ACTHIV 2017: A State-of-the-Science Conference for Frontline Health Professionals
HIV Pathogenesis: What the clinician needs to know

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Disclosures

Grants
Bristol Myers Squibb, Gilead, Merck, ViiV

Consultant
Abbvie, Bristol Myers Squibb, Gilead, Janssen, Merck, Teva, ViiV
Objectives

• Identify how HIV pathogenesis impacts antiretroviral therapy and outcomes
• Define how HIV infection influences end organ disease
Natural History of Untreated HIV Infection

Viral Dynamics

Productively Infected CD4+ Lymphocytes

Activated Uninfected CD4+ Lymphocytes

Infected Resting Memory CD4+ Lymphocytes

Activated Uninfected CD4+ Lymphocytes

Long-lived Cells

Productively Infected CD4+ Lymphocytes

Activated Uninfected CD4+ Lymphocytes

Activated Uninfected CD4+ Lymphocytes

Infected Resting Memory CD4+ Lymphocytes

Activated Uninfected CD4+ Lymphocytes

Viral Dynamics

Antiretroviral Therapy

Long-lived Cells

Viral Dynamics

Productively Infected CD4+ Lymphocytes

Activated Uninfected CD4+ Lymphocytes

Infected Resting Memory CD4+ Lymphocytes

T_{1/2} \sim 1 \text{ day}

\text{Log}_{10} \text{RNA}

T_{1/2} \sim 20 \text{ min.}

Activated Uninfected CD4+ Lymphocytes

Antiretroviral Therapy

Long-lived Cells

Viral Dynamics

Productively Infected CD4+ Lymphocytes

Activated Uninfected CD4+ Lymphocytes

Infected Resting Memory CD4+ Lymphocytes

Activated Uninfected CD4+ Lymphocytes

Long-lived Cells

% >95%

$T_{1/2}$~1 day

$T_{1/2}$~20 min.

<5%

$T_{1/2}$~2-4 weeks

Log$_{10}$ RNA

**Viral Dynamics**

*Productively Infected CD4+ Lymphocytes*
- T½ ~ 1 day
- >95%

*Activated Uninfected CD4+ Lymphocytes*
- T½ ~ 20 min.

*Infected Resting Memory CD4+ Lymphocytes*
- T½ ~ 6 months - years

*Long-lived Cells*
- <1%

*Activated Uninfected CD4+ Lymphocytes*
- <5%

*Viral Dynamics*
Cure Research
THE CHALLENGE OF VIRAL RESERVOIRS IN HIV-1 INFECTION

Joel N. Blankson, Deborah Persaud, and Robert F. Siliciano

Observed $t_{1/2}$ of latent reservoir = 44 months

Possible acceleration of decay by intensification

Prolonged survival of memory T cells and progeny

Intermitotic $t_{1/2}$ of memory T cells = 6 months

Latent reservoir may be 60-fold higher than previous estimates.
“Managing” the Cellular Reservoir

• Minimize size
  – Early therapy
  – Eradication by cytotoxic treatment
  – Induction of latent virus for clearance
  – Decreasing cell susceptibility to infection

• Enhancing clearance
  – Enhancing HIV-specific immune responses e.g. therapeutic vaccine, early therapy
  – Immunotherapy
  – Novel targeted cytotoxic agents
Semen May Harbor HIV Despite Effective HAART: Another Piece in the Puzzle

Philippe Halfon\textsuperscript{1,}\textsuperscript{*}, Claude Giorgetti\textsuperscript{2}, Hacène Khiri\textsuperscript{3}, Guillaume Pénaranda\textsuperscript{4,}\textsuperscript{*}, Philippe Terriou\textsuperscript{2}, Géraldine Porcu-Buisson\textsuperscript{2}, Véronique Chabert-Orsini\textsuperscript{2}

4% of Plasma HIV RNA – negative are positive in semen.
HIV-1 Viral Escape in Cerebrospinal Fluid of Subjects on Suppressive Antiretroviral Treatment

