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When Does the CD4+ Cell Count Plateau? Evidence from Subjects Treated with a Lopinavir/ritonavir-based Regimen for Up to 7 Years

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Background

Suppressive combination antiretroviral therapy leads to a rapid increase in CD4+ T-cell counts during the first several weeks of therapy. Thereafter, the rate of CD4+ T-cell increase gradually decreases.

For various reasons, it remains difficult to determine how long CD4+ T-cell counts can continue to increase:

- Large intra-individual variability
- A relatively small number of studies with long-term data available
- Methodology for determining whether a plateau has been reached: graphical inspection is attractive for practical purposes but relatively subjective, and segmented linear models (analyzing week A to week B, week B to week C, etc., separately) are dependent on the choice of segments and may suffer from small sample sizes within each segment.

Previous studies have generally suggested a CD4+ T-cell count plateau 3–4 years after treatment initiation. We present an analysis using data from a 7-year study in antiretroviral-naïve subjects (Study 720) receiving a lopinavir/ritonavir (LPV/r)-based antiretroviral regimen evaluating whether CD4+ T-cell counts plateau in subjects receiving potent, suppressive antiretroviral therapy.

Methods

We analyzed CD4+ T-cell count changes from baseline in 100 antiretroviral-naïve subjects treated with LPV/r + stavudine + lamivudine for up to 7 years (360 weeks). Nonlinear regression was used to fit the following model to the CD4+ T-cell count data:

$$CD4 = \begin{cases} a + bt + ct^2 & \text{if } t < t_p \\ p & \text{if } t \geq t_p \end{cases}$$

This segmented model fits a quadratic relationship up to time t_p followed by a plateau (p) after time t_p (i.e., t_p is the time of plateau). The model fit requires the curve to be continuous (the sections meet at t_p) and smooth (the first derivatives or slopes are the same at t_p); therefore, the value of t_p is determined by the model fit (i.e., the model provides least-squares estimates of plateau time and plateau level).

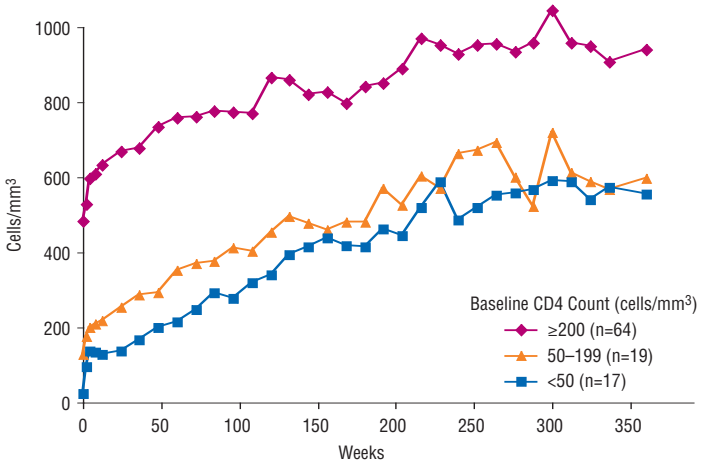
Separate models were fit by stratum of baseline CD4+ T-cell count (<50 cells/mm^3, 50–199 cells/mm^3, ≥200 cells/mm^3).

To assess the variability of the estimated time of plateau, bootstrap replications (n=4000) were performed for each stratum of baseline CD4+ T-cell count. The sample size of each replication was equal to the original sample size, with observations from the original data set selected randomly with replacement. The model-fitting procedure was repeated for each bootstrap replicate, and the distribution of resulting bootstrap estimates of plateau times was summarized by box-and-whisker plots.

Results

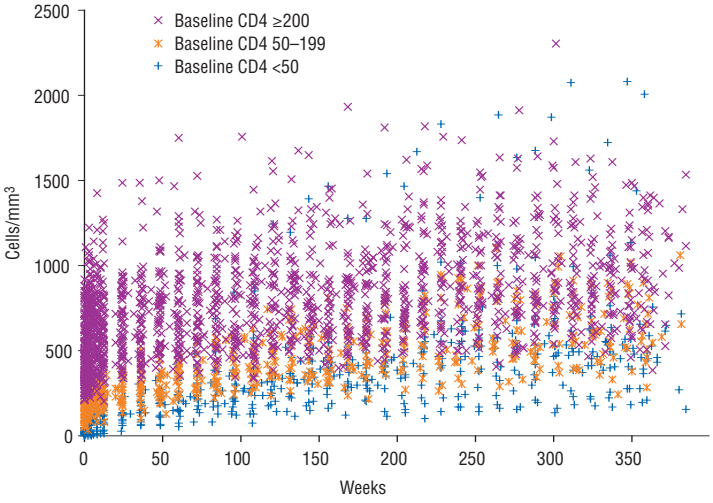
- 100 subjects were included in the analysis. 17 had baseline CD4+ T-cell count <50 cells/mm^3, 19 had baseline between 50 and 199 cells/mm^3, and 64 had baseline CD4+ count ≥200 cells/mm^3.
- Mean CD4+ T-cell count values over time are shown in Figure 1 by baseline CD4+ T-cell count category. Mean increases in CD4+ T-cell count from baseline to year 7 were 532, 476, and 495 cells/mm^3 for subjects with baseline CD4+ T-cell count <50, 50–199, and ≥200 cells/mm^3.

