HIV and AIDS

Human Immunodeficiency Virus
Acquired Immune Deficiency Syndrome

HIV is a retrovirus that infects lymphocytes and macrophages
As of 2016,

People living with HIV infection = 38 million

1.1 million deaths in 2015

cumulative AIDS-associated deaths worldwide -- ~35 million
cumulative AIDS-associated deaths worldwide -- ~35 million
Adults and children estimated to be living with HIV, 2015
By WHO region

Number of people, by WHO region

- **Eastern Mediterranean**: 330,000 [240,000–490,000]
- **Western Pacific**: 1,400,000 [1,100,000–2,000,000]
- **Europe**: 2,500,000 [2,300,000–2,700,000]
- **Americas**: 3,400,000 [3,000,000–3,900,000]
- **South-East Asia**: 3,500,000 [3,000,000–4,100,000]
- **Africa**: 25,500,000 [23,000,000–28,400,000]

Total: 36,700,000 [34,000,000–39,800,000]

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

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Where did HIV originate?

Non-human primates in Africa

SIV → HIV in isolated human populations in Africa
Potentially as early as the 1800’s
Probably from “bush meat”

Late 1800’s – mid 1900’s

• Increased travel between countries
• Vaccination programs (reused needles)
• “Sexual revolution”
Sooty mangabeys

SIVsm
Chimpanzees

SIVcpz
HIV-1
most prevalent -- pandemic AIDS
~90% of global cases
most virulent
from chimpanzees

HIV-2
mostly confined to West Africa
less virulent
from Sooty Mangabees
HIV Transmission

HIV is found in the blood, semen, or vaginal fluid of an infected person.

*HIV is transmitted in 3 main ways:*

- Having sex (anal, vaginal, or oral) with infected person
- Sharing needles and syringes with infected person
- Being exposed (fetus or infant) to HIV before or during birth or through breast feeding
Symptoms

Primary Infection – asymptomatic or “acute retroviral syndrome” – flu like symptoms

Stage 1 – no symptoms or lymph node swelling

Stage 2 – minor weight loss, skin problems, upper respiratory infections

Stage 3* – unexplained chronic diarrhea, chronic fever, oral yeast infections, bacterial infections, pulmonary TB, acute necrotizing inflammation of the mouth

Stage 4* – opportunistic infections and cancers correlated with HIV infections

*some people with Stage 3 and all people with Stage 4 symptoms have AIDS
HIV infection to the development of AIDS-related symptoms

range = 2 - 15 years in the absence of anti-retroviral therapy.

wide variation in disease progression.

~10% of HIV-infected people progress to AIDS within 2 to 3 years
HIV infection to the development of AIDS-related symptoms

AIDS –
when untreated, average survival rates
~1 year

--with early intervention (when infected with HIV but before showing clinical signs)
~20 years

http://youtu.be/hI1w5l7I2wU
Viral replication

Obligate intracellular parasite

1) Virus enters cell
2) Copies of viral genome are made
3) Capsid proteins are made
4) New virus is packaged
5) Mature virus leaves cell
HIV Life-Cycle – HIV is a Retrovirus

HIV genome is made of RNA

HIV uses a protein called reverse transcriptase to make a DNA copy of its genome

The DNA copy of the genome is spliced in to one of your chromosomes and will be copied with your genome every time the infected cell undergoes cell division
HIV Life-Cycle – HIV is a Retrovirus

HIV has 3 proteins that are very different from your proteins:

reverse transcriptase
integrase
protease
The HIV Life Cycle

HIV medicines in six drug classes stop HIV at different stages in the HIV life cycle.

1. Binding (also called Attachment): HIV binds (attaches itself) to receptors on the surface of a CD4 cell.
   - CCR5 Antagonists

2. Fusion: The HIV envelope and the CD4 cell membrane fuse (join together), which allows HIV to enter the CD4 cell.
   - Fusion inhibitors

3. Reverse Transcription: Inside the CD4 cell, HIV releases and uses reverse transcriptase (an HIV enzyme) to convert its genetic material—HIV RNA—into HIV DNA. The conversion of HIV RNA to HIV DNA allows HIV to enter the CD4 cell nucleus and combine with the cell's genetic material—cell DNA.
   - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
   - Nucleoside reverse transcriptase inhibitors (NRTIs)

4. Integration: Inside the CD4 cell nucleus, HIV releases integrase (an HIV enzyme). HIV uses integrase to insert (integrate) its viral DNA into the DNA of the CD4 cell.
   - Integrase inhibitors

5. Replication: Once integrated into the CD4 cell DNA, HIV begins to use the machinery of the CD4 cell to make long chains of HIV proteins. The protein chains are the building blocks for more HIV.

