The immune profile in HIV: A useful signature in future HIV research?

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Despite widespread availability of effective antiretroviral therapy (ART), people living with HIV (PLWH) still experience excess morbidity and mortality relative to the general population, being driven primarily by non-AIDS, age-related conditions such as cardiovascular disease and malignancy. Globally, as the population of PLWH grows older, the relative contribution from these age-related conditions to overall morbidity and mortality is likely to increase.¹

Despite this increased risk of non-AIDS related conditions in treated PLWH, cohort studies have reported improvements in life expectancy in PLWH with some reporting estimates approaching that of the general population.^{2,4} This disparity between studies demonstrating higher comorbidity and mortality risk in PLWH, but yet, at least some, PLWH achieving normal life expectancies relative to the

general population suggests a heterogeneity of risk within populations of PLWH on effective ART. Although much research has focused on inflammation, immune dysfunction and microbial translocation as potential drivers of non-AIDS risk in PLWH, a strategy to identify vulnerable individuals at risk of non-AIDS conditions is currently lacking. However, current evidence does point to a central role for host immune responses to both HIV infection and ART, an individual's 'immune risk profile', which may play a central role in driving increased risk of non-AIDS morbidity.

Effective, immune-mediated host responses to viral infections are mediated through Th1 pathways, involving CD8+ T lymphocytes, natural killer (NK) T-cells and dendritic cells.⁵ HIV acquisition is often accompanied by a reduction in the CD4+ T cell count and an associated increase in the CD8+ T cell count resulting in an abnormal, inverted CD4:CD8 T-cell ratio. While viral suppression with effective ART may restore CD4+ T cell counts to pre-infection levels, the CD8+ T cell count often remains elevated with only a small proportion of PLWH normalizing their CD4:CD8 ratio.^{6,7} Associations between lower CD4:CD8 ratios and higher prevalence of non-AIDS comorbidities in treated PLWH has been demonstrated in a number of studies,⁸⁻¹⁰ suggesting an association between persistent immune dysfunction (reflected in failure to normalize the CD4:CD8 ratio) and adverse clinical outcomes.

The relationship between CD4+ and CD8+ responses to normalization of CD4:CD8 ratios (>1) were examined in a study by our group which demonstrated significant associations between higher naïve CD8+ T-cell populations and normalization of the CD4:CD8 ratios to >1,⁷ findings since validated in other studies.¹¹ These data suggest that, while lower CD4:CD8 ratios are associated with worse outcomes, higher CD4:CD8 ratios are associated with

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preserved naïve CD8⁺ T-cell repertoires, which in animal studies are associated with better antiviral immune responses¹² suggesting a link between individual immune responses to ART in PLWH and subsequent risk of non-AIDS morbidity and mortality.

Markers of T cell activation and exhaustion have also been shown to be increased in PLWH despite long-term viral suppression.¹³ However, whether these differences are driven by HIV infection itself or by co-infection by other viruses, specifically cytomegalovirus (CMV) is a subject of debate. A recent study of T cell senescence in a large, predominantly male population of participants with and without HIV, reported increased T-cell senescence in those with HIV that was largely explained by high rates of CMV co-infection, which exceeded 90% in the population of PLWH. Regardless of the underlying cause, such persistent T cell abnormalities in PLWH may be an important contributor to additional comorbidity and mortality risk within this population.

In addition to disturbances of the adaptive immune system, reflected in T-cell dysfunction, dysregulation of innate immunity, systemic inflammation and gut microbial translocation have also been consistently demonstrated in PLWH. In a study of ART-naïve PLWH who initiated therapy, we demonstrated persistently raised soluble CD14 (sCD14), a monocyte marker of innate immune activation. The CD14 receptor on monocytes binds bacterial lipoprotein polysaccharide (LPS), a by-product of gut microbial translocation. Consistent with these changes being driven by altered microbial translocation, we observed increases in intestinal fatty acid binding protein (iFABP), a marker of impaired gut endothelial integrity, accompanying the increases in sCD14 seen with ART initiation.¹⁴ These data are consistent with other studies in PLWH that have linked monocyte activation, lower CD4:CD8 ratio and systemic inflammation (interleukin 6 (IL-6) and D-dimer) with adverse outcomes such as accelerated atherosclerosis and both cardiac-related and all-cause mortality.^{15,16}

The relationship between persistent immune abnormalities and ART is complex. Although,

