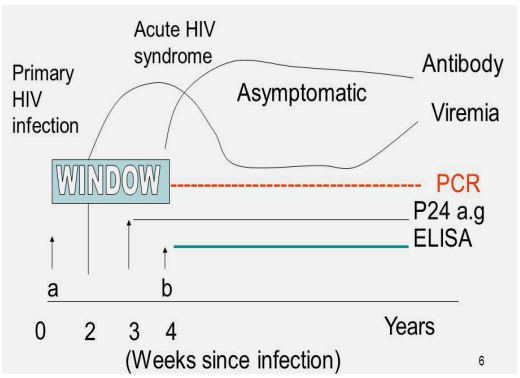
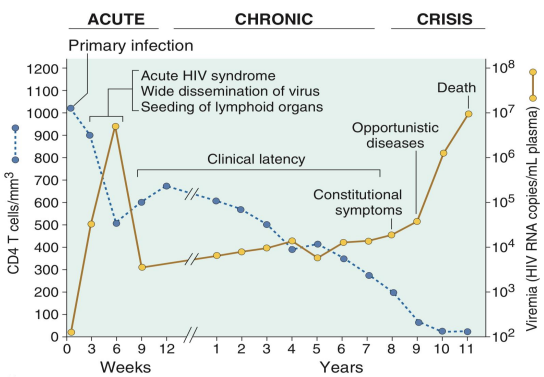


Figure B



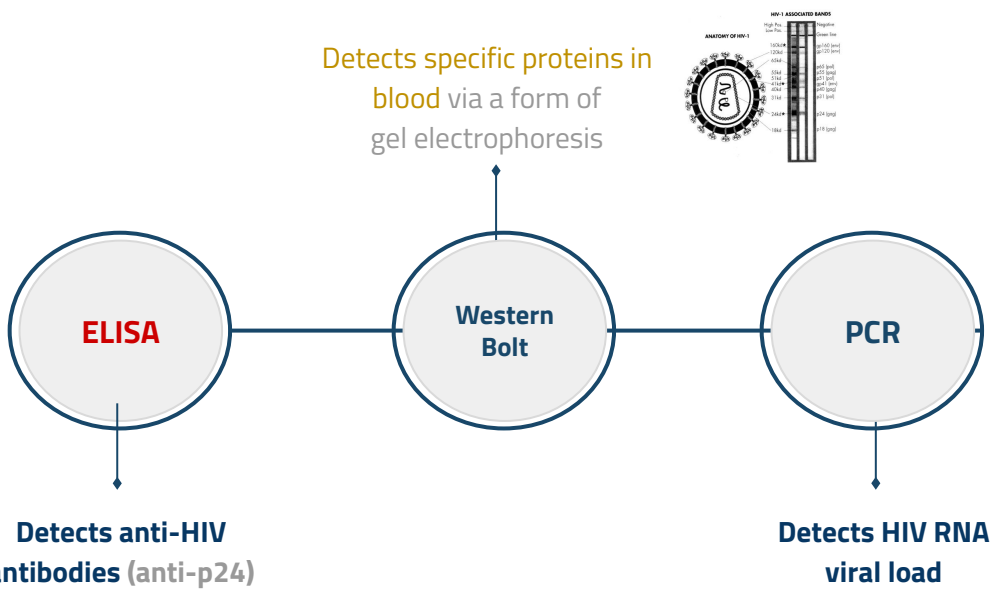
Diagnosis and Management

Laboratory Markers of HIV Infection

- **Viral Load → Marker of HIV replication**
- **CD4 count → Marker of immunological damage**

★ **Remember: The virus is targeting CD4 cells (Inversely proportional). Unless infection is managed, and virus replication is inhibited, CD4 will decrease.**

Diagnosis: Diagnostic Approach



- **PCR:** (If viral load is low for a few years, then you are managing the patient very well
- **For diagnosis, PCR and p24 are not usually used because they're expensive and time consuming. Instead, we use ELISA because it is cheaper. The only problem with ELISA is LATE DETECTION (4-8 weeks of infection) compared to PCR and p24.**

Management

- Treatment is recommended as soon as possible. **It can't cure HIV** (#micro: doesn't eradicate infection) but **helps to keep HIV patients healthier** (#micro: by inhibiting viral replication) and **prevent HIV transmission** (#micro: minimize chance of viral transmission, not inhibit it).
  Anti-retroviral therapy (ART):
  - Reverse transcriptase inhibitors
  - Protease inhibitors
  - Fusion inhibitors
- Post exposure prophylactic treatment (PEP): within max 72 hours after exposure for 28 days