6. Assembly: New HIV proteins and HIV RNA move to the surface of the cell and assemble into immature (noninfectious) HIV.

7. Budding: Newly formed immature (noninfectious) HIV pushes itself out of the host CD4 cell. The new HIV releases protease (an HIV enzyme). Protease acts to break up the long protein chains that form the immature virus. The smaller HIV proteins combine to form mature (infectious) HIV.
   - Protease inhibitors (PIs)
HIV Infection

Cell surface proteins required for HIV entry

CD4

and either CCR5 or CXCR4
CD4 Binding

- gp120
- V3 loop
- gp41
- CD4

Co-receptor Binding

- CCR5/CXCR4
HIV Infection

HIV infects cells of the immune system

- CD4+ cells (= T helper cells)
- macrophages
- microglia (macrophage-like cells in the brain)
Many tissues/organs in the body are part of the immune system.
All the cells in the immune system are born in the bone marrow
Role of the Immune System

protection against invaders

Recognition

self vs. non-self

Response

destroy non-self components
Two Branches of the Immune System

Innate immunity

- physical and chemical attributes
  -- antibacterial proteins
  -- phagocytosis by macrophages

Acquired immunity

-- specificity
-- adaptiveness
-- self vs. non-self recognition
-- memory
Types of White Blood Cells

Antigen presenting cells

cells like macrophages and neutrophils that phagocytose foreign cells or viruses and show other WBCs that there is a foreign invader present

B lymphocytes

produce antibodies against foreign invader

T lymphocytes

activate all other immune system cells lyse foreign cells or virally infected cells
T-cells

Helper T-cells – key to activating immune responses

Cytotoxic T-cells and Natural killer cells – recognize aberrant cells and kill them
B-cells activated when surface-bound antibody recognizes pathogen or toxin

multiply – make many cells producing same antibody

secrete antibody into blood stream

Also need cytokines from T helper cell activation to get full B cell activation
1) Invading pathogen (antigen) engulfed by antigen presenting cell (APC)
2) APC activates T helper cell ($T_H$)
3) Activated $T_H$ activates other immune cells
4) $T_H$ activates B cells
   B cells produce antibodies to destroy pathogen
5) $T_H$ activates macrophages (M)
   M engulf and destroy pathogen
6) $T_H$ activated cytotoxic T cells ($T_C$)
   $T_C$ produce peforin (●) to kill pathogen
How can B cell and T cells respond to so many different antigens?

Every day you make millions of B and T cells (each with its own unique receptor)

Those cells live about 1 month –
if they encounter a match to their receptor they are activated to respond

if not – they undergo apoptosis to make room for the new B and T cells
How can B cell and T cells respond to so many different antigens?

2.5 x $10^7$ T Cell Receptor possibilities

2.0 x $10^9$ B Cell Receptor (Antibody) possibilities
Symptoms and CD4+ cell counts in HIV infection
Not everyone infected with HIV develops AIDS.

**Table 1: Definitions of non-progressors.**

<table>
<thead>
<tr>
<th></th>
<th>EC</th>
<th>VC</th>
<th>LTNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ cell count (cells/µL)</td>
<td>&gt;350</td>
<td>&gt;350</td>
<td>&gt;350</td>
</tr>
<tr>
<td>Viral load (copies/mL)</td>
<td>&lt;50</td>
<td>50–200</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>Duration of infection (years)</td>
<td>*</td>
<td>*</td>
<td>&gt;7</td>
</tr>
<tr>
<td>CART</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tbody>
</table>

*Duration of infection is not used in the definition of controllers in this review.

EC = Elite Controllers

VC = Viremia Controllers

LTNP = Long-term nonprogressors
Not everyone infected with HIV develops AIDS.

up to 5 percent of individuals have stable CD4+ T cell counts and no symptoms even after 12 or more years

What is different about these individuals?

- genetic factors
- neutralizing antibodies
Symptoms and CD4+ cell counts in HIV infection
A mutation in CCR5 makes individuals resistant to HIV infection.

