OUTLINE

- HIV PATHOGENESIS
- EPIDEMIOLOGY
- IMMUNOLOGY
- HEPATITIS A VACCINE RESEARCH
ABBREVIATIONS AND JARGON

- **PI** PROTEASE INHIBITOR
- **NA** NUCLEOSIDE ANALOGUE (NUKE)
  - **NRTI** NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR
- **NNRTI** NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NON-NUKE)
- **HAART** HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)
  - TRIPLE OR COMBINATION THERAPY OR COCKTAIL
  - PI + 2 NA OR NNRTI + 2 NA
  - HEART
AGING AND HIV

- BACKGROUND EPIDEMIOLOGY
  - PRIOR TO 1989, BLOOD PRODUCTS WERE MAJOR RISK FACTOR
    - 1% AGE 13-49 YEARS
    - 6% AGE 50-59 YEARS
    - 28% AGE 60-69 YEARS
    - 64% AGE ≥70 YEARS
## RECENT EPIDEMIOLOGY

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>50 YEARS</th>
<th>13-49 YEARS</th>
</tr>
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<tbody>
<tr>
<td>MALE</td>
<td>84%</td>
<td>79%</td>
</tr>
<tr>
<td>RACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHITE</td>
<td>39%</td>
<td>38%</td>
</tr>
<tr>
<td>BLACK</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td>HISPANIC</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>RISK FACTOR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAY/BISEXUAL</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>IDU</td>
<td>19%</td>
<td>26%</td>
</tr>
<tr>
<td>HETEROSEXUAL</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>NONE REPORTED</td>
<td>26%</td>
<td>16%</td>
</tr>
<tr>
<td>AIDS-DEFINING DX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV ENCEPHALOPATHY</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>WASTING</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>OTHER OI</td>
<td>38%</td>
<td>36%</td>
</tr>
<tr>
<td>IMMUNOSUPPRESSION</td>
<td>52%</td>
<td>58%</td>
</tr>
</tbody>
</table>

MMWR 1998;47:21
HIV AND AGING: CO-MORBIDITY

- Advancing age is risk factor for many infectious diseases.
- Older HIV-positive patients have shorter AIDS-free interval and shorter survival.
- Rapid progression may be due to delayed diagnosis or HIV-related or non-HIV-related comorbidity.

13% of ≥50 died within one month of AIDS DX versus 6% of 13-49.
Figure 1: Survival in HIV-infected seropositive haemophiliacs patients by age at seroconversion and expected survival based on mortality rates for uninfected patients subdivided by age and severity of haemophilia.
Within each age-at-seroconversion group estimates are censored when fewer than five HIV-seropositive patients remain at risk.

Figure 2: Development of AIDS in haemophilia patients and survival after a diagnosis of AIDS by age at seroconversion. Within each group estimates are censored when fewer than five people remain at risk.
**IMPACT OF AGING ON HIV PROGRESSION**

**LANCET 2000;355:1131-37**

<table>
<thead>
<tr>
<th>AGE</th>
<th>MEDIAN SURVIVAL</th>
<th>MEDIAN TIME TO AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>12.5 (12.1-12.9)</td>
<td>11.0 (10.7-11.7)</td>
</tr>
<tr>
<td>25-34</td>
<td>10.9 (10.6-11.3)</td>
<td>9.8 (9.5-10.1)</td>
</tr>
<tr>
<td>35-44</td>
<td>9.1 (8.7-9.5)</td>
<td>8.6 (8.2-9.0)</td>
</tr>
<tr>
<td>45-54</td>
<td>7.9 (7.4-8.5)</td>
<td>7.7 (7.1-8.6)</td>
</tr>
<tr>
<td>55-64</td>
<td>6.1 (5.5-7.0)</td>
<td>6.3 (5.5-7.2)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>4.0 (3.4-4.6)</td>
<td>5.0 (4.0-6.2)</td>
</tr>
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</table>
RECONSTITUTION OF T-CELL IMMUNITY

- PROGRESSIVE LOSS OF THYMIC FUNCTION BEGINNING AT AGE SIX YEARS
  - LOSE CD45RA (AND L-SELECTIN)
  - GAIN CD45RO
  - HAART IN CHILDREN (1-16 YEARS)
    - LARGER INCREASE <6 YEARS VS >6 YEARS

- FOLLOWING CHEMOTHERAPY, INVERSE RELATION BETWEEN AGE (1-24YRS) AND CD4+ T-CELL NUMBER
  - CD4+ T-CELL CORRELATED WITH CD4+CD45RA+

- FOLLOWING BURNS, IT TAKES A 40 YEAR OLD TWICE AS LONG AS A 20 YEAR OLD TO REPLACE CD4+ CELLS

- CHEMOTHERAPY FOR BREAST CANCER (33-69)
  - NO RELATION BETWEEN AGE AND CD4 RECOVERY
Figure 1. Relation between Age and Reconstitution of CD4+ T Lymphocytes.

