Clinical Manifestations of HIV/AIDS

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Does HIV infection equal AIDS?

- No!
- HIV infection means HIV is replicating in the body.
- AIDS-A specific diagnostic condition in which HIV antibodies are present and an opportunistic disease has occurred.
The Human Immunodeficiency Virus
Lentivirus Genomes

**Structural Proteins**
- Gag-p17 MA, p24 CA, p7 NC, and p2 (p1?)
- Gag-Pol-p160
- Pol-p10 PR, p66/p51 RT, p33 IN
- Env (gp160): gp120 SU, gp41 TM

**“Accessory” Proteins**
- Vif-p23
- Vpr-p15
- Tat-p14
- Rev-p19
- Vpu-p16
- Nef-p27
HIV Lifecycle

HIV Lifecycle and Therapeutic Targets

A. amphotericin B detergents defensins
B. soluble CD4
C. CCR-5/CXCR4 inhibitors
D. RT Inhibitors lamivudine stavudine zidovudine zalcitabine nevirapine
E. dicitteoyttartaric acids diketoacids Shionogi Compound
F. protease inhibitors saquinavir ritonavir indinavir nelfinavir
G. ribozymes gene therapy antisense RNA RNAI
The Clinical Manifestations of AIDS
Diagnosis of HIV Infection

1. Positive ELISA

2. 

- gp120
- p66
- p51/55
- gp41
- p33
- p24
- p17
Common Viral Opportunistic Pathogens

- The Herpes viruses:
  - Herpes simplex virus types 1 and 2 (HSV-1 & HSV-2)
  - Cytomegalovirus (CMV)
  - Varicella zoster (VZV)
  - Kaposi’s sarcoma Herpes virus (KSHV)
  - Epstein-Barr Virus (EBV)

- Human papillomavirus (HPV)

Common Viral Co-Infections:

- Hepatitis B and C, Herpes simplex type 2, KSHV, papillomavirus.
Herpes simplex virus types 1 and 2
Cytomegalovirus Retinitis
Varicella zoster virus
Varicella zoster virus
Fungal Opportunistic Pathogens

- *Pneumocystis carinii*
  - pneumonia
- *Candida albicans*
  - thrush
- *Cryptococcus neoformans*
  - meningitis
Pneumocystis carinii Pneumonia
Histology of *Pneumocystis carinii* Pneumonia.
Oral Thrush - *Candida* species
Protozoal Opportunistic Pathogens

- *Toxoplasma gondii* – Central nervous system
- *Giardia lamblia* – Gastrointestinal tract
- *Cryptosporidium* species – Gastrointestinal tract
Toxoplasma gondii
Giardia lamblia: Giardiasis
Bacterial Opportunistic Pathogens

- *Mycobacterium avium intracellulare* or *Mycobacterium avium* complex

Common Bacterial Co-Infections

- *Treponema pallidum*
- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
Mycobacterium avium intracellulare or Mycobacterium avium complex
AIDS-Associated Malignancies

- Viral-induced lymphoid enlargement:
  - PGL

- Viral-induced Neoplasia:
  - Lymphoma (EBV)
  - CNS Lymphomas (EBV)
  - Kaposi’s sarcoma (KSHV)
  - Cervical cancer (HPV)
Lymphoid enlargement: Persistant Generalized Lymphadenopathy
Lymphoma
Kaposi’s sarcoma
Other AIDS-Defining Illnesses

HIV Infection Plus:

- HIV encephalopathy (or dementia).
- Wasting syndrome.
- Idiopathic thrombocytopenia purpura.
- HIV-associated peripheral neuropathy.
Pediatric AIDS

- Similar opportunistic pathogens as adult EXCEPT *Mycobacterium tuberculosis*.
- Additionally, bacterial infections are greatly increased.
- Failure to thrive (gain weight) is a typical manifestation.
Streptococcus pyogenes and/or Staphylococcus aureus infection.
Haemophilus influenzae: Acute otitis media
Summary of Opportunistic Pathogens

