Correspondence

Class of Antiretroviral Therapy and CD4+ T Cell Count Recovery: Independence Questioned

To the Editor—I would like to congratulate Khanna et al. [1] for their study, which investigated risk factors associated with poor increases in the $CD4^+$ T cell count in a Swiss cohort of HIV-1–infected patients. A priori knowledge of these factors would be very useful in clinical practice to aid in the selection of the combination antiretroviral therapy (ART) regimen that is most likely to optimize immunologic recovery.

In terms of increases in the $CD4^+$ T cell count, however, Khanna et al. [1] reported "similar" (nonsignificant) effects for boosted protease inhibitors (PIs; 452 recipients; median increase, 343 cells/μL), nonnucleoside reverse-transcriptase inhibitors (NNRTIs; 251 recipients; median increase, 255 cells/μL), and nonboosted PIs (2590 recipients; median increase, 310 cells/μL). In contrast, a large, systematic review [2] reported significant differences in $CD4^+$ T cell count among recipients of these ART classes after 48 weeks of treatment: for boosted PIs (1002 recipients), the increase was 200 cells/μL; for NNRTIs (6705 recipients), the increase was 173 cells/μL; and for PIs (4602 recipients), the increase was 179 cells/μL. Importantly, the superior and statistically significant effect on the $CD4^+$ T cell count associated with boosted PI ART was also noted in multivariate analysis [2]. It remains uncertain whether the discordant conclusions of these 2 studies resulted from differences in statistical power, from the statistical model used (Cox vs. linear regression), or from bias adjustment.

I would also like to point out that, in the 2 studies cited in the Discussion section to support the absence of a statistically significant difference in effect between boosted PIs and NNRTIs, the one randomized study [3] included atazanavir without ritonavir—that is, a nonboosted PI.

In my opinion, the results reported by Khanna et al. [1] should not undermine the fact that PIs [4], but not NNRTIs, modulate activation of peripheral blood $CD4^+$ T cells and decrease their susceptibility to apoptosis, both in vitro and in vivo. This occurs independently of HIV replication inhibition [5]. Of note, low doses of ritonavir increase PI exposure to these cells, without additional hepatic toxicity, compared with administration of nonboosted PIs [6].

Of interest, the authors reported that hepatitis C virus (HCV)–coinfected individuals were significantly less likely to have an increase in the $CD4^+$ T cell count. They speculated, "Whether coinfection with HCV or a poorer adherence to ART in this group of primarily injection drug users is responsible for this observation remains to be shown" [1, p. 1099]. Of note, this group of patients was also significantly less likely to be prescribed boosted-PI ART (21% were HIV-HCV coinfected, compared with 35% of patients in the nonboosted PI group). Arguably, you cannot adhere to a regimen that your physician did not prescribe to you. It would be interesting to know whether HCV infection status remained significant in the subgroup of patients who had access to more-potent boosted PIs.

In conclusion, the superior effect of commencement of an ART regimen that includes boosted PIs should be considered in the context of risk factors for poor likelihood of recovery of the $CD4^+$ T cell count, including among HIV-HCV–coinfected persons.

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Reply to Parienti

To the Editor—Parienti [1] highlights important study results and findings regarding the effect of different combined

antiretroviral treatment (cART) modalities on increases in the $CD4^+$ T cell count and on immune reconstitution. In fact, many studies indicate that boosted protease inhibitor (PI) therapy, compared with nonnucleoside reverse-transcriptase inhibitor (NNRTI) therapy, leads to greater increases in the $CD4^+$ T cell count [2]. It is likely that the discrepancy between those data and the data from our study resulted from a larger number of included patients in the study by Bartlett et al. [2]. In that study, 53 trials were included in the analysis, for a total of 14,264 patients in 90 treatment arms. As a consequence, smaller differences between the study groups in the median $CD4^+$ T cell count after 48 weeks became statistically significant. However, it is unlikely that these small differences between treatment groups in the $CD4^+$ T cell count will have clinical consequences, such as a higher proportion of opportunistic infections.

Of importance, most of these studies reported that older age, lower baseline $CD4^+$ T cell count, and low baseline viral loads were followed by lower increases in the $CD4^+$ T cell count, regardless of whether those increases were measured in absolute numbers (compared with baseline values) or whether the study measured the percentage of patients who reached specific $CD4^+$ T cell count thresholds. Because many patients (~50%) who initiate combination ART switch treatment regimen during the first year of treatment [3], there has been a lack of long-term studies of immune recovery in the context of specific treatments or treatment modalities. A recent study in Switzerland found that 36 first-line regimens were initially administered and that, in 53% of cases, these regimens were changed during the first year [4]. Therefore, it is likely that questions such as which regimen is best for immune reconstitution can only be answered through large trials conducted over long periods. With this in mind, we cannot exclude the possibility that patients with suboptimal $CD4^+$ T cell count recoveries switched treatments earlier in the course of therapy, leading to a "leveling off," compared with different treatments received by patients remaining in the analysis [5].

