MODULE ONE

TB Basic Science

Treatment Action Group
TB/HIV Advocacy Toolkit
Topics to be covered

- What is Tuberculosis?
- TB bacteria and what is unique about it.
- How is TB different from HIV?
- How is TB transmitted?
- Important players in the immune response.
- How does our immune system react to TB?
- The difference between latent TB infection and active TB disease
- Challenges to TB control in context of HIV
- Advocacy priorities
History of TB
“If the importance of a disease for mankind is measured by the number of fatalities it causes, then tuberculosis must be considered much more important than those most feared infectious diseases”

Robert Koch, March 24, 1882
A brief history of TB

- TB has been found in the mummies of ancient Egyptians and Andean Indians demonstrating that it has been in humans for thousands of years.

- Was first identified by Dr. Robert Koch in 1882.

- Around the turn of the 20th century, TB was referred to as “consumption.”
Fundamental Concepts
What is TB?

- The scientific name for the TB microbe is *mycobacterium tuberculosis* or MTB.

- Beneath a microscope, it has a long rodlike shape and thick, waxy-looking coat.
What is TB? (cont’d)

- Bacteria are single-celled organisms which can exist either independently or as parasites (dependent upon another organism for life).
- MTB is a type of mycobacteria
  - *myco* means “waxy” in Latin and refers to MTB’s waxy-looking cell wall.
  - There are 70 different types of mycobacteria.
What is TB? (cont’d)

- The thick waxy cell wall allows the germ to spread through the air and survive outside of the body.

- The nature of the cell wall means that it retains specific staining dyes after being washed in acidic solutions ("acid-fast bacillus")
TB reproduction

- Unlike most bacteria, which divide within minutes or hours, MTB splits in two once every 16 to 20 hours.

- This asexual process is known as binary fission.

- MTB has all the necessary genetic material to reproduce so it does not require a host.
Critical differences between TB and HIV

a) MTB is a huge bacteria made of a fatty cell wall, and many proteins.
b) MTB stores its genetic material as DNA.
c) DNA is more stable than RNA because it has a proofreading mechanism that regulates its mutations.
d) MTB is a relatively complex organism and has ~4,000 genes.
e) It reproduces by dividing in two in a process called binary fission.
f) MTB has been infecting humans for thousands of years.

a) HIV is a tiny retrovirus made of just a few proteins and a glycolipid (sugar-fat-protein) envelope.
b) HIV stores its genetic material as RNA.
c) RNA has no regulating mechanism hence copies often contain changes or mutations.
d) HIV is a relatively simple organism and has nine genes.
e) HIV tricks our own cell’s genetic machinery to replicate.
f) HIV has been around for about 70 years.
How is TB transmitted?
How is TB transmitted?

- TB is transmitted through the air from exposure to bacilli in the saliva of infected persons and sputum coughed up from their lungs.

- Once inhaled, the droplets can push their way into the lungs, settling in tiny air sacs known as alveoli.
Factors that may affect TB transmission

- Not all persons exposed to MTB become infected!
- Factors related to the person with TB (index case):
  - whether they are sputum smear-positive (high or low bacillary load);
  - have cough;
  - are on AND adhering to their TB medication regimen
- Factors related to the person being exposed to MTB (contact):
  - Closeness and frequency of contact with index case
  - age of contact-young children and older adults may be at increased risk for transmission
- Environmental factors:
  - ventilation;
  - size of room or space;
  - duration of exposure; and
  - sunlight or Ultraviolet (UV) light
Who’s who in the immune response?
Our Immune response
Some of the “players” include...

**ANTIGEN -PRESENTING CELLS** - (macrophages 😞 and dendritic cells) patrol the body looking for germs.

**CD4 T-CELLS** - act as coordinator of the immune response, instructing other cells to attack specific invading germs.

**CD8 T-CELLS** - are involved in cell-to-cell killing. When ordered by CD4 T cells, they seek out and destroy cells that have been infected by a specific germ.

**B CELLS** - are immune cells that, when instructed by the CD4 T cells, make antibodies.

**ANTIBODIES** - are sticky proteins that attach to germs, marking them for destruction by the immune system or hampering their ability to reproduce. Antibodies are specific to the germ (bacteria, virus, or other harmful toxins).

**CYTOKINES** - are small signaling proteins that help immune cells communicate.

Adapted from CSTEP curriculum: Project Inform and A&PIWC

Section 4 • Who’s who in Immune Response
How does the immune system respond to TB?

The immune system sends out an army of immune cells. Chief among them are dendritic cells and macrophages.
How does the body respond?

Dendritic cells and macrophages transport MTB to the lymph nodes, which act as the communication and meeting center for the immune system.

In the lymph nodes, the cells chop up the TB bacilli and present it to the CD4 T cell, which coordinates the immune response.
Immune Response

Antibody Response (or Humoral)
- B-Cells
- Antibodies
- Attacks germs outside of cell (e.g. germs in blood)

Cellular Response
- CD8 T cells
- Cell-to-cell killing
- Attacks germs inside of cells (e.g. infected cells)

Bone Marrow
B-cells

Th2
CD4 T cell

Th1

CD8 T cells

Thymus
Immune response
Before going any further...
what is the difference
between latent TB infection
and active TB disease?
What is the difference between TB infection and TB disease?