Arvid Edén,1 Dietmar Fuchs,4 Lars Hagberg,1 Staffan Nilsson,1 Serena Spudich,6 Bo Svennerholm,2 Richard W. Price,5 and Magnus Gisslén1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CSF viremic (n = 7)</th>
<th>CSF aviremic (n = 62)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46 (36–64)</td>
<td>45 (22–71)</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex, no. (%) of patients</td>
<td>4 (57)</td>
<td>45 (73)</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, × 10^6 cells/L</td>
<td>620 (400–810)</td>
<td>525 (390–642)</td>
<td></td>
</tr>
<tr>
<td>CD4 nadir, × 10^6 cells/L</td>
<td>133 (40–200)</td>
<td>150 (68–213)</td>
<td></td>
</tr>
<tr>
<td>CSF HIV-1 RNA level, copies/mL</td>
<td>121 (54–213)</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>CPE rank</td>
<td>1.6 ± 0.5</td>
<td>1.7 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>CPE-2010 rank</td>
<td>7.3 ± 0.76</td>
<td>7.4 ± 1.23</td>
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</tr>
<tr>
<td>CSF neopterin level, nmol/L</td>
<td>9.2 (6.6–16.2)</td>
<td>5.1 (4.4–8.4)</td>
<td></td>
</tr>
<tr>
<td>Plasma neopterin level, nmol/L</td>
<td>7.2 (6.1–8.0)</td>
<td>7.6 (5.1–10.3)</td>
<td>NS</td>
</tr>
<tr>
<td>WBC count, × 10^6 cells/L</td>
<td>1 (1–6)</td>
<td>1 (1–3)</td>
<td>NS</td>
</tr>
<tr>
<td>Time on ART, months</td>
<td>77 (67–101)</td>
<td>35 (17–59)</td>
<td>.002</td>
</tr>
</tbody>
</table>

NOTE. Data are median value (interquartile range) or mean value ± standard deviation, unless otherwise indicated. All subjects had plasma HIV-1 RNA <50 copies/mL. ART, antiretroviral therapy; CSF, cerebrospinal fluid; CPE, CNS penetration effectiveness; NS, not significant; WBC, white blood cell count.

10% of Plasma HIV RNA – negative are positive in CSF

Procedure and Events

- Ablative chemotherapy
- Total body XRT
- Graft vs. host
- Transplant with CCR5Δ32 homozygous donor

New Hope of a Cure for H.I.V.

BY ANDREW POLLACK
NOVEMBER 28, 2011

VIRUS-FREE Timothy Brown of San Francisco had two bone-marrow transplants to treat leukemia, and H.I.V. can no longer be detected in his body. (Heidi Schumann for The New York Times)

HIV Pathogenesis beyond viremia and cure
Consequences of Stopping ART: SMART Trial

Continuous antiretroviral therapy throughout follow-up (n = 2752)

HIV-1-infected patients with CD4+ cell count > 350 cells/mm³
(N = 5472)
95.4% treatment experienced

ART stopped/deferred until CD4+ <250 cells/mm³ then started to increase CD4+ to >350 cells/mm³ (n = 2720)

## SMART: Primary Endpoint and Components

<table>
<thead>
<tr>
<th>Event</th>
<th>Events</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of Disease or Death</td>
<td>164</td>
<td>2.5</td>
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<tr>
<td>Death</td>
<td>84</td>
<td>1.9</td>
</tr>
<tr>
<td>Serious HIV Events</td>
<td>21</td>
<td>6.1</td>
</tr>
<tr>
<td>Severe Complications*</td>
<td>114</td>
<td>1.5</td>
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</tbody>
</table>

*CVD, Renal, Hepatic Events (fatal/nonfatal)

SMART and START Studies: Disease Risk

- Combined analysis of SMART and START studies (n=10,157)
  - AIDS events (n=123)
  - Serious non-AIDS events (n=244)
  - CVD (n=103)
  - Cancer (n=117)
  - Death (n=118)
  - AIDS and serious non-AIDS events (n=359)

- Immune preservation through immediate and continuous ART significantly reduces the risk of AIDS and non-AIDS events
  - Cancer risk reduction did not vary by type of cancer

Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration


Differences That Could Explain Progression

Many Qualitative and Quantitative Differences Between Different Hosts Could Explain Pathogenic and Non-Pathogenic Course of Infection

<table>
<thead>
<tr>
<th></th>
<th>Sooty Mangabey</th>
<th>African Green</th>
<th>Rhesus Macaque</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5 CD4 T-cell depletion</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Preferential Th17 loss</td>
<td>--</td>
<td>--</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Enteropathy</td>
<td>--</td>
<td>--</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Microbial translocation</td>
<td>--</td>
<td>--</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Acute immune activation</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Downregulate active immune activation</td>
<td>√</td>
<td>√</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Chronic immune activation</td>
<td>--</td>
<td>--</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

