Beyond HIV/AIDS 101: HIV Pathophysiology to Medical Intervention

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National Minority AIDS Education & Training Center

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Pre-Test
The GI associated lymphoid tissue constitutes the largest immune compartment in the body:

a. True
b. False
c. Unsure
The following are HIV enzymes:

a. Protease
b. Reverse transcriptase
c. Intergrase
d. a and c
e. all of the above
f. unsure
Review the structure
Box # 3 is the Nucleocapsid:

a. True
b. False
c. Unsure
Workshop Objectives

Upon the conclusion of this workshop, participants will have an enhanced ability to:

- Discuss Lifecycle of HIV
- Explain CD4 cell and Host defenses systems
- Describe Natural History of HIV Disease
- Identify immune response to HIV
HIV Structure
HIV Structural Biology

**Products of the HIV Genome**
- Two Envelope Proteins
- Three Structural Proteins
- Three Enzymes
- Six Accessory/Regulatory Proteins
HIV Envelope Proteins
HIV Envelope Proteins
HIV Envelope

gp160 = Precursor Polypeptide

gp41  gp120
HIV Envelope
HIV Envelope (with Glycan Shield)
HIV Structural Protein
HIV Structural Protein
Matrix (p17 antigen)
HIV Matrix Protein (p17 antigen)
HIV Structural Protein
HIV Structural Protein
Capsid (p24 antigen)
HIV Capsid Protein (p24 antigen)
HIV Core
HIV Core

HIV RNA

Nucleocapsid (p7)
HIV Core
HIV Envelope and Structural Proteins

1. Capsid (p24)
2. Envelope
3. Nucleocapsid (p7)
4. Matrix (p17)
HIV Envelope and Structural Proteins

- Envelope
  - gp120
  - gp41
- Capsid (p24)
- Nucleocapsid (p7)
- Matrix (p17)
HIV Accessory/Regulatory Proteins

- Net (negative factor)
- Rev
- Tat (transactivator of transcription)
- Vpr (viral protein R)
- Vpu (viral protein U)
- Vif (viral infectivity factor)
HIV Enzymes

Reverse Transcriptase
- p66
- p51

Integrase

Protease
Host (Human) Cell: HIV Receptors

- CD4 Receptor
- CCR5 Co-Receptor
- CXCR4 Co-Receptor
• What are the three HIV enzymes?

1. ______________________________________

2. ______________________________________

3. _______________________________________
Host Cellular Receptors
CD4, CCR5, & CXCR4
CD4 T-Helper Cell Subtypes

<table>
<thead>
<tr>
<th>Th Group</th>
<th>Cell Products</th>
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<tbody>
<tr>
<td>Th1</td>
<td>Interleukin-12R, Interferon-γ, Interleukin-2</td>
</tr>
<tr>
<td></td>
<td>Interleukin-17A, Interleukin-17F, Interleukin-21, Interleukin-22</td>
</tr>
<tr>
<td>Th2</td>
<td>Interleukin-4R, Interleukin-4, Interleukin-13, Interleukin-5</td>
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</tbody>
</table>
Pathogenesis and Natural History of HIV
Natural History of Untreated HIV

The graph illustrates the natural history of untreated HIV, focusing on the decline of CD4 cell count over time. The y-axis represents CD4 cell count, ranging from 0 to 1000, while the x-axis represents years, from 0 to 15.

Key points:
- **Acute HIV:** The initial phase characterized by a rapid decline in CD4 cell count.
- **Acute CD4 Depletion:** A significant drop in CD4 cell count during the first year, labeled as Year 1.

The graph shows a steep decrease in CD4 cell count during the first year, indicating the acute phase of HIV infection, followed by a slower decline over subsequent years.
Natural History of Untreated HIV
Natural History of Untreated HIV
Natural History of Untreated HIV

Diagram showing the decline of CD4 cell count over time, with a peak during acute HIV and a prolonged period of immune activation.
Normal Intestine

CD4

CD8
Normal Intestine

Acute HIV Infection
Normal Intestine

Acute HIV Infection

Destruction of CD4 Cells in Gut
Normal Intestine

Acute HIV Infection

Destruction of CD4 Cells in Gut

Profound Loss of Intestinal CD4 Cells
Reasons for Massive Gut Mucosal CD4 Depletion

- The Largest reservoir of immune cells in the body
  - GI Associated lymphoid tissue is largest immune compartment

- Large Population of Preferred Target Cells for Acute Infection
  - Gut 50-70% express CCRS
  - Blood 10-20% express CCRS

- Dense Clustering of Cells in GI Mucosa
  - Close proximity leads to cell-to-cell HIV transmission
  - Binding to Integrin Receptor (alpha-4, beta7)
  - Integrin receptor preferentially expressed on gut CD4 cells
Normal Gut
CD4 Depleted Gut: Consequences

Enteropathy
- Diarrhea
- Malabsorption
- Increased Gut Permeability

CD4 Depleted Gut
CD4 Depleted Gut: Bacterial Translocation
Gut Involvement in Chronic Inflammatory State

- Massive Gut CD4 Cell Depletion
- Structural Damage Enteropathy
- Increased Gut Permeability
- Increased Bacterial LPS
- Bacterial Translocation
- Chronic Inflammation
Natural History Phases: Interventions

• **Phase 1: Acute CD4 Depletion**
  — Gut depletion severe within 4 weeks
  — Vaccine that would lessen effect on “GALT”

• **Phase 2: Inflammatory and Immune activation**
  — Antiretroviral Therapy: ? Optimal Timing
  — Gut Repair/Restoration
  — Specific Anti-Inflammatory/Immunosuppressant

• **Phase 3: Immune Suppression**
  — OI Treatment and Prophylaxis
  — Antiretroviral Therapy
The Effects of HIV Infection on Endothelial Function

- Endothelial dysfunction and/or injury is pivotal to the development of cardiovascular and inflammatory pathology.

- Entry of virus into endothelial cells may occur via CD4 antigen.

- Nevertheless, endothelial activation, enhanced adhesiveness of endothelial cells, endothelial cell proliferation and apoptosis.

- In HIV infection, dysfunctional or injured endothelial cells increases the potential for tissue injury, inflammation and remodeling, and accelerate the development of cardiovascular disease.
It's QUESTION TIME!!
Post-Test
The following are HIV enzymes:

a. Protease
b. Reverse transcriptase
c. Intergrase
d. a and c
e. all of the above

✓
Review the structure
Box # 3 is the Nucleocapsid:

a. True
b. False
The GI associated lymphoid tissue constitutes the largest immune compartment in the body:

- a. True
- b. False
Acknowledgements

David H. Spach, MD

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Thank You!