**CCR5Δ32**

Heterozygotes have better survival rates.

Homozygotes cannot be infected with HIV strains that use CCR5 (but are still susceptible to strains that use CXCR4).
One man was cured

He had leukemia and needed a bone marrow transplant

A donor match who had the $\text{CCR5}^{\Delta 32}$ mutation was identified

Timothy Ray Brown
Destruction of the Immune System

1) gp120 on infected $T_H$ cells
   – recognized by cytotoxic T cells and B-cells

2) soluble gp120
   binds to CD4+, stimulates killing of non-infected cells that have gp120 on surface
3) infected $T_H$ cells form synctia infected cells with gp120 on the surface bind and fuse with healthy $T_H$ cells ultimately causes cell lysis

4) viral budding ruptures $T_H$ cells
Destruction of the Immune System

5) $T_H$ cell maturation is inhibited 
   (so not making more $T_H$ cells)

6) Programmed cell death
   gp120 may stimulate PCD
   when binds to CD4+
Net effect –

as $T_H$ cells ↓ immune response ↓

AIDS <200 CD4+ cells/μL
Antiviral Drugs to treat HIV Infection

Reverse Transcriptase Inhibitor

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

HIV uses an enzyme called reverse transcriptase to make DNA copies of its RNA genome.

Human cells do not have RT
Antiviral Drugs to treat HIV Infection

Protease Inhibitors

HIV proteins are made as one long polyprotein which is then cleaved into the individual proteins by the HIV Protease.

Human cells do not have this protease.
Integrase Strand Transfer Inhibitors (INSTIs)

HIV has Integrase – a protein required for the DNA copy of the genome to be integrated into the host chromosome.
Antiviral Drugs to treat HIV Infection

Fusion Inhibitor

CCR5 Antagonists
Block the ability of HIV to get into CD4+ cells by targeting CCR5

Viral Response to Drugs –
develop drug resistance – mutation based
Life Cycle Review

https://youtu.be/odRyv7V8LAE
Example of a rapid HIV test

Read results in 10 -12 minutes
Vaccine possibilities

1) protect against HIV infection
2) lower viral load in infected individuals

Most vaccines have focused on the envelope protein gp120. Strong neutralizing antibody responses can be detected but have not been maintained.

AIDSVAX – did not protect (halted trials in 2003)

STEP study
vaccine clinical trial (Merck Co. & NIH)
aimed at inducing T-cell responses
study halted (in 2008) when determined that the vaccine did not protect against infection
Vaccine possibilities

RV144
trial in Thailand, 16,000 adult volunteers

Short term – first 12 months -- ~60% effective
but then protection decreases rapidly

Potential for improved protection
if give booster vaccines regularly
Antiretroviral therapy coverage and number of AIDS-related deaths, global, 2000–2015

Sources: GARPR 2016; UNAIDS 2016 estimates.
<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Range</th>
<th>Subcategory</th>
<th>Total</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Number of people living with HIV in 2015</td>
<td>36.7 million</td>
<td>[34.0 million – 39.8 million]</td>
<td>Adults</td>
<td>31.8 million</td>
<td>[30.1 million – 33.7 million]</td>
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<tr>
<td></td>
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<td></td>
<td>Women</td>
<td>16.0 million</td>
<td>[15.2 million – 16.9 million]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Children (&lt;15 years)</td>
<td>3.2 million</td>
<td>[2.9 million – 3.5 million]</td>
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<tr>
<td>People newly infected with HIV in 2015</td>
<td>2.1 million</td>
<td>[1.9 million – 2.4 million]</td>
<td>Adults</td>
<td>1.9 million</td>
<td>[1.7 million – 2.1 million]</td>
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<td>Children (&lt;15 years)</td>
<td>240 000</td>
<td>[210 000 – 280 000]</td>
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<tr>
<td>AIDS deaths in 2015</td>
<td>1.1 million</td>
<td>[940 000 – 1.3 million]</td>
<td>Adults</td>
<td>1.0 million</td>
<td>[1.2 million – 1.5 million]</td>
</tr>
<tr>
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<td></td>
<td>Children (&lt;15 years)</td>
<td>190 000</td>
<td>[170 000 – 220 000]</td>
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Source: UNAIDS/WHO estimates.