CD4:CD8 ratio and CD8+ cell count for prognosticating mortality in HIV-infected patients on antiretroviral therapy

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In people living with HIV (PLWH), immune compromise is largely due to a decrease in CD4$^+$ T-lymphocyte (CD4) cells, resulting in increased rates of human immunodeficiency virus (HIV)-associated morbidity and mortality as CD4$^+$ cell count declines. Previously, it was common to defer initiation of antiretroviral therapy (ART) in asymptomatic PLWH until their CD4$^+$ cell count declined below a certain threshold, which has changed throughout the years based on updated guidelines, increasing access to ART, and lower drug prices. There is increasing evidence that early initiation of combination ART/ highly-active ART offers benefit even in individuals with relatively high CD4$^+$ cell counts, as demonstrated in trials such as the Strategic Timing of Antiretroviral Treatment (START) study (1) and Temprano study (2).

The START trial was a randomized controlled trial that enrolled PLWH with a CD4$^+$ cell count greater than 500 cell/μL. The primary endpoint was any serious AIDS-related event, serious non-AIDS related event, or death from any cause. The findings in this trial showed that the primary endpoint occurred in significantly fewer individuals who were started immediately on ART rather than when their CD4$^+$ cell count dropped below 350 cell/μL. Furthermore, more than two-thirds of primary end points occurred in PLWH with a CD4$^+$ cell count over 500 cells/μL. The Temprano study was a 2-by-2 factorial, 1:1 superiority trial that enrolled PLWH with a CD4$^+$ cell count less than 800 cells/μL. Participants were enrolled into one of four treatment groups: deferred ART based on country-specific WHO criteria at the time of the study, deferred ART plus 6-month isoniazid preventive therapy (IPT), early/immediate ART initiation, and early/immediate ART plus 6-month of IPT. The primary end point was a composite of AIDS-related diseases, non-AIDS-defining cancer, non-AIDS-defining invasive bacterial disease, or death from any cause. The risk of death or severe HIV-related illness was independently lower in the early ART and IPT groups compared to the deferred ART and non-IPT groups.

As a result of these studies and others, there is widespread consensus that PLHW should be started on ART as soon as possible after HIV diagnosis to prevent unnecessary morbidity and mortality associated with deferred ART initiation. In addition, Temprano provided evidence that IPT can help prevent tuberculosis-related morbidity and mortality. Although most AIDS-related deaths occur in PLWH with a CD4$^+$ cell count <350 cells/μL, the results of these trials show that PLWH on ART with higher CD4$^+$ cell counts still experience significant morbidity and mortality from both infectious and non-infectious causes. The CD4$^+$ cell count and HIV RNA measurement (HIV viral load or VL) continue to be the two most commonly-used markers for monitoring immune recovery and treatment effectiveness for individuals on ART, but increasing evidence shows that these markers are insufficient for prognosis of non-AIDS related morbidity and mortality in individuals virally suppressed on ART. Are there other markers that may help predict

morbidity and mortality in this population?

$CD8^+$ T-lymphocyte ($CD8^+$) cell counts increase in response to acute infection and remain raised in HIV and other chronic infections. The CD4:CD8 ratio naturally decreases with age, is associated with increased mortality, and is a marker of both acute and chronic inflammation (3). Thus, it has been suggested that both $CD8^+$ cell count and CD4:CD8 ratio may be additional prognostic markers for morbidity and mortality in PLWH. Prior to ART initiation the combined $CD4^+$ and $CD8^+$ T-lymphocyte levels remain near constant, with a gradual decline of $CD4^+$ cells and increase in $CD8^+$ cells until the transition from HIV infection to AIDS, where a sharp decline in both $CD4^+$ and $CD8^+$ cells is observed (4). After initiation of ART, a negative correlation between changes in $CD4^+$ and $CD8^+$ cell count has been observed (5) with an increase in $CD4^+$ cell count and decrease in $CD8^+$ cell count. This suggests that a declining $CD8^+$ cell count or increasing CD4:CD8 ratio along, with undetectable HIV VL, could be markers for effective antiretroviral treatment and a good prognosis.

In a recent issue of *Clinical Infectious Diseases*, Trickey *et al.* report on their investigation into whether CD4:CD8 ratio or $CD8^+$ cell count is independently associated with all-cause, AIDS, and non-AIDS-related mortality in PLWH on ART with suppressed HIV VL and $CD4^+$ cell count ≥350 cells/μL (3). They used data from the Antiretroviral Therapy Cohort Collaboration (ART-CC), a collection of 13 European and North American cohorts of PLWH. Eligible participants were enrolled between 1996 and 2010, had to be ART-naïve, and were aged ⩾16 years of age when they started on ART with at least three antiretroviral drugs. Follow-up began after ART initiation when the participant's $CD4^+$ cell count first reached 350 cells/μL or greater, a $CD8^+$ cell count was first recorded, and HIV VL was <200 copies/μL or undetectable.