Figure 1. Mean CD4+ Cell Count Values Over Time in Study 720



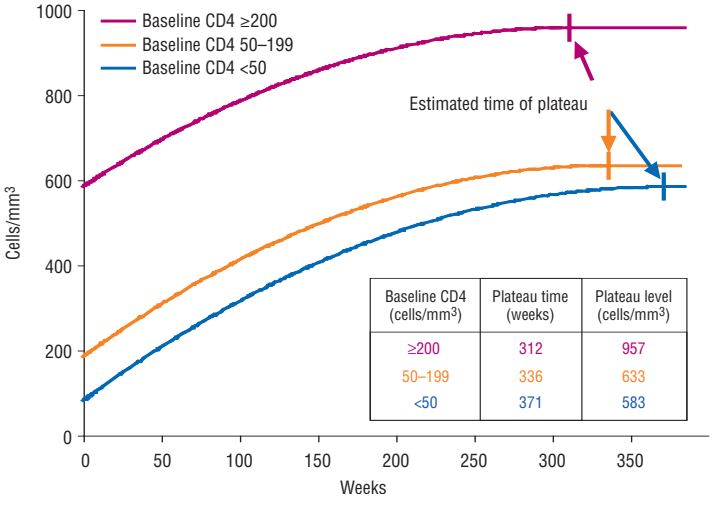
- Individual CD4+ T-cell count data across the entire study are displayed in Figure 2. At week 360 (or final visit, for subjects discontinuing prior to week 360), 91% of subjects had CD4+ T-cell counts above 350 cells/mm^3, 75% above 500 cells/mm^3, and the overall median was 740 cells/mm^3.

Figure 2. Individual CD4+ Cell Count Values Over Time in Study 720



- Fitted models are displayed in Figure 3. For subjects with baseline CD4+ T-cell counts <50 cells/mm^3, a plateau was observed beginning at week 371 at a level of 583 cells/mm^3. For subjects with baseline CD4+ T-cell counts between 50–199 or ≥200, corresponding values were week 336 at 633 cells/mm^3 and week 312 at 957 cells/mm^3, respectively.

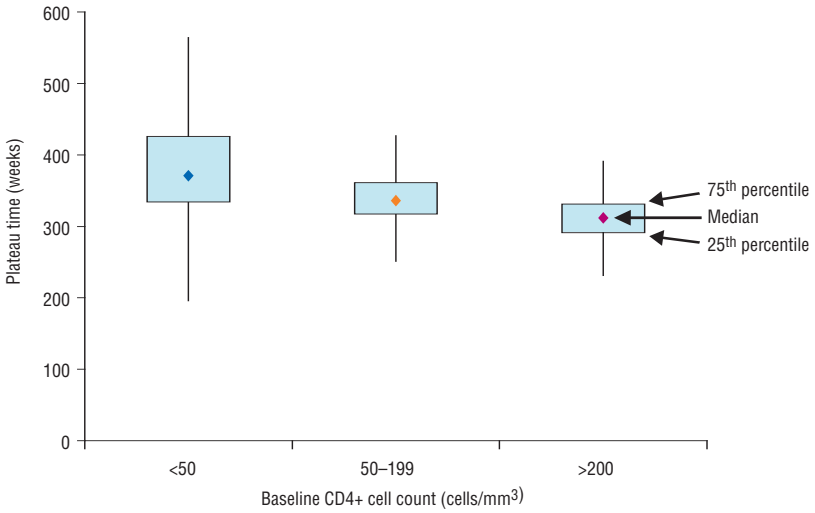
Figure 3. Fitted CD4 Cell Count Model with Estimated Plateau Time



Baseline CD4 (cells/mm^3)	Plateau time (weeks)	Plateau level (cells/mm^3)
≥200	312	957
50–199	336	633
<50	371	583

- Bootstrap replicates (see Methods) were used to assess variability of estimated plateau times. The distributions of estimated plateau times are displayed in Figure 4. The differences between the distributions of values for the <50 group compared to the ≥200 group suggest that CD4+ T-cell counts continued increasing for a longer period of time in those who started with very low CD4+ T-cell counts.