Absolute CD4+ T-lymphocyte counts were measured in the peripheral blood of patients approximately six months after the completion of chemotherapy. The correlation coefficient was calculated by the Spearman rank-correlation method.
HIV-INDUCED IMMUNE PATHOGENESIS

- CHARACTERISTIC LOSS OF HELPER CD4+ T-CELLS
- INFECTION OF PERIPHERAL CD4+ T-CELLS
  - PREFERENTIAL INFECTION OF CD45RO+ CELLS
- DESTRUCTION OF THYMUS
- FUNCTIONAL CONSEQUENCES ARE LOSS OF:
  - NEOANTIGENS
  - ALLOANTIGENS
  - MITOGENS
IMMUNE RECONSTITUTION

- HAART IS HIGHLY EFFECTIVE IN REDUCING VIRAL LOAD AND INCREASING NUMBERS OF CD4+ T-CELLS
- MECHANISMS:
  - MOBILIZATION OF LYMPHOCYTES
  - DECREASED DESTRUCTION
  - INCREASED DIFFERENTIATION FROM THYMIC PRECURSORS
IMMUNE RECONSTITUTION AFTER HAART

THREE DISTINCT PHASES

FIRST 4 WEEKS: INCREASE IN OF CD45RO T-CELLS, CD8 T-CELLS, B-CELLS; THOUGHT TO REPRESENT RECIRCULATION

NEXT SEVERAL MONTHS: REDUCTION IN T-CELL ACTIVATION MARKERS, WITH DECLINE IN CD8 T-CELLS

6-12 MONTHS: RISE IN CD45RA T-CELLS, PRESUMABLY THYMIC-DERIVED

RECOVERY OF FUNCTION?

REACTIVITY AGAINST RECALL ANTIGENS
INCOMPLETE REGENERATION OF T-CELL RECEPTOR DIVERSITY
EFFECTS OF AGING ON IMMUNE RECONSTITUTION

MANFREDI, et al AIDS 2000;14:1475

12 mo F/U

AGE <35 ≥55
N 84 21
BASELINE VL 4.5 log 4.7 log
Δ VL -1.8 log -1.9 log
BASELINE CD4 231/µl 212/µl
Δ CD4 +114/µl +72/µl
EFFECTS OF AGING ON IMMUNE RECONSTITUTION


95 PERSONS, 48 mo F/U

AGE CD4

<35  +374
35-44  +318
>44  +196

NEGATIVE PREDICTORS OF CD4 RECOVERY

AGE, NADIR CD4
EFFECT OF AGE ON RECOVERY OF CD4 NUMBER 
VIARD et al, JID 2001; 183: 1290-4

Figure 1. Kaplan-Meier curves of time to increase in CD4 cell count of ≥200 × 10^6 cells/L after start of HAART in subjects in 4 age quartiles.
EFFECT OF AGE ON RESPONSE TO HAART

<table>
<thead>
<tr>
<th>AGE</th>
<th>#</th>
<th>BASELINE</th>
<th>8-12 WEEKS</th>
<th>24-28 WEEKS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CD4</td>
<td>VL</td>
<td>CD4</td>
</tr>
<tr>
<td>2-6 yr</td>
<td>20</td>
<td>384</td>
<td>5.4</td>
<td>+144</td>
</tr>
<tr>
<td>6-18 yr</td>
<td>21</td>
<td>176</td>
<td>5.2</td>
<td>+71</td>
</tr>
<tr>
<td>26-39 yr</td>
<td>18</td>
<td>126</td>
<td>4.7</td>
<td>+85</td>
</tr>
<tr>
<td>50-73 yr</td>
<td>19</td>
<td>163</td>
<td>4.5</td>
<td>+77</td>
</tr>
</tbody>
</table>
IMMUNE RECONSTITUTION IN OLDER HIV+ MEN

