HIV / AIDS Pathogenesis 2

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VA North Texas Health Care System UT Southwestern Medical Center
Objectives

- Characterize HIV-1 (classification, structure and life cycle)
- Describe the clinical course and immunopathology of untreated HIV infection
- Describe the clinical course and immunopathology of treated HIV infection
- Explain the principles of antiretroviral therapy
Outline

- HIV-1 Virology
  - Classification / Structure / Life Cycle
- Natural History of untreated HIV-1 Infection
  - Acute and Chronic HIV Infection
  - Factors modifying disease progression
- Natural History of treated HIV-1 Infection
  - Scope of Immune Reconstitution & Activation
  - HIV-associated non-AIDS morbidity (HANA)
- Antiretroviral Therapy
  - Principles / Objectives
  - HIV Reservoirs and Kinetics on HAART
  - Obstacles to Cure
What is the goal of HAART?

- 1988 – mid 90s:
  - Prolong life

- Late 90s – mid 2000s:
  - Restore immune system
  - Prevent AIDS durably by preventing resistance

- Since mid 2000s:
  - Avoid toxicities
  - Avoid non-AIDS events (SMART study 2006)
  - Restore / maintain quality of life
  - Achieve normal life expectancy

- Since 2010s:
  - Reduce transmissions
What is not (yet) the goal of HAART?

- Eradication
- Functional Cure
What does HAART achieve?

- Protection of (most?) activated lymphocytes from infection
- Shut down of intra-individual viral evolution:
  - gag and env genes (no new “immune-escape” mutations)
  - pol gene no new ARV mutations
- “Immune Reconstitution” (to a significant degree)
What doesn’t (long-term) HAART achieve?

- Normalization of peripheral CD8 counts and activation
- Normalization of peripheral CD4 counts
  - if started too late
  - if (?)
- Normalization of tissue (e.g. GALT) immune activation
- Normalization of life-expectancy (unproven)
HAART Does Not Fully Restore Life Expectancy

Life expectancy at age 33.0 years

Estimated life lost with current standard of care: 11.92 years

N=8,091, mult. US cohorts

HAART Does Not Fully Restore Life Expectancy

- US veterans with HIV - No cohort – real patients - no censoring

3 year Risk of AIDS off and on HAART

CD4s don’t predict OIs well on HAART

J Infect Diseases 2011;203:364-71
"Non AIDS" Deaths More Common

<table>
<thead>
<tr>
<th>Source</th>
<th>Non AIDS</th>
<th>Leading Causes</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>NY Death Certificates</td>
<td>26%</td>
<td>Alcohol/drug abuse (31%), CVD (24%), Cancer (21%)</td>
<td>Ann Int Med 2006;145:397-406</td>
</tr>
<tr>
<td>Barcelona Death Certificates</td>
<td>60%</td>
<td>Liver (23%), Infection (14%), Cancer (11%), CVD (6%)</td>
<td>HIV Med 2007;8:251-8</td>
</tr>
<tr>
<td>HOPS Chart Rev.</td>
<td>63%</td>
<td>Liver (18%), CVD (18%), Pulmonary (16%), Renal (12%), GI (11%), Infection (10%), Cancer (8%)</td>
<td>JAIDS 2006;43:27-34</td>
</tr>
<tr>
<td>Cascade Chart Rev.</td>
<td>63%</td>
<td>Liver (20%), Infections (24%), Unintentional (33%), Cancer (10%), CVD (9%)</td>
<td>AIDS 2006;20:741-9</td>
</tr>
</tbody>
</table>
## Risk of death after experiencing an AIDS or serious non-AIDS event during SMART or ESPRIT