Silvestri G. J Med Primatol 2008; 2:6-12
SMART: Changes in D-Dimer and IL-6 Levels

- Suggests HIV viremia effect on endothelium, leading to increased tissue factors and initiation of coagulation cascade

*DC patients on ART at baseline with HIV RNA ≤400 copies/mL

ART and T Cell Immune Activation

T cell activation declines during long-term ART, but remains elevated, even after many years of viral suppression

Hunt, et al. JID 2003
Pathogenesis of PHI: SIV Model

Bacterial Translocation

Benchley et al. Nat Medicine 2006
HIV immune activation

- gut
- CD4 depletion
- enteropathy
- low thymic output
- LT fibrosis
- T/B cell dysfunction

Target cells

Immune activation

Non-AIDS morbidity and mortality
- inflammation
- tissue damage
- coagulopathy

Immune deficiency

Poor pathogen control

Courtesy of D. Douek
Potential Interventions

- **Anti-infective therapy:**
  - CMV, EBV, HSV, HCV/HBV

- **Microbial translocation:**
  - sevelamer, colostrum, rifaximin

- **Anti-coagulants:**
  - low dose warfarin, dabigatran, aspirin, clopidogrel

- **Chemokine receptor inhibitors:**
  - maraviroc

- **Anti-inflammatory drugs:**
  - Chloroquine
  - Minocycline
  - NSAIDs (COX-2i, aspirin)
  - Methotrexate
  - Talidomide, pentoxyfyl (TNF inhibitors)
  - Biologics (e.g., TNF inhibitors, IL-6 inhibitors, anti-PD1)

  - **Statins**
Rosuvastatin Treatment Reduces Markers of Monocyte Activation in HIV-Infected Subjects on Antiretroviral Therapy

Nicholas T. Funderburg, Ying Jiang, Sara M. Debanne, Norma Storer, Danielle Labbate, Brian Caggett, Janet Robinson, Michael M. Lederman, and Grace A. McComsey

Funderburg NT, et al. CID 2014; 58588-594
Statins in HIV-infected Patients with Arterial Inflammation

Study Design

CCTA screening
FDG PET/CT screening
40 Randomized
Placebo
Once a day
Baseline
3 months
Once a day
Atorvastatin
20 mg, once a day
40 mg, once a day
12 months

Both groups received lifestyle and dietary counseling based on NCEP guidelines and Therapeutic Lifestyle Changes (TLC) diet.

Key Inclusion Criteria:
- Age 18-60
- HIV+
- Stable anti-retroviral therapy
- LDL < 130 mg/dL
- Evidence of subclinical atherosclerosis
  - One or more plaque on coronary CTA
  - TBR > 1.6

Key Exclusion Criteria:
- History or symptoms of cardiovascular disease
- Critical coronary stenosis
- AST or ALT greater than 3 times upper limit of normal
- Creatinine >1.5 mg/dL
- Treatment for active liver or renal disease
- Acute infectious illness within 3 months

Statin Effect on Atherosclerosis

Change in noncalcified plaque volume

Plaque regression/progression and CAC

Randomized Trial to Prevent Vascular Events in HIV

Asymptomatic HIV+ patients with no history of CVD

Screening And Consent

Randomization

Placebo

Pitavastatin 4mg/day

Intervention

Mechanistic Study

Coronary plaque, vascular inflammation, immune activation

Mechanistic Primary Endpoint

CV Death MI Unstable Angina Stroke Arterial Revasc

Clinical Primary Endpoint

Individual components of primary endpoint

All cause death

Incidence/Progression of noncalcified plaque; High-risk plaque

Inflammatory, immunological, metabolic biomarkers

Predictors of statin effects

Statin safety and non AIDS comorbidities: DM, Infections, Cancer

Secondary Endpoints
Conclusion

• HIV replication occurs at a high rate with high levels of turnover allowing for rapid selection of viruses that escape immune and ARV pressure
• Viral reservoir (cellular, CNS, other) is established quickly after infection and remains obstacle for cure
• Enhanced inflammation and immune activation persists in face of suppressive ARVs
  – This may lead to ongoing end organ disease and morbidity
  – Better understanding pathogenesis and how to target this process may enhance the lives of chronically infected individuals
Thank You!!