Many people incorrectly use the terms TB infection and TB disease interchangeably.

Latent TB infection (aka LTBI) refers to the period of time when the immune system has been successful in containing the MTB and preventing disease.

Active TB disease refers to the time when TB breaks out of latency and causes disease.
Latent TB infection

- TB-specific CD4 and CD8 T cells travel into the lung to contain TB bacilli and eliminate infected cells.

- Cytokines (cellular chemical messengers) released by these cells also activate macrophages in a way that helps them break down and dispose of MTB (process known as phagocytosis).

- As a result, instead of being eliminated from the body, the TB microbe is encased in a hard shell, known as a tubercle.
Phagocytosis

a. Ingestion of the pathogen and the formation of an internal pocket called a phagosome.

b. Normally, a cytokine called interferon gamma (IFN-γ) activates macrophages in a way that promotes the phagosome to fuse with another pocket called a lysosome (which contains substances capable of breaking down the pathogen). The new phagolysosome disposes of the pathogen. **MTB has the ability to block this process in order to survive in the macrophage’s phagosome and prevent its transport to the lysosome for degradation and disposal.**

c. Waste material is expelled
Latent TB infection

The tubercles are contained by TB-specific CD4 and CD8 T cells in an immunological prison called a granuloma that can keep TB from causing disease and spreading it to other people.

When in this stage of latency, TB bacilli change their diet so that they require very little oxygen to survive and can remain dormant or reproduce at very low levels.
Immunologic memory

In a matter of weeks after the initial infection, TB is usually contained by the immune system.

Most (about 90%) of the newly-generated TB-specific CD4 and CD8 T cells are no longer needed and they die off in a process called apoptosis (cell suicide).
Immune Response

- Once the germ has been “dealt with” the immune system slows down.
  - A small number of “memory cells” remain
  - If exposed to the same germ again - the memory cells will "remember" and mount a response that is more rapid than the first time the immune system responded to the germ.

Section 5: Immune response

Adapted from CSTEP curriculum: Project Inform and A&PIWC
Immune response

In HIV-negative persons, the body’s immune system usually keeps TB infection under control. In fact, most people with latent TB infection never develop TB disease. Only 1 in 10 cases ever progresses to active TB.

On the other hand, HIV-positive persons with LTBI have an annual risk of about 10 percent of developing TB disease. In other words, they have a 1 in 10 chance every year of progressing to active disease.
How does LTBI progress to Active Disease?

Latent TB infection can progress to active disease when the body becomes weak from disease, malnutrition, immune suppression, or even old age.

When the immune system is compromised, the tubercles may begin to multiply and break out of the granulomas, damaging the lung tissue creating cavities.
Active TB disease

- Active TB disease may manifest in the lungs (pulmonary TB) and/or in other parts of the body (extrapulmonary TB).

- Pulmonary TB is the most common form of TB disease.

- Pulmonary TB expels pus into the lungs, which a person with TB may cough up in spit or sputum.

- Extrapulmonary TB (EPTB) is rare in adults with healthy immune systems but occurs in up to 40% of TB cases among people with HIV (rarely involves a single organ) and children.
Challenges to TB control in TB/HIV coinfection
Challenges: Extra-pulmonary TB (EPTB)

- People with HIV are more likely to have extrapulmonary TB. Sites that can be affected include:
  - **Miliary TB** is TB disseminated throughout the body.
  - **Tuberculosis lymphadenitis** is found in the lymph nodes, and is the most common form of EPTB.
  - **Pleural TB** is found in the pleural cavity around the lungs and is the most common form of EPTB in people with HIV.
  - **Skeletal TB** is found in the bones and joints.
  - **Tuberculosis meningitis** is found in the central nervous system.
  - **Gastrointestinal TB** is found in the gastrointestinal tract.
  - **Genitourinary TB** is found in genitourinary tract.
  - **Tuberculosis peritonitis** is found in the pelvic cavity.
  - **Tuberculosis pericarditis** is infects the membrane around the heart (pericardium).
Challenges: smear-negative TB

People with HIV and children have fewer TB bacteria in their sputum due to fewer functioning CD4 and CD8 T cells. In healthy immune systems CD4 and CD8 T cells expel TB into the sputum.

As CD4 T cells are lost and compromised due to HIV infection, CD8 T cells lose the directional support they need to do their job and become impaired in their ability to kill TB-infected cells.

When this happens, the chance of smear-negative TB increases because fewer TB bacilli are released in the sputum.

Up to 61% of people coinfected with HIV and TB generate smear-negative tests, meaning the sputum smear test comes up negative incorrectly indicating that the person does not have TB.
Advocacy priorities

- The need for basic understanding of TB is essential for newer and better prevention and infection control strategies, vaccines, diagnostics, and treatments.

- The newly revised *Global Plan to Stop Tuberculosis 2011-2015* now includes fundamental or basic science research in its research priorities.

- High burden countries need to increase their investment in basic science research and programs.
A brief review...

- Name two differences between TB and HIV.
- What is binary fission?
- What does “AFB” refer to?
- How is TB transmitted? Name one factor that may impact TB transmission.
- What are antigen-presenting cells?
- What is the difference between latent TB infection and active TB disease?
- Why are people with HIV more likely to have smear-negative TB?