

Immunology and Natural History of HIV/AIDS

**Part A: Module A1
Session 5**



Objectives

1. Understand how the normal immune system works
2. Describe the HIV lifecycle and its effect on the immune system
3. Describe the stages of disease progression, including symptoms, laboratory findings and management of primary infection and seroconversion



The Normal Immune System

- Protects the body
- Consists of skin, mucus membranes, lymphoid organs and tissues
- All of its components are vital in the production and development of lymphocytes
- B-cells and T-cells are produced from stem cells in the bone marrow
- B-cells recognize specific antigen targets and secrete specific antibodies



The Normal Immune System, continued

- T-cells regulate the immune system and kill cells that bear specific target antigens
- CD4+ cells are T-helper cells that activate B-cells, CD8 and macrophages when a specific antigen is present
- Phagocytes include PMNs, monocytes and macrophages
- The complement system consists of 25 proteins



CD4 cells

- Are a type of T cell
- Play critical role in orchestrating immune system response to infection
- When infected by HIV, the CD4 cell is destroyed
 - Can count the numbers of CD4 cells per milliliter of blood, called “CD4 count”
 - Once the CD4 count gets low, the body can’t mount an adequate immune response to infection
 - Infections are now caused by agents that the body would ordinarily be able to handle (“opportunistic” infections)
 - Patients then die of some other illness that resulted from the weakened immune system due to HIV infection

Human Immunodeficiency Virus

- HIV is a retrovirus that uses its RNA and the host's DNA to make viral DNA. It has a long incubation period.
- HIV consists of a cylindrical center surrounded by a sphere-shaped lipid envelope. The center consists of two single strands of RNA.

