Human Immunodeficiency Virus Infection
PHAR 6124

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Outline

• Introduction
• Epidemiology
• Transmission
• Pathogenesis
• Detection, diagnosis & monitoring
• Natural history

Historical Perspective

• AIDS = acquired immunodeficiency syndrome
  – 1981 → first recognized as a distinct clinical entity
  – First described in a group of young homosexual males with profound immune system deficits
• HIV or human immunodeficiency virus →
  recognized as the cause of AIDS in 1984

Classification of HIV

• Retrovirus → 2 forms: DNA provirus and enveloped RNA-containing infectious virus
• Retroviruses transcribe viral RNA into DNA to optimally replicate
• Member of Retroviridae class of viruses
  – 3 distinct subfamilies:
    1. oncovirus
    2. spuvirus
    3. lentivirus → HIV; characterized by their indolent, infectious cycle

Classification of HIV

11 clades (subgroups)

F  H  I
lentivirus

HIV-1

HIV-2

3 lineages

<table>
<thead>
<tr>
<th>Group M</th>
<th>Group N</th>
<th>Group O</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  B  C  D  E  F  G  H  I  J  K</td>
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<td></td>
</tr>
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</table>

A  B  C  D  E  F  G  H  I  J  K

• HIV-1-B → responsible for the epidemic in North America & Western Europe

Origin of HIV Infection

• Evidence suggests HIV in humans resulted from cross-species transmission (zoonosis)
  – primates → simian immunodeficiency virus (SIV)
• HIV-1 → similar to SIVcpz (chimpanzees)
• 1959 → earliest known human infection (Central Africa)
• Spread → modern transportation, promiscuity, and drug abuse
AIDS Epidemic Update: 2005

- The overall number of people living with HIV is increasing worldwide
  - Exception: Caribbean (prevention, education)
- Steepest increases in HIV were seen in Eastern Europe, Central and East Asia
- Globally, sub-Saharan Africa continues to be the most affected region

UNAIDS and WHO Joint Annual Report: released November 21, 2005

AIDS Epidemic Update: 2005

- Access to HIV treatment has improved:
  - 250,000 to 350,000 deaths averted
  - >1,000,000 people in low and middle-income countries live longer, better lives
- Knowledge of safe sex and HIV remains low in many countries where prevalence is high and growing

UNAIDS and WHO Joint Annual Report: released November 21, 2005

Adults & Children Living with HIV: End 2005

<table>
<thead>
<tr>
<th>Region</th>
<th>Number</th>
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<tbody>
<tr>
<td>Western Europe</td>
<td>720,000</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>510,000</td>
</tr>
<tr>
<td>South &amp; South-East Asia</td>
<td>7,4 million</td>
</tr>
<tr>
<td>East Asia &amp; Pacific</td>
<td>570,000</td>
</tr>
<tr>
<td>Total</td>
<td>40.3 million</td>
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Adults & Children Newly Infected with HIV during 2005

<table>
<thead>
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<tbody>
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<td>Western Europe</td>
<td>22,000</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>67,000</td>
</tr>
<tr>
<td>South &amp; South-East Asia</td>
<td>990,000</td>
</tr>
<tr>
<td>East Asia &amp; Pacific</td>
<td>140,000</td>
</tr>
<tr>
<td>Australia &amp; New Zealand</td>
<td>20,000</td>
</tr>
<tr>
<td>Total</td>
<td>4.9 million</td>
</tr>
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</table>

Adult & Child Deaths 2° AIDS during 2005

<table>
<thead>
<tr>
<th>Region</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>1,200</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>58,000</td>
</tr>
<tr>
<td>South &amp; South-East Asia</td>
<td>480,000</td>
</tr>
<tr>
<td>East Asia &amp; Pacific</td>
<td>41,000</td>
</tr>
<tr>
<td>Australia &amp; New Zealand</td>
<td>6,000</td>
</tr>
<tr>
<td>Total</td>
<td>3.1 million</td>
</tr>
</tbody>
</table>

