Immunodeficiencies

Part 2: HIV and AIDS

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Outline

- HIV
  - Antiretroviral therapy
  - History + life cycle
  - Causes + consequences
- Immunodeficiency
- AIDS
History of HIV

1st reports of acquired immunodeficiency in homosexual men

Origin of HIV epidemic

1980

1900
Worldwide spread of HIV
HIV attachment to host cells

Receptor: CD4
Co-receptor: CXCR4 or CCR5

HIV Lifecycle

1. **Fusion**
2. **Uncoating**
3. **Reverse transcription**
4. **Integration (strand transfer)**
5. **Transcription**
6. **Translation**
7. **Assembly**
8. **Budding**

**Key Components**:
- **Viral DNA**
- **Human Genomic DNA**
- **Viral RNA**
- **Protein chains**
- **Viral proteins**
Early events in HIV-infection

Figure 1
Phases of infection following exposure to human immunodeficiency virus (HIV). Infection begins with transmission across a mucosal barrier, either by a cell-free virus, infected cell, or virion attached to dendritic cells (DCs) or Langerhans cells (LCs). Early low-level propagation probably occurs in partially activated CD4+ T cells, followed by massive propagation in activated CD4+ T cells of the gut-associated lymphoid tissue lamina propria. Dissemination of HIV to other secondary lymphoid tissues and establishment of stable tissue viral reservoirs ensue. Immune response lags behind the burst of viremia and provides only partial control of viral replication. Adapted from Reference 5. Abbreviations: CTL, cytotoxic T lymphocyte; PD-1, programmed death 1.
Establishment of HIV latency

Siliciano et al, 2011
Effect of acute HIV infection on CD4+ T cell subsets

Acute HIV infection infects CCR5+ CD4+ T cells (mainly effector memory)

CD4+ T cell depletion in chronic infection

- Continuous infection in lymph nodes/mucosa
- Generation of new short-lived CD4+em
- Death of CD4+cm
- Destruction of lymph-node architecture

AIDS:
- CXCR4-tropic HIV infects naive and resting memory cells
- Critical loss of CD4+em and CD4+cm

Typical course of untreated HIV disease

- **Primary HIV Infection**
- **Asymptomatic**
- **Opportunistic infections/ AIDS, death**

Plasma HIV RNA (cp/ml)
CD4+ T cell count (/µl)

2-12 Weeks

2-14 years

1-6 years
Extreme courses of HIV disease

RAPID PROGRESSOR

Seroconversion

~5%

ELITE CONTROLLER

~1%
Unusual course of HIV disease: Non-progression despite high viremia

Viremic non-progressor

CD4 T cells/μl

HIV RNA (cp/ml)

0.1%

Rotger et al, Journal of Clinical Investigation, in press
Comparative AIDS Research:

HIV-1 humans
Viremic non progressors

SM & AGM

SIVmac Chinese RM s
SIVsmE660 RM s
SHIVsf162p3

SIVmac PTMs

HIV-1 humans
„usual progressors“

HIV-2 humans

HIV-1 humans
elite controllers

Silvestri et al, CROI 2010
Non-pathogenic vs pathogenic SIV/HIV disease

Non-pathogenic  Pathogenic

- AIDS  No  YES
- CD4 T cell depletion  No  YES
- Viral load  High  High
- CCR5 expression on T cells upon activation  No  Yes
- Microbial translocation  No  Yes
- IMMUNE ACTIVATION  No  Yes
HIV-associated damage to the GI-tract fuels immune activation.
Pathogenic vs non-pathogenic HIV/SIV disease

Pathogenic: (most) humans, macaques

Non-pathogenic: Sooty mangabey

Immune activation
- increased proliferation and activation of T cells
- increased susceptibility to apoptosis
- high levels of proinflammatory cytokines and chemokines
- high levels of interferon-stimulated genes

Immune activation and HIV

- CD4 depletion enteropathy
- Reduced delivery
- Microbial translocation
- Depletion of CD4+ T cells (T-em and T-cm) fibrosis of lymph nodes
- Immune activation cytokine switch

Adapted from Douek et al. Annu Rev Med 2009
Mechanisms of CD4+ T cell depletion: not only the virus!

<table>
<thead>
<tr>
<th>Destruction of CD4+ T cells</th>
<th>Impaired CD4+ T-cell production</th>
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<tbody>
<tr>
<td>Direct destruction of infected cells (&lt;1%!!)</td>
<td>Direct effects of virus</td>
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<tr>
<td>- Virus (envelope, Vpr) mediated apoptosis</td>
<td>- Infection-mediated death of progenitor cells</td>
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<td>- Disruption of cell membranes</td>
<td>- Destruction of stromal network for haematopoiesis</td>
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<td>Indirect induction of death in uninfected cells</td>
<td>Indirect effects</td>
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<td>- Cytolysis by HIV-specific cytolytic T cells/NK cells</td>
<td>- Cytokine dysfunction</td>
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<td>- Triggering of apoptosis upon immune activation</td>
<td>- Opportunistic infections of bone marrow</td>
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<td>- Apoptosis following interaction with antigen-presenting cell</td>
<td>- Infiltrating malignancies</td>
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<td>- Myelotoxic drugs</td>
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Dysbiosis of the Gut Microbiota Is Associated with HIV Disease Progression and Tryptophan Catabolism

Ivan Vujkovic-Cvijin et al.
Sci Transl Med 5, 193ra91 (2013);
DOI: 10.1126/scitranslmed.3006438

Fig. 1. Gut bacterial microbiota composition in HIV-infected subjects differs from that of HIV-uninfected risk-matched control subjects.