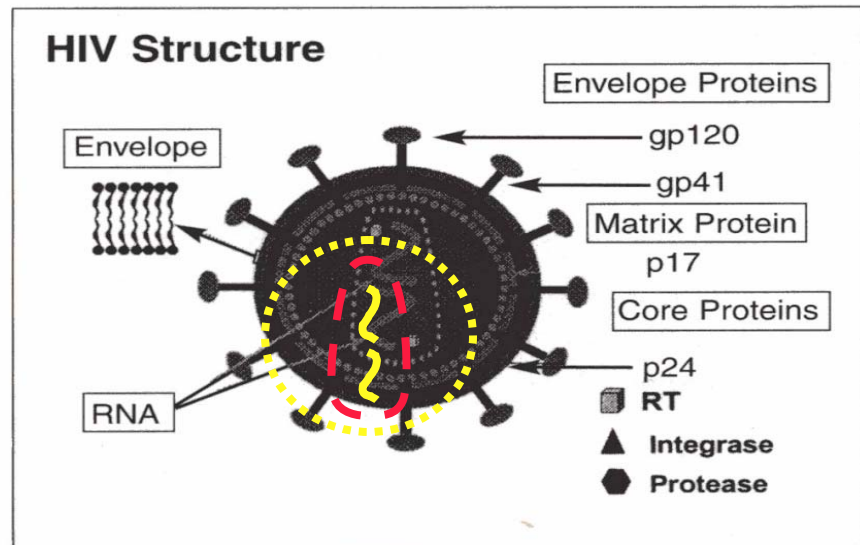


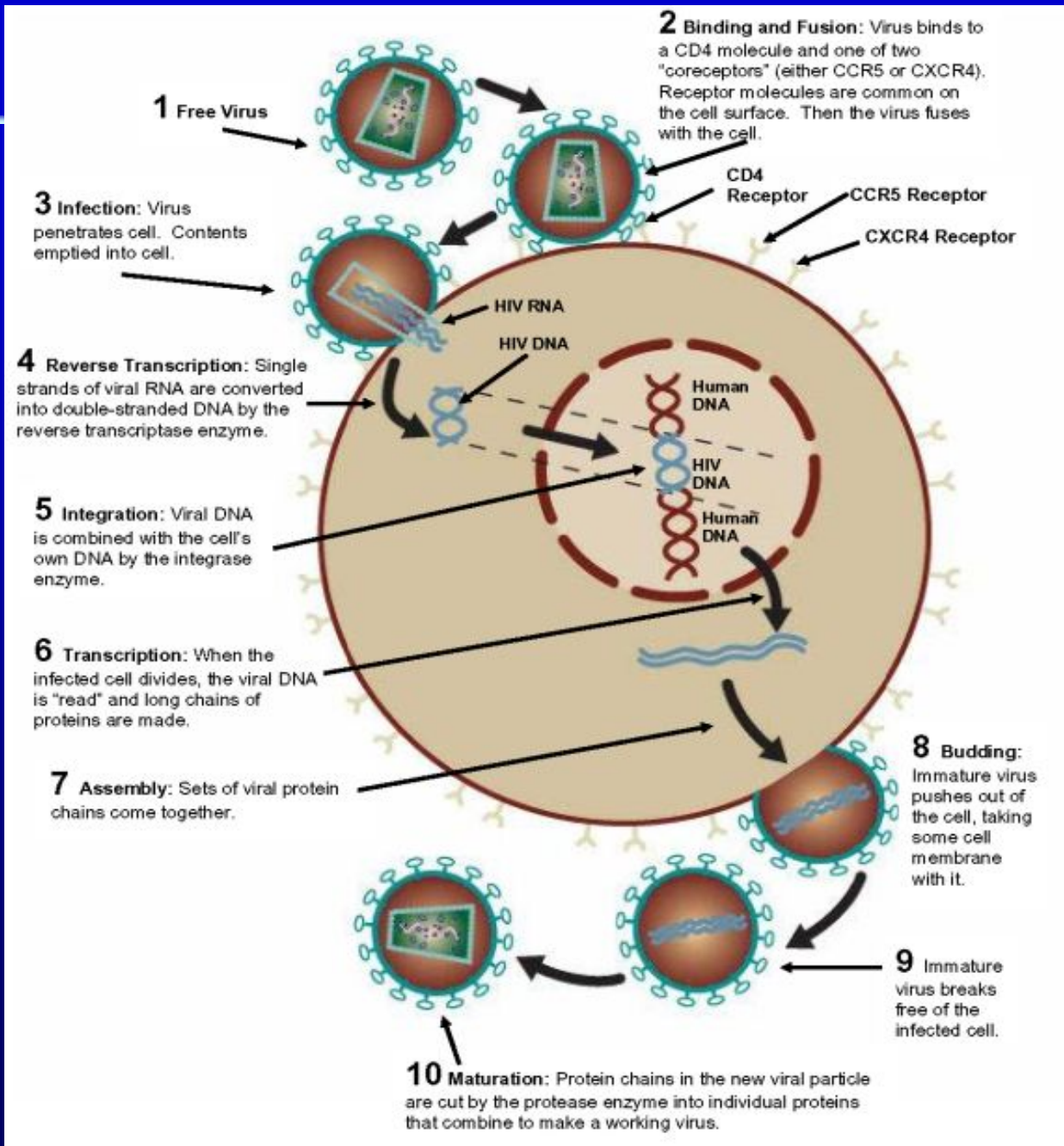
Figure 3. The Human Immunodeficiency Virus

- HIV causes severe damage to and eventually destroys the immune system by utilizing the DNA of CD4+ lymphocytes to replicate itself, destroying the CD4+ lymphocyte.



HIV Lifecycle

- Host cells infected with HIV have a very short lifespan.
- HIV continuously uses new host cells to replicate itself.
- Up to 10 million individual viruses are produced daily.
- During the first 24 hours after exposure, the virus attacks or is captured by dendritic cells (type of phagocyte) in mucous membranes and skin.
- Within five days of exposure, infected cells make their way to lymph nodes and then to the peripheral blood, where viral replication becomes very rapid.