- CD4+/CD8+ lymphocytes are critical in immunity to:
  - Intracellular bacteria
  - Viruses
  - Fungi
  - Protozoa
  - Viral-induced cancers
  - New bacterial infections (no memory)

Therefore, in AIDS these opportunists are seen with high frequency!
Viral Load-Typical
Viral Load - Longterm Non-Progressor
Viral Load-Rapid Progressor
Viral Load:

- Directly measures the number of viral genomes in blood.
- Indirectly measures the number of virions in the blood.
- Predicts time to AIDS.
- Predicts time to death.
- Is important in determining when to start anti-retroviral therapy.
- Is best used in conjunction with CD4 count.
HIV Therapies

HIV Lifecycle and Therapeutic Targets

A. amphotericin B
detergents
defensins

B. soluble CD4

C. CCR-5/CXCR4 inhibitors

D. RT Inhibitors
- lamivudine
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diketoacids
Shionogi Compound

F. protease inhibitors
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- ritonavir
- indinavir
- nelfinavir

G. ribozymes
gene therapy
antisense RNA
RNAi
FDA-Approved RT Inhibitors

- **NRTIs (8)**
  - Abacavir
  - Didanosine
  - Emtricitabine
  - Lamivudine
  - Stavudine
  - Tenofovir
  - Zalcitabine
  - Zidovudine

- **NNRTIs (3+1)**
  - Delavirdine
  - Efavirenz
  - Nevirapine
  - Etravirine (Phase III)

- **NtRTIs (1)**
  - Tenofovir disoproxil fumarate

- **Co-formulations (3)**
  - Combivir (ZDV+LMV)
  - Trizivir (ZDV+LMV+ABA)
  - ATRIPLA (EFV+EMT+TNF)
FDA-Approved Protease Inhibitors (10)

- Amprenavir
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir/Ritonavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir
Entry Inhibitors (1+1)

- Maraviroc (FDA-approved, August 2007)
- Vicroviroc (Phase IIb/III completed)
Fusion Inhibitors

- Enfuvirtide
Integrase Inhibitors (1+1)

- Raltegravir (FDA approved, October 2007).
- Elvitegravir (Phase IIb/III completed)
HIV Therapy-Complications

- Short-term toxicities
- Long-term toxicities
- Drug resistance
When to initiate therapy?

- Dept. of Health & Human Services Rec’s

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>CD4 count</th>
<th>RNA level</th>
<th>Rec.</th>
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</thead>
<tbody>
<tr>
<td>AIDS (Symp.)</td>
<td>Any</td>
<td>Any</td>
<td>Rx</td>
</tr>
<tr>
<td>AIDS (Asymp.)</td>
<td>&lt;200/mm³</td>
<td>Any</td>
<td>Rx</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>200-350/ mm³</td>
<td>Any</td>
<td>Offer Rx</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt;200-350/ mm³</td>
<td>&lt;20,000</td>
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<tr>
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<td>&gt;55,000</td>
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</tbody>
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DHHS Preferred Initial Regimens

- Efavirenz + lamivudine + (zidovudine or tenofovir or stavudine) = 1 NNRTI + 2 NRTIs
- Lopinavir/ritonavir + lamivudine + (zidovudine or stavudine) = Boosted PI + 2 NRTIs
Adherence to HAART and control of HIV replication

<table>
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<tr>
<th>Adherence to HAART</th>
<th>Viral load &lt;400 @ 6 months</th>
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<tbody>
<tr>
<td>&gt;95% adherence</td>
<td>78%</td>
</tr>
<tr>
<td>90-95% adherence</td>
<td>45%</td>
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<tr>
<td>80-90% adherence</td>
<td>33%</td>
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<tr>
<td>70-80% adherence</td>
<td>29%</td>
</tr>
<tr>
<td>&lt;70% adherence</td>
<td>18%</td>
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Changing patterns of anti-HIV therapy

FDA Approved Medications

Year

The Bottom Line:

- You will see HIV-infected individuals in your practice.
- AIDS is likely to remain a public health problem for the foreseeable future.
- New infections will continue to occur due to the perception HIV is no longer a problem.
- New drugs will be available by the time you enter the clinics.