<table>
<thead>
<tr>
<th>Nonfatal event</th>
<th>No. with event</th>
<th>No. (%) of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>286</td>
<td>47 (16.4)</td>
</tr>
<tr>
<td>Serious AIDS(^a)</td>
<td>78</td>
<td>29 (37.2)</td>
</tr>
<tr>
<td>All other AIDS(^b)</td>
<td>221</td>
<td>25 (11.3)</td>
</tr>
<tr>
<td>Serious non-AIDS</td>
<td>435</td>
<td>115 (26.4)</td>
</tr>
<tr>
<td>CVD</td>
<td>208</td>
<td>24 (11.5)</td>
</tr>
<tr>
<td>MI</td>
<td>93</td>
<td>7 (7.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>40</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td>CAD</td>
<td>133</td>
<td>11 (8.3)</td>
</tr>
<tr>
<td>Renal</td>
<td>14</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>26</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Malignancies(^c)</td>
<td>207</td>
<td>77 (37.2)</td>
</tr>
<tr>
<td>Lung</td>
<td>44</td>
<td>30 (68.2)</td>
</tr>
<tr>
<td>Prostate(^d)</td>
<td>25</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Anal</td>
<td>29</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>AIDS or serious non-AIDS</td>
<td>696</td>
<td>154 (22.1)</td>
</tr>
</tbody>
</table>

*AIDS 2010;24:697-706*
Non-AIDS mortality dominates on long-term HAART

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients</th>
<th>Hazard ratio (95% CI) per 100 cells/µL CD4 rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>227</td>
<td>0.49 (0.42 - 0.56) Univariate, 0.56 (0.49 - 0.63) Multivariate</td>
</tr>
<tr>
<td>Non-AIDS</td>
<td>80</td>
<td>0.81 (0.73 - 0.90) Univariate, 0.86 (0.78 - 0.94) Multivariate</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>188</td>
<td>0.63 (0.56 - 0.70) Univariate, 0.65 (0.58 - 0.73) Multivariate</td>
</tr>
<tr>
<td>AIDS, non-AIDS or death</td>
<td>335</td>
<td>0.64 (0.57 - 0.72) Univariate, 0.70 (0.62 - 0.78) Multivariate</td>
</tr>
</tbody>
</table>
Immune Reconstitution

- Initial rapid increase in CD4+ T cells
  - mostly memory CD4+ T cells, skewed TCR repertoire
  - likely to reflect redistribution of memory CD4+ cells
  - cannot replace lost T cell specificities
- Followed by slow steady rise in CD4+ T cells
  - naïve CD4+ T cells
  - derived from the thymus (?)
  - can eventually replace lost T cell specificities
  - Plateau phase reached after 2-12 years
- CD8 cells remain elevated (+ 1 SD > normal) even after 15 y of suppressive HAART
Positive Predictors for Immune Reconstitution on ART

- High Nadir CD4 count
- High Viral Load
- Younger Age
- Shorter Duration of HIV Infection
- Few or no treatment interruptions
- No chronic viral hepatitis B or C, no diss. MAC

Clinical Correlates of Immune Reconstitution on ART

- Return of pathogen-specific immunity
- Prophylactic therapy for opportunistic pathogens can safely be stopped
- Long-term recovery of immunity is possible
Immune Reconstitution

*Inflammatory Syndrome* (IRIS)

- Occurs in 10-25% of patients starting HAART
- Case definition
  - Documented response to anti-retroviral therapy
  - Clinical deterioration of an infectious or inflammatory condition temporally related to ART initiation.
  - Symptoms cannot otherwise be explained
- Important pathogens: Mycobacteria, Cryptococci, CMV
  - Sometimes life threatening: TB meningitis
- Not important pathogens: P.jiroveci, Toxoplasma gondii
- Treatment: Reassurance, Steroids

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1 INSHI Case Definition

Drechsler, Battegay Current Opinion in HIV and AIDS 2006, 1:56–61
Immune activation in peripheral blood CD8+ T-cells after 8 years of HAART

