HIV Virus: The Road from Infection to Infection to Death

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Objectives

- Describe the HIV virus life cycle
- Understand the relationship between the HIV viral load and the CD4 count
- Differentiate between HIV from AIDS
- List 2 Opportunistic Infections related to HIV infection
- Describe the role of Post-Exposure Prophylaxis in the context of HIV exposure
- List three classes of antiretrovirals and explain their mechanism of action
HIV - History

• Discovered when studying the possible relationship of viruses causing cancer
• Researchers in the U.S. and Paris simultaneously discovered the virus
  – Luc Montagnier of the Pasteur Institute (left)
  – Robert C. Gallo of NIH (currently U. of Maryland) (right)
HIV - Discovery

Discovery of an unknown virus

Patient with swollen lymph nodes

T cells from lymph nodes are cultured

~2 weeks

Virus replication

Infected cells fuse and many die.

© The Nobel Committee for Physiology or Medicine 2008   Illustration: Annika Röhl
Electron microscopy identifies retroviral particles budding from infected T cells.
Nobel Prize (2008)
HIV – the virus

• Retrovirus
• RNA virus with an RNA nucleoprotein core surrounded by a lipid envelope
• Core contains RNA, protease, reverse transcriptase, and integrase
• Rapid replication (up to 1 million times per day)
• Rapid replication results in various mutations in the RNA
Structure of HIV Virus

- surface envelope protein
- transmembrane envelope protein
- protease
- nucleocapsid
- reverse transcriptase
- lipid bilayer
- matrix
- capsid
- viral genome
- integrase
HIV-1 vs HIV-2

- Two known types: HIV-1 and HIV-2
  - HIV-1 is more common and more often results in AIDS
- HIV-2 is concentrated in African continent
- HIV-1 is spread throughout the world including the US, Europe, Asia, and South America
- HIV-2 is genetically closer to the Simian Immune Virus (SIV) than to HIV-1
- HIV-1 is divided into 4 clades (B,C,D,E)
  - Clade B: U.S., Europe, S. America, Australia
Infection with HIV

• Most commonly exposure to infected blood
  – Intravenous drug users
  – Sexual contact (MSM)
• Acutely onset of symptoms similar to influenza with the exception of the presence of lymphadenopathy
• Symptoms self-resolving in the acute phase of infection
• Often not diagnosed until pregnancy or hospitalization with an opportunistic infection
### Post-Exposure Prophylaxis (PEP) Occupational Exposure

#### Table 1: Exposure and transmission risk/exposure

<table>
<thead>
<tr>
<th>Type of exposure with known HIV+ source</th>
<th>Estimated risk of HIV transmission/exposure³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive anal intercourse (RAI)</td>
<td>1/120</td>
</tr>
<tr>
<td>Use of contaminated injecting equipment</td>
<td>1/150</td>
</tr>
<tr>
<td>Occupational needlestick injury</td>
<td>1/333</td>
</tr>
<tr>
<td>Receptive vaginal intercourse</td>
<td>1/1,000²</td>
</tr>
<tr>
<td>Insertive anal or vaginal intercourse</td>
<td>1/1,000²</td>
</tr>
<tr>
<td>Receptive fellatio with or without ejaculation</td>
<td>Not measurable³</td>
</tr>
<tr>
<td>Insertive fellatio</td>
<td>Not measurable</td>
</tr>
<tr>
<td>Cunnilingus</td>
<td>Not measurable</td>
</tr>
<tr>
<td>Bites etc.</td>
<td>Not measurable</td>
</tr>
<tr>
<td>Other trauma</td>
<td>Not measurable</td>
</tr>
<tr>
<td>Non-occupational exposure of intact mucous membrane and skin</td>
<td>Not measurable</td>
</tr>
<tr>
<td>Community needle-stick injury</td>
<td>Not measurable</td>
</tr>
</tbody>
</table>
Modes of Transmission

• Blood to Blood:
  – Intravenous drug use (sharing syringes)
  – Sexual transmission
  – Occupational exposure
    • “Patient to Provider” and “Provider to Patient”
  – Transfusions (prior to 1985)
  – Vertical transmission (mother to fetus)
  – Others such as tattoo, cocaine use, and other high risk activities