Global Epidemiology

14,000 new HIV infections/day in 2005

- > 95% are in low and middle income countries
- ≈ 2000 are in children < 15 years old
- ≈ 12,000 are in persons 15-49 years old
  - Almost 50% are women
  - About 50% are 15-24 year olds

www.who.org
United States Epidemiology

- Estimated incidence as of December 2005
  - 1,200,000 living with HIV
  - Approximately 43,000 new HIV cases per year
  - Women, ethnic minorities (African-Americans & Hispanics) and adolescents are disproportionately affected
- Cumulative AIDS cases (adults, adolescents, children) reported to the CDC through 2003:
  - 892,875 (500,395 deaths)

www.cdc.gov

Minnesota Epidemiology

- December 31, 2004 → 5,002 persons are assumed alive and living with HIV/AIDS
  - 2,835 living with HIV infection
  - 2,167 living with AIDS
- Includes 689 persons who first reported with HIV/AIDS elsewhere & moved to MN

www.health.state.mn.us

HIV Transmission

1. Sexual – most common
   - Receptive anal – risk is 0.1-3% per act
   - Receptive vaginal – risk is 0.1-0.2% per act
   - Oral – risk not well defined
- Probability of transmission increases when index partner has more advanced disease and a high viremia
- Highest risk persons: ulcerative STD’s, multiple partners, partners of intravenous drug users (IVDUs)

HIV Transmission

2. Parenteral – broadly includes contaminated blood exposure through:
   - IVDU – used needles or injection-paraphernalia; 25% of AIDS cases in the United States
   - Blood products or organ transplants – < 1% of infection reports; risk is < 1%
   - Needlestick – occupational exposure; most are 2nd to percutaneous injury; risk is 0.3%
HIV Transmission

3. Perinatal or vertical transmission
   – ≈ 25% risk in absence of drug treatment;
   – < 2% transmission rate with drug treatment
   – Breast-feeding carries a significant risk (’03 data)
   • Most common cause of pediatric infection
   • Infections occur during or near time of birth due to exposure to ruptured membranes
     – Goal → Treat infected mother
   • C-section reduces transmission in select cases

Virus-Host Interactions

• HIV-1 uses viral envelope glycoproteins (gp120, gp41) and target cell receptors for attachment and entry into host cells
  • Target cells:
    – CD4 (cluster designation-4) lymphocytes (primary)
    – Macrophages
    – Dendritic cells
  • Target cell receptors:
    – CD4
    – CCR5 and CXCR4 (chemokine co-receptors)

HIV-1 Life-Cycle

• Essential Steps:
  – Attachment to cellular receptors and fusion with the target cell membrane
  – Penetration into the cytoplasm and release of RNA genome
  – HIV-1 RNA genome is reverse transcribed into a linear viral DNA duplex
  – Linear viral DNA is incorporated into a pre-integration complex that enters the host cell nucleus

**HIV-1 Life-Cycle**

- Essential Steps:
  - Linear viral DNA becomes the precursor for **integrated** proviral DNA → the template for viral transcription
  - The template is transcribed into mRNA encoding essential viral proteins
  - mRNA is exported from the host cell nucleus back into the cytoplasm where it is translated
  - Functional proteins are synthesized and assembled into a mature retroviral particle

One CD4 cell is capable of producing 1000-3000 viral particles!

**Detection of HIV-1**

- Primary test
  - Enzyme linked immunosorbent assay (ELISA)
  - Detects antibodies against HIV-1
  - Repeat in duplicate; 1 or both reactive → confirm
- Confirmatory tests
  - Western blot – most common
  - Indirect immunofluorescence assay (IFA)
- Established HIV-1 infection = a reactive ELISA & a positive Western blot

**Prognostic Markers for HIV-1**

1. **Viral load** – quantifies the degree of viremia by measuring the amount of HIV-1 RNA in plasma or other biological fluid

- FDA approved HIV-1 viral load assays:
  - Reverse transcriptase polymerase chain reaction assay (Amplicor v.1.5, Roche Diagnostics)*
  - Nucleic acid amplification test (NucliSens QT, Organon Teknika)
  - Signal amplification nucleic acid probe assay (VERSANT v.3.0, Bayer)

* Most widely used technique

1. **Viral load**

- Used to monitor disease progression and response to treatment
- Reported as # viral RNA copies/mL
- Reductions reported in base 10 logarithm

- Example:
  - 100,000 copies/mL → 10,000 copies/mL
  - $10^5$ copies/mL → $10^4$ copies/mL
  - Change is $1 \log_{10}$
Prognostic Markers for HIV-1

- Minimal change in viral load considered statistically significant (2 standard deviations) is a 3-fold or 0.5 log_{10} copies/mL change
- Goal of therapy is to reach below assay's limit of detection:
  - < 50 copies/mL (Amplicor v.1.5)
  - < 75 copies/mL (VERSANT v.3.0)
  - < 80 copies/mL (NucliSens QT)
- Should reach by 16-24 weeks of therapy