CD38+ HLA-DR+ CD4 T cells

% CD38+HLA-DR+ CD4 T cells

- **start HAART**
- 1 year HAART
- long-term HAART
- control

- < 200 baseline CD4
- > 200 baseline CD4

J Immunol 2008;181:1573-1581
CD4-cells in sigmoid submucosa

N=23 Mean Baseline CD4 count = 183

$r^2 = 0.7, p = 0.02$

Mucosal Immunol 2008;1:382-88
p24 in Lymph Node biopsies

before HAART

aviremic after 2 years of HAART

Infection 32 2008 No. 2
Immune Reconstitution in US veterans

\[ n=6,372, \text{BL VL}>1000, \text{HAART naïve at BL}, \text{HAART adherence always} \geq 80\% \]
Not everybody’s immune system is equal…

n=6,372, BL VL>1000, HAART naïve at BL, HAART adherence always≥80%
Mortality Risk Factor: “Normal” CD4

CD4 Stratum reached
- <250
- 250-389
- 390-529
- 530-719
- ≥720

Mortality in Percent

Years

n=14,800, US Veterans, VL suppressed

Drechsler JIAPAC 2014; 13(2)
# Mortality Risk Factor: “Normal” CD4

Annual CD4 average reached

<table>
<thead>
<tr>
<th>CD4 Range</th>
<th>Univariate Model</th>
<th>Multivariate Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥720 cells/µL (=ref)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>530-719 cells/µL</td>
<td>&lt;0.001</td>
<td>1.48 (1.19-1.85)</td>
</tr>
<tr>
<td>390-529 cells/µL</td>
<td>&lt;0.001</td>
<td>1.6 (1.29-2)</td>
</tr>
<tr>
<td>250-389 cells/µL</td>
<td>&lt;0.001</td>
<td>2 (1.62-2.48)</td>
</tr>
<tr>
<td>&lt;250 cells/µL</td>
<td>&lt;0.001</td>
<td>3.26 (2.64-4.02)</td>
</tr>
</tbody>
</table>

Drechsler JIAPAC 2014; 13(2)  

n=14,800, US Veterans, VL suppressed
HIV-associated non-AIDS events

May be related to immune activation and/or persistent subclinical immune deficiency

- Cardiovascular Disease / Dyslipidemia
- Non-AIDS defining cancers
- Liver fibrosis
- CKD
- Osteoporosis
- Cognitive Dysfunction
- Non-AIDS related infections
How can HIV induce atherosclerosis? Through Inflammation and activation of macrophages.
HAART and dyslipidemia

Cardiovascular risk factors in HIV-positive patients and the impact of protease inhibitors

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² Abteilung für Endokrinologie, Universitätsspital Zürich

My 1st poster (Swiss ID society 1998…)

Graph showing non-HDL-Cholesterol levels with a p-value of <0.01 and a threshold of 160 mg/dL.
Data Collection on Adverse Events of Antiretroviral Drugs

![Graph showing adjusted relative rates for protease inhibitors and nonnucleoside reverse-transcriptase inhibitors versus exposure (yr).]
MACS Cohort: Lipids Before and After HIV Infection

Correlation of highest TC value before HIV seroconversion and highest TC value after HAART (and before AHLP) initiation in 323 individuals (p<0.001).
TC in HIV-infected US veterans on HAART depends on HAART use…
...and on CD4 recovery, viral suppression and type of HAART
HIV as independent RF for CAD