Take home messages

Infection with HIV usually occurs by sexual transmission, blood transfusion, mother to infant or accidental exposure

HIV targets the immune system and primarily infects CD4 positive lymphocytes

Immunodeficiency associated with HIV infections **is mainly due to reduction in CD4** positive helper lymphocyte numbers

Increased viral load, significant reduction in CD4 lymphocytes and opportunistic infections are the hallmarks of progression to AIDS

SUMMARY

HIV mode of transmission

- Sexually (genital od colonic mucosa)
- Perinatally (mother to infant)
- Parenterally (blood transfusions, needles, ,etc...)
- Accidental occupational exposure

Cell targets of HIV

Cells which express **CD4 receptor, such as:**

- **Brain:** macrophages and glial cells
- **Skin:** langerhans cells
- **Lung:** alveolar macrophages
- **Bone marrow:** lymphocytes
- **Lymph nodes and thymus:** lymphocytes and dendritic cells
- **Blood, semen, vaginal fluids:** macrophages
- **Colon, duodenum, rectum:** chromaffin cells

Properties of HIV

Structure		**Envelope proteins: 1) gp 120 2) gp41** **Capsid protein:** p24 (anti-HIV antibodies are against p24, anti-p24 antibodies)
Pathogenesis		1. **Envelope protein gp120 binds to host CD4 receptor AND coreceptor. CXCR4 and CCR5 (chemokine receptors)** 2. **HIV (Retrovirus) enters cell** 3. Reverse transcriptase makes DNA copy of RNA 4. Integrase enzyme integrates viral DNA with host DNA 5. HIV makes it own proteins 6. New HIV forms and leaves the cell (budding process)
CD4 depletion & dysfunction	**Direct**	• Elimination of infected cells by virus-specific immune responses • Loss of plasma membrane integrity because of viral budding
	Indirect	• Apoptosis • **Autoimmunity** • **Syncytium formation: most commonly in the brain**
Cytokine dysregulation	**Increase**	Increased expression of pro-inflammatory cytokines: • TNF-alpha, IL-1,IL-6, IL-10, IFN-gamma
	Decrease	Disruption and loss of immunoregulatory cytokines: • IL-2, IL-12 • CD8 and NK
Infection Course		• Seroconversion: it takes 4 - 8 weeks after HIV infection for the antibodies to appear. • **Window period: The time between infection and detectability of HIV antibodies, begins at the time of infection and can last 4 to 8 weeks.** • **Levels of viral load post seroconversion correlate with risk of progression of disease.**

Progression of infection to AIDS

- **Increased viral load**
- **Significant reduction in CD4 lymphocytes:** CD4+ T cell count **less than** 200 cells/mm^3
- **Opportunistic infections & tumors (kaposi's sarcoma)**

QUIZ

★ = focused on in class

Q1) ★ What is the CD4 T cell count of a person with HIV infection that progressed to AIDS?

A	300 cells/mm^3	B	400 cells/mm^3	C	200 cells/mm^3	D	250 cells/mm^3

Q2) Which of the following is a chemokine receptor (coreceptor) that HIV must bind to for infection of cells?

A	CD4 receptor	B	MHC II	C	CXCR4	D	CXCR5

Q3) Which of the following is NOT increased as a result of cytokine dysregulation by HIV?

A	IL-2	B	TNF-alpha	C	IFN-gamma	D	IL-6

Q4) ★ Which of the following proteins allows attachment of HIV to cells?

A	gp41	B	gp120	C	p17	D	p24

Q5) Which of the following is a DIRECT mechanism of CD4 dysfunction?

A	Autoimmunity	B	Apoptosis	C	Syncytium formation	D	Loss of membrane integrity

Q6) Autoimmunity is an INDIRECT mechanism of CD4 dysfunction?

A	True	B	False	C		D	

Q7) What are the target cells of HIV?

A	Glial cells	B	Dendritic cells	C	Macrophages	D	All the above

Q8) ★ In which organ is syncytium formation most commonly seen?

A	Bone marrow	B	Skin	C	Brain	D	Lung

Q9) ★ Window period: it is the time between infection and detectability of antibodies?

A	True	B	False	C		D	

Q10) ★ Gradual reduction in number of circulating CD4 cells is <u>inversely</u> correlated with the viral load:

A	True	B	False	C		D	

Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
C	C	A	B	D	A	D	C	A	A

Team Leader

Sarah Alobaid

Organizer

Sarah Alaidarous

Note Takers

Sarah Alaidarous

Faisal Alomri

Summary

Sarah Alobaid

Immunologyteam439@gmail.com

IMMUNOLOGY
TEAM 439