



## A games of T-cells: Can the CD4/CD8 ratio be a useful, actionable biomarker to improve outcomes in HIV



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### Abstract:

HIV treatment guidelines currently differ on whether or not the CD4/CD8 ratio of treated HIV patients has a role to play in clinical decision-making. Some Europeans guidelines find utility in the ratio while others either discourage following the ratio or are silent on the topic. Given that abnormally low CD4/CD8 ratios are associated with poorer response to vaccines and if severe enough (<0.4) higher morbidity and mortality, we looked at case series and individual clinical decisions such as switching to integrase inhibitors to determine to further our understanding of when normalization was possible. Cases were drawn from several different situations including Ethiopia, the Wisconsin Department of Corrections and our VA hospital. Surprisingly while it is more difficult to get ratio recovery in patients with very low CD4 counts, we found it does occur sometimes only after >5 years of therapy both in the US and in Ethiopia. In general ratio recovery occurs easier in younger patients and in females, which is consistent with data on the ratio from mice. We made a 3 minute video oriented to patients explaining what is known about ratio recovery in People Living with HIV. Future work need to delineate if the goal of ratio normalization for women should be higher than >1.0, and if the goal should be age appropriate or not.

International HIV Guidelines Regarding Monitoring Lymphocyte Subsets				
Guideline	CD4	CD8	CD4/CD8 Ratio	Notes
US Department of Health and Human Services (USDHHS) Adult and Adolescent HIV <sup>1</sup>	Absolute CD4 cell count at diagnosis, prior to ART, and every 3-6 months intervals (can be annual if CD4 > 500 - 550 cells/mm <sup>3</sup> for >2 years)	"Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful and is more expensive than monitoring CD4 count alone; therefore, it is not routinely recommended (BIII)"	CD4/CD8 Ratio	Ratings of recommendations: B (moderate)  Evidence of recommendations: III (expert opinion)
USDHHS Pediatric HIV <sup>2</sup>	Absolute CD4 cell count is recommended for monitoring immune status in children of all ages, with CD4 % as an alternative for children aged <5 years	No recommendation	No recommendation	Frequency of CD4 testing is dependent on age, time since diagnosis, and clinical stability
International Antiviral Society -USA Panel <sup>3</sup>	Absolute CD4 cell count at diagnosis, prior to ART, and every 3-6 months until HIV RNA is suppressed and CD4 cell count is above 350 for 3 years	No recommendation	No recommendation	
WHO HIV <sup>4</sup>	Absolute CD4 cell count at diagnosis	No recommendation	No recommendation	The use of CD4 cell count for ART response monitoring can be stopped in settings where routine viral load monitoring is available and people are stable on ART
British HIV Association <sup>5</sup>	Absolute CD4 cell count and percentage at diagnosis, prior to ART, and every 3-12 months depending on stability	No recommendation	No recommendation	
European AIDS Clinical Society <sup>6</sup>	Absolute CD4 cell count and % at diagnosis, prior to ART, and every 3-6 months (can be annually if stable on ART and CD4 count >350 cells/μl)	CD8 absolute count and % is optional at diagnosis, prior to ART, and every 3-6 months	Ratio is recommended at diagnosis, prior to ART, and every 3-6 months "CD4/CD8 ratio is a stronger predictor of serious outcomes"	No ratings of recommendations or evidence provided

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2. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at <https://aidsinfo.nih.gov/guidelines/html/2/pediatric-artv0>. Published 2017. Accessed January 30, 2018.  
3. Günthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. (1538-3598) (Electronic).  
4. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. July 2017. Geneva: World Health Organization; Available at <http://apps.who.int/iris/bitstream/handle/10665/255648/1/9789241550062-eng.pdf?ua=1>. Published 2017. Accessed January 30, 2018.  
5. British HIV Association guidelines on the routine investigation and monitoring of HIV-1-positive adults. Available at <http://www.bhiva.org/documents/GuidelinesMonitoring2016/BHIVA-Monitoring-Guidelines.pdf>. Published 2016. Accessed January, 2018.  
6. European AIDS Clinical Society Guidelines. Available at [http://www.easociety.org/files/guidelines\\_3.1-english.pdf](http://www.easociety.org/files/guidelines_3.1-english.pdf). Published 2017. Accessed January 30, 2018.

