HIV Pathogenesis
New insights

Charles Hicks, M.D
Professor of Medicine
University of California, San Diego
Learning Objectives

• Upon completion of this presentation, learners should be better able to:
  – Select appropriate antiretroviral therapy based on an understanding of HIV pathogenesis.
  – Initiate preventive therapy for opportunistic infections using data based on risk of OIs by CD4 count.

• There will be no off-label discussions in this presentation.
“The time has come to close the book on infectious diseases. We have basically wiped out infection in the United States.”
“Even without mutation, it is always possible that some hitherto obscure parasitic organism may escape its accustomed ecological niche and expose the dense human populations that have become so conspicuous a feature of the earth to some fresh and perhaps devastating mortality.”

- William H. McNeill

“Plagues and People”, 1976
Dengue Type 4 Infections in U.S. Travelers to the Caribbean

Dengue type 4 infections have been confirmed in 2 U.S. travelers who recently returned from St. Barthelemy, a small island in the French West Indies. These are the first documented cases of dengue type 4 ever reported in the Western Hemisphere.

On April 1, 1981, a Chicago resident had an acute febrile illness typical of classical dengue; symptoms included myalgia, headache, severe retro-orbital pain, and lower back pain. On April 4 he developed a diffuse rash over his torso. When acute- and convalescent-phase serum specimens collected on April 1 and April 14 were tested at CDC, there were diagnostic rises in hemagglutination-inhibition and complement-fixation titers to dengue type 4. The patient recovered completely after a few days.

When the laboratory diagnosis of dengue 4 was made in association with a travel history to the West Indies, the patient was contacted for additional information and a confirmatory serum specimen. This specimen also had dengue antibody titers similar to those of the convalescent-phase specimen.

The patient reported that he had traveled from Chicago to St. Barthelemy, stopping only for brief periods to change planes at the airports in San Juan, Puerto Rico, and St. Martin, West Indies. He stayed on St. Barthelemy from March 13 to March 27 and flew back to Chicago, again with only brief airport stops in St. Martin and San Juan. The patient stated that an outbreak of dengue was thought to be occurring on St. Barthelemy.

Serologic test results for other specimens from U.S. travelers that had recently been evaluated at CDC were reviewed to determine whether any other patients with a history of possible exposure in the Western Hemisphere had findings suggestive of dengue type 4 infection. Another patient, a Virginia resident who had traveled in the French West Indies, had an antibody pattern compatible with 1 or more previous dengue or other flavivirus infections. Results of tests of a second serum specimen obtained from the patient later in convalescence documented secondary dengue type 4 infection. The patient visited St. Barthelemy in April; he developed a typical dengue-like illness on April 17. The patient also recalled that residents of St. Barthelemy believed an outbreak of dengue was occurring.

The Pan American Health Organization and the Caribbean Epidemiology Center (CAREC) have been informed; they in turn have notified health officials throughout the Caribbean.

 Reported by R Merrick, MD, Illinois Masonic Medical Center, Chicago; KT Reddi, MD, Chicago Dept of Health; BJ Francis, MD, State Epidemiologist; Illinois State Dept of Public Health; RS Brown, MD, Gloucester, Va.; JM Owens, MD, GB Miller, Jr, MD, State Epidemiologist, Virginia State Dept of Health; Vector-Borne Diseases Div, Virology Div, San Juan Laboratories, Center for Infectious Diseases, CDC.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES / PUBLIC HEALTH SERVICE
Estimated AIDS Cases in the United States and Puerto Rico Cumulative through 1983  N = 4,793

Each Dot Represents 50 Cases

Note. Data have been adjusted for reporting delays. Data are presented for AIDS cases reported to CDC through June 2008. All data are provisional.
In 2010, in the U.S. and 5 U.S. dependent areas, the estimated cumulative number of AIDS diagnoses among adults and adolescents was 1,153,674. The estimated cumulative number of AIDS diagnoses ranged from two in American Samoa to 199,176 in New York.
Kunst Museum, Basel, Switzerland
Pathophysiology of HIV Infection
How many days on average does it take for HIV to pass from its original site of entry to being widely disseminated?

A. 5 days
B. 11 days
C. 21 days
D. 60 days
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

HIV at Surface of CD4 Lymphocyte
HIV impacts CD4 Cells in the GALT and mucosal tissues

Viral-host Dynamics

- About $10^{10}$ (10 billion) virions are produced daily.
- Each infected cell produces enough virus to infect 10 new cells (replicative rate of 10).
- Average life-span of an HIV virion in plasma is ~6 hours.
- Average life-span of an HIV-infected CD4 lymphocytes is ~1.6 days.
- Theoretically, ART that is >90% effective (which we have) should reduce the replicative rate to <1, thereby extinguishing infection.

Adapted from: Lederman, M et al. Immunopathogenesis of HIV Infection. HIV Insite Knowledge Base, Oct 2004
HIV Evasion Methods

- Makes 10 billion copies/day → rapid mutation of HIV antigens
- Integrates into host DNA
- Depletes CD4 lymphocytes
- Down-regulates MHC-I process
- Impairs Th1 response of CD4 helper T lymphocyte
- Infects cells in regions of the body where antibodies penetrate poorly, e.g., the central nervous system

Adapted from: Lederman, M et al. Immunopathogenesis of HIV Infection. HIV Insite Knowledge Base, Oct 2004
HIDE AND SEEK

1. HIV invades T cells and turns them into virus-producing factories

2. As long as those factories are operating, antiviral drugs can find the infected T cells and suppress production

3. But it turns out that some of those infected T cells—the so-called memory T cells—remain idle for years or even decades, providing a lingering source of renewed infection

Source: Time
B-Lymphocyte, Immune System, T-Killer, T-Helper, Suppressor
How long does HIV persist in cells in the setting of viral suppression in the blood?

A. 90 days
B. 6-8 months
C. 4-5 years
D. >50 years
HIV Persists despite suppressive therapy

Frequency of Latently Infected CD4+ T Cells as a Function of Time on HAART

- $t_{\frac{1}{2}} = 44.2$ months
- 73.4 years

- **Arm A**: RAL first (immediate intensification)
- **Arm B**: Placebo first (deferred intensification)
Activation and Elimination
Time Course of HIV Infection: Immunological and Virological Markers

- HIV Plasma Viral RNA (Determined by Quantitative Competitive - RNA PCR; RNA level exceed viral titers by an average of 60,000 - fold)
- HIV Plasma Viremia (Determined by quantitative endpoint dilution culture)
- CD4+ T Lymphocyte Count (cells per mm³)

Clinical Progression:
- Primary Infection
- Clinical Latency
- Possible Acute HIV Syndrome
- Wide Dissemination of Virus Seeding of Lymphoid Organs
- Opportunistic Diseases
- Constitutional Symptoms
- Death

Strategies to reduce and/or control HIV reservoirs

- Spontaneous or Induced Reversal of Latency
- Elimination of expressing cells
  - Stimulation and recruitment of immune effector cells
  - Targeted antibody or antibody-drug conjugate delivery
  - No Infection of CD4+T-cells

Modified from Romas Geleziunas et al.
How does HIV lead to T-cell depletion?

• The virus is **cytopathic** - leads to accelerated destruction of both mature CD4+ T cells and immature progenitor cells

• The virus is **antigenic** - triggers a chronic inflammatory response that facilitates viral replication and spread
Source: International AIDS Education Project
CVD: Why Is This a Problem?

• HIV- and ART-induced dyslipidemia
  – Persistently low HDL cholesterol
  – Poor response to statin and fibrate therapies
  – DDIs
  – Polypharmacy and pill burden

• Some ART may increase CV risk

• High rates of other risk factors, especially smoking

• Lipoatrophy and central adiposity

• Chronic immune activation and inflammation

HDL, high-density lipoprotein.
Rates of MI May Be Higher in HIV-Positive Patients

- Rates of AMI compared in HIV-positive and HIV-negative patients at 2 Boston hospitals
  - N of about 4000 for HIV-positive patients and about 1.0 million for HIV-negative patients
  - 8-year period from 1996 to 2004

- How much of this difference is medication related?

AMI, acute myocardial infarction; MI, myocardial infarction; RR, relative ratio.
Opportunistic Infections

MAJOR COMPLICATIONS IN THE COURSE OF HIV INFECTION

Kaposi’s Sarcoma

Lymphoma

400

Tuberculosis

Herpes zoster, thrush, HSV

CNS Disorders (HIV)

Bacterial infections, esophageal candidiasis

Wasting

Pneumocystosis

Toxoplasmosis

Atypical mycobacteriosis

CMV, cryptosporidiosis, microsporidiosis

PML

Source: International AIDS Education Project
Development of AIDS is like an impending train wreck

Viral Load = Speed of the train
CD4 count = Distance from cliff
Attempting to treat HIV infection based on our understanding of its pathogenesis
Entry of HIV into cells occurs by the virus attaching to what cell surface structures?

A. CD4 molecule only
B. CD8 molecule only
C. Chemokine co-receptor (CCR5 or CXCR4)
D. Both CD4 and a chemokine co-receptor
To enter a cell, HIV uses the CD4 receptor and a co-receptor, either CCR5 or CXCR4.
Integrated Approaches to HIV Treatment

- Reverse Transcriptase Inhibitors
- Protease Inhibitors
- Integrase Inhibitors
- Entry Inhibitors

Various PI, NRTIs, NNRTIs

- CCR5 antag
- T-20
- CXCR4

Particle assembly

Viral gag-pol protein cleavage

Translation

Viral RNA

RNA integration

nucleus

Cytosol

cDNA

Viral RNA

Reverse Transcription

Integrated Approaches to HIV Treatment
“Half of what we have taught you is wrong. Unfortunately, we do not know which half.”

– C. Sidney Burwell, M.D.
Address to the graduation class
Harvard Medical School