Estimating the Optimal CD4 Count for HIV-infected Individuals to Start Antiretroviral Therapy

Bryan Shepherd
Department of Biostatistics
Vanderbilt University Medical Center

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Optimal timing of HAART is unclear

Current guidelines recommend starting when CD4+ lymphocyte count (CD4) falls below 350 cells/mm$^3$

Evidence comes from observational studies of HAART initiators and is subject to lead-time and selection bias
ART-CC study, Lancet, 2002
Lead-time Bias

Lead time bias: Only followed people from the time they started HAART.

Ideal analysis: randomize people with CD4 > 500 to start HAART first time CD4 below 500 versus first time CD4 below 200. Start follow-up at the time of randomization.
Applied Cole et al., *Stat Med* 2004

- impute leadtimes and unseen events with pre-HAART data

24,444 patients followed from start of HAART on or after 1998.

Imputed lead times using 21247 patients from pre-HAART era.

Favored starting HAART sometime before CD4 drops below 350.

Limitations
- Relied on historical data
- Compared hazard ratios – not directly estimating optimal CD4
NA-ACCORD Study (NEJM 2009)

Applied Hernan et al., Basic Clin Pharmacol Toxicol 2006
- treat observational data as if they came from trial where individuals are randomized to one of 2 treatment starting rules
- artificially censor individuals when their data is no longer compatible with one of the rules

17,517 asymptomatic patients from 1996-2005.
- CD4 > 500 versus CD4 ≤ 500 (n=2220 and 6935)
- CD4=351-500 versus CD4 ≤ 350 (n=2084 and 6278)

Concluded HAART should be initiated at CD4 > 500.

Limitations
- those who died within 6 months before HAART initiation assigned delayed group
- compared broad CD4 ranges – not estimating optimal CD4
NA-ACCORD and ART-CC Results Applied to Our Cohort

**3 Month CD4 Window**
- 500 vs 400
  - Not Adjusted
  - Adjusted
- 400 vs 300
  - Not Adjusted
  - Adjusted
- 300 vs 200
  - Not Adjusted
  - Adjusted

**6 Month CD4 Window**
- 500 vs 400
  - Not Adjusted
  - Adjusted
- 400 vs 300
  - Not Adjusted
  - Adjusted
- 300 vs 200
  - Not Adjusted
  - Adjusted
Recent Analyses

Robins et al., *Stat Med* 2008

- extended Hernan et al. to more than 2 treatment starting rules
- selects the optimal treatment starting rule
- not yet employed

**Ideal Randomized Trial**

- multi-armed trial
- rule is *start HAART when CD4 measured below x*
- patients randomly assigned a value of $x$ between 201-750
- inclusion criteria of HAART-naive and CD4 in a certain range
- outcome is health status (utility) $k$ months after study entry.
- What rule maximizes health?
There are 550 possible initiation rules
Very large randomized trial would have few subjects per arm
  for example, 11,000 subjects implies only 20 per arm.
Borrow information by fitting flexible regression model.
Observational Data Mimicking Randomized Trial

- multi-armed trial
- inclusion criteria of HAART-naive and CD4 in a certain range
- rule is \textit{start HAART when CD4 measured below }x
- patients’ HAART/CD4 history consistent with which rules
- Not randomized so need to incorporate methods to address potential bias
- outcome is health status (utility) k months after “study entry”.
- What rule maximizes health?
Our Cohort

Comprehensive Care Center, Nashville TN

- Vanderbilt-Meharry Center for AIDS Research
- Outpatient clinic
- 2011 patients with at least 2 visits from 1998-2007
- Healthcare coverage available to virtually all HIV-infected Tennesseans

1034 Patients met Inclusion Criteria

- HAART/ART naive
- No prior AIDS-defining event
- CD4 within 200-749
Rule: *start HAART within 3 months of CD4 first measured below* $x$

$x$ was chosen to be 201-750.

3 months was chosen for practical reasons.
- patients come approximately every 3 months for a visit

Definitions
- Time 0 was chosen as time of first CD4 measurement below 750.
- Follow-up ended at death, Dec 31, 2007, or last clinic visit for persons LTFU.
- We considered health at $k=6, 12, 24, \text{ and } 36 \text{ months.}$
A. Utility 1: CD4 count–based

- Asymptomatic
- ADE, NADE
- Death

B. Utility 2: Quality of Life

- Asymptomatic
- Cytomegalovirus and fungal infections
- Pneumocystis carinii pneumonia
- Other ADE, NADE
- Death
Regimen Rules in Randomized Trial

Rule: *Start HAART within 3 months of CD4 first measured below x*

Suppose patient assigned $x = 400$

- if first CD4 measurement below 400 was 350 and patient started HAART within 3 months of this measurement, then patient was adherent to assigned rule.
  - Note: patient was also consistent with all rules from $x = 399, \cdots, 351$.

- if first CD4 measurement below 400 was 350 and patient did not start HAART within 3 months of this measurement, then patient was non-adherent to assigned rule.