### Additional info and ongoing updates at: Gameoftcells.medicine.wisc.edu



Check out:  
GameofTcells.medicine.wisc.edu

for updates on epic battles the immune system has with cancer, a variety of microbes (viruses, bacteria, fungi, and parasites) as well as battles with itself.

#### References:

1. Santagostino, Alberto, Germano Garbaccio, and Angela Pistorio. "An Italian National Multicenter Study for the Definition of a Reference Ranges for Normal Values of Peripheral Blood Lymphocyte Subsets in Healthy Adults." *Haematologica* 84 (1999): 499-504. Web.
2. Shao, Ming-Jun, Yi-Jun Zhu, Ting-Er Qiu, Min Hu, and Yun-Qin He. "Changes in the Level of Immunoglobulins and CD4/CD8 Ratio in Young and Aged Mice with Estradiol Deficiency." *Immunological Investigations* 46.3 (2017): 305-13. Web.
3. McBride, J and Striker, R. "Imbalance in the Game of T cells: What the CD4/CD8 ratio can tell us about HIV and Health" *PLOS Pathogens* 2017
4. Serrano-Villar, S, Moreno, S et. Al. Different impact of the raltegravir versus efavirenz on CD4/CD8 ratio recovery in HIV infected patients *Journal of Antimicrobial Chemotherapy*, 2016

### Background:

- CD4 helper/inducer cells and CD8 cytotoxic/suppressor cells are two phenotypes of circulating T lymphocytes.
- The ratio of these two cell types has recently emerged as an indicator of a healthy immune system.
- Generally, ratios between 1.5 and 2.5 are considered normal; however, there are different factors that may impact this ratio, such as sex, age, ethnicity, genetics, and infections. Currently, there is no accepted "normal" CD4/CD8 ratio and definitions of "normal" vary across different hospital systems.
- With the advent of modern ART, the use of absolute CD4 count and HIV viral load no longer serve as accurate indicators of patient risks. The CD4/CD8 ratio may more accurately describe a patient's risk of immune dysfunction and the co-morbidities associated with this condition.
- Lower ratios are associated with worse outcomes.