ART undoubtedly provides a survival benefit to PLWH through halting CD4⁺ T cell decline, reducing systemic inflammation and preventing AIDS illnesses, there is emerging evidence of independent changes to the CD8⁺ T cell count and CD4:CD8 ratio specific to the type of ART regimen used.^{17,18} Specific ART regimens may also independently impact an individual's risk of specific comorbidities, such as cardiovascular and bone disease. For example, the nucleoside reverse transcriptase inhibitor abacavir has been associated with both increases in platelet reactivity¹⁹ and lower expression of platelet-specific soluble glycoprotein VI, which is associated with cardiovascular events in the general population. These changes may explain the reversible increased risk of myocardial infarction observed in PLWH treated with abacavir.²⁰ Likewise, reductions in bone mineral density (BMD), also worsen after ART initiation and although the mechanism underlying this is unknown, there is some evidence suggesting an interplay between gut wall integrity and T cell differentiation upon ART initiation, which may perhaps explain these observed reductions in BMD.²¹

Although these data suggest that PLWH with persistent immune dysfunction (lower CD4:CD8 ratios, innate immune activation and systemic inflammation) are at higher risk of a number of non-AIDS co-morbidities, results of interventional studies targeting inflammation and innate immune activation to reduce co-morbidities in PLWH have generally been disappointing.^{22,23} This may reflect either poor choice of intervention or a failure within these studies to target those subjects with a specific host 'immune risk profile' who would benefit most from these interventions. We consider the current lack of detailed host profiling to identify those subjects who would benefit most from these interventions to be a significant factor holding back this important field of research.

There is increasing evidence that host genomics may play a part in immune responses to viral infections. For example, genotypic variation in interferon lambda genes can lead to differential expression of interferon lambda (IFNL), with commonly occurring

polymorphisms in IFNL4 associated with enhanced antiviral responses in chronic hepatitis C infection.^{24,25} Interestingly, IFNL is also necessary for effective gastrointestinal tract immunity,²⁶ which may have particular implications in HIV co-morbidities given the association between microbial translocation, innate immune activation and age-related morbidity and mortality. Further research is required to determine the role, if any, of these host genotypic characteristics and host immune response to HIV infection, which may in turn impact non-AIDS related morbidity and mortality.

It is becoming increasingly clear that not only are these biological pathways implicated in host responses associated with co-morbidities, but many are also implicated in effective host responses necessary to effect successful eradication of HIV infection. Clinical cure of HIV is a goal which has evaded researchers for a number of reasons, including the high genetic diversity of the HIV virus, the inability of PLWH to mount effective, HIV-specific antiviral immune responses and the ability of integrated HIV to persist in a latent form that escapes immunosurveillance but is capable of re-establishing infection upon ART interruption. Current cure strategies focus on the ‘shock and kill’ approach, which relies on inhibiting HIV replication with ART, ‘awakening’ latently infected cells using latency reversal agents (LRA) and intervening with therapeutic vaccines to induce host immune responses capable of identifying and eradicating infected cells.

Unfortunately, results from clinical trials of LRA have been disappointing, with poor host immune responses implicated²⁷ with the HIV-reservoir size in dormant T-cells an independent factor influencing development of favorable and unfavorable outcomes.²⁸ We would argue that the same inability to currently identify those individuals with the ‘immune risk phenotype’ that would favor a more robust antiviral immune response may also explain these disappointing results in human studies and point to a role for biologically phenotyping host responses to inform which host immune responses are necessary for effective cure

strategies. A host with a more dysfunctional immune profile, characterized by T-cell expansion and terminal T-cell differentiation with associated high levels of systemic inflammation and innate immune activation may not respond optimally when challenged with cure strategies relative to a profile characterized by greater naïve T-cell reserve and lower systemic inflammation.

Currently these views remain purely speculative and further work is required to explore and test whether there is an ‘immune risk phenotype’ or biological profile that determines outcomes in PLWH. However, these intriguing preliminary data suggest a potential to ‘biologically profile’ PLWH to identify specific groups: 1) those with profiles consistent with poor immune responses, persistent immune activation and/or systemic inflammation who carry a higher risk of comorbidities, and 2) those with optimal immune responses on ART, less inflammation and immune-profiles suggesting better antiviral immune responses who are potentially ideal candidates for cure strategies. Such a radical approach to host immune profiling has the potential to transform research into HIV comorbidities and HIV cure. Host immune profiling offers the potential to individualize goal-directed management of HIV, achieve optimal responses to specified treatments and interventions and ensure the correct resources are directed appropriately to those who would benefit from them most.

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