- if patient started HAART before CD4 measured below 400 he would be non-adherent.
Regimen Rules in Observational Data

Rule: *Start HAART within 3 months of CD4 first measured below x*

With which x are each patient’s CD4 and HAART initiation history compatible?
### Assigning regimen rules compatible with patient data

**Table:** A few examples

<table>
<thead>
<tr>
<th>Patient</th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>400</td>
<td></td>
<td></td>
<td>350</td>
<td></td>
<td></td>
<td>HAART</td>
</tr>
<tr>
<td>B</td>
<td>250</td>
<td></td>
<td></td>
<td>300</td>
<td></td>
<td></td>
<td>HAART</td>
</tr>
<tr>
<td>C</td>
<td>350</td>
<td>180</td>
<td>190</td>
<td></td>
<td>200</td>
<td></td>
<td>HAART</td>
</tr>
</tbody>
</table>

Rules: *Start HAART within 3 months of CD4 measured below x*

- Patient A compatible with $x = 351, \ldots, 400$.
- Patient B compatible with no $x$, censored at month 4.
- Patient C compatible with no $x$, censored at month 5.
Assigning regimen rules compatible with patient data

### Table: A few more examples

<table>
<thead>
<tr>
<th>Patient</th>
<th>Month</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>D</td>
<td>400</td>
<td></td>
<td>HAART</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>400</td>
<td>250</td>
<td>HAART</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>450</td>
<td></td>
<td>250</td>
<td></td>
</tr>
</tbody>
</table>

Rules: *Start HAART within 3 months of CD4 measured below x*

- Patient D compatible with $x = 401, \ldots, 750$.
- Patient E compatible with $x = 251, \ldots, 750$.
- Patient F compatible with $x = 201, \ldots, 250$. 
Potential Bias

Observational Study

- Patients were not randomly assigned treatment rules
- Many patients not followed k months and so were censored.
  - artificial censoring
  - LTFU
  - end-of-study censoring
- Censored patients may be different than those remaining in study

We account for potential by incorporating covariates using inverse-probability weights.
Simple Illustrative Example:

- Women are twice as likely to remain in the study than men 
  (eg, 0.8 vs 0.4)
- Therefore a man who remains in the study is given twice as much weight 
  (eg, 1/0.8 = 1.25 vs 1/.4 = 2.5)

Logistic regression with covariates, both at time 0 and time varying, used to predict probability of remaining in the study/starting HAART at a specific month.

- Covariates: age, sex, race, injection drug use as HIV risk factor, most recent CD4, CD4%, HIV-1 RNA, time since most recent laboratory measurements, time in care.

Weights truncated at 2.5th and 97.5th percentiles
### Weighted Least Squares Regression

<table>
<thead>
<tr>
<th>id</th>
<th>x</th>
<th>y</th>
<th>w</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>301</td>
<td>100</td>
<td>1.1</td>
</tr>
<tr>
<td>1</td>
<td>302</td>
<td>100</td>
<td>1.1</td>
</tr>
<tr>
<td>1</td>
<td>303</td>
<td>100</td>
<td>1.2</td>
</tr>
<tr>
<td>1</td>
<td>304</td>
<td>100</td>
<td>1.2</td>
</tr>
<tr>
<td>1</td>
<td>305</td>
<td>100</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td>441</td>
<td>205</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>442</td>
<td>205</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>443</td>
<td>205</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Fit weighted least squares estimator of model

\[
E(Y_x) = \beta_0 + \beta_1 x + \beta_2 x^2 + \beta_3 x^3 + \beta_4 x^4 + \beta_5 x^5 + \beta_6 x^6
\]

.
Our Cohort

- 2011 patients with at least 2 provider visits
- 1034 met inclusion criteria
  - 430 excluded because first pre-HAART CD4 < 750 was under 200
  - 42 had no pre-HAART CD4 < 750
  - 232 had prior ADE
  - 240 had been on prior non-HAART ART
  - 33 had prior ADE and prior ART
- 73% male, 42% African American, 8% IDU
- median age 35 (IQR 28-42)
- median CD4 at study entry 403 (IQR 301-528)
- median follow-up 35 months (IQR 14-65)
- median visits per year 6.4 (IQR 4.5-9.5)
- 60% started HAART during follow-up; median time to HAART was 4.1 months (IQR 1.7-17.3)
- median CD4 prior to HAART was 342 (IQR 264-462)
93 (9%) died
82 (8%) had ADE (25 of these later died)
20 (2%) had an NADE (7 of these later died)

**Table:** Number with events and censored

<table>
<thead>
<tr>
<th>month</th>
<th>death</th>
<th>ADE</th>
<th>NADE</th>
<th>asympt.</th>
<th>Censored</th>
<th>LTFU</th>
<th>EOS</th>
<th>artif.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>3</td>
<td>11</td>
<td>8</td>
<td>852</td>
<td>79</td>
<td>40</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>14</td>
<td>10</td>
<td>715</td>
<td>115</td>
<td>96</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>18</td>
<td>24</td>
<td>11</td>
<td>519</td>
<td>176</td>
<td>170</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>32</td>
<td>33</td>
<td>14</td>
<td>390</td>
<td>217</td>
<td>211</td>
<td>137</td>
<td></td>
</tr>
</tbody>
</table>
Distribution of Regimen Rules

A. Histogram of HAART Initiation Rules
Distribution of Utility 1

C. Histogram of Utility 1

CD4 count–based Utility

Frequency
Illustrative Analysis

Distribution of Weights

B. Histogram of Inverse Probability Weights

Weights

Frequency

0
10000
30000
50000

1.0 1.5 2.0 2.5
Weighted Least Squares Regression

D. Utility 1 maximized at CD4 Rule = 554
Distribution of Utility 2

E. Histogram of Utility 2

Quality-of-Life Utility

Frequency
Weighted Least Squares Regression

F. Utility 2 maximized at CD4 Rule = 354
Estimates and 95% CI of optimal CD4 to initiate HAART

<table>
<thead>
<tr>
<th>Months</th>
<th>CD4 Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>300</td>
</tr>
<tr>
<td>12</td>
<td>400</td>
</tr>
<tr>
<td>24</td>
<td>500</td>
</tr>
<tr>
<td>36</td>
<td>600</td>
</tr>
</tbody>
</table>

- Utility 1
- Utility 2
### Secondary Analyses

**Restricting Candidate Rules to CD4=201-500**

**Table:** Estimated Optimal CD4 (95% CI)

<table>
<thead>
<tr>
<th>Utility</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CD4-based</td>
<td>495 (468-522)</td>
<td>554 (459-750)</td>
<td>489 (427-750)</td>
<td>509 (460-750)</td>
</tr>
<tr>
<td>2. CD4-based (rest.)</td>
<td>428 (413-500)</td>
<td>449 (402-500)</td>
<td>500 (402-500)</td>
<td>471 (410-500)</td>
</tr>
<tr>
<td>3. QOL</td>
<td>337 (201-442)</td>
<td>354 (288-386)</td>
<td>358 (294-750)</td>
<td>475 (287-750)</td>
</tr>
<tr>
<td>4. QOL (rest.)</td>
<td>341 (201-396)</td>
<td>355 (263-375)</td>
<td>371 (266-500)</td>
<td>384 (265-500)</td>
</tr>
</tbody>
</table>
## Secondary Analyses

### Efavirenz-based Regimens

**Table:** Estimated Optimal CD4 (95% CI)

<table>
<thead>
<tr>
<th>Utility</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CD4-based</td>
<td>495 (468-522)</td>
<td>554 (459-750)</td>
<td>489 (427-750)</td>
<td>509 (460-750)</td>
</tr>
<tr>
<td>2. CD4-based (EFV)</td>
<td>520 (493-550)</td>
<td>509 (428-559)</td>
<td>464 (418-554)</td>
<td>485 (413-577)</td>
</tr>
<tr>
<td>3. QOL</td>
<td>337 (201-442)</td>
<td>354 (288-386)</td>
<td>358 (294-750)</td>
<td>475 (287-750)</td>
</tr>
<tr>
<td>4. QOL (EFV)</td>
<td>286 (201-421)</td>
<td>320 (201-380)</td>
<td>337 (263-453)</td>
<td>336 (201-512)</td>
</tr>
</tbody>
</table>
### Other Utilities

**Table:** Estimated Optimal CD4 (95% CI)

<table>
<thead>
<tr>
<th>Utility</th>
<th>Months of follow-up (k)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CD4-based</td>
<td>554 (459-750)</td>
</tr>
<tr>
<td>2. QOL</td>
<td>354 (288-386)</td>
</tr>
<tr>
<td>3. Survival</td>
<td>201 (201-750)</td>
</tr>
<tr>
<td>4. ADE-free survival</td>
<td>201 (201-436)</td>
</tr>
<tr>
<td>5. ADE/NADE-free survival</td>
<td>327 (201-451)</td>
</tr>
<tr>
<td>6. CD4-based with regimen changes</td>
<td>414 (381-448)</td>
</tr>
<tr>
<td>7. QOL with regimen changes</td>
<td>201 (201-201)</td>
</tr>
<tr>
<td>8. CD4-based without NADE</td>
<td>563 (480-750)</td>
</tr>
<tr>
<td>9. QOL without NADE</td>
<td>334 (293-378)</td>
</tr>
</tbody>
</table>
Strengths
- Directly Estimated Optimal CD4 for starting HAART
- No arbitrary classifications needed
- Incorporated NADEs and other information
- Considered modern, EFV-based regimens

Limitations
- Smaller sample size and few events
- Results dependent on choice of utility
- Rules based on measured CD4 only
- Analyses ignore impact of HAART initiation on HIV transmission
- Observational study
Acknowledgements

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