Table 2. Rates of AMI

<table>
<thead>
<tr>
<th>Status</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>80-89</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uninfected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>19,805</td>
<td>4,209</td>
<td>1,120</td>
<td>148</td>
</tr>
<tr>
<td>No. of AMI events</td>
<td>218</td>
<td>66</td>
<td>36</td>
<td>14</td>
</tr>
<tr>
<td>AMI rates per 1000</td>
<td>2.2</td>
<td>3.3</td>
<td>6.7</td>
<td>21.5</td>
</tr>
<tr>
<td>person-years (95% CI)</td>
<td>(1.9-2.5)</td>
<td>(2.6-4.2)</td>
<td>(4.8-9.2)</td>
<td>(12.7-36.4)</td>
</tr>
<tr>
<td><strong>HIV Infected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>9,342</td>
<td>2,065</td>
<td>557</td>
<td>56</td>
</tr>
<tr>
<td>No. of AMI events</td>
<td>171</td>
<td>46</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>AMI rates per 1000</td>
<td>3.9</td>
<td>5.0</td>
<td>10.0</td>
<td>13.5</td>
</tr>
<tr>
<td>person-years (95% CI)</td>
<td>(3.3-4.5)</td>
<td>(3.8-6.7)</td>
<td>(6.7-14.7)</td>
<td>(4.3-42.0)</td>
</tr>
<tr>
<td>Incidence rate ratio (95%)</td>
<td>1.80</td>
<td>1.53 (1.03-1.08)</td>
<td>1.50</td>
<td>0.63</td>
</tr>
<tr>
<td>(1.47-1.21)</td>
<td>2.26</td>
<td>(0.86-2.57)</td>
<td>(0.12-2.25)</td>
<td></td>
</tr>
</tbody>
</table>

Freiberg M JAMA Int Med 2013, 173 614-22
Principles of HAART
Antiretroviral Drug Approval

[cART]

Softer & better

HAART

1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015

AZT ddI ddC d4T 3TC ddI SQV RTV NVP EFV APV RTV<sub>NFV</sub> IDV<sub>DLV</sub> EFV<sub>APV</sub> TDF LPV/r ETV RAL MVC DRV TPV TAF TAF RPV EVG DGV
Antiretroviral Therapy: Facts of HIV Replication

- $10^9$ to $10^{10}$ virus particles produced per day
- $10^3$ to $10^4$ virus particles per life span of activated CD4 cell (2-3 days)
- Typically 8 cell divisions per activation cycle, $\rightarrow 10^5$ to $10^6$ virus particles per activation burst
- RT mutation rate $\sim 3 \times 10^5$/bp/cycle
- HIV genome = $10^4$ bp
- Every possible mutation occurs $10^4$-$10^5$ times/d
- Simultaneous triple and quadruple mutations are rare
- Potent combination therapy is required to inhibit the emergence of resistant HIV
Development of Resistance

Original Virus Quasispecies

Selection Pressure exerted by Drugs

Minority Quasispecies with reduced susceptibility

HIV RNA Level

New Virus Quasispecies

Resistant virus

Time
HIV-1 RNA Response in Subjects With M184V (M184V Present by Week 12)


300 mg BID (n=14)

3TC monotherapy

Weeks

Mediation decrease
HIV RNA log copies/mL
## How Quickly Resistance Can Occur Depends on the Viral Load

<table>
<thead>
<tr>
<th>Viral Load</th>
<th>Days Before Mutation Arises</th>
</tr>
</thead>
<tbody>
<tr>
<td>300,000</td>
<td>0.1</td>
</tr>
<tr>
<td>30,000</td>
<td>1</td>
</tr>
<tr>
<td>3,000</td>
<td>10</td>
</tr>
<tr>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>30</td>
<td>1,000</td>
</tr>
</tbody>
</table>

Adapted from Siliciano, 2002
Start ART

greatest risk for selecting resistant HIV

< 400 cop
Cell Culture assays

\[ \frac{C_{\text{min}}}{IC_{50}} \]

\[ 1 \quad 10 \quad 100 \quad 1000 \quad 10000 \]

NRTI, NNRTI, PI, FI, II

3TC, ABC, AZT, d4T, ddl, FTC, TDF, EFV, NVP, DLV, TMC125, TMC278, APV, ATV, DRV, IDV, LPV, NFV, SQV, TPV, T20, T1249, L870812, RAL, GS9137

Nature medicine July 2008
Remember:

- “Potent combination therapy is required to inhibit the emergence of resistant HIV”
- “Potency” of an antiretroviral = Inhibitory potential x Genetic vulnerability x Forgiveness
- Example of great inhibitory potential but also great genetic vulnerability: 3TC/FTC (point mutation)
- Example of negligible genetic vulnerability: modern boosted PIs
- Example of great forgiveness: efavirenz (t½: 10-14d)
- There is no magic “number of active drugs” needed, it is the number of concomitant mutations needed to arise simultaneously that determines likelihood of treatment failure
- The “fourth ARV” is the immune system
First phase: mean half-life 0.9-1.6 days and occurs over the first 7 to 10 days = Death of productively infected CD4+ cell

Second phase: dying off longer-lived cells (e.g. macrophages)
Third phase: latently infected memory T cells, ½ life many years
‘Undetectable’ = ‘fairly low VL’

Latently infected cells occasionally release virus
Time to eradication...

**Slow decay of latently infected CD4^+ T cells**

Time to eradication > 73.4 years

Finzi et al., Nature Med., 1999
A

Not this

Shen L et al. JACI 2008

Start HAART

Ongoing replication

Plasma HIV-1 RNA (copies/ml)

Limit of detection (50 copies/ml)

Time on HAART (yrs)
Env Sequence genetic distance during and after multiple ART interruptions (Swiss Spanish STI trial)

Joos B et al. PNAS 2008
HAART Intensification

- In most (but not all) studies, treatment intensification is not associated with measurable changes in plasma HIV RNA levels, immune activation, or HIV-specific responses
  - Dinosaur PNAS 09; Gandhi IAS 09; McMahon CID 10;
- In other studies using more precise measures of replication, an effect of intensification may be evident, but this does not affect plasma HIV RNA levels
  - Buzon, CROI 10, Yukl CROI 10, Hatano JID 2013
- Ongoing viral replication is not likely to be a major cause of persistent viremia, but it is possible that low-level virus replication persists and that this virus will remain a barrier to eradication
Ongoing HIV replication despite HAART?

- Against
  - viral evolution studies
  - Intensification studies

- However:
  - Low levels of ongoing replication may occur without detectable evolution
  - Replication may occur sporadically
  - Replication may occur in a subset of patients on HAART:
    - an increase in “2-LTR excision circles” was observed both after raltegravir intensification studies, predominantly in PI-treated patients. (Buzon et al 2010, Hating JID 2013)
    - = unintegrated viral DNA that becomes fused by cellular enzymes
Ongoing HIV replication despite HAART?

- Postulated/hypothesized mechanisms:
  - Low ARV penetration rates into some (lymphatic) tissues
  - Cell to cell transmission manyfold more effective than cell-free transmission
Prospects for “Cure”

- Likelihood of virology relapse decreases after prolonged HAART (≥5 years): improved HIV-specific immunity vs. lower number of latently infected cells
VL rebound probability after prolonged HAART

JAIDS 2011;55:460-65
Prospects for “Cure”

- Likelihood of virology relapse decreases after prolonged HAART (≥5 years): improved HIV-specific immunity vs. lower number of latently infected cells?
- Proof of concept study to mimic “Berlin Patient” experience by modulating autologous T-cells (CCR5 deletion) successful
- $^{213}$Bi-labeled monoclonal gp41 antibodies reduced proviral load in HAART treated humanized mice
Obstacles for “Cure”

C By-subject total HIV-1 DNA over time

DNA copies/10^6 CD4+ T-cells

Years on ART

CID 2014;59:1312-21
Obstacles for “Cure”

- Vast majority of latently infected cells are resting central memory CD4 cells which have been proven to be difficult to activate.
- Activation of these cells may not be “enough” in the absence of strong CTL responses (reversion to latency).
- Number of CD4 cells with replication competent virus may be 60x higher than previously thought.
- Majority of HIV-specific CD4 cells are latently infected.
- Some pluripotent hematopoietic progenitor cells (CD34+) may be infected.
Obstacles for “Cure”

- Other lymphotropic viruses without prospects for “cure”: EBV, CMV, KSV, HBV, HTLV-1
Inhibitory Potential at 24 hours (Forgiveness)

Nature medicine July 2008