HIV-1 RNA Measurement Continuum

< 50 > 75,000

*Example of limits for Roche Amplicor RT-PCR assay

HIV-1 RNA Response

<table>
<thead>
<tr>
<th>WEEK</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38,000</td>
<td>&gt;75,000</td>
</tr>
<tr>
<td>2</td>
<td>6,000</td>
<td>60,000</td>
</tr>
<tr>
<td>4</td>
<td>250</td>
<td>900</td>
</tr>
<tr>
<td>8</td>
<td>&lt;50</td>
<td>&lt;50</td>
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<tr>
<td>12</td>
<td>&lt;50</td>
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<tr>
<td>16</td>
<td>&lt;50</td>
<td>1000</td>
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<tr>
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<td>9,000</td>
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<tr>
<td>24</td>
<td>&lt;50</td>
<td>32,000</td>
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<tr>
<td>32</td>
<td>&lt;50</td>
<td>&gt;75,000</td>
</tr>
<tr>
<td>48</td>
<td>&lt;50</td>
<td>&gt;75,000</td>
</tr>
</tbody>
</table>

Prognostic Markers for HIV-1

2. CD4 lymphocyte count

- Normal for adults: 500 to 1600 cells/µL or 40% to 70% of all lymphocytes
- Marker of disease progression and response to treatment
- Reductions → opportunistic infections and AIDS malignancies

Prognostic Markers for HIV-1

- CD4 count is the most important consideration in deciding to start therapy
- A significant change (2 standard deviations) is ≈ 30% in absolute CD4 count and 3% in CD4 percentage
- On therapy (first regimen), expect an increase in absolute CD4 count of 100-150 cells/mm^3/yr until a threshold is reached

CD4 Count Response

<table>
<thead>
<tr>
<th>WEEK</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>275</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>290</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
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<td>380</td>
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<tr>
<td>20</td>
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<td>400</td>
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<tr>
<td>24</td>
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<td>420</td>
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<td>32</td>
<td>40</td>
<td>430</td>
</tr>
<tr>
<td>48</td>
<td>10</td>
<td>450</td>
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</tbody>
</table>
Prognostic Markers for HIV-1

- Prognosis is described best when viral load measurement is used along with CD4 lymphocyte count

Center for Disease Control’s AIDS Case Definition: 1993

<table>
<thead>
<tr>
<th>CD4 Count (absolute &amp; %)</th>
<th>A asymtomatic acute HIV-1</th>
<th>B symptomatic not A or C</th>
<th>C AIDS-indicator conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500 cells/mm³ or &gt;28%</td>
<td>A1</td>
<td>B1</td>
<td>C1</td>
</tr>
<tr>
<td>200-499 cells/mm³ or 14-28%</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
</tr>
<tr>
<td>&lt;200 cells/mm³ or &lt;14%</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
</tr>
</tbody>
</table>

Relationship Between CD4 Count & AIDS Malignancies/OIs

- Bacterial skin infections
- Varicella zoster virus (VZV), Kaposi’s sarcoma (KS)
- Oral Candidiasis
- Pneumocystis carinii pneumonia (PCP)
- Non-Hodgkin’s lymphoma (NHL)
- Herpes simplex virus (HSV) infections
- Cryptococcal meningitis
- Cytomegalovirus (CMV) infections
- Mycobacterium-avium complex (MAC)

Clinical Presentation

1. Primary infection or acute retroviral syndrome:
   - Flu-like: fever, sore throat, fatigue, weight loss
   - Maculopapular/morbilliform rash: 40-80%
   - Diarrhea, lymphadenopathy, night sweats: >50%
   - Aseptic meningitis: 25%
   - Symptoms last approximately 2 weeks
   - High viral load (>50,000 copies/mL in adults)
   - Wide dissemination: CNS, lymph tissue

Initial Viral Load (Set-point) & Disease Progression
Viral Set-point Predicts Progression of HIV-1 Disease

Clinical Presentation

2. Clinical Latency (NOT virologic latency):
   - Absence of symptoms
   - Low or undetectable viral load
   - Persistent decrease in CD4 count over time
   - HIV replication in reservoirs: CNS, testes, retina, resting CD4 lymphocytes
   - Usually persists for years

Clinical Progression

3. Symptomatic Disease:
   - Constitutional symptoms: fatigue, weight loss, night sweats, fever
   - Opportunistic infections: PCP, MAC
   - Opportunistic malignancies: KS
   - Death occurs without drug treatment