Immunodeficiencies

Part 2: HIV and AIDS

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Outline

- HIV
  - Immune deficiency
    - Causes + consequences
    - Antiretroviral therapy
  - History + life cycle
  - AIDS

Diagram:

- HIV
  - Immunodeficiency
    - Antiretroviral therapy
  - AIDS

Legend:
- HIV
- Immunodeficiency
- Antiretroviral therapy
- AIDS
Origin of HIV epidemic

1980
1st reports of acquired immunodeficiency in homosexual men

1900
Origin of HIV epidemic
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. Viral DNA
5. 3'-processing
6. Pre-Integration Complex
7. Integration (strand transfer)
8. Nucleus
9. Human Genomic DNA
10. Transcription
11. Viral RNA
12. Translation
13. Protein chains
14. Viral proteins
15. Assembly
16. Budding
17. Viral DNA
18. RNA
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) and CD4+ T cell count (/µl)

2-12 Weeks

2-14 years

1-6 years
Extreme courses of HIV disease

RAPID PROGRESSOR

- Seroconversion
- CD4 T cells/µl: ~5%

ELITE CONTROLLER

- HIV RNA (cp/ml): ~1%
Unusual course of HIV disease: Non-progression despite high viremia

Viremic non-progressor

Rotger et al, Journal of Clinical Investigation, in press
Non-pathogenic vs pathogenic SIV/HIV disease

<table>
<thead>
<tr>
<th></th>
<th>Non-pathogenic</th>
<th>Pathogenic</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>No</td>
<td>YES</td>
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<tr>
<td>CD4 T cell depletion</td>
<td>No</td>
<td>YES</td>
</tr>
<tr>
<td>Viral load</td>
<td>High</td>
<td>High</td>
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<tr>
<td>CCR5 expression on T cells upon activation</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Microbial translocation</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>IMMUNE ACTIVATION</td>
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</table>
HIV-associated damage to the GI-tract fuels immune activation

Healthy

HIV-pos

Bacterial translocation

Immune activation
Pathogenic vs non-pathogenic HIV/SIV disease

Pathogenic: (most) humans, macaques
Non-pathogenic: Sooty mangabeys

Plasma HIV RNA (cp/ml)
CD4 -cells (/µl)

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

Depletion of CD4+T cells (T-em and T-cm) fibrosis of lymph nodes

Reduced delivery

CD4 depletion enteropathy

Microbial translocation

Immune activation cytokine switch

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

## Destruction of CD4$^+$ T cells

- **Direct destruction of infected cells (<1%!!):**
  - Virus (envelope, Vpr) mediated apoptosis
  - Disruption of cell membranes

- **Indirect induction of death in uninfected cells:**
  - Cytolysis by HIV-specific cytolytic T cells/NK cells
  - Triggering of apoptosis upon **immune activation**
  - Apoptosis following interaction with antigen-presenting cell

## Impaired CD4$^+$ T-cell production

- **Direct effects of virus:**
  - Infection-mediated death of progenitor cells
  - Destruction of stromal network for haematopoiesis

- **Indirect effects:**
  - Cytokine dysfunction
  - Opportunistic infections of bone marrow
  - Infiltrating malignancies
  - Myelotoxic drugs

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Adapted from McCune, Nature 2001
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>
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<td>Functional T cell</td>
<td>+++</td>
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<td>Partial Exhaustion I</td>
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<tr>
<td>Deletion</td>
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HIV
Consequences of HIV-induced immunodeficiency

Primary HIV Infection

Asymptomatic

Opportunistic infections/AIDS, death

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
Moderate Immunodeficiency

- Lymphadenopathy
- Thrombopenia
- Oral hairy leukoplakia
- Herpes zoster
- Oral thrush
- Cervical dysplasia
- Cervical carcinoma
- Rezid. bact. pneumonia
- Tuberculosis
- Kaposi-Sarcoma

Severe Immunodeficiency

- Candida esophagitis
- Pneumocystis jiroveci pneumonia
- Malignant Lymphoma
- Persist. ulcerous *H.simples*
- Cytomegalovirus retinitis
- Cryptosporidiosis
- HIV-encephalopathy
- progressive multifocal leukencephalopathy
- Histoplasmosis

Very Severe Immunodeficiency

- Cerebral toxoplasmosis
- Cryptococcosis
- Disseminated *M.avium* infection
- Diss. *M.genavense* Infection

Opportunistic Diseases and CD4 lymphocyte count

- CD4/μl
  - 500
  - 200
  - 100
HIV Lifecycle And Existing Drug Targets

**HIV Drugs**

- Fusion inhibitors
- RT inhibitors
- CCR5 inhibitors
- Integrase inhibitors
- Protease inhibitors

HIV entry:
- Fusion
- Uncoating

HIV reverse transcription:
- Reverse transcription

HIV integration:
- Integration (strand transfer)

HIV transcription:
- Viral RNA
- Translation

HIV assembly:
- Protein chains
- Viral proteins

HIV replication:
- Viral DNA
- Transcription
- Integration complex

HIV maturation:
- Budding

HIV viral components:
- Human Genomic DNA
- Viral DNA
- RNA

HIV reverse transcription components:
- Viral RNA
- Protein chains
Indications for ART 2019

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

CD4 levels over time:
- Viremia

CD4 levels:
- 700
- 500
- 200
Effect of antiretroviral therapy

Primary HIV Infection

Asymptomatic

ART

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

2-12 Weeks

2-14 years
Successful cART is associated with increases in CD4+ T-cell responses to HCV and CMV

Rohrbach et al, GUT 2011
New opportunistic infections

Inzidence per 100 py

Median CD4 T cell increase

Months post ART

-6 0 3 6 9 12 15

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200
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)

Very slow decay of the latent reservoir

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

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

Siliciano et al, Nature Medicine, 2003

H. Günthard, CROI 2018
Broadly neutralizing antibodies did not prevent viral rebound after ART interruption.
The search for the best HIV antibodies

Induction of almost identical bnAbs in two patients with fully different genetic background

40 virus panel

Kouyos, Rusert & Kadelka et al., Nature 2018
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

Latently infected CD4+ T cell

Host genome
Integrated HIV-1 genome

LRA
Gp120
HIV-1 proteins

Presentation of HIV-1 peptides
MHC I
HIV-1 mRNA

Transcriptionally active HIV-1-infected cell

“Shock”

Transcription initiation

“Kill”

Dying infected CD4+ T cell

Immune system
Cytopathic effects

Dying infected CD4+ T cell

HDAC inhibitors
PKC agonists
TLR agonists ...

Uninfected CD4+ T cell

HIV remission (cure?): A very rare event

CCR5d32hom!
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**
  - A highly adaptable pathogen
  - Not only due to direct viral effects
  - A preventable disease

- **Antiretroviral therapy**
- **Immunodeficiency**