Introduction

- Heterogeneity with regard to both rate of increase and apparent plateau of CD4+ T lymphocyte cell count (CD4) has been noted following effective antiretroviral therapy (HAART) initiation.
- A significant proportion of individuals who initiate HAART fail to achieve adequate quantitative CD4 reconstitution despite sustained viral suppression.
- Vitamin D has immunoregulatory functions and may serve as a potential target for intervention to improve CD4 recovery following HAART initiation.

Materials and methods

Study Sample and Design

- Participated were those studied in the Multicenter AIDS Cohort Study (MACS).
- Initiated HAART under observation
- Censored at 2 years post HAART initiation if viral suppression (HIV RNA<50 copies/mL) wasn’t achieved
- Those achieving viral suppression were censored at viral failure (HIV RNA>50 copies/mL) or administratively censored at end of study follow-up

Statistical Analysis

Adjustment of Vitamin D 25 levels for seasonal variation

- Linear regression model with 25(OH)D as the dependent variable and the season of blood collection as a categorical independent variable (January-March, April-June, July-September, October-December).
- Residuals of the model were added to the model intercept to adjust out the seasonal variation

Modeling of CD4 rebound following HAART initiation

- Negative exponential non-linear mixed effects model with three random effects used to model change in CD4 count after HAART initiation
- Exposure: Post-HAART 25(OH)D and 1,25(OH)2D measurements from immuno-affinity purification and liquid chromatography tandem mass spectrometry assay
- Examined covariates: CD4 at HAART initiation, Age at HAART initiation, black race, injection drug use (IDU) & pre-2000 HAART era
- Final model:

\[
\text{Mean}_{\text{CD4}} = \beta_0 + \beta_1 \times \text{Age} + \beta_2 \times \text{Years since HAART} + \beta_3 \times \text{CD4 at HAART} + \beta_4 \times \text{IDU} + \beta_5 \times \text{Pre-2000 HAART} + \varepsilon
\]

Reduction in e=10

Results

- There were 636 HIV-infected men with post HAART 25(OH)D and 1,25(OH)2D measurements and at least 1 CD4 measurement

Baseline Characteristics

- Serum 25(OH)D Group

<table>
<thead>
<tr>
<th>Serum 25(OH)D Group</th>
<th>Black</th>
<th>HAART ERA</th>
<th>HAART pre-2000 era</th>
<th>HAART 2000-2004 era</th>
<th>HAART pre-2004 era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>25.8</td>
<td>25.8</td>
<td>25.8</td>
<td>25.8</td>
<td>26.5</td>
</tr>
<tr>
<td>%</td>
<td>52.8</td>
<td>52.8</td>
<td>52.8</td>
<td>52.8</td>
<td>52.8</td>
</tr>
<tr>
<td>Median</td>
<td>14.9</td>
<td>14.9</td>
<td>14.9</td>
<td>14.9</td>
<td>14.9</td>
</tr>
<tr>
<td>SD</td>
<td>10.2</td>
<td>10.2</td>
<td>10.2</td>
<td>10.2</td>
<td>10.2</td>
</tr>
</tbody>
</table>

Conclusion

- There is substantial heterogeneity in the final CD4 asymptote achieved following HAART initiation, which is only partially explained by CD4 at HAART initiation.
- Levels of that active form of Vitamin D - 1,25(OH)2D - following HAART initiation appear to be associated with a small increase in the rate of CD4 recovery.

Acknowledgments

- The authors thank all the collaborators, staff, and participants of the Multicenter AIDS Cohort Study (MACS). Data in this manuscript were provided by the Multicenter AIDS Cohort Study (MACS) with centers at Baltimore, Chicago, Los Angeles, Pittsburgh, and Data Coordinating Center at the Johns Hopkins University Bloomberg School of Public Health.
- The MACS website is located at aidscohortstudy.org.
- The authors would like to thank all the collaborators, staff, and participants of the Multicenter AIDS Cohort Study (MACS). Data in this manuscript were provided by the Multicenter AIDS Cohort Study (MACS) with centers at Baltimore, Chicago, Los Angeles, Pittsburgh, and Data Coordinating Center at the Johns Hopkins University Bloomberg School of Public Health.

Serum 25(OH)D Group

- Black
- HAART ERA
- HAART pre-2000 era
- HAART 2000-2004 era
- HAART pre-2004 era

Distributions of Vitamin D and CD4

- Serum 25(OH)D Group
- Tertile 1
- Tertile 2
- Tertile 3

<table>
<thead>
<tr>
<th>Vitamin D description (25D: ng/mL)</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>16.9</td>
<td>16.9</td>
<td>16.9</td>
</tr>
<tr>
<td>SD</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Median</td>
<td>8.7</td>
<td>8.7</td>
<td>8.7</td>
</tr>
<tr>
<td>P-value</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Predicted CD4 rebound by CD4 at HAART initiation

- Estimated Parameter
- Effect of Post-HAART 25(OH)D (per 10 ng/mL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Asymptote</th>
<th>Time to 75%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptote</td>
<td>18 cells lower on average</td>
<td>0.11</td>
<td>0.58</td>
</tr>
<tr>
<td>Time to 75%</td>
<td>Median time 10% faster</td>
<td>0.71</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Overall Tertile 1 Tertile 2 Tertile 3

- Overall Tertile
- 1 Tertile
- 2 Tertile

<table>
<thead>
<tr>
<th>Vitamin D description (25D: ng/mL)</th>
<th>Overall Tertile 1</th>
<th>Overall Tertile 2</th>
<th>Overall Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptote</td>
<td>66%</td>
<td>44%</td>
<td>70%</td>
</tr>
<tr>
<td>Time to 75%</td>
<td>89%</td>
<td>0.9%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Correlation between:

- Rate of Decay and Intercept
- Rate of Decay and Asymptote
- Intercept and Asymptote

- Rate of Decay and Intercept
- 0.6 (i.e. Lower start, Faster rise)
- Rate of Decay and Asymptote
- 0.7 (i.e. Faster rise, Lower finish)
- Intercept and Asymptote
- 0.2 (i.e. Higher start, Higher finish)

The Adjusted Effect of Vitamin 25(OH)D

- Estimated Parameter
- Effect of Post-HAART 25(OH)D (per 10 ng/mL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Asymptote</th>
<th>Time to 75%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptote</td>
<td>2 cells higher on average</td>
<td>0.71</td>
<td>0.02</td>
</tr>
<tr>
<td>Time to 75%</td>
<td>Median time 3% faster</td>
<td>0.71</td>
<td>0.02</td>
</tr>
</tbody>
</table>

References