• HIV is unlikely to be transmitted through other bodily fluids such as saliva, sweat, tears or contact skin
Infection with HIV

- HIV-1 infection may be divided into three subtypes based on surface receptor affinity:
  - CCR5 tropic (HIV virus only binds to CCR5)
  - CXCR4 tropic (HIV virus only binds to CXCR4)
  - Dual tropic (see next slide)
  - Dual Mixed tropic (see next slide)
- CCR5 tropic is more common in early infection
- Mixed or Dual-Mixed tropic infections are more common in treatment experienced patients
Tropism

CCR5 Tropic

CXCR4 Tropic

Dual Tropic

CD4 CELL SURFACE
Immunity to HIV Infection

- DNA Mutation (alleles) called CCR5 delta-32 mutation results in natural increased immunity to HIV infection:
  - Homozygous individuals with 1 allele on each chromosome for delta-32
    - >90% immunity to HIV due to the lack of CCR5 receptors
  - Heterozygous individuals with 1 allele on one chromosome only for delta-32
    - ~50% immunity and slower progression to AIDS due to less CCR5 receptors
- Prevalent in approximately 10% of persons with European dissent
Natural Immunity

- CCR5 Tropic
- CXCR4 Tropic
- Dual Tropic

CD4 CELL SURFACE

CXCR4
Important Definitions

• HIV Syndrome/Infection:
  – A general term used to identify the condition when a human is infected with HIV

• Acquired **Immune Deficiency** Syndrome (AIDS)
  – Defined as a severe case of HIV infection where the hosts immune system is severely depressed due to the HIV infection
    • CD4+ <200
    • History/Presence of Opportunistic Infections (OI)
Role of Antiretroviral Therapy

• 5 major classes of antiretroviral therapy:
  – Nucleoside/Nucleotide Reverse Transcriptase Inhibits (NRTI/NtRTI)
  – Non-Nucleoside Reverse Transcriptase Inhibitors (nNRTIs)
    • First Generation
    • Second Generation
  – Protease Inhibitors (PI)
  – Integrase Inhibitors (II)
  – Entry Inhibitors
    • gp-120 inhibitor
    • CCR5 inhibitor
HIV - Therapy

• Combination therapy with three or more agents is required for the suppression of HIV

• Highly Active Antiretroviral Therapy (HAART) consists of:
  – 2 NRTIs \textit{plus one of the following}
    • 1 PI (boosted/unboosted)
    • 1 nNRTI
    • 1 Integrase Inhibitor

• Mega-HAART is therapy with HAART plus an additional 1-3 agents
  – Utilized in patients with high degree of resistance to antiretroviral therapy
HIV- Therapy

**NRTIs:**
- Zidovudine (AZT)
- Lamivudine (3TC)
- Emtricitabine (FTC)
- Abacavir (ABC)
- Stavudine (d4T)
- Didanosine (ddI)
- *Tenofovir (TDF)*

**nNRTIs:**
- Nevirapine (NVP)
- Efavirenz (EFV)
- Ertavirine (ETR)
- Rilpivirine (RPV)

**PIs:**
- Amprenavir (APV)*
- Fosamprenavir (fAPV)*
- Indinavir (IDV)*
- Atazanavir (ATV)*
- Tipranavir (TPV)*
- Darunavir (DRV)*
- Lopinavir (LPV)*
- Saquinavir (SQV)*
- Nelfinavir (NFV)
- *Ritonavir (RTV)*

**Integrase Inhibitor:**
- Raltegravir

**Entry Inhibitor:**
- Maraviroc
- Enfuvirtide (ENF)
HIV Life Cycle

HIV fusion with host cell membrane

Matrix protein

HIV core

HIV RNA

HIV DNA

DNA integrates with host DNA

New virus protein

New viral RNA

RT

Host cell

Nucleus

Host cell

Mature HIV

HIV attachment to host cell

Virus budding

Virus assembly

Migration to cell surface
Resistance to NRTIs
Resistance to NRTIs

Resistance by ATP-Mediated Excision of the Nucleoside Analogue

Drug-sensitive virus

Drug-resistant virus

ATP

Thymidine analogue mutations allow ATP to bind to reverse transcriptase

Excision of nucleoside analogue from viral DNA by ATP
Resistance to nNRTIs