Replication errors

- HIV makes many errors (mutations) during reverse transcription (taking RNA into DNA)
- Some of these mistakes make virus unable to replicate or makes it weaker
- Some of these mutations are responsible for reducing the effect of ARVs
 - Concept of *resistance*
 - To be discussed in a later lecture



Natural History: The Chronology of HIV-Induced Disease

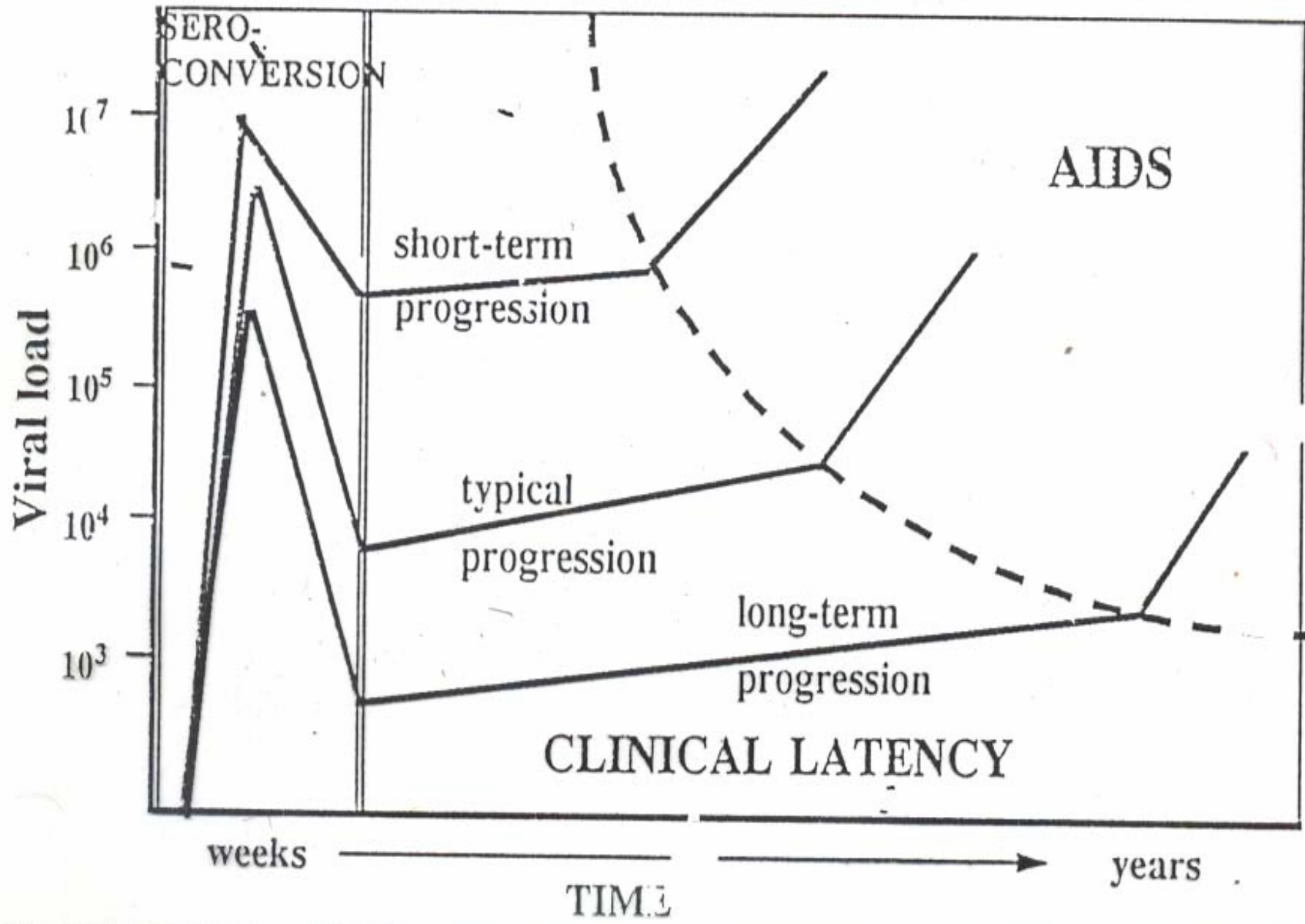
1. Primary HIV Infection and Seroconversion

