Immunodeficiencies

Part 2: HIV and AIDS

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Andri Rauch
Universitätsklinik für Infektiologie
Inselspital PKT2B – 3010 Bern
andri.rauch@insel.ch
Outline

HIV

History + life cycle

Causes + consequences

Antiretroviral therapy

Immunodeficiency

AIDS
Origin of HIV epidemic

1st reports of acquired immunodeficiency in homosexual men

1900

Origin of HIV epidemic

1980

1st reports of acquired immunodeficiency in homosexual men
Worldwide spread of HIV

Adult prevalence %

- 15.0 – 34.0%
- 5.0 – <15.0%
- 1.0 – <5.0%
- 0.5 – <1.0%
- 0.1 – <0.5%
- <0.1%
HIV attachment to host cells

Receptor: CD4
Co-receptor: CXCR4 or CCR5

HIV Lifecycle

1. **Fusion**
2. **Reverse transcription**
3. **3’-processing**
4. **Integration (strand transfer)**
5. **Pre-Integration Complex**
6. **Uncoating**
7. **Assembly**
8. **Viral RNA**
9. **Viral proteins**
10. **Protein chains**
11. **Translation**
12. **Transcription**
13. **Viral DNA**
14. **RNA**
15. **Viral DNA**
16. **Human Genomic DNA**
17. **Nucleus**
Early events in HIV-infection

Day 0

- Infected donor cell
- HIV virion
- Langerhans cell
- Epithelial cell
- Endocytic compartment
- Resting memory T cell
- Activated memory T cell
- Stromal DC
- Lymphatic vessel
- Venule
- Macrophage
- Monocytic precursor cell

Day 3

- Transport to regional lymphnodes
- Entry into blood stream
- Widespread dissemination (Brain, Spleen, Gut, Lymph Nodes...)

Hladik et al, Nat Rev Immunol 2008
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**

2-12 Weeks

**Asymptomatic**

2-14 years

**Opportunistic infections/ AIDS, death**

1-6 years

Plasma HIV RNA (cp/ml)

CD4+ T cell count (/μl)
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

Rotger et al, Journal of Clinical Investigation, in press
What determines HIV-disease progression?

* „Usual“ PROGRESSOR*
* RAPID PROGRESSOR*
* ELITE CONTROLLER*
* VIREMIC NON-PROGRESSOR*
Comparative AIDS Research:

HIV-1 humans
Viremic non progressors

HIV-2 humans

HIV-1 humans
„usual progressors“

HIV-1 humans
elite controllers

Silvestri et al, CROI 2010
### Non-pathogenic vs Pathogenic SIV/HIV Disease

<table>
<thead>
<tr>
<th></th>
<th>Non-pathogenic</th>
<th>Pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>No</td>
<td>YES</td>
</tr>
<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>
</tr>
<tr>
<td>CCR5 expression on T cells upon activation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Microbial translocation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>IMMUNE ACTIVATION</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</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

- 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
When Immune Activation Turns To The Dark Side

<table>
<thead>
<tr>
<th>Good</th>
<th>Bad</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anti-viral innate immune response</td>
<td>• Target cell generation</td>
</tr>
<tr>
<td>• Restoration of memory CD4 T cells</td>
<td>• HIV replication</td>
</tr>
<tr>
<td></td>
<td>• Thymic dysfunction</td>
</tr>
<tr>
<td></td>
<td>• T and B cell exhaustion</td>
</tr>
<tr>
<td></td>
<td>• Macrophage/DC activation</td>
</tr>
<tr>
<td></td>
<td>• Cytokine/Chemokine secretion</td>
</tr>
<tr>
<td></td>
<td>• Lymph node fibrosis</td>
</tr>
<tr>
<td></td>
<td>• Generalized tissue fibrosis</td>
</tr>
<tr>
<td></td>
<td>• Coagulation cascade activation</td>
</tr>
<tr>
<td></td>
<td>• … … …</td>
</tr>
</tbody>
</table>

Adapted from D. Douek
Markers of inflammation and gut barrier dysfunction predict mortality independently of CD4 count and virus load.
Persistent, Albeit Reduced, Chronic Inflammation in Persons Starting Antiretroviral Therapy in Acute HIV Infection

Irini Sereti,1 Shelly J. Krebs,3,4 Nittaya Phanuphak,9 James L. Fletcher,9 Bonnie Slika,3,4 Sutheeraporn Pinyakorn,3,4 Robert J. O’Connell,3,4 Adam Rupert,5 Nicolas Chomont,10 Victor Valcour,9 Jerome H. Kim,3,4,9 Merlin L. Robb,3,4 Nelson L. Michael,3,4 Daniel C. Douek,6 Jintanat Ananworanich,3,4,11 and Netanya S. Utay7,2; for the RV054/SEARCH 010, RV304/SEARCH 013 and SEARCH 011 protocol teams
# 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
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 controls.

