Acute HIV infection and Prospects for Optimizing the Immune Response with Quantitative Modeling

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Harvard Medical School
47 year old male

Present to MGH ED with an 8 day history of:

- Fever to 102.5
- Headache
- Photophobia
- Myalgias and arthralgias
- Nausea and vomiting

3rd visit to health care system
47 year old male

Additional history:
MSM
Recent unprotected sex with an HIV infected partner
PMH: prior history of syphilis

Exam:
- Fever
- Cervical lymphadenopathy
- Rash (started on torso spread to limbs and scalp)
Diagnosis

Acute HIV Infection
Viral Infections and Immunity

• Three outcomes of a viral infection
  – Death
  – Eradication
  – Chronic infection

    Latency ⇔ Viral activity
Chronic Infection: Viral Latency and Replication

Immune Response

VZV, HSV, EBV, CMV

HIV
HIV Terminology

Viral Load = Speed of the train
CD4 count = Distance from cliff
Acute HIV Infection
Acute HIV Infection
Early events and Diagnosis

- CD4
- HIV RNA
- ELISA/WB
- Acute HIV Sx
- 2-6 wks
- 2-8 wks
- 6 months

CTL
The level of HIV in the blood stream following seroconversion predicts disease progression.

Lyles et al, 2000

HIV Viral Load

Interquartile ranges

- Rapid Progression: 59,987
- Slow Progression: 28,240
- Interquartile ranges: 11,843

One year
Partial Control

Why can’t the immune system more effectively control HIV replication?
Viral factors

Host genetic factors

Host immune responses
Neutralizing Antibodies

New virus assembly

B cell
Why do neutralizing antibodies fail?

- Viral debris
- Rapid evolution and diversification
- Inadequate T cell “help”
New virus assembly

2-3 Days

CTL

Soluble factors
If CTL are present, why is the immune response not more effective in HIV infection?
HIV-Specific T Helper Cells are impaired in all stages of disease

1. Activation
2. Clonal expansion
3. Cytokine secretion
Critical relationship between CD4 and CD8
What happens to HIV-specific T helper cells?
Acute HIV infection
Acute HIV Infection
Early events and Diagnosis

CD4
HIV RNA
ELISA / WB
CTL

Acute HIV Sx
2 - 6 wks
2 - 8 wks
6 months

Rapid
Mod.
LTNP
Treatment

Should individuals with Acute HIV-1 infection be treated with antiretroviral therapy?
<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preservation of HIV-specific cellular</td>
<td>Toxocities and unknown long-term risks</td>
</tr>
<tr>
<td>immune responses</td>
<td></td>
</tr>
<tr>
<td>Opportunity for structured treatment</td>
<td>Short- and long-term clinical benefits are not</td>
</tr>
<tr>
<td>interruption</td>
<td>well-defined</td>
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<tr>
<td>Lowering of HIV-1 set point</td>
<td>Resistance acquisition</td>
</tr>
<tr>
<td>Limitation of viral evolution and diversity</td>
<td>Limitation of future antiretroviral therapy</td>
</tr>
<tr>
<td>Decreased transmission</td>
<td>options</td>
</tr>
<tr>
<td>Mitigation of acute retroviral symptoms</td>
<td>Quality of life impact</td>
</tr>
<tr>
<td></td>
<td>Cost</td>
</tr>
</tbody>
</table>

Kassutto et al, *Clinical Infectious Diseases* 2006
HIV-Specific T helper cells

Can treatment initiated during acute HIV infection preserve HIV-specific T helper cells?
What happens to HIV-specific T helper cells?

Pathogenesis hypothesis:
• HIV-specific T helper cell responses are generated and subsequently lost during acute infection

Treatment hypothesis:
• Treatment with ARV during acute infection will protect these responses from being lost
CD4 cells

Activation & Expansion

Infection

Impairment
CD4 cells & Expansion

Activation & Expansion

Antiretroviral therapy
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute</th>
<th>Early</th>
<th>total n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>35</td>
<td>37</td>
<td>102</td>
</tr>
<tr>
<td>[IQR]</td>
<td>[31,39]</td>
<td>[34,43]</td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>94</td>
<td>94</td>
<td>102</td>
</tr>
<tr>
<td>HIV Risk Factor MSM (%)</td>
<td>82</td>
<td>81</td>
<td>94</td>
</tr>
<tr>
<td>White race (%)</td>
<td>77</td>
<td>78</td>
<td>102</td>
</tr>
<tr>
<td>Mean baseline VL (copies/mL)</td>
<td><strong>5.61 million</strong> (11,000-95 million)</td>
<td>382,000 (2800-2.95 million)</td>
<td>75</td>
</tr>
<tr>
<td>(range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline CD4 (cells/mm³)</td>
<td>445</td>
<td>567</td>
<td>100</td>
</tr>
<tr>
<td>(range)</td>
<td>(42-1093)</td>
<td>(170-981)</td>
<td></td>
</tr>
</tbody>
</table>

*Kassutto et al, CID 2006*
Control
chronic
acute
LTNP

Stimulation index

control chronic acute acute LTNP
No Rx Rx

Elite controllers

Rosenberg et al, Science 1997
Clinical Point

• Immune damage occurs in the earliest stages of acute HIV infection: there appears to be a “window of opportunity” to reverse this damage with treatment

• Highly drug resistant virus can be transmitted during acute infection: viral genotyping is recommended if treatment is initiated
If treatment during acute infection restores immune responses similar to the elite controller phenotype...

Can treatment initiated during acute HIV infection be discontinued?
Lessons from Berlin
Lisziewicz et al, NEJM 340 (21), 1999
Augment HIV-specific immunity
Hypothesis
Can therapy be discontinued?

