

# Immunology of HIV And Brief Overview of Opportunistic Infections

# Objectives



1. Briefly describe the natural history and immunology of HIV
2. Learn the difference between HIV and AIDS
3. Define the term *Opportunistic Infection (OI)*
4. Describe why people living with HIV/AIDS are susceptible to OIs

# 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

# HIV



- Discovered in the early 1980s, but was around before that
  - Called a retrovirus → medicines used against it are called “antiretrovirals”
- Attacks several types of cells, but most importantly uses the CD4 cell
  - Invades the CD4 cell
  - Tricks the CD4 cell to make more HIV
  - Then kills the CD4 cells
- Produces billions (1,000,000,000’s) of viruses a day
  - Can measure how many viruses are present: “viral load”

# Natural History



- HIV gains entry into CD4 cells and multiplies inside them, eventually destroying them.
- As CD4 cell count decreases and viral load increases, the immune defences are weakened.
- People infected with HIV eventually become vulnerable to special infections, called “opportunistic” infections.
- Without ARV treatment, HIV progresses to symptomatic disease and AIDS and death

# Natural History of HIV Infection



## Seroconversion

- \* Infection with HIV, antibodies develop

## Asymptomatic

- \* No signs of HIV, immune system controls virus production

## Symptomatic

- \* Physical signs of HIV infection, some immune suppression

## AIDS

- \* Advanced immune suppression, opportunistic infections, end-stage disease

# 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.

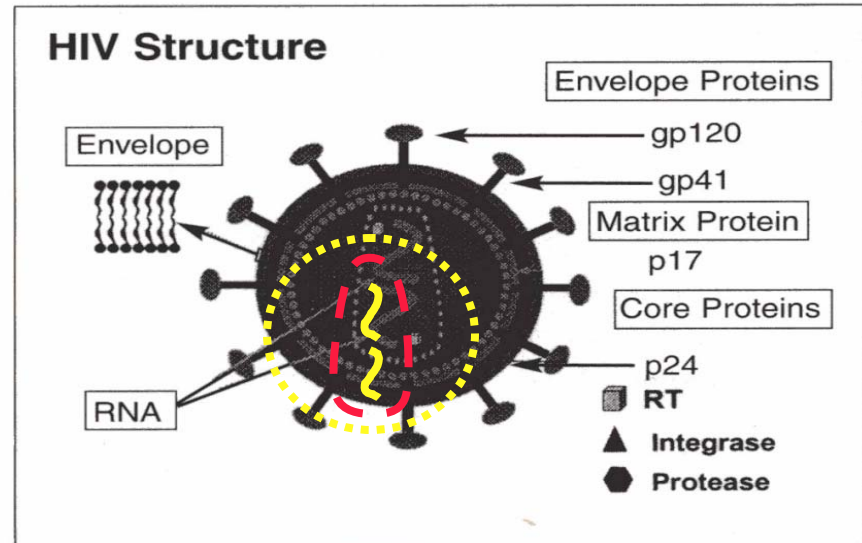


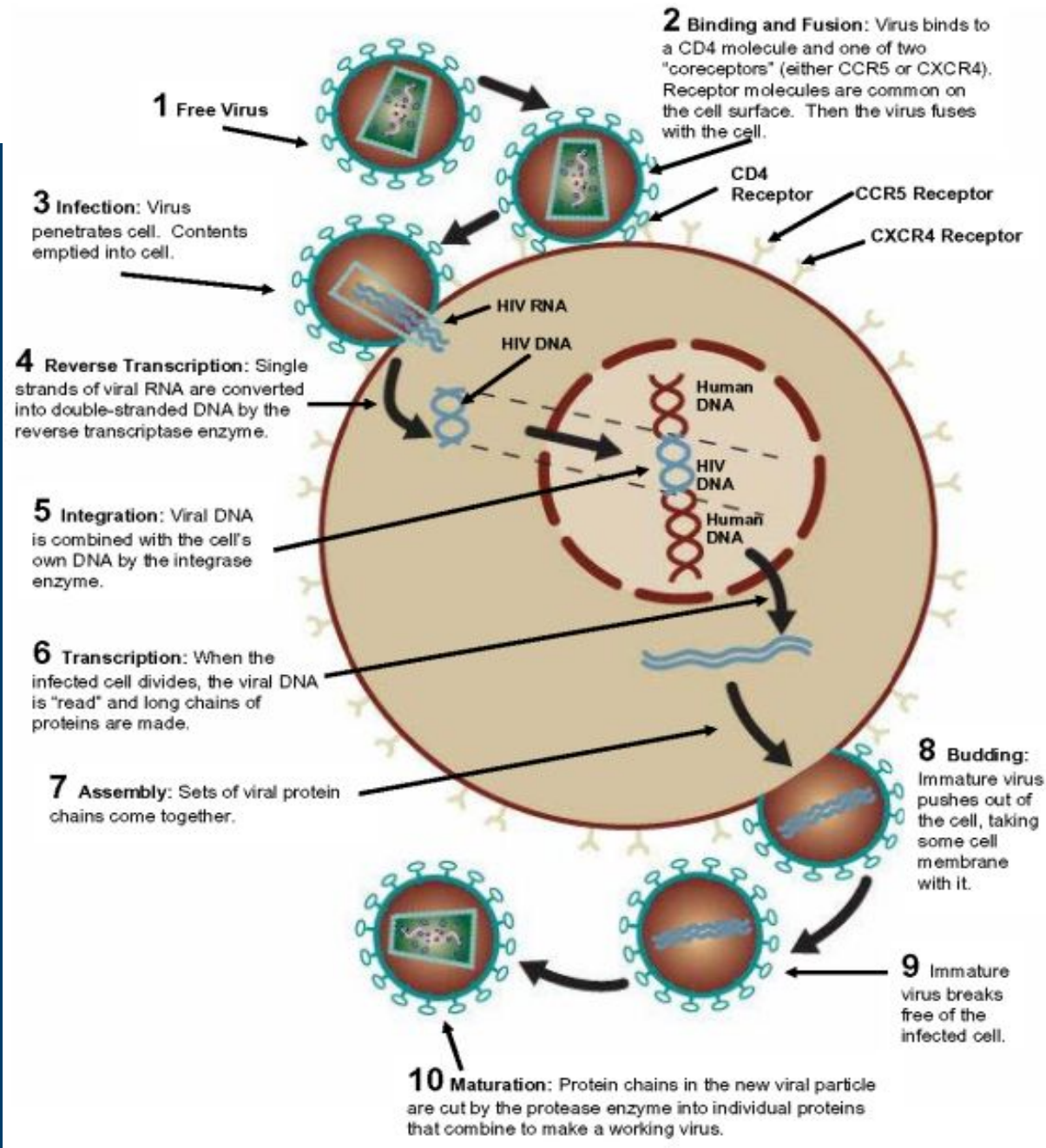
Figure 3. The Human Immunodeficiency Virus

- 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.