It is impossible to judge whether this could have introduced a bias—in particular, bias against the effect of boosted PIs—in one direction or another. As noted by Parienti [1], we did not assess our patients with regard to the lower viral load threshold of 50 copies/mL, because with use of this criterion, the number of patients would have been too low to assess different unchanged treatments over such long periods. It would also be difficult to examine in larger cohorts, because "blips" may contribute to measurements >50 copies/mL. In our study, 34.4% of patients developed detectable HIV-1 RNA levels after month 6. In patients for whom HIV-1 RNA levels were consistently undetectable during the 48-month period and who received boosted PI therapy, an increase in the $CD4^+$ T cell count of 393 cells/μL was noted, compared with 274 cells/μL among patients with consistently undetectable levels who received NNRTI therapy—a difference of 119 cells/μL in favor of boosted PIs. However, the number of patients was too small and the interquartile ranges for $CD4^+$ T cell counts were too large to reach statistical significance in a multivariate regression model that compared immune responses. In addition, the median increases in the $CD4^+$ T cell counts did not differ significantly. As pointed out by Parienti [1], treatment with PIs may have had a positive effect on the increase in the $CD4^+$ T cell count, because apoptosis of these cells did not occur. This is a reasonable explanation for the slightly higher—but not significantly different—median $CD4^+$ T cell count in the boosted PI group. It was not our aim to examine specific treatment combinations for the contribution of individual drugs to immune reconstitution (i.e., for each drug combination in conjunction with differences in the nucleoside reverse-transcriptase inhibitor backbone) [6, 7]. However, we confirmed that zidovudine treatment led to significantly lower increases in the $CD4^+$ T cell count. In addition, hepatitis C virus–coinfected patients who received boosted PIs had significantly lower $CD4^+$ T cell counts at 48 months (410 vs. 593 cells/μL; $P = .03$).

As acknowledged by Parienti [1], our main finding—that $CD4^+$ T cell count increases were similar among persons who received different cART modalities—is meaningful [5]. Over the long term, most HIV–infected cART recipients experience normalization of $CD4^+$ T cell counts [8]. In that study, patients with low baseline $CD4^+$ T cell counts (<200 cells/μL) had significant increases in the $CD4^+$ T cell counts even after 5 years of cART. The study by Mocroft et al. [8] did not define which specific cART regimen was associated with the fastest normalization of the $CD4^+$ T cell count; however, the fact that patients who experienced optimal viral responses to treatment had increases in their $CD4^+$ T cell counts, even up to 5 years after commencement of cART, supports our findings. Thus, longer durations of cART and longer observation periods may yield or reveal similar increases in the $CD4^+$ T cell count. As stated above, switches in the regimen are frequently observed during the first year, and patients with more significant increases in the $CD4^+$ T cell count may have been selected. On the other hand, our findings provide an important piece of information for clinicians: if a patient tolerates a particular treatment regimen, and if the $CD4^+$ T cell count increases as expected during the first year of therapy, additional increases are to be expected.

We would like to support the notion that, for a given patient, it would be very useful to select an optimal regimen in terms of immunological recovery with prior knowledge of the risks. At this moment, for individual patients, it is difficult to assess specific risk factors and to determine which treatment, in the long term, is most beneficial in terms of immune reconstitution. Finally, we should acknowledge that individual immune responses

(such as cellular immune responses to specific pathogens), which are often determined on the basis of numeric and functional $CD4^+$ T cell count recovery, might not depend completely on $CD4^+$ T cell counts attained. The importance of specific immune responses was demonstrated in a recent study of the development of brain lymphoma in HIV-infected patients that occurred despite normal $CD4^+$ T cell counts [9].

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Fatal Acute Varicella-Zoster Virus Hemorrhagic Meningomyelitis with Necrotizing Vasculitis in an HIV-Infected Patient

To the Editor—A 41-year-old woman was transferred to our institution with a 2-day history of fever, headache, neck pain, and progressive flaccid quadriparesis. She had a background of HIV infection diagnosed 15 years earlier, with no prior AIDS-defining illness. Three weeks before presentation, her $CD4^+$ T cell count was 155 cells/μL (her nadir; $CD4^+$ cell percentage, 7%), and her HIV RNA level was 6000 copies/mL. One week later, antiretrovirial therapy (ART) was changed from lamivudine, nevirapine, and abacavir to lamivudine, raltegravir, and ritonavir-boosted atazanavir because of immunological and virological failure.

The patient was febrile (temperature, 38.6°C), drowsy, confused, and hypophonic and had neck stiffness and a flaccid quadriparesis. Reflexes other than triceps jerks were absent. Sensory findings were not evaluable. Results of cranial nerve examination were normal. Six vesicular lesions were noted on her anterior chest examination.

Results of brain CT were normal, and lumbar puncture revealed xanthochromic CSF. Opening pressure was 15 cm H_20; the patient's protein concentration was extremely elevated, at 39.0 g/L (normal range, 0.15–0.4 g/L), her glucose level was 2 mmol/L (normal range, 2.5–4.5 mmol/L), and her RBC count was 1400 cells/μL, with 40 polymorphs and 2 lymphocytes. Her serum glucose level was 6.9 mmol/L. Gram stain revealed no organisms. The patient's $CD4^+$ T cell count had decreased to 83 cells/μL (CD4 cell percentage, 9%). Assessment of HIV load was not performed.

Intravenous dexamethasone, acyclovir,

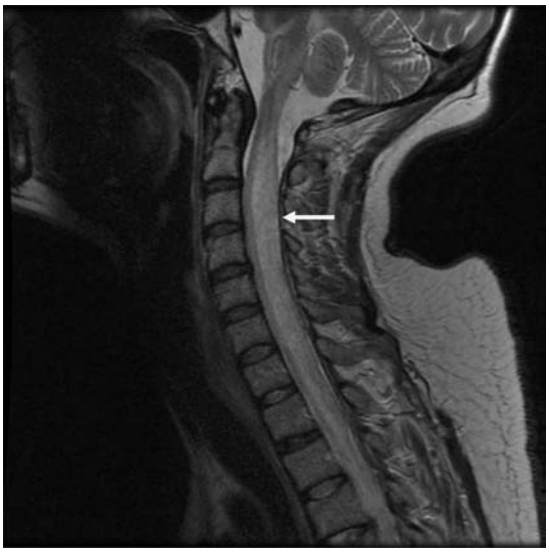

Figure 1. MRI of the patient's cervical cord. The T2 sequence demonstrated severe cord swelling suggestive of cord infarction.