HIV Pathogenesis and Natural History

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Learning Objectives

• Describe key features of HIV pathogenesis and natural history

• Explain how these key features inform HIV treatment paradigms

• Describe how these features may contribute to non-AIDS complications during ART

• Identify how these features impact research efforts to cure HIV
Where did HIV come from?
Simian Immunodeficiency Virus (SIV)

Keele et al, Science, 2006
Monkeys Don’t Use This
HIV is genetically similar to naturally occurring SIV in Chimpanzees
SIV->HIV Transmission Event

- Probably circa 1931
- Monkey poaching industry
- Kinshasa, Congo
  - 1959 HIV+ plasma
- Further human to human spread facilitated by:
  - Adaptation in humans
  - Transmission networks (truck drivers)

Korber et al, Science, 2000
How does HIV replicate within cells?
HIV Life Cycle
An Animated Video

Janet Iwasa, PhD
U Utah

www.ScienceofHIV.org
HIV Life Cycle

1. BINDING
On the surface of a T-cell, HIV binds to a CD4 receptor and one of two co-receptors—CXCR4 or CCR5.

2. FUSION
The virus fuses with the host cell membrane and releases its genetic material (RNA) into the cell.

3. REVERSE TRANSCRIPTION
The single-stranded HIV RNA is converted into double-stranded HIV DNA by the reverse transcriptase enzyme.

4. INTEGRATION
After the HIV DNA enters the cell's nucleus, the enzyme integrase cuts the cell's DNA and inserts the HIV DNA into it.

5. TRANSCRIPTION AND TRANSLATION
The enzyme RNA polymerase makes RNA copies of DNA. HIV RNA is either inserted into new virus particles or processed and translated into HIV proteins.

6. ASSEMBLY
The long protein chains are cut into individual proteins by the enzyme HIV protease. A new virus is assembled with these proteins and HIV RNA.

7. RELEASE
The new virus particle is released from the host cell, taking with it part of the cell's membrane, and capable of infecting other cells.

https://www.flickr.com/photos/5winfographics/9037451756/
Important Characteristics of HIV Life Cycle

• Error-prone reverse transcriptase
  – Makes a mistake EVERY 3rd time it replicates

• Each day, 10 billion new virions made and up to 1 billion new CD4+ T cells infected!
  – Each drug resistance mutation is present in at least one virus in every person with HIV

• HIV rapidly evolves in the face of selection pressures (drugs or the immune response)
  – Need 3 drugs with different resistance patterns to prevent selection of drug-resistant viruses.

Coffin/Swanstrom, CSH PM, 2013
Massive Genetic Diversity of HIV


Challenge of an HIV Vaccine
Another Key Characteristic of HIV Life Cycle: Latency

• HIV integrates into DNA of resting T cells and persists indefinitely in “Latent Reservoir”
  – Primary barrier to curing HIV

• Once treatment started, it must be continued indefinitely to prevent viral rebound.

• Drug resistance mutations persist in latent reservoir even during suppressive ART.
  – Once resistant, always resistant!
Natural history of HIV infection within an infected individual
Exposure to HIV at mucosal surface (sex)

Virus collected by dendritic cells, carried to lymph node

HIV replicates in CD4 cells, released into blood

Virus spreads to other organs


Slide courtesy of Charles Hicks
Importance of Gut-associated Lymphoid Tissue in Acute HIV

- Gut has ~50% all CD4 T cells in body
- Majority are
  - CCR5+ (fat targets)
  - Activated (virus factories)
- 60% of all CD4 T cells lost from gut in 1st 2 wks

HIV Natural History: Acute HIV

- Cytotoxic T cell response
- Neutralizing antibodies
- Loss of “virus factories” in gut

Which of the following are typical symptoms of acute HIV infection?

1. Mono- or influenza-like illness
2. Sepsis syndrome
3. Oral candidiasis
4. 1 and 3 only
5. 1, 2 and 3
Insert Web Page

This app allows you to insert secure web pages starting with https:// into the slide deck. Non-secure web pages are not supported for security reasons.

Please enter the URL below.

https://api.cvent.com/polling/v1/api/polls/sp-r63j4y

Note: Many popular websites allow secure access. Please click on the preview button to ensure the web page is accessible.
Symptoms of Acute HIV

- Severe Flu-like illness (mono-like)
  - Fever, rash, LN, sore throat
- Diarrhea, Nausea/Vomiting
- Oral, genital ulcerations
- Oral thrush
- Aseptic meningitis (10%)

Hecht, AIDS, 2002
Transmission Risk Highest during Early HIV Infection – Rakai, Uganda

Wawer, JID, 2005
Immunologic and Clinical Benefit of Early ART (at CD4>500): START Trial

### AIDS Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
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<td>TB</td>
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<tr>
<td>Bacterial Infection</td>
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<td>Lymphoma</td>
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<td>Non-AIDS Cancer</td>
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### Non-AIDS Events

Guidelines now suggest starting ART in all regardless of disease stage.

*START trial, NEJM, 2015*
Remember to Test for Acute HIV!

- Mono-like illness in person *potentially* at risk should prompt HIV Ab *and* Viral Load testing
- Early diagnosis alters patient behavior and prevents further transmission!
- Early diagnosis and treatment may also decrease morbidity over the long-term.
Why can’t the immune system control HIV?
Adaptive Immune Response to HIV

Walker and Burton, Science, 2008
Problems with Neutralizing Antibody Response Against HIV

• Develops too late (3 weeks)

• Resistant viruses constantly selected
  – One step ahead of immune system

• HIV envelope is “shielded” by sugars, making it hard for antibodies to bind.