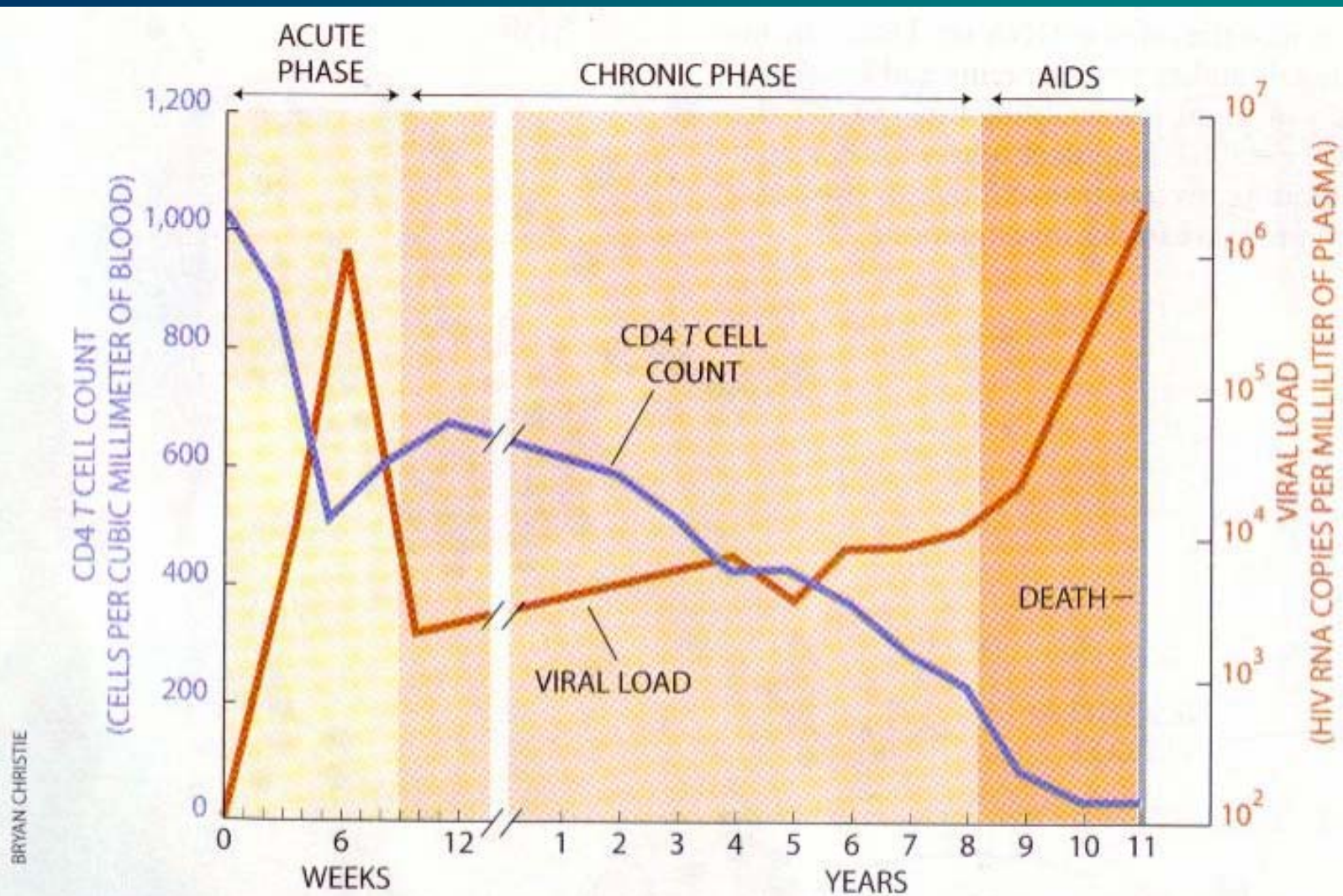


# Replication errors



- 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

# Clinical Course of *Untreated* HIV Infection



SOURCE: Anthony Fauci et al. in *Annals of Internal Medicine*, Vol. 124; 1996

# War analogy



- Immune system: Military
- CD4 cells: Generals/soldiers
- HIV: Enemies

# The Invasion



- When HIV (the enemy) first enters the body, it uses the body's OWN generals to reproduce itself
- Makes many, many more enemies
  - May be over a million (1,000,000) viruses in each ml of blood!
- Kills many soldiers and generals
- May make a person sick with flu-like symptoms: "acute retroviral syndrome"

# Seroconversion / Acute HIV Infection



- Clinical manifestations resolve as antibodies to the virus become detectable in patient's serum.
- Patients then enter a stage of asymptomatic infection lasting months to years.