### Data sources VA, UW and Ethiopia:

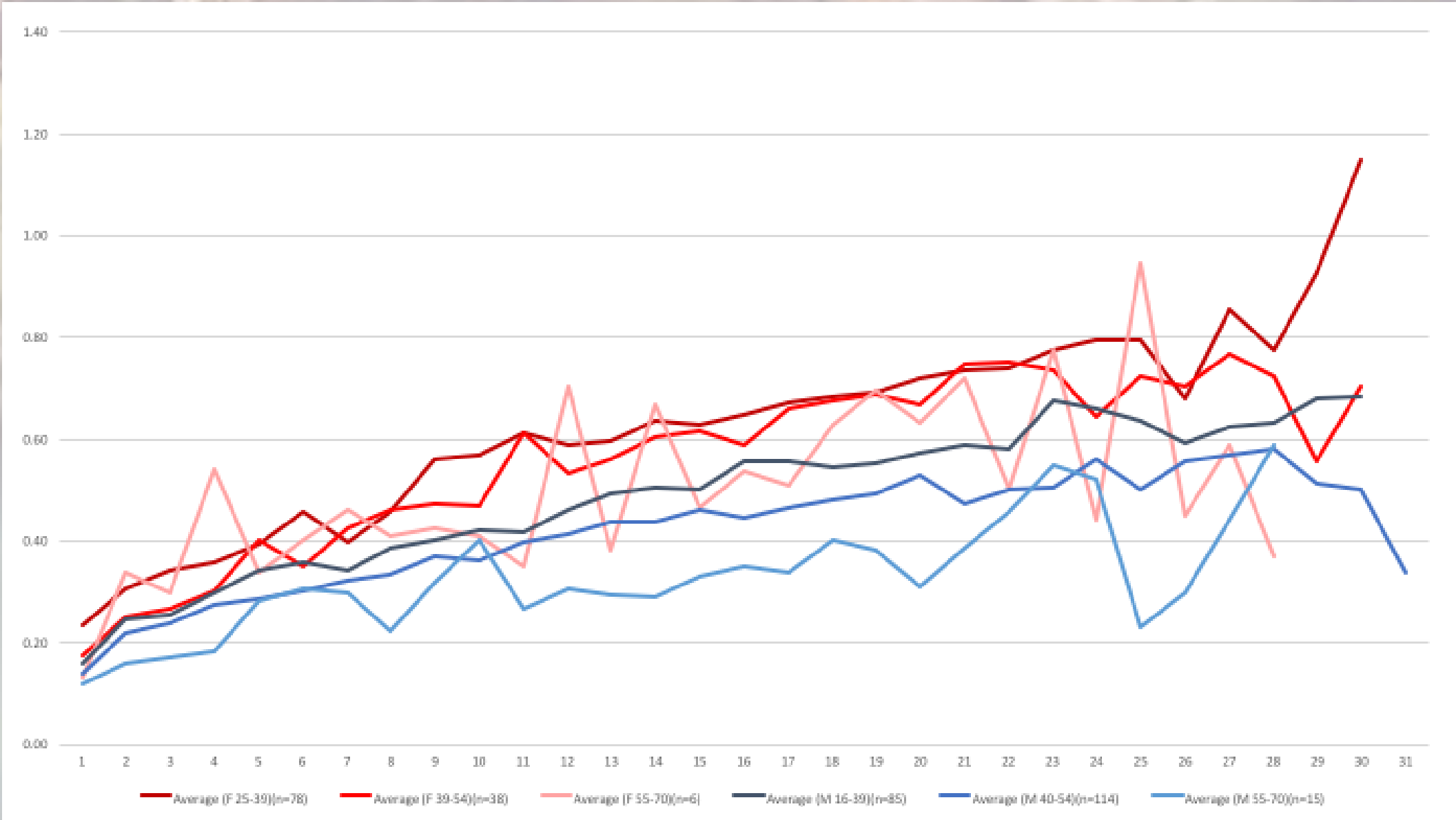


Figure 1: Composite of 336 Ethiopian patients on therapy, 2/3 males and 1/3 females over ~15 years. The group that is consistently above 1.4 is highly enriched for females, and the patients with no real improvement in the ratio is highly enriched for men.

