ACTHIV 2019: A State-of-the-Science Conference for Frontline Health Professionals
HIV Pathogenesis

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Describe the current understanding of HIV pathogenesis and the natural history of infection
• Explain the relationship between pathogenesis and HIV treatment decisions
• Describe how pathogenesis relates to comorbidities and non-AIDS complications in people living with HIV infection
• Relate HIV pathogenesis to the unique challenges facing HIV cure interventions
Faculty and Planning Committee Disclosures
Please consult your program book or the Conference App.

There will be no off-label/investigational uses discussed in this presentation.
Outline

• HIV viral life cycle
  – Consequences for antiretroviral therapy
  – Implications for HIV cure efforts

• Immunologic consequences of HIV infection
  – Immune deficiency/Inflammation
  – Immune disruptions in antiretroviral-treated patients

• Looking forward
The Life Cycle of HIV

1. HIV attaches to surface receptors on target cells (CD4 + CCR5 or CXCR4)

www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle
The Life Cycle of HIV

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7. The viral protease cleaves proteins to mature the virus particle

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The Life Cycle of HIV: Antiretroviral targets

Which stages in the viral life cycle are targets of current antiretroviral therapies?

a) 3
b) 4
c) 7
d) All of the above
The Life Cycle of HIV: **Antiretroviral targets**

1. Maraviroc *HIV cure interventions*
2. T-20
3. NRTIs, NNRTIs (Tenofovir, 3TC, Rilpivirine etc)
4. Integrase inhibitors (Dolutegravir, Raltegravir)
5. *HIV cure interventions*
6. *No current targets*
7. Protease inhibitors (Darunavir etc)

www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle
Key features of the HIV life cycle for treatment

- Antiretroviral drug targets throughout the life cycle
- Error-prone reverse transcriptase (step 3)

Coffin and Swanstrom, Cold Spring Harbor Perspectives in Medicine, 2013
Key features of the HIV life cycle for treatment

- Antiretroviral drug targets throughout the life cycle
- Error-prone reverse transcriptase (step 3)
- High rate of replication:
  - Up to 10 billion virions per day

Coffin and Swanstrom, Cold Spring Harbor Perspectives in Medicine, 2013
Key features of the HIV life cycle for treatment

- HIV rapidly evolves to escape from selection pressure from either the immune system or antiretroviral therapy.
- Therapy with multiple drugs prevents the selection of resistant viruses.
- The genetic diversity of HIV is a challenge to the development of an effective vaccine.

Coffin and Swanstrom, Cold Spring Harbor Perspectives in Medicine, 2013
The other half of the HIV Life Cycle: Latency

Images modified from www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle
The other half of the HIV Life Cycle: Latency

- HIV integrates into the host DNA and persists indefinitely
- The latent reservoir holds an “archive” of resistance mutations
- This reservoir obligates lifelong therapy
The other half of the HIV Life Cycle: Latency

- Cells with integrated DNA but no virus RNA production
  - do not trigger the immune system
  - are not targeted by any antiretroviral therapies

- Some strategies for HIV cure have been focused on turning ON the integrated HIV genomes to allow the cells to be recognized and eliminated....
Key Features of the HIV lifecycle:

Why does the immune system fail to control HIV?

• CD8\(^+\) T cell responses are limited by
  – Immune escape due to high mutational rate
  – HIV specific functions to evade the immune response
  – Depletion of CD4\(^+\) T cells decreases the ”help” available to CD8 responses
Key Features of the HIV lifecycle:
Why does the immune system fail to control HIV?

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- Broadly neutralizing antibody responses
  - Develop too late to be effective in primary infection
  - Selection of resistance variants
  - Difficulty in eliciting neutralizing antibody responses in uninfected individuals
HIV pathogenesis: when and why to start treatment

When should antiretroviral therapy be started?

a) When the CD4 count is <350
b) When the CD4 count is <500
c) When the viral load is >100,000 copies/mL
d) As soon as the patient is willing to take medication
Immunologic consequences of HIV infection

Immunologic consequences of HIV infection

- Local Infection
- Trafficking to the lymph node

Immunologic consequences of HIV infection

Local Infection

Trafficking to the lymph node

Hematogenous dissemination

Immunologic consequences of HIV infection

Local Infection

 Trafficking to the lymph node

Hematogenous dissemination

Immunodeficiency + Inflammation

Immunologic consequences of HIV infection: *Immunodeficiency*

![Graph](chart.png)

Coffin and Swanstrom, *Cold Spring Harbor Perspectives in Medicine*, 2013
CD4⁺ T cell depletion

- TB, HSV, Bacterial infections
- PCP
- Toxoplasmosis, Cryptococcosis
- CMV
- *Mycobacterium avium* Complex

Adapted from Wilcox and Saag, Gut, 2008
CD4⁺ T cell depletion...Not just in the blood

- Gut-associated lymphoid tissue is highly enriched for CD4⁺ T cells
- Up to 60% of CD4⁺ T cells are lost from the gut during acute infection

Brenchley J, et al., J Exp Med, 2004; Brenchley JM, Nature Med, 2006; Figure adapted from Mehandru, S., www.prn.org
CD4$^+$ T cell depletion...Not just in the blood

- This loss of cells leads to defective barrier function
  - Increased translocation of bacterial products
  - Increased systemic inflammation

Brenchley J, et al., J Exp Med, 2004; Brenchley JM, Nature Med, 2006; Figure adapted from Mehandru, S., www.prn.org
Inflammation is a driver of HIV pathogenesis

• Early in the epidemic, T cell activation was shown to be associated with disease progression:
  – ▲ CD8⁺ T cell activation ▲ Hazard ratio of 2 for disease progression
  – Supported by data from natural hosts of SIV
  – Contributes to immune dysfunction in untreated disease

Giorgi et al., JID, 1999; Deeks et al., Blood 2004; Hunt et al., JID 2003; Silvestri et al., Immunity, 2003
Inflammation is a driver of HIV pathogenesis

• Early in the epidemic, T cell activation was shown to be associated with disease progression:
  – ▲ CD8+ T cell activation ▲ Hazard ratio of 2 for disease progression
  – Supported by data from natural hosts of SIV
  – Contributes to immune dysfunction in untreated disease

Does inflammation resolve with initiation of antiretroviral therapy?

Giorgi et al., JID, 1999; Deeks et al., Blood 2004; Hunt et al., JID 2003; Silvestri et al., Immunity, 2003
Inflammation persists during antiretroviral therapy

Hunt et al., JID 2003; Hunt et al., PLoS One 2011
There are multiple drivers of inflammation in HIV

Deeks, Lewin, and Havlir, Lancet 2013
Inflammation and HIV-associated comorbid diseases

Which of the following comorbid conditions is associated with inflammation?

a) Cardiovascular disease
b) Cognitive dysfunction
c) Frailty
d) Metabolic diseases
e) All of the above

Peterson and Baker, Curr Opin Infect Dis, 2019.
Inflammation contributes to HIV-associated comorbid diseases

- Cardiovascular disease
- Cognitive dysfunction
- Frailty
- Bony disease
- Metabolic diseases

Clinical Challenges:

- Reducing residual inflammation in treated disease
- Quantifying risk for comorbidities

Peterson and Baker, Curr Opin Infect Dis, 2019; Triant et al., Circulation, 2018
Looking forward: *the frontiers of HIV pathogenesis*

- **HIV Cure**
  - Gene editing
  - Bone marrow transplantation strategies

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Looking forward: the frontiers of HIV pathogenesis

- HIV Cure
  - Latency reversal agents

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Looking forward: the frontiers of HIV pathogenesis

• HIV Cure
  – Latency reversal agents
  – Immune modulation:
    • Therapeutic vaccines
    • Broadly neutralizing antibodies

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Looking forward: the frontiers of HIV pathogenesis

- Reducing residual immune activation
  - Reducing excess risk from traditional risk factors
  - Biomarker discovery to risk stratify patients
  - Therapeutic interventions to reduce inflammation
  - Optimal therapeutic choices to minimize complications
Summary

• The life cycle of HIV identifies multiple points for intervention and highlights the challenges of inducing effective immunity
• HIV leads to depletion of CD4+ T cells with associated susceptibility to infections
• HIV leads to gut barrier disruption and increased translocation of microbial products
• HIV infection leads to T cell activation and innate immune activation which is associated with disease progression in untreated disease
• Despite ART and viral suppression there is residual immune activation that is linked to comorbidities
• Looking forward: novel interventions to achieve cure, ongoing work to identify biomarkers of inflammatory risk and to develop interventions to reduce inflammation
Thank you

- Peter Hunt, MD UCSF
- Conference organizers
- Bartlett Clinic Johns Hopkins University