Options Project: Overview and Treatment Issues

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MACS: Progression to AIDS by Viral RNA and CD4 after Seroconversion

Proportion with AIDS (median f/u=5.4 year)

- RNA<10k CD4>500
- RNA<10k CD4<500
- RNA>10k CD4>500
- RNA>10k CD4<500

Mellors, Annals, 1995;122:578
MACS: Progression to AIDS by Viral RNA and CD4 after Seroconversion

Proportion with AIDS (median f/u=5.4 year)

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Proportion with AIDS (median f/u=5.4 year)

Mellors, Annals, 1995;122:578
Questions

- Can we understand why some people progress rapidly and others progress slowly?
- Can we do something to intervene and move people toward the lower viral load group?
Options Project Overview
(April 2010)

- 1351 screened since May 1996
- 619 enrolled in long-term follow-up
  - 297 in current follow up
- 11,981 plasma specimens, 8,300 PBMC (cells) specimens stored
- 7,337 plasma aliquots, 8,194 PBMC aliquots withdrawn
- Key support from NIH Program Project grant
- Supported 11 successful NIH grants
- Over 70 articles
Collaborative Model with Interdisciplinary Research

- **PHP:**
  - Jim Kahn
  - Chris Pilcher
  - Steve Deeks
  - Brad Hare
  - Jason Barbour
- **Jay Levy**
- **Division of Experimental Medicine**
  - Doug Nixon
  - Mike McCune
- **Blood System Research Institute**
  - Mike Busch
  - Philip Norris
  - Eric Delwart
- **Robert Grant**
- **Serena Spudich**
- **Jorge Oksenberg**
- **CAPS**
  - Margaret Chesney
  - Steve Morin
- **Monogram Biosciences**
- **Core Immunology lab**
  - Barry Bredt
  - Elizabeth Sinclair
- **LCV- Teri Liegler**
- **ASB- Yvonne de Souza, Eileen Wong**
- **AIEDRP Network**
- **UCSD (Susan Little, Davey Smith, Doug Richman)**
- **Harvard collaborations (Bruce Walker, Marcus Altfed, Todd Allen)**
- **Swedish Institute of Infectious Diseases (Sarah Palmer, Annika Karlsson)**
Key Elements for Success

- Strong staff
  - Lisa Loeb, Lisa Harms, Ed Diaz, Lauren Poole, Clarissa Ospina-Norvell, Gerald Spotts, Tony Ling
- Referring providers, clinics, and organizations
- Dedicated participants
What is the effect of early treatment?
AIEDRP Observational Treatment Analysis

- Hecht et al, JID, 2006
- Subjects Enrolled at AIEDRP sites
  - ≤ 6 months of HIV seroconversion
- Treatment group:
  - Started HAART within 6 months of seroconversion
  - Took ≥ 12 weeks of HAART
  - Stopped HAART for ≥ 4 weeks
  - Divided into those who started HAART ≤ 2 weeks of seroconversion (acute) vs > 2 weeks (early)
- Untreated group:
  - Followed at least 24 weeks without HAART
Untreated vs Acute Tx vs Early Tx Viral load
CD4 T-cell count Untreated vs Acute TX vs Early Tx
ACTG 5217, The SETPOINT Study Design (Hogan et al, CROI, 2010)

Primary Endpoints: \( \log_{10} \text{HIV-1 RNA at Wk 72} \) (Arms A/B) and \( \text{Wk 36 (Arm B)} \)

*88% chose provided regimen – alternatives allowed
Efficacy analysis included 79 subjects

Step 2 eligibility by Wk 72 among 79 subjects enrolled at least 72 weeks prior to the DSMB review

<table>
<thead>
<tr>
<th>Met Step 2 criteria</th>
<th>Arm A (Rx)</th>
<th>Arm B (No Rx)</th>
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<tbody>
<tr>
<td>By wk 72</td>
<td>4/39 (10%)</td>
<td>20/40 (50%)</td>
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<tr>
<td>By wk 36</td>
<td>0/39 (0%)</td>
<td>11/40 (27.5%)</td>
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Arm A had better outcome on the primary endpoint (p=0.005) at wk 72 as well as at wk 72 (Arm A) vs. wk 36 (Arm B) (p=0.002)

DSMB recommended stopping study due to inability to answer primary question re. virologic setpoint and low probability that above outcome would change
Time to Meeting Step 2 Eligibility Criteria (96 Weeks)

- Weeks from Randomization
- Probability Not Experienced Failure
- Log rank test: P<0.001
- Number at Risk:
  - Arm A: 7 failures
  - Arm B: 23 failures

Weeks from Randomization

0 12 24 36 48 60 72 84 96

Number at Risk

65 59 54 49 44 36 30 25 19

Arm A
Arm B

Probability Not Experienced Failure

0.2 0.4 0.6 0.8 1.0

Arm A: 7 failures
Arm B: 23 failures
Time to Meeting Step 2 Eligibility
Starting at Wk 36 Arm A vs. Wk 0 Arm B

Weeks off Treatment

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<tr>
<th>Probability Not Experienced Failure</th>
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<tr>
<td>1.0</td>
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<td>0.8</td>
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Arm A vs. Arm B

Number at Risk

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<tr>
<th>Arm A</th>
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<tr>
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Arm A: 7 failures
Arm B: 23 failures

Weeks off Treatment
Treatment Conclusions

- Acute treatment may improve VL and CD4 for at least 72 weeks after treatment cessation
- Possible modest benefits of limited treatment during acute treatment but not compelling
- CD4+ T-cell counts often go to < 350 within 2 years in persons with symptomatic acute HIV. Early treatment helps prevent this “immunologic failure.”
- Questions remain about whether there is a safe period of untreated HIV (Kitahata et al, NEJM, 2009)
- Acute/early treatment still needs to be individualized and may be particularly appropriate in those with low CD4/high VL
What is the effect of IL-2?
Proportion of Participants with HIV RNA < 50 copies/ml

Week from start of HAART

% HIV RNA<50

0% 10% 20% 30% 40% 50% 60% 70% 80%

Early IL-2
Control
Mean CD4 T-Cell Count by IL-2 Group

CD4 count (cells/ul)

Week after starting HAART

Early IL-2
Control

* P<0.05
IL-2 Conclusions

- IL-2 effectively increases CD4+ T-cells without increasing viral load
- ESPRIT and SILCAAT studies found that increased CD4 counts from IL-2 do not translate into clinical benefit (NEJM, 2009; 1548-59)