- Will HIV-1-specific immune responses generated and maintained during acute infection be enough to control viremia?
- Can a “snap-shot” of autologous virus further boost the immune system?
Multiple Treatment Interruptions
Can therapy be discontinued?

![Graph showing viral load (copies/ml) over years off therapy. The viral load increases as the years off therapy increase, surpassing the 50,000 copies/ml threshold around 3 years off therapy.]
“STI”
Structured treatment interruption

Several patterns have emerged

- Failure
- Transient control of viremia with sudden loss of containment
- Control (durability?)

• This strategy works 50% of the time... Are we doing it correctly?

Rosenberg et al, Nature 2000
Kaufmann et al, PLoS Med 2004
Treatment Interruption Strategies

Terminal Treatment
Discontinuation
Terminal Treatment Discontinuation

- ACTG 5187
- Four gene DNA vaccine
- 20 subjects *treated* during acute HIV infection
- Randomized to DNA vaccine versus placebo
- After 4\textsuperscript{th} vaccination (week 30), ARV was discontinued

1. Median viral load in placebo group (3.7 log_{10}) 5,012 copies/ml

2. This is markedly different from expected VL based on MAC’s data (28,000 copies)

3. CD4 counts remained stable during treatment interruption

Future Directions: Sorting it all out

• More questions then answers...
• Is treatment interruption a viable clinical strategy?
• Should individuals with acute infection be treated at all?
• Can we rely on clinical trials to sort it all out?
Future Directions: Modeling Biomedical Problems

- Multidisciplinary collaboration is essential
- MGH-NCSU
- Physician-Scientists do not understand math!
- Be prepared for skepticism
- Be the “science behind the science”
Smarter Trial Design

• In the absence of clinical data, physicians rely on “experience”, “expert opinion” and “educated guessing”

• Can sophisticated mathematical and statistical models of Acute HIV infection more effectively design clinical trials?
HIV dynamic models and control

Possible model for within-subject dynamics:
HIV dynamic models and control

Model for within-subject dynamics: $s = 7$ "states"

\[
\begin{align*}
\dot{T}_1 &= \lambda_1 - d_1 T_1 - \{1 - \epsilon_1 u(t)\} k_1 V_I T_1 \\
\dot{T}_2 &= \lambda_2 - d_2 T_2 - \{1 - f \epsilon_1 u(t)\} k_2 V_I T_2 \\
\dot{T}_1^* &= \{1 - \epsilon_1 u(t)\} k_1 V_I T_1 - \delta T_1^* - m_2 E T_1^* \\
\dot{T}_2^* &= \{1 - f \epsilon_1 u(t)\} k_2 V_I T_2 - \delta T_2^* - m_2 E T_2^* \\
\dot{V}_I &= \{1 - \epsilon_2 u(t)\} 10^3 N_T \delta (T_1^* + T_2^*) - cV_I - \{1 - \epsilon_1 u(t)\} \rho_1 10^3 k_1 T_1 V_I \\
&\quad - \{1 - f \epsilon_1 u(t)\} \rho_2 10^3 k_2 T_2 V_I \\
\dot{V}_{NI} &= \epsilon_2 u(t) 10^3 N_T \delta (T_1^* + T_2^*) - cV_{NI} \\
\dot{E} &= \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E
\end{align*}
\]

- $\theta = (\lambda_1, d_1, \epsilon_1, k_1, \ldots)$ plus initial conditions
- Observable: $CD4 \text{ count} = T_1 + T_1^*$, $viral \text{ load} = V_I + V_{NI}$
- $u(t) = ARV \text{ input at } t \ (0 \leq u(t) \leq 1, \ 0 = \text{off}, \ 1 = \text{on})$
Mathematical-statistical framework

Predictive capability:

Patient #14

CD4$^+$ T-cells / ul

0 200 400 600 800 1000 1200 1400 1600

Virus copies/ml

0 $10^0$ $10^1$ $10^2$ $10^3$ $10^4$ $10^5$

0 200 400 600 800 1000 1200 1400 1600

time (days)
Population Based Simulation
100 “virtual” patients
Design of a clinical trial

**Trial schema:** 1/2 pts randomized to ARV, 1/2 pts to no ARV
Conclusions...

- The early events in acute HIV infection may represent a unique “window of opportunity” for treatment.
- It is not known whether treatment during acute infection is the correct thing to do.
- STI may have a role in management of treated during acute infection but optimal approach not known.
- Can Quantitative modeling be used to optimize the design and conduct of clinical trials?
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  - Shuhua Hu
Solid Organ Transplantation
Solid Organ Transplantation

• Every transplant requires a Donor and a Recipient
• Unless the donor and recipient are a perfect genetic match, the recipient immune system will reject the transplanted organ
• Rejection ultimately results in failure of the transplanted organ
• Every transplant recipient must take immunosuppressive therapy to prevent rejection

•
Solid Organ Transplantation

- Every transplant recipient must take immunosuppressive therapy to prevent rejection
- Transplant recipients are pharmacologically immunosuppressed and therefore much more susceptible to serious infection
- A major problem in immunosuppressed patients is the reactivation of latent viruses such as CMV, VZV, HSV and EBV
The Balance of Immunosuppression

Rejection

Infection
Latency vs re-activation: a delicate balance

Immune pressure
May result in rejection

Viral latency

Viral replication
Latency vs re-activation: a delicate balance

Intermittent periods of viremia and control
Can modeling be used to inform and optimize immunosuppression strategies?
What is measurable?

- Donor and Recipient tissue type/genetics
- Serologic status
- Pre-transplantation immune responses
- Post-transplantation immune responses
- Drug-level of immunosuppression*
- Levels of viremia over time
- Graft function
- Tissue activity (via biopsy)
- Activity of other viruses