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 European guidelines find utility in the ratio while others do not exclude 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 integrate inhibitors to determine if ratio 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 a 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 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.

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:

Preliminary results:

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

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.

Figure 3: Large variance exists in post-menopausal women and a current range of a normal ratio is unknown (red bars).

Figure 4: This patient showed good HIV suppression ratio (pneumocystis potentially due to parasites) reduced both his CD4 and CD8 (left & right panel) after that despite the CD4 recovery, the ratio remained low corresponding to the rise in viral load.

Figure 5: This patient’s CD4 largely plateaued despite antiviral suppression but achieved a higher ratio with switch to a integrate containing regimen.

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

Figure 7: This patient is an example of a “Post-Treatment Control”. She was infected, became pregnant, and started therapy virtually simultaneously. These factors may have resulted in a low reservoir that could be controlled by her own immune system once HIV therapy was stopped.

Additional info and ongoing updates at: GameofCells.medicine.wisc.edu

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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:

References:


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


5. British HIV Association guide lines on the routine investigation and monitoring of HIV-1-positive adults. Available at


7. McIntosh, 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


10. 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