Genera in HIV untreated subjects:
- Neg. correlation with gut-barrier enhancing cytokines
- Pos. correlation with T cell activation cytokines
# CD8-T cell exhaustion

Adapted from Freeman et al, J Exp Med 2006

<table>
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<tr>
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<th>IFN-γ</th>
<th>TNF-α</th>
<th>IL-2</th>
<th>CTL</th>
<th>Proliferative Potential</th>
<th>Antigen Load</th>
<th>CD4 Help</th>
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<tr>
<td>Functional T cell</td>
<td>+++</td>
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<td>++</td>
<td>+++</td>
<td>Low</td>
<td>High</td>
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<td>Partial Exhaustion I</td>
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<td>+/-</td>
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<td>Low</td>
<td>High</td>
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<td>Partial Exhaustion II</td>
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<td>-</td>
<td>+</td>
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<td>Full Exhaustion</td>
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<td>Low</td>
<td>Low</td>
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<td>Deletion</td>
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Consequences of HIV-induced immunodeficiency

- **Primary HIV Infection**
  - 2-12 Weeks
  - Plasma HIV RNA (cp/ml)
    - Maximal peak
- **Asymptomatic**
  - 2-14 years
  - CD4+ T cell count (/µl)
  - Stable count
- **Opportunistic infections/ AIDS, death**
  - 1-6 years
    - Declining count

Plasma HIV RNA (cp/ml)
CD4+ T cell count (/µl)
CD4 T\(^+\) cells: At the center of immune defense

Fauci et al, Harrison's Principles of Internal Medicine, 17th edition
HIV Drugs

HIV Lifecycle And Existing Drug Targets

- **Fusion inhibitors**
- **Reverse transcriptase inhibitors**
- **RT inhibitors**
- **Protease inhibitors**
- **Integrase inhibitors**
- **Integrase inhibitors**

**HIV Drugs**

**Fusion**

**Uncoating**

**Assembly**

**Budding**

**Transcription**

**Translation**

**3'-processing**

**Integration (strand transfer)**

**Pre-Integration Complex**

**Viral DNA**

**Viral RNA**

**Protein chains**

**Viral proteins**

**Viral DNA**

**RNA**

**Human Genomic DNA**

**Nucleus**

- **CCR5 inhibitors**
- **Integrase inhibitors**
- **Viral DNA**
Indications for ART 2017

- Pregnancy
- Post-exposure prophylaxis
- Acute HIV-Infektion
- ART irrespective of CD4 T cell count
Effect of antiretroviral therapy

Plasma HIV RNA (cp/ml)
CD4+ T cell count (/µl)
Successful cART is associated with increases in CD4⁺ T-cell responses to HCV and CMV.
New opportunistic infections

In incidence per 100 py

Median CD4 T cell increase

Months post ART

Median CD4 T cell increase
Persistent, Albeit Reduced, Chronic Inflammation in Persons Starting Antiretroviral Therapy in Acute HIV Infection


Panel A: CRP levels in HIV-negative, 4thG1, 4thG2, 4thG3, and Chronic Untreated groups. Median CRP levels are 0.26, 0.81, 3.15, 1.37, and 1.94, respectively.

Panel B: sCD14 levels in HIV-negative, 4thG1, 4thG2, 4thG3, and Chronic Untreated groups. Median sCD14 levels are 0.79, 1.20, 1.64, 1.57, and 1.51, respectively.

Panel C: D-Dimer levels in HIV-negative, 4thG1, 4thG2, 4thG3, and Chronic Untreated groups. Median D-Dimer levels are 0.17, 0.17, 0.28, 0.33, and 0.47, respectively.

Panel D: sCD14 levels over time on ART, with significant differences indicated by "P < .005" for 4thG1 and 4thG3 compared to 4thG2.

Panel E: CRP levels over time on ART, with significant differences indicated by "P < .001" for 4thG1 compared to 4thG2.

Panel F: D-Dimer levels over time on ART, with significant differences indicated by "P < .001" for 4thG1 compared to 4thG2.
Early ART reduces viral reservoir

Strain et al, JID, 2005
Schmid et al, Plos One, 2010

…but cure is still not (yet) achievable (with very few exceptions)

H. Günthard, CROI 2018

Very slow decay of the latent reservoir

The viral outgrowth assay measures
$t_{1/2} = 44$ months

It would take 60 years to eradicate a low reservoir estimate of $10^5$ cells!

Siliciano et al, Nature Medicine, 2003
Broadly neutralizing antibodies did not prevent viral rebound after ART interruption
Strategies for reducing the latent reservoir

- Early ART
- Shock and kill
- Therapeutic vaccine
- bNabs with effector functions
- Immune modulation
  - ICB-Ab
  - DART
  - IFNs
- Direct targeting of HIV infected cells

Size of latent HIV-1 Reservoir

H. Günthard, CROI 2018
Shock and kill strategy

IRIS
Immune reconstitution inflammatory syndrome

“Unmasking “ of subclinical infections due to restored immune responses

Subclinical/silent infection  IRIS

Antiretroviral Combination Therapy

CD4

Therapy OI
Decrease in death rate in Switzerland since introduction of highly active antiretroviral therapy (HAART)
Life expectancy in HIV-positive individuals and in the general population in Switzerland

A. Gueler et al, and M. Egger for the Swiss HIV Cohort Study and Swiss National Cohort
Changing causes of death in the SHCS

Ruppik et al, CROI 2011
Summary

- HIV
- Immunodeficiency
- AIDS

- Not only due to direct viral effects
- A highly adaptable pathogen
- A preventable disease

Antiretroviral therapy