- Clinical features
- Seroconversion illnesses

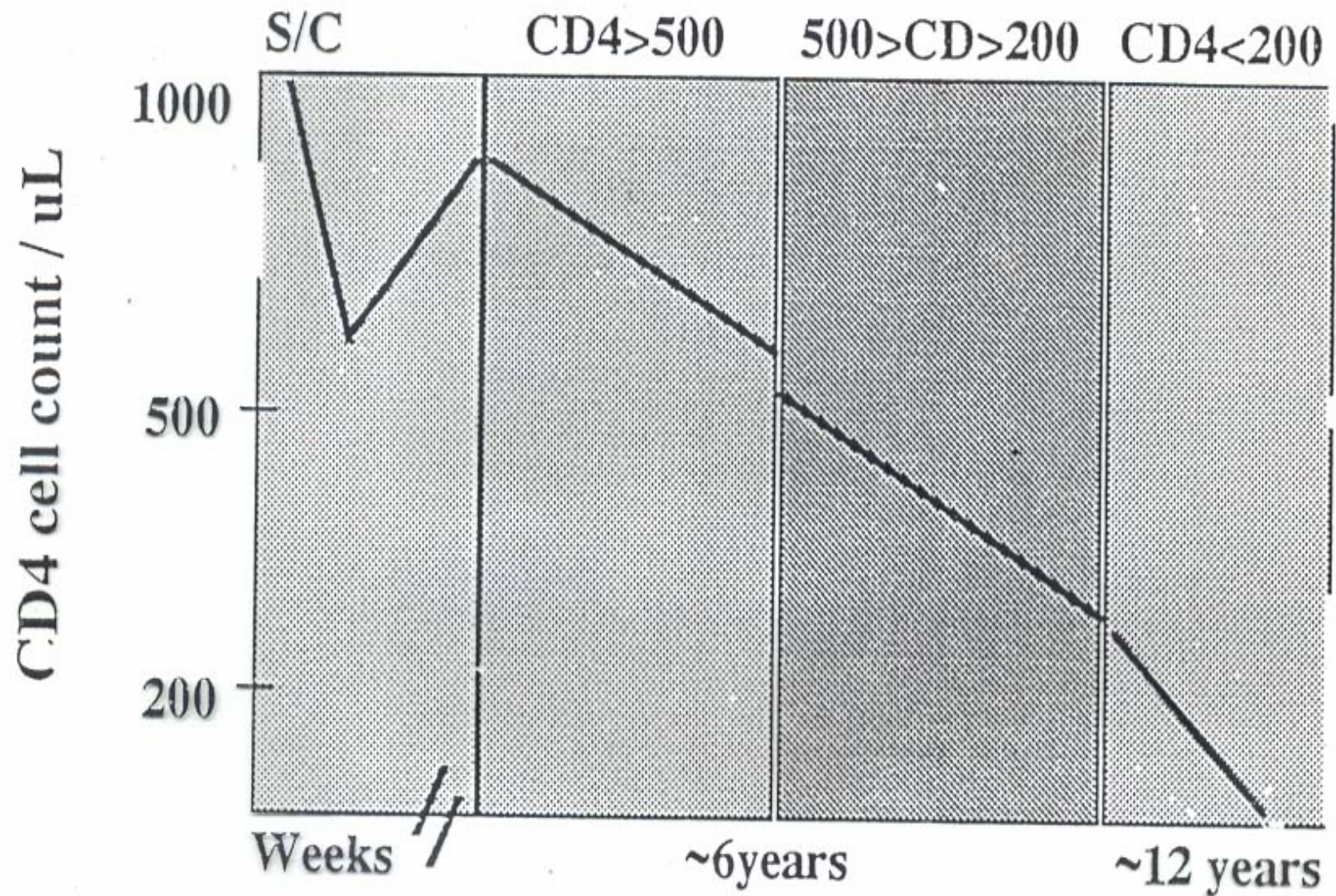
2. Stages of Disease Progression

- Early immune depletion
- Intermediate immune depletion
- Advanced immune depletion

VIRAL LOAD AND COURSE OF INFECTION



CD4 CELLS & THE COURSE OF INFECTION



From Crowe et al MJA, 164: 1996

Primary HIV Infection and Seroconversion

Clinical Features

- On first exposure, there is a 2-4 week period of intense viral replication before the onset of an immune response and clinical illness.
- Acute illness lasts from 1-2 weeks and occurs in 53% to 93% of cases.
- Clinical manifestations resolve as antibodies to the virus become detectable in patient serum.
- Patients then enter a stage of asymptomatic infection lasting months to years.