# Win, Lose or Draw?



- So now, there are plenty of enemies and plenty of soldiers
  - We can count them: “viral load”, “CD4 count”
  - Seems on the outside like there is a “draw”
    - \* But plenty of warfare is taking place
- Slowly, but surely, the enemy kills off more of the soldiers
  - May take 8-10 years in adults who newly got infected for them to get seriously ill
    - \* Some people are rapid progressors (3-5 years)
    - \* Others are long-term non-progressors (may take 15 years or longer)
    - \* Called “latent phase”

# Latent Stage



- During this stage, level of virus in blood is very low
- Generally lasts for five years or more
- See gradual immune depletion over time
- Patients are usually symptom-free
- CD4 count may be above 500 to start and then will drop

# Latent Stage



- As the CD4 cell count drops, infections commence and persist or increase
- Over time, mild infections, particularly of skin and mucosal surfaces, start to appear
- Examples include skin rashes and oral thrush

# WHO Clinical Classification System



- Stage I:** Asymptomatic, generalized lymphadenopathy
- Stage II:** Weight loss <10%, prurigo, fungal nail infection, herpes zoster, recurrent URTIs
- Stage III:** Weight loss > 10%, chronic diarrhea or fever, oral candidiasis /HL, pulmonary TB, severe bacterial infections
- Stage IV:** AIDS-defining illnesses: e.g HIV wasting syndrome, PCP, brain toxoplasmosis, candida oesophagitis, extra-pulmonary TB, CMV retinitis, Kaposi's sarcoma, non-Hodgkins lymphoma and/or performance score 4: bedridden >50% of the day during the last month

# Meanwhile....



- The military is protecting the body against all disease-causing organisms
- Because there are plenty of soldiers, these other organisms don't cause many problems
  - If given the chance, they *would* cause problems, but can't because the soldiers are patrolling the body
    - \* Example: ordinary people may not try to rob a bank when there is a lot of security around, but if there is no security, then some might try

# Waiting for the right opportunity



- But when HIV kills enough soldiers, those other organisms can now attack the body
  - Called "*opportunistic infections*" because they wait around for the right *opportunity* to cause disease
    - \* Wait for there to be too few soldiers (CD4 cells) to protect the body
    - \* Examples: thrush, TB, cryptococcal meningitis, oesophageal candidiasis, PCP
  - These organisms can kill the person if not treated

# The Empire Strikes Back



- If, somehow, you could give the few remaining soldiers some weapons, things will likely get better
- Weapons: antiretrovirals!!!
  - Military first needs training on how to use these weapons
    - \* ARV training, adherence training, etc.
    - \* Patient education
- Now, the few remaining soldiers can fight off the increasing numbers of enemies

# Recruiting more soldiers



- Enemies: now dead *or hiding*
- Military can now recruit more soldiers and train more generals
- The other “opportunistic” organisms that caused problems when there weren’t many soldiers, now can’t cause problems because there are more soldiers to protect the body

# OI overview



- Individuals with HIV/AIDS acquire diseases that also affect otherwise healthy people
  - May have more severe course, however
- Individuals with HIV/AIDS may also acquire diseases that would not cause disease in otherwise healthy people
  - They are susceptible because of weakened immune system
  - Opportunistic infections - infections that would not cause disease in an otherwise healthy person

# OI Overview



People with HIV/AIDS are especially susceptible to OIs due to:

- Suppression of their immune system
- Psychological stress, which can influence the immune system
- Depletion of nutritional status

# Opportunistic Infections



- May be the initial presentation of HIV
  - May have otherwise ignored or not had previous symptoms
  - May not have wanted VCT or thought it was even necessary
- Are often signs of immunologic deterioration
  - Tend to occur as CD4 counts drop
  - In children < 1 year of age, may get opportunistic infections with “normal” CD4 counts

# Opportunistic infections



- May need closer follow-up if OIs occur
- Prevention and treatment of disease may prolong life and improve a patient's quality of life
- Response to ARVs will prevent most OIs
  - If OIs occur while on ARVs, think about poor adherence and/or resistance

*Opportunistic infections are the  
main reason why people with  
HIV die!*

# 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 for sure
- 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 (or had only food acquisition problems and not wasting syndrome), and her CD4 count was above 200
- Oral thrush is not an AIDS-defining illness

# AIDS



- Advanced Immune Depletion (CD4 cell  $<200$ / mL) or having ever had WHO stage IV illnesses.
- Viral loads tend to increase, and patients become less able to work or perform other normal functions
- Patients are at high risk for more opportunistic infections
  - Opportunistic infections are the main reason why patients with AIDS die!
- Antiretroviral medication should be started if patient is ready

# 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