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

Padraig M. C. McGettrick[1,], Elena Alvarez Barco[2], Greg Kaminskiy[3], Patrick W. G. Mallon[4*]*

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 co-morbidities 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

[1]MB BCh BAO, MRCPI, HIV Molecular Research Group, UCD School of Medicine, Catherine McAuely Education and Research Centre, Nelson Street, Dublin 7, Dublin, Ireland, Department of Infectious Diseases, Mater Misericordae University Hospital, Eccles Street, Dublin 7, Ireland; [2]BSc, PhD, HIV Molecular Research Group, UCD School of Medicine, Catherine McAuely Education and Research Centre, Nelson Street, Dublin 7, Dublin, Ireland; [3]MD, National Medical Research Centre of Phthisiopulmonology and Infectious Diseases, Moscow, Russian Federation; [4]BSc FRACP MB BCh BAO PhD, HIV Molecular Research Group, UCD School of Medicine, Catherine McAuely Education and Research Centre, Nelson Street, Dublin 7, Dublin, Ireland, Department of Infectious Diseases, Mater Misericordae University Hospital, Eccles Street, Dublin 7, Ireland.

*Corresponding author: Padraig McGettrick, MB BCh BAO, MRCPI, HIV Molecular Research Group, UCD School of Medicine, Catherine McAuely Education and Research Centre, Nelson Street, Dublin 7, Dublin, Ireland, Department of Infectious Diseases, Mater Misericordae University Hospital, Eccles Street, Dublin 7, Ireland. Padraig.mcgettrick@ucd.ie

Article downloaded from www.germs.ro
Published June 2018

ISSN 2248 – 2997
ISSN – L = 2248 – 2997

preserved naïve CD8+ T-cell repertoires, which in animal studies are associated with better antiviral immune responses[12] 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 reactivity[19] 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 implicated[27] 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.

Conflicts of interest: PMCM has received sponsorship to attend meetings and conferences from Gilead Sciences, Janssen Cilag and MSD. EAB and GK have no conflicts of interests. PWGM is currently receiving grants to his institution, is serving on advisory boards and speaking engagements for, and/or receives honoraria from Gilead Sciences, Bristol Myers Squibb, Janssen Cilag, and MSD.

Funding: None to declare.

Authors' contribution statement: All authors have contributed equally to this manuscript.

References

1. McGettