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Evidence of a Decrease in CD4 Recovery Once Back on Antiretroviral Therapy After Sequential ≥ 6 Weeks Antiretroviral Therapy Interruptions

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To the Editor

The implementation of short-term (less than 12 weeks) interruptions of suppressive antiretroviral therapy (ART)¹ is not uncommon in clinical management of HIV infection. Studies to date on planned, supervised, short-term ART interruptions (TIs) have shown that although sequential TIs do not result in decreased levels of viral rebound, they also do not seem to have a negative impact on the return of CD4⁺ T-cell count to preinterruption levels once ART is reinitiated and viral resuppression achieved. We have revisited this finding by assessing changes in CD4⁺ and CD8⁺ T-cell count in chronically suppressed HIV-1–infected subjects after a maximum of 8 sequential TIs and ART-mediated viral suppression.

Our study cohort comprised of 21 chronically suppressed HIV-1–infected subjects participating in 2 sequential studies based in Philadelphia: (a) an initial study of chronically suppressed HIV⁺ patients randomized to a maximum of 4 sequential TIs (2, 4, and 6 weeks and a final open-ended TI) (results from this study are described in PLoS medicine²) and (b) an observational study of 13 of the 21 subjects from the initial study, undergoing a maximum of 4 additional TIs (3 TIs of 6 weeks each and 1 open-ended TI). Recruitment characteristics were age ≥ 18 years, on ART (≥ 3 drugs), CD4 count >400 cells per microliter at entry with a history of nadir CD4 ≥ 100 cells per microliter, and plasma HIV-1 RNA (viral load) <50 copies per milliliter at entry with >6 months history of <500 copies per milliliter as described.² For analysis purposes, 2 groups were used as follows: (a) group 1 ($n = 21$): patients with number of TIs varying from 1 to 8 and (b) group 2 ($n = 11$): patients undergoing all 8 TIs. All ART interruptions were followed by resumption of ART and resuppression to plasma HIV-1 RNA <50 copies per milliliter before any subsequent TI. Clinical parameters (viral load and CD4⁺ and CD8⁺ T-cell count) were measured by Quest Diagnostics (Horsham, PA) every 4 weeks on ART and every 2 weeks during TIs. All subjects were recruited and followed at the Jonathan Lax Immune Disorder Clinic in Philadelphia. Informed consent was obtained from all patients in this study, and human experimentation guidelines of the US Department of Health and Human Services and of the authors' institutions were followed. Statistic analysis and modeling were performed using R, version 2.6.2.

Patients ($n = 21$) were followed for an average of 1079 days (standard error [STE] = 113.25 days). As expected, comparison of CD4⁺ and CD8⁺ T-cell count at beginning and end of each TI showed a decrease in CD4⁺ T-cell count when viral rebound was present (data not shown). To further assess how the CD4⁺ and CD8⁺ T-cell count change over time as a result of multiple

sequential TIs, mixed effect models were applied using the CD4⁺ and CD8⁺ T-cell count at the start of each TI when ART-mediated viral resuppression to plasma HIV-1 RNA <50 copies per milliliter was achieved (“TI baseline” values). The variation in measurement of CD4⁺ and CD8⁺ T-cell count that could be associated with the method used was also accounted in this model. Initial results for changes in TI baseline CD4⁺ T-cell count over time showed a significant 18.9% decrease from 683.91 cells per cubic millimeter (first starting mean CD4⁺ T-cell count baseline on ART) to 554.63 cells per cubic millimeter (last mean CD4⁺ T-cell count baseline on ART) over the entire period of 8 TIs ($n = 11$, $P = 0.001$). In further defining whether the decrease observed was equal across all TIs, an inflection point was applied to the model (Fig. 1). A significant change was not detected in TI baseline CD4⁺ T-cell levels for any of the groups during the first 4 TIs, though the point estimate for the slope was negative for group 2 ($n = 11$). In contrast, a significant trend of decrease in TI baseline CD4⁺ T-cell count was observed for both groups ($n = 21$, $P = 0.029$; $n = 11$, $P = 0.024$) after the fourth TI, which was also the first TI with duration longer than 6 weeks. Interestingly, no change was found in TI baseline CD8⁺ T-cell count on ART over the entire period of 8 TIs.

Conclusions of a decreased recovery of CD4⁺ T cells after ART reinitiation and viral suppression after each TI were also supported by 2 time point comparisons, using Wilcoxon signed rank tests, of CD4⁺ and CD8⁺ T-cell count at study entry and at baseline of each sequential ART interruption. Results showed a significant decrease in CD4⁺ T-cell count after the seventh (group 1: $P = 0.042$; group 2: $P = 0.019$) and eighth (group 1: $P = 0.007$; group 2: $P = 0.007$) interruption of ART. As observed before, no change was observed on CD8⁺ T-cell count at these time points for any of the analysis groups.

We now provide the first evidence of a potential “cost” of repeated TIs with duration ≥ 6 weeks on CD4⁺ T-cell count after reinitiation of the same ART regimen and achievement of viral suppression to <50 copies per milliliter. Although observations by us and others^{2–7} do not support an immediate immunological “cost” of short-term TIs (<6 weeks) on CD4⁺ T-cell count, our present findings now define a potential incremental 2%–3% “cost” in recovery of CD4⁺ T-cell count on ART after each TI of ≥ 6 weeks. Although therapy interruptions for clinical management purposes or due to other causes (therapy supply lapses in resource-limited settings) are likely to continue to occur, our data now shows that ≥ 6 weeks viral replication can have a limited but negative impact on the degree of recovery of immune reconstitution after ART reinitiation. However, it is also acknowledged that our data also reconfirms that short-term TIs are unlikely to affect immune reconstitution once on ART and that the limited impact on CD4 recovery, documented here for longer TIs, would not represent a major criteria by itself preventing a longer TI from being considered, if clinically warranted.

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REFERENCES

1. Azzoni L, Papasavvas E, Montaner LJ. Lessons learned from HIV treatment interruption: safety, correlates of immune control, and drug sparing. *Curr HIV Res* 2003;1:329–342. [PubMed: 15046257]

2. Papasavvas E, Kostman JR, Mounzer K, et al. Randomized, controlled trial of therapy interruption in chronic HIV-1 infection. *PLoS Med* 2004;1(3):e64. [PubMed: 15630469]
3. Dybul M, Chun TW, Yoder C, et al. Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: effects on virologic, immunologic, and toxicity parameters. *Proc Natl Acad Sci U S A* 2001;98:15161–15166. [PubMed: 11734634]
4. Dybul M, Nies-Kraske E, Daucher M, et al. Long-cycle structured intermittent versus continuous highly active antiretroviral therapy for the treatment of chronic infection with human immunodeficiency virus: effects on drug toxicity and on immunologic and viro-logic parameters. *J Infect Dis* 2003;188:388–396. [PubMed: 12870120]
5. Martinez-Picado J, Frost SD, Izquierdo N, et al. Viral evolution during structured treatment interruptions in chronically human immunodeficiency virus-infected Individuals. *J Virol* 2002;76:12344–12348. [PubMed: 12414975]
6. Ortiz GM, Wellons M, Brancato J, et al. Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. *Proc Natl Acad Sci U S A* 2001;98:13288–13293. [PubMed: 11687611]
7. Oxenius A, Price DA, Gunthard HF, et al. Stimulation of HIV-specific cellular immunity by structured treatment interruption fails to enhance viral control in chronic HIV infection. *Proc Natl Acad Sci U S A* 2002;99:13747–13752. [PubMed: 12370434]

FIGURE 1.

The CD4⁺ T-cell count over sequential therapy interruptions. Shown is estimated log₁₀ baseline CD4⁺ T-cell count for the group of 21 HIV-1-infected patients based on mixed effect model. The model is fitted with 2 slopes, with 1 inflection point at the fourth interruption. The random effects include the intercept and the first slope.