Figure 4. Box-and-Whisker Plots of Bootstrap Estimates of Plateau Times by Baseline CD4+ Count



Sensitivity analyses provided results similar to the primary analysis:

- Analyzing CD4+ T-cell count change from baseline instead of CD4+ T-cell count value: estimated plateau times were 302, 348, and 373 weeks for the ≥200, 50–199, and <50 groups, respectively.
- Analyzing only those subjects who completed the study: estimated plateau times were 310, 369, and 360 weeks for the ≥200, 50–199, and <50 groups, respectively.

Discussion

Determining the time at which CD4+ T-cell count is no longer increasing is challenging due to large within-subject variability and the gradually slowing rate of CD4+ T-cell count increase that is typically observed.

Unlike methods of graphical inspection and segmented linear models, our model provides an explicit estimate of the time of CD4+ T-cell count plateau. We used it to evaluate CD4+ T-cell counts in subjects treated with a LPV/r-based regimen for up to 7 years in study 720. Subjects with very low baseline CD4+ T-cell counts (<50 cells/mm^3) appeared to demonstrate increases throughout the entire 7-year treatment period, while those with higher baseline CD4+ T-counts reached a plateau between years 6 and 7. Notably, however, the group with lowest baseline CD4+ T-cell counts did not "catch up" to the other groups, and whether all subjects in that group will be able to achieve "normal" CD4+ T-cell counts, even with continued suppressive therapy, remains unclear. At the least, it would apparently require several more years of therapy.

Results of this study compare favorably with others analyzing long-term CD4+ T-cell count trajectories (Table 1) in subjects who have started on their first antiretroviral regimen. Compared to the only study that identified continued CD4+ T-cell count increases beyond 5 years (ATHENA cohort, Gras, et al. 2006), the current study using a LPV/r-based regimen compared favorably: mean increases from baseline to year 7 for subjects with baseline CD4+ T-cell counts of <50, 50–199, and ≥200 were 532, 476, and 495, respectively, for the current study, and 449, 429, and approximately 412, respectively, for the ATHENA cohort. The overall increases in the current study are consistent with reports that ritonavir-boosted PI regimens result in higher CD4+ T-cell increases compared to other regimens (Bartlett 2005) and that LPV/r-based regimens had larger annual increases compared to other boosted PI regimens (Mocroft 2006).

Table 1. Comparison with Other Studies Evaluating Long-term CD4+ T-cell Trajectories in Subjects Receiving Combination Antiretroviral Therapy.

Reference	Study	Follow-up time, No. of subjects	Summary of CD4+ T-cell count findings
Tarwater 2001	MACS cohort	3½ years n=314	Plateau at 2–3½ years after treatment initiation
Kaufmann 2002	Observational cohort (Australia)	4 years n=95	Plateau during the third year of treatment
Kaufmann 2003	Swiss cohort	4 years n=2235	Plateau after 2–3 years
Garcia 2004	Observational cohort (Barcelona)	~5 years n=861	Plateau after 4–5 years
Keruly 2006	Observational cohort (Baltimore)	5 years n=261	Plateau after 1–3 years
Le Moing 2006	APROCO cohort	5 years n=870	Plateau after 3 years
Esteve 2006	PISCIS cohort	5+ years n=1452	Plateau after 4 years except subjects with baseline <100 cells/mm^3
Gras 2006	ATHENA cohort	7 years n=529	Small increases between years 5–7 for subjects with baseline <500 cells/mm^3
Current analysis	Study 720	7 years n=100	Plateau between years 6 and 7 (baseline ≥50 cells/mm^3) or after year 7 (baseline <50 cells/mm^3)

Conclusions

- Based on a model that explicitly identifies a time of CD4+ T-cell count plateau, antiretroviral-naïve subjects treated with a LPV/r-based regimen had increases for at least 6–7 years.
- Subjects with lower baseline CD4+ T-cell counts had longer durations of CD4+ T-cell count increases (plateau after 7 years for subjects with baseline CD4+ <50 cells/mm^3, compared to a plateau at 6 years in subjects with baseline values of ≥200 cells/mm^3).
- However, CD4+ T-cell count values did not “catch up” to those who started with higher CD4+ T-cell counts at baseline.
- Results from this analysis of LPV/r-treated subjects compare favorably to previous studies that have suggested a plateau for CD4+ T-cell increases at earlier timepoints, lower final CD4+ T-cell counts, or both.

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