Primary outcomes were all-cause and cause-specific mortality hazard ratios for tertiles of CD4:CD8 ratio [0–0.40, 0.41–0.64 (reference), >0.64], $CD8^+$ cell count [0–760, 761–1,138 (reference), >1,138 cells/μL], and the shape of associations using cubic spines. Cause of death was determined by ICD-10 codes or free text, and for the latter classification two clinicians independently classified each death. If the cause of death could not be concluded from ICD-10 codes or free test, deaths were labeled as "unclassifiable", and if the cause of death was unknown, these deaths were labeled as "unknown". Deaths due to an AIDS-defining condition and/or that occurred when there was a $CD4^+$ cell count <100 cells/μL were classified as AIDS-related. All other deaths, excluding "unknown" deaths, were considered to be non-AIDS related.

For all individuals at 10 years, after initiation of ART mean $CD8^+$ cell count declined from 1,040 cells/μL at baseline to 942 cells/μL at 1 year and plateaued around 930 cells/μL, which is above the range of 209–924 cells/μL which is considered normal in the general population (6). Mean $CD4^+$ cell count increased steadily from 507 to 678 cells/μL at 10 years; mean CD4:CD8 ratio increased from 0.49 at baseline to 0.58 at 1 year, then more gradually to 0.73 after 10 years, still significantly lower than the mean CD4:CD8 ratio of 1.8 in the general population (6).

$CD8^+$ cell counts showed a U-shaped association with all-cause mortality, with the lowest mortality rates near the median $CD8^+$ cell count value and the highest rates at the $CD8^+$ cell count extremes. The highest all-cause mortality rate was associated with the highest $CD8^+$ cell counts. This association was statistically significant but not prognostic for all-cause mortality; CD4:CD8 ratio showed no association with all-cause mortality. Similarly, $CD8^+$ cell count had a U-shaped association with non-AIDS-related mortality, but this was neither statistically significant nor prognostic. There was no association with CD4:CD8 ratio and non-AIDS-related mortality. Conversely, $CD8^+$ cell count and CD4:CD8 ratio were both associated with AIDS-related mortality to a statistically-significant degree (P=0.016 and 0.037, respectively). AIDS-related mortality declined with increasing CD4:CD8 ratio and with decreasing $CD8^+$ cell count. The upper tertiles of both CD4:CD8 ratio and $CD8^+$ cell count were both prognostic for AIDS-related deaths. The adjusted hazard ratio (aHR) for AIDS-related mortality for the lowest versus middle (reference) tertile of CD4:CD8 ratio was 1.28 (95% CI, 0.95–1.73); the aHR for the highest versus middle tertile of $CD8^+$ cell count was 1.36 (95% CI, 1.01–1.84). Both CD4:CD8 ratio and $CD8^+$ cell count were prognostic for AIDS-related deaths to a statistically significant degree.

Thus, neither CD4:CD8 ratio nor $CD8^+$ cell count showed any prognostic ability to predict all-cause mortality in PLWH in this population. This study had a sample size of almost 50,000 individuals, which was significantly larger when compared to previous studies. Individuals included in this study came from a wide range of countries across a variety of high-resource settings, so these findings are likely to be generalizable to similar settings. Although the study authors found that CD4:CD8 ratio and $CD8^+$ cell count were not prognostic for all-cause mortality, there were other interesting observations from this study. Both low CD4:CD8 ratio and high $CD8^+$ cell count were associated

with increased all-cause mortality, suggesting that there was excessive AIDS-related mortality in a population with suppressed HIV VL and relatively high $CD4^+$ cell counts. Furthermore, $CD8^+$ cell count decreased sharply after ART initiation but remained elevated at a baseline above that of a general population. This suggests a need for early HIV diagnosis and ART initiation before the $CD8^+$ cell count elevates to levels that may be difficult to recover from.

Hoenigl *et al.* analyzed CD4/CD8 ratios in 90 individuals diagnosed with acute HIV infection (AHI) between 2007–2014 in relation to (I) signs and symptoms of AHI and (II) early versus delayed antiretroviral initiation (7). They found that CD4/CD8 ratios were significantly lower in those reporting signs and symptoms of AHI at the time of HIV diagnosis compared to those who did not report symptoms. In addition, lower CD4/CD8 ratios were associated with a longer duration of signs and symptoms of AHI and were observed in those who sought medical attention for their symptoms. Lastly, very early ART initiation (within 40 days of estimated date of infection) was associated with a significant increase compared to delayed ART initiation (greater than 40 days since estimated date of infection). Thus, very early ART initiation may lead to a greater increase in CD4/CD8 ratios.

We still have much to learn regarding why PLWH with reconstituted immunity still suffer greater morbidity and mortality from both infectious and non-infectious causes than the general population. Although $CD8^+$ cell count appears to be a marker for chronic inflammation, this biomarker alone does not appear to reliably prognosticate non-AIDS related mortality in PLWH. Further investigation into the pathogenesis of chronic inflammation associated with HIV, better candidate biomarkers to diagnose this, and better treatment options are all clearly warranted.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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