Graph showing the CD4+ counts over time (Baseline, 1-3 months, 3-6 months, 6-12 months) with different line colors and styles for CD4+, CD4+45RA, and CD4+45RO.
EFFECTS OF AGE ON IMMUNE RECONSTITUTION FOLLOWING HAART

PRIMARY HYPOTHESIS:
- RETURN OF NAÏVE CD4+ T-CELLS IS THE CRITICAL DETERMINANT OF FUNCTIONAL IMMUNE RECONSTITUTION FOLLOWING HAART

SECONDARY HYPOTHESIS:
- THERE ARE INTRINSIC DEFECTS IN NAÏVE CD4+ T-CELLS IN HEALTHY ELDERS
OBJECTIVES

- TEST NAÏVE CD4 T-CELL FUNCTION BY IMMUNIZATION WITH A NEOANTIGEN (HEPATITIS A VACCINE)
- EVALUATE T-CELL RECEPTOR DIVERSITY IN NAÏVE CD4 T-CELLS
- EXAMINE CHANGES IN EXPRESSION OF ADHESION MOLECULES AND CYTOKINE PROFILES
SITES

- GAINESVILLE VA MEDICAL CENTER
- ALACHUA COUNTY PUBLIC HEALTH DEPARTMENT
- UNIVERSITY OF FLORIDA
  - ADULT INFECTIOUS DISEASES CLINIC
  - PEDIATRIC INFECTIOUS DISEASES CLINIC
ENTRY CRITERIA

- ALL ANTI-HAV AB SERONEGATIVE AND PREVIOUSLY VACCINATED AGAINST TETANUS
- HEALTHY VOLUNTEERS
  - HIV (-) NO KNOWN IMMUNOLOGICAL PROBLEM
- HIV (+) NAÏVE
  - NEVER ON HAART; DUAL NUCLEOSIDES ALLOWED
- HIV (+) HAART
  - ON PROTEASE INHIBITOR (PI) OR NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI) PLUS TWO NUCLEOSIDE ANALOGUES (NA) > 1 YR
  - VL < 50 COPIES/ML OR >1.5 LOG DROP
SUBJECTS

- HEALTHY CONTROLS, N=25
  - HIV (-)
  - AGE 2-78

- HIV (+) NAÏVE, N=9
  - NEVER ON THERAPY OR DUAL NA
  - AGE 17-66

- HIV (+) ON HAART, N=32
  - TRIPLE THERAPY > 1 YEAR
  - AGE 3-62
PROTOCOL

- WEEK 0:
  - ☑ VACCINATE WITH HEPATITIS A AND TETANUS
  - ☑ BLOOD DRAW

- WEEK 4:
  - ☑ RE-VACCINATE WITH HEPATITIS A
  - ☑ BLOOD DRAW

- WEEK 8:
  - ☑ BLOOD DRAW
EFFECT OF AGE ON ANTIBODY RESPONSE TO HEPATITIS A VACCINE

$R^2 = 0.56, \ p < 0.01$
EFFECT OF AGE ON ANTIBODY RESPONSE TO HAV IN HIV(+) PERSONS NOT ON THERAPY

[Graph showing the relationship between age and HAV antibody titer.]
EFFECT OF AGE ON ANTIBODY RESPONSE TO HAV VACCINE IN PATIENTS ON HAART
RECOVERY OF NAIVE CD45 RA CELLS AND HAV ANTIBODY RESPONSE
FURTHER STUDIES

- EXAMINATION OF RESPONSE AFTER 4-5 YEARS OF HAART
- TETANUS ANTIBODY
- SEPARATION OF CD4+45RA+ AND CD4+45RO+ T-CELLS
  - T-CELL RECEPTOR REPERTOIRE DIVERSITY
  - PROLIFERATION TO HEP A, TETANUS, AND PHA
SUMMARY

- THERE IS A SIGNIFICANT AGE-RELATED DECLINE IN SERUM ANTI-HAV Ab RESPONSE
- HIV INFECTION ROBS PERSONS OF THEIR NAÏVE CD4 T-CELL FUNCTION
- MINIMALLY RESTORED BY HAART
  - NO DIFFERENCE IN PI OR NNRTI BASED REGIMENS
  - NOT INFLUENCED BY BASELINE CD4
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