Primary HIV Infection and Seroconversion, continued

Seroconversion Illness

- Manifests as a flu-like syndrome: fever, myalgia, etc.
- Neurological symptoms: HIV in CSF, aseptic meningoencephalitis, etc.
- Gastrointestinal symptoms: mucocutaneous ulceration, pharyngeal edema, etc.
- Dermatological symptoms: rash, urticaria, etc.

- Laboratory Findings
 - First 1-2 weeks:
 - Profound reduction in CD4, CD8 lymphocyte counts
 - Peripheral lymphocytosis
 - Mild thrombocytopenia
 - First 2-6 weeks:
 - Antibodies to HIV develop but may not be detected by standard testing for 6 weeks to 6 months.
 - HIV antigen may be detected in serum before antibodies



Stages of Disease Progression

- Early Immune Depletion (CD4 cell count $> 500/\mu\text{L}$)
 - During this stage, level of virus in blood is very low
 - HIV replication taking place mostly within lymph nodes
 - Generally lasts for five years or more
 - Persistent Generalized Lymphadenopathy (PGL) without other symptoms may be noted
 - Usually symptom-free, but several autoimmune disorders may appear



Stages of Disease Progression, continued

- Intermediate Immune Depletion
(CD4 cell count between 500 and 200/ μL)
 - Immune deficiency increases
 - Infections commence and persist or increase as the CD4 cell count drops
 - Consider commencing first-line ARV therapy
 - Less severe infections, particularly of skin and mucosal surfaces, appear



Stages of Disease Progression, continued

- Advanced Immune Depletion (CD4 cell $<200/\mu\text{L}$)
 - Patients get more opportunistic infections and cancers
 - Viral loads tend to increase, and patients become less able to work or perform other normal functions
 - Antiretroviral medication should be started if patient is ready



HIV and AIDS

What is the difference between HIV and AIDS?



Does this person have AIDS?

Based on the information given,
determine whether these patients have AIDS:

- 26 year old HIV+ female, obese, resolved cryptococcal meningitis
- 29 year old HIV+ female, very thin, CD4 360
- 34 year old male, HIV+ with thrush in the mouth
- 44 year old male with pulmonary TB, deep chronic cough, thin, bed-ridden
- 33 year old HIV+ male, never had major illness, CD4 180
- 32 year old female with chronic diarrhea over one month and weight loss of more than 10% of her body



AIDS

- Acquired Immunodeficiency Syndrome
 - Syndrome: constellation of signs, symptoms or illnesses
 - Not everyone with AIDS will have the same symptoms or signs or illnesses
 - Is an advanced stage of HIV illness
 - Certain clinical conditions lead to automatic AIDS diagnosis
 - Certain immunologic criteria will lead to AIDS diagnosis



Criteria for AIDS

- HIV+ patient has ever had a CD4 count less than 200
 - People whose initial CD4 < 200, but improve on HAART have AIDS
- HIV+ patient ever had certain clinical conditions
 - HIV wasting syndrome (wt loss of > 10% body weight, unexplained chronic diarrhea or weakness and unexplained fever)
 - Cryptococcal meningitis, esophageal candidiasis, extrapulmonary tuberculosis, cerebral toxoplasmosis, PCP, Kaposi's sarcoma, others



Staging, continued

- Only two of the cases we presented had AIDS
- AIDS cases:
 - Cryptococcal meningitis in HIV+ patient
 - Note, she was not wasted
 - 33 year old man with CD4 180
 - Note, he had never been majorly ill
- Two were not noted to be HIV+ (TB patient and the one with chronic diarrhea)
- One lady may have been thin all of her life, and her CD4 count was above 200
- Oral thrush is not an AIDS-defining illness



Summary

- An understanding of the immunology and natural history of HIV will help greatly in understanding antiretroviral therapy
- HIV primarily infects, uses, and then destroys CD4 cells while producing more of itself
- As the CD4 count drops, a patient becomes more symptomatic and susceptible to opportunistic infections
- AIDS is an advanced form of HIV infection, defined by certain clinical features or a $CD4 < 200$.
 - For the most part, you cannot just look at someone and tell if they have AIDS