14. Fabre LF, Clayton AH, Smith LC, et al. Association of major depression with sexual dysfunction in men. *J Neuropsychiatry Clin Neurosci.* 2013; 25:308–318.
15. Khera M. Patients with testosterone deficit syndrome and depression. *Arch Esp Urol.* 2013;66:729–736.

Immunodeficiency at the Start of Combination Antiretroviral Therapy: Steady Improvement or Step Changes?

To the Editors:

The IeDEA and ART-CC Collaborations[1] recently described CD4 cell counts at the start of combination antiretroviral therapy (cART) in low-, middle-, and high-income countries. The findings accurately highlight the global problem of HIV-positive individuals initiating cART at CD4 cell counts below those recommended currently in the treatment guidelines in 2002–2010. We believe, however, that the analysis could have benefited from 2 main additions.

First, the authors modeled CD4 at cART initiation linearly. This methodology does not allow for the expected nonlinear changes to CD4 at cART initiation as guidelines changed throughout the years of analysis. One would expect to see an increase in CD4 at cART initiation in 2006 and 2009 after changes to WHO guidelines recommending earlier antiretroviral therapy initiation.[2] Modeling techniques, such as restricted cubic splines,[3] would allow the CD4 at cART initiation to move freely by the year of cART initiation.

Second, as the authors point out in the discussion, one possible reason for lower median CD4 at cART initiation may be late presentation to HIV care.[4] The aim of this work is to aid delivery of public health strategies and interventions, so it is important to know if messages should be geared to more frequent testing or earlier treatment initiation. It would, therefore, be useful if the analysis could be stratified by those who started cART shortly after the first presentation to HIV care (eg, at the next visit after the first available CD4) compared with those under long-term follow-up.

Finally, it should be considered that median CD4 at initiation in this analysis is likely to overestimate the true median at initiation, as those who do not initiate are not included in this analysis.

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REFERENCES

1. Avila D, Althoff KN, Mugglin C, et al. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. *J Acquir Immune Defic Syndr.* 2014;65: e8–e16.
2. World Health Orginization. *Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach: 2010 Revision*. Geneva, Switzerland: WHO Press; 2010.
3. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med.* 1989;8:551–561.
4. Antinori A, Coenen T, Costagiola D, et al. Late presentation of HIV infection: a consensus definition. *HIV Med.* 2011;12:61–64.

Authors' Reply: Immunodeficiency at the Start of Combination Antiretroviral Therapy: Steady Improvement or Step Changes?

To the Editors:

We thank Ashley Olson et al[1] for their interest in our study of CD4 cell counts in more than 350,000 patients who started combination antiretroviral therapy (ART) from low-, middle-, and high-income countries during the years 2002–2010,[2] based on the International Epidemiological Databases to Evaluate AIDS[3] and the ART Cohort Collaboration.[4] In response to their first point, we found a steady increase in CD4 cell counts rather than step changes following the change in WHO guidelines on when to start ART in 2006 and 2009. We modeled CD4 counts both using additive and linear mixed-effects models, but there was virtually no difference in the fit of the 2 models. The effect of the change in the guidelines was thus gradual, rather than stepwise. This may be because of the understandable lag between a change in WHO guidelines and individual country-level implementation resulting in gradual rather than stepwise increases. Interestingly, our separate analysis of CD4 measures at the start of ART in children showed that trends were clearly nonlinear, although there was again little evidence of stepwise increases following guideline changes.[5]

We agree with Olson et al that the late presentation for HIV care is one reason for the late start of ART, and that stratifying the analysis by the time from presentation with HIV infection to start of ART would be interesting. Unfortunately, the date of the first presentation was not generally recorded in the cohorts participating in the International epidemiological Databases to Evaluate AIDS. Also, where recorded, the definitions of the first presentation varied. Of note, the first presentation will often not have taken place at the facility where ART was subsequently initiated.

Finally, we were a bit puzzled by the correspondents' statement "that median CD4 at initiation in this analysis is likely to overestimate the true median at initiation, as those who do not initiate are not included in this analysis." Surely, the CD4 count at initiation can only be studied in patients who initiate ART. However, as we discussed in our paper,[2] CD4 cell counts at the start of cART were missing in some patients, and these patients were more likely to be from low- and middle-income countries

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and in more advanced stages of HIV infection than patients with CD4 counts. It is thus likely that our estimates of median CD4 cell counts at cART initiation were biased upward for these countries.

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REFERENCES

1. Olson AD, Turkova A, Szubert AJ. Immunodeficiency at the start of combination antiretroviral therapy: steady improvement or step changes? *J Acquir Immune Defic Syndr*. 2015;68:e16.
2. Avila D, Althoff KN, Mugglin C, et al. Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries. *J Acquir Immune Defic Syndr*. 2014;65:e8–e16.
3. Egger M, Ekouevi DK, Williams C, et al. Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. *Int J Epidemiol*. 2012;41:1256–1264.
4. May MT, Ingle SM, Costagliola D, et al. Cohort profile: Antiretroviral Therapy Cohort Collaboration (ART-CC). *Int J Epidemiol*. 2014;43:691–702.
5. Koller M, Patel K, Chi BH, et al. Immunodeficiency in children starting antiretroviral therapy in low-, middle- and high-income countries. *J Acquir Defic Syndr*. 2014;68:62–72.