• Some broadly neutralizing antibodies (BNAb) also recognize host proteins
  – “Selected out” in B cell development (anti-cardiolipin antibodies in Lupus)
Problems with Cytotoxic CD8+ T cells

• Arrive too late (lost ½ body’s CD4 T cells by wk 3)
• Because they are peptide-specific, a single point mutation can lead to “immune escape”
• HIV “hides” from CD8+ T cells by decreasing MHC expression in infected cells (HIV nef protein), blocking antigen presentation
• HIV preferentially infects HIV-specific CD4+ T cells, which need to give “help” to CD8+ T cells
• Inflammation impairs T cell function (exhaustion)
Why does HIV cause AIDS?
Development of AIDS is like an impending train wreck

Viral Load = Speed of the train
CD4 count = Distance from cliff

J. Coffin, XI International Conf. on AIDS, Vancouver, 1996
Opportunistic Infections
MAJOR COMPLICATIONS IN THE COURSE OF HIV INFECTION

Kaposi’s Sarcoma

Lymphoma

Tuberculosis

Herpes zoster, thrush, HSV

CNS Disorders (HIV)

Bacterial infections, esophageal candidiasis

Wasting

Pneumocystosis

Toxoplasmosis

Atypical mycobacterioses

CMV, cryptosporidiosis, microsporidiosis, PML

CD4/mm³

Time

Courtesy of Chuck Hicks
Are there mechanisms other than CD4 depletion that contribute to disease?

Do they persist during ART?
An Important Clue from Nature

Sooty Mangabey
- Infect with SIV
- High Levels of Viral Replication
- **No AIDS, normal lifespan**
- *Minimal* Immune Activation

Rhesus Macaque
- Infect with SIV
- High Levels of Viral Replication
- **AIDS and death**
- *Massive* Immune Activation

Silvestri, Immunity, 2003
T Cell Activation Remains Abnormally High During ART-mediated Viral Suppression

Causes of Persistent Immune Activation During ART-mediated Viral Suppression

HIV production and replication

ART toxicity, lipodystrophy, and traditional risk factors

Cytomegalovirus and other copathogens

Loss of regulatory cells

\( T_{\text{reg}} \) → \( T_{\text{eff}} \)

Inflammation

\( \uparrow \) Monocyte activation
\( \uparrow \) T-cell activation
\( \uparrow \) Endothelium adhesion
Dyslipidaemia
Hypercoagulation

Comorbidities
(cardiovascular disease, cancer, kidney disease, liver disease, osteopenia/osteoporosis, neurocognitive disease)

Deeks, Lewin, and Havlir, Lancet 2013
Many age-associated morbidities increased in treated HIV

- Cardiovascular disease [1-3]
- Cancer (non-AIDS) [4]
- Bone fractures / osteoporosis [5,6]
- COPD [12]
- Liver disease [7]
- Kidney disease [8]
- Cognitive decline [9]
- Non-AIDS infections [10]
- Intermediate-Stage Macular Degeneration [13]
- Frailty [11]

Inflammation **Strongly and Durably Predicts Morbidity / Mortality in Treated HIV Infection**

(IL-6 + D-dimer Score)  


**SMART / ESPRIT / SILCAAT**  
(Median Current CD4: 500; Nadir: 181)

*Years*  
**Cum. % of pts with event**

<table>
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<th>Quartiles:</th>
<th>q4 (highest)</th>
<th>q3</th>
<th>q2</th>
<th>q1 (lowest)</th>
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**HR: 1.64 per 2-fold increase**

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**START**  
(CD4>500)

*Months*  
**Cumulative % with event**

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**HR: 1.61 per 2-fold increase**

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Ongoing research efforts to reduce immune activation

• Address traditional risk factors
  – Smoking, substance use, diet / exercise, HTN

• Clinical endpoint study of statins underway (REPRIEVE)

• Several proof of concept studies to identify optimal targets to reduce inflammation
What about HIV cure?
The “Berlin Patient”

Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.
Bone Marrow Transplant and Very Early ART Not Sufficient for Curing HIV

[Diagram showing the time in remission for different methods of treatment, including typical rebound after ART cessation, Boston patients method: Stem cell transplants, Mississippi baby method: Early ART initiation, Visconti cohort/post treatment controllers method: Early ART initiation, French teenager method: Early ART initiation, Timothy Brown is the only person who has sustained remission after discontinuing ART, The Berlin Patient (Timothy Brown) method: Chemotherapy + 2 full stem cell transplants.]

https://www.avert.org/professionals/hiv-science/searching-cure
Ongoing research efforts toward an HIV cure

- Gene therapy to render cells resistant or to engineer an effective immune response.
- Improve immune response to the virus
  - Therapeutic vaccination
  - Broadly neutralizing antibodies
  - Therapies to decrease immune exhaustion
- Make latent cells “visible” to the immune system
Summary

• Rapid HIV mutation/replication rate = rapid evolution
  – Virus is always one step ahead of the immune response
  – Need 3 drugs to prevent selection of \textit{pre-existing} mutants

• Latency is primary barrier to HIV cure
  – Also means that drug resistance mutations get “archived”

• Remember to test for acute HIV (with VL)!
  – Opportunity to prevent transmission and progression

• Immunodeficiency not just due to CD4 depletion
  – Functional immune defects present even at high CD4

• Next frontier: blocking inflammation and HIV cure