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

<table>
<thead>
<tr>
<th>Condition</th>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Functional T cell</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Partial Exhaustion I</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Partial Exhaustion II</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Full Exhaustion</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Deletion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

HIV

Adapted from Freeman et al, J Exp Med 2006
Consequences of HIV-induced immunodeficiency

- **Primary HIV Infection**: 600 to 10^6
- **Asymptomatic**: 200 to 10^4
- **Opportunistic infections/AIDS, death**: 1-6 years

- **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
Opportunistic Diseases and CD4 lymphocyte count

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

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

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

CD4/μl
- 500
- 200
- 100

Moderate Immunodeficiency

Immunodeficiency
Prophylaxis and maintenance treatment

PCP – Toxo- primary prophylaxis

MAC prophylaxis

Secondary prophylaxis = maintenance TTT

Secondary prophylaxis

Secondary prophylaxis

Secondary prophylaxis

Secondary prophylaxis

CD4/µl
HIV Lifecycle And Existing Drug Targets

**HIV Drugs**

- **Fusion** inhibitors
- **Reverse transcription** inhibitors
- **Uncoating** inhibitors
- **Protease inhibitors**
- **Integrase inhibitors**

**Key Steps**

1. **Fusion**
2. **Uncoating**
3. **Uncoating**
4. **RT inhibitors**
5. **3’-processing**
6. **Pre-Integration Complex**
7. **Integration (strand transfer)**
8. **Nucleus**
9. **Assembly**
10. **Budding**
11. **Translation**
12. **Viral proteins**
13. **Protein chains**
14. **Viral RNA**
15. **Human Genomic DNA**
16. **Viral DNA**
17. **RNA**
18. **3’-processing**
19. **Integrase Inhibitors**
20. **CCR5 inhibitors**

**Viral DNA**

**RNA**
Traditional indications for ART

- Pregnancy
- Post-exposure prophylaxis
- Acute HIV Infektion
- Progressive immunodeficiency:
  - Symptomatic Infection
  - CD4 cut-off (350 or higher?)

Graph showing CD4 levels over time with lines indicating different states such as viremia and progressive immunodeficiency.
START: Strategic Timing of AntiRetroviral Treatment Trial

Study Design and Baseline Characteristics

START is an international randomized trial comparing immediate ART (CD4 >500 cells/µL) versus deferred ART (CD4 <350 cells/µL)

- Primary endpoint is the development of a serious AIDS event, a serious non-AIDS event (CVD, ESRD, decompensated liver disease, non-AIDS cancer), or death from any cause

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=4685</th>
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<tbody>
<tr>
<td>Age (yr)*</td>
<td>36 (29, 44)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1257 (27)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2086 (45)</td>
</tr>
<tr>
<td>Black</td>
<td>1410 (30)</td>
</tr>
<tr>
<td>Time since HIV diagnosis (yr)*</td>
<td>1.0 (0.4, 3.1)</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)*</td>
<td>651 (584-765)</td>
</tr>
<tr>
<td>Baseline HIV-RNA (copies/mL)*</td>
<td>12,759 (3019-43,391)</td>
</tr>
<tr>
<td>TDF Usage</td>
<td>89% in both groups</td>
</tr>
</tbody>
</table>

* Median (IQR)

- On May 15, 2015 at a planned interim review, the international Data & Safety Monitoring Board recommended that participants in the deferred arm who were not already on ART should be offered ART and follow-up should continue with all subjects on therapy
Primary Results: combined outcome

<table>
<thead>
<tr>
<th></th>
<th>Immediate ART</th>
<th>Deferred ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with Event (%)</td>
<td>42 (1.8%)</td>
<td>96 (4.1%)</td>
</tr>
<tr>
<td>Rate/100PY</td>
<td>0.60</td>
<td>1.38</td>
</tr>
<tr>
<td>HR (Imm/Def)</td>
<td>0.43 (95% CI: 0.30 to 0.62, p&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

“Combination antiretroviral therapy (ART) should be recommended for all HIV-positive persons regardless of CD4+ count.”
“Combination antiretroviral therapy (ART) should be recommended for all HIV-positive persons regardless of CD4+ count.”
**Primary Results: serious non-AIDS events**

<table>
<thead>
<tr>
<th></th>
<th>Immediate ART</th>
<th>Deferred ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with Event (%)</td>
<td>29</td>
<td>47</td>
</tr>
<tr>
<td>Rate/100PY</td>
<td>0.42</td>
<td>0.67</td>
</tr>
<tr>
<td>HR (Imm/Def)</td>
<td>0.61 (95% CI: 0.38 to 0.97, p=0.04)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Immediate</th>
<th>Deferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>CVD</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Liver/renal</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Deaths (other)</td>
<td>7</td>
<td>13</td>
</tr>
</tbody>
</table>

“Combination antiretroviral therapy (ART) should be recommended for all HIV-positive persons regardless of CD4+ count.”

Lundgren D, et al. IAS 2015. Vancouver, CAN. Oral # MOSY03
Pregnancy

Post-exposure prophylaxis

Acute HIV-Infection

ART irrespective of CD4 T cell count

Indications for ART 2017

CD4

Viremia

t
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

Inzidence per 100 py

Median CD4 T cell increase

Months post ART
IRIS
Immune reconstitution inflammatory syndrome

“Unmasking” of subclinical infections due to restored immune responses

Subclinical/silent infection  IRIS

Antiretroviral Combination Therapy
Decrease in death rate in Switzerland since introduction of highly active antiretroviral therapy (HAART)

BAG Bull 2010

Men
Women

Antiretroviral therapy
Life expectancy in HIV-positive individuals and in the general population in Switzerland
Changing causes of death in the SHCS

Ruppik et al, CROI 2011
Summary

- HIV: A highly adaptable pathogen
- Immunodeficiency: Not only due to direct viral effects
- AIDS: A preventable disease
- Antiretroviral therapy