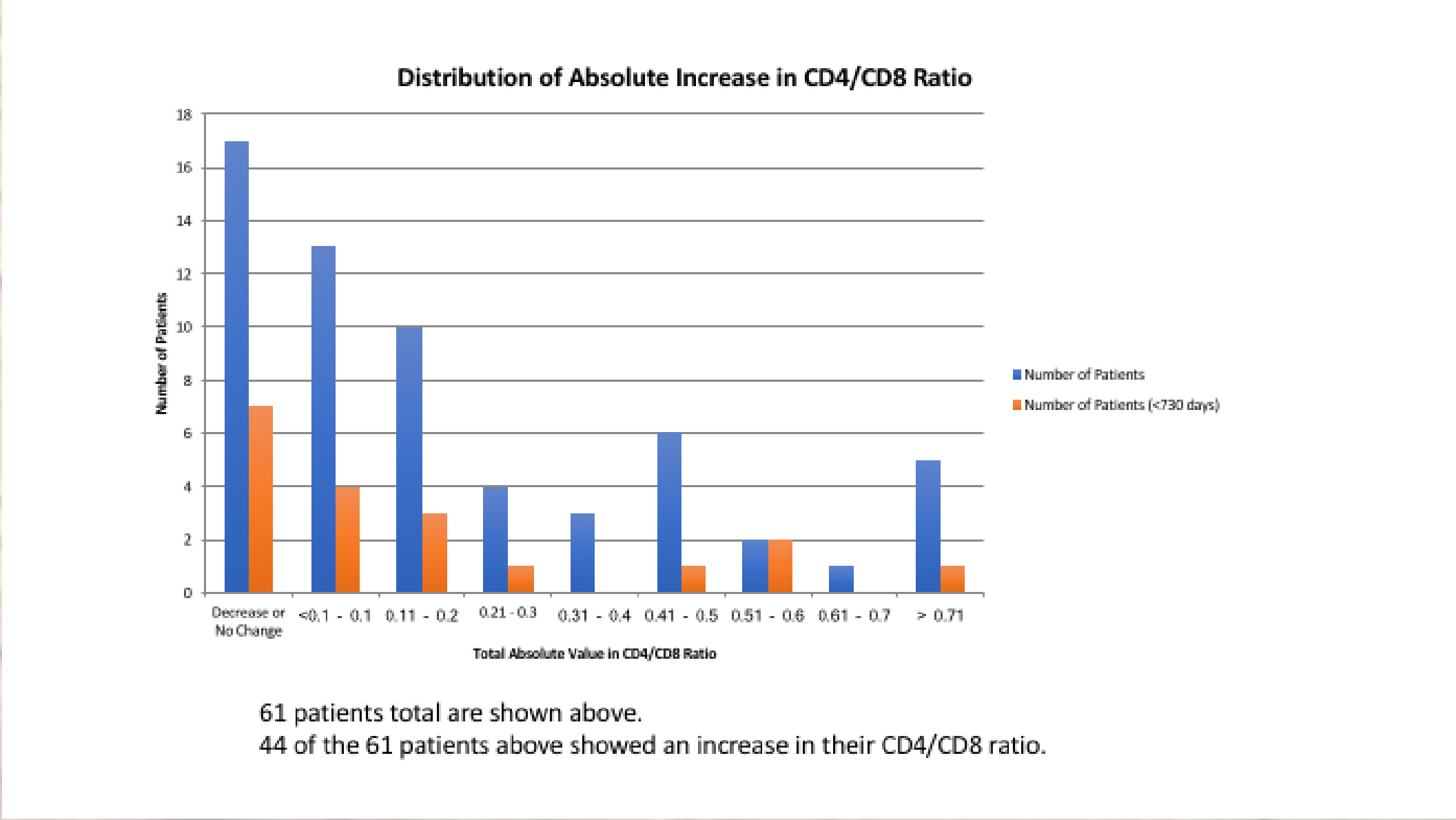


Figure 2: While there is wide variation generally patients with HIV who are incarcerated in the Wisconsin Department of corrections have a increase in their ratio, and this increase is associated with the length of incarceration, meaning the longer patients are incarcerated then the more likely for those entering with a low ratio, there will be a large improvement.

### Preliminary results:

### Ratio could be one measure of the reservoir and possible progression and recovery of HIV disease

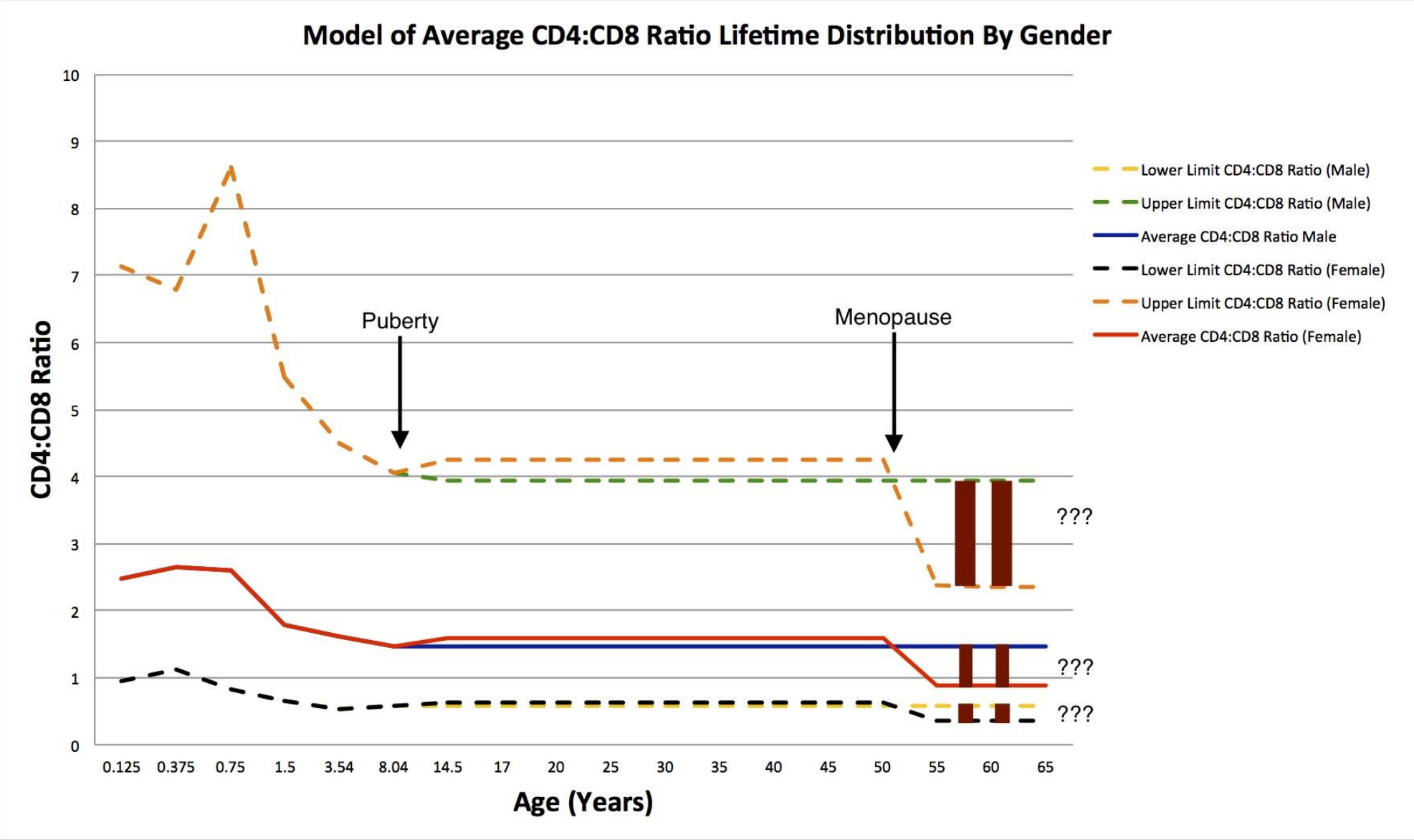


Figure 3: Large variance exists in post-menopausal women and a current range of a normal ratio is unknown (red bars)<sup>1,2</sup>.

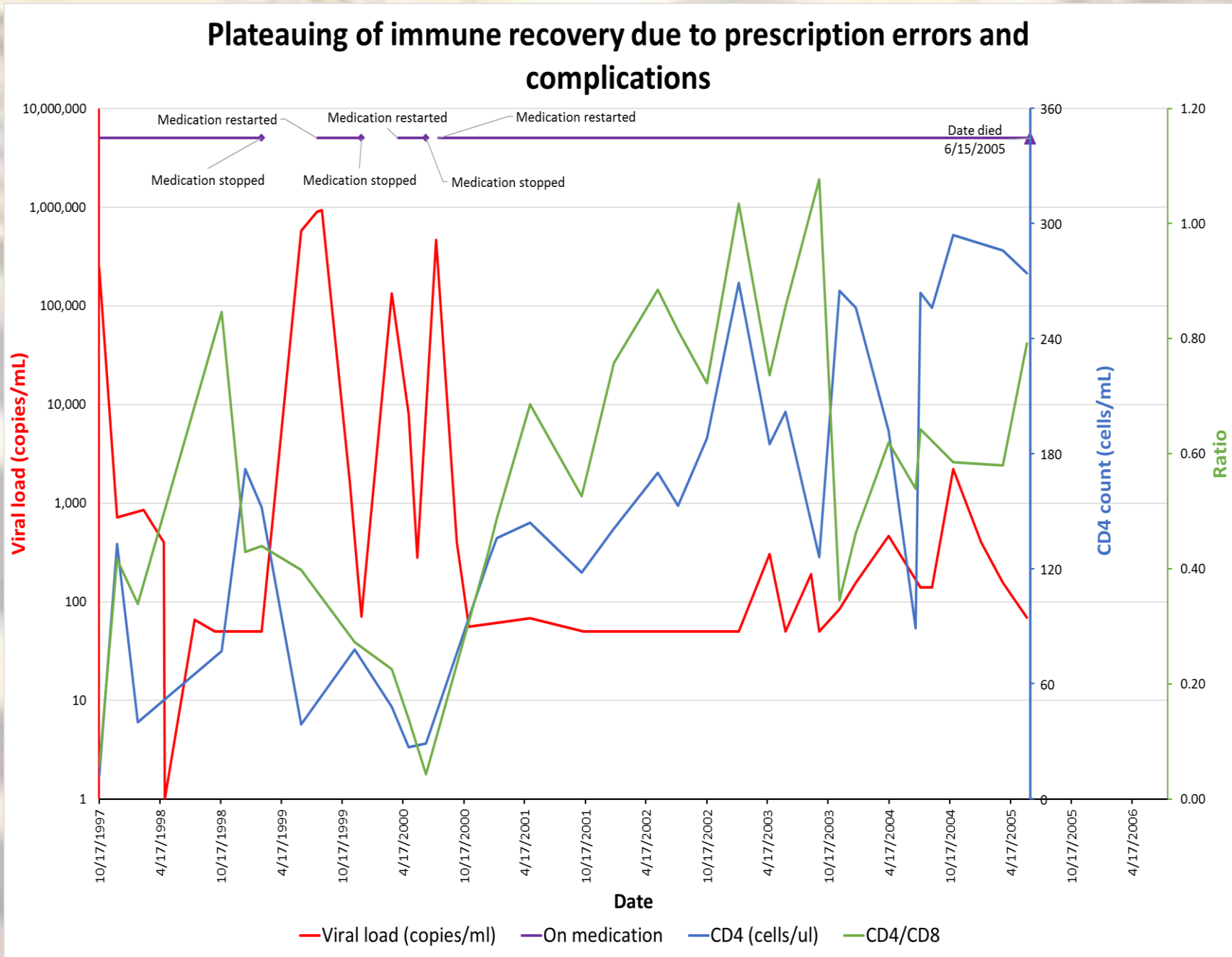


Figure 4: The patient showed good HIV suppression until pancytopenia (potentially due to ganciclovir) reduced both his CD4 and CD8 cells in October 2003. After that, despite the CD4 recovery, the ratio remained low corresponding to the rise in viral load.

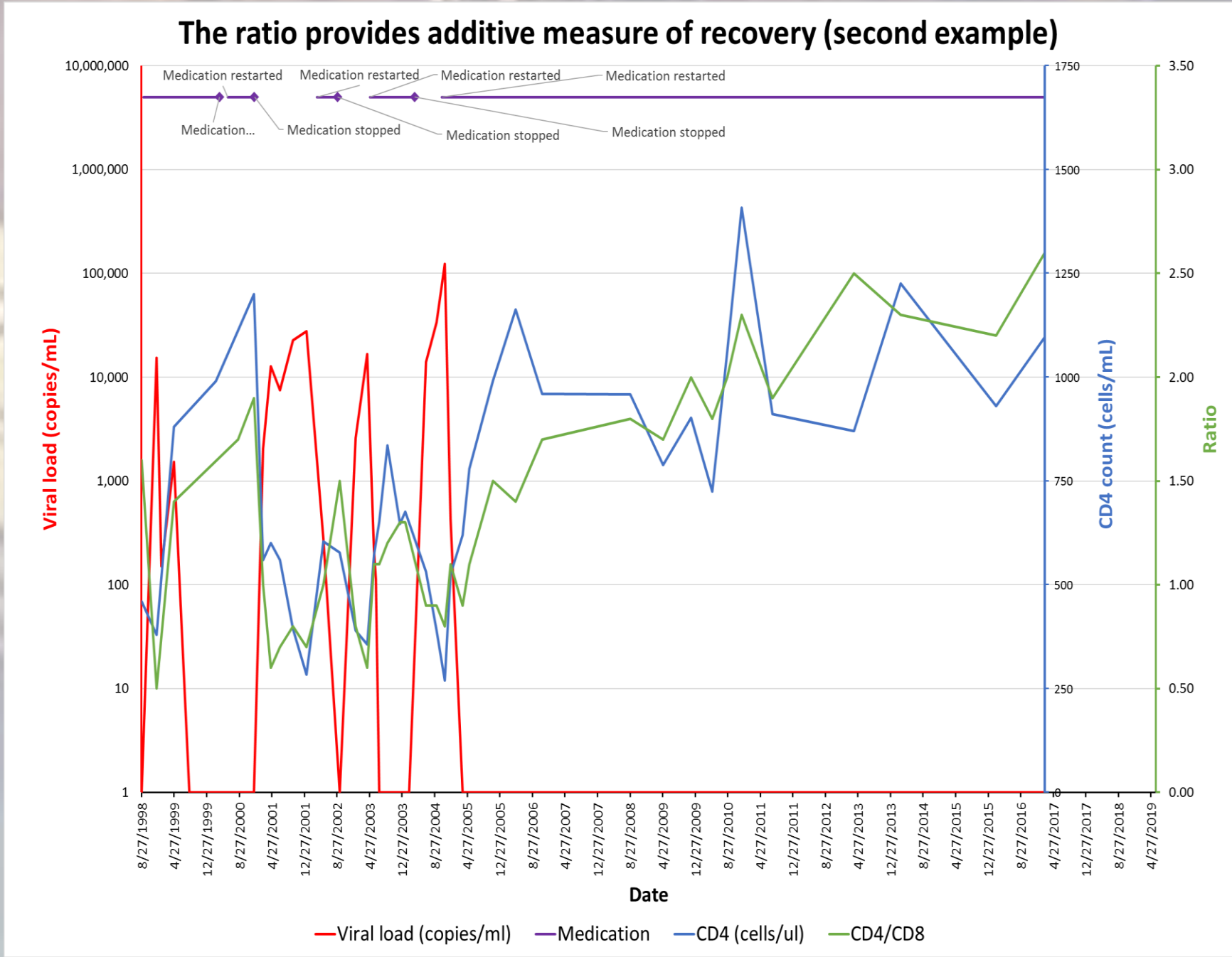


Figure 6: The CD4/CD8 ratio can be a potential additive measure of the recovery. The ratio fluctuated much less than the CD4 count corresponding more closely to the stability of the disease. In 2004 she switched to raltegravir/darunavir dual regimen.

### Possible Spoilers:

- HIV AB quantification may be an easy way to link ratio with reservoir.
- Treatment discontinuation occurs "naturally". Unfortunately, after prison discharge, will it be protective of viral relapse?
- Veteran's Affairs data contains NK immunological cell counts. Can machine learning uncover a new ratio?
- Should the goal of a cure be a supranormal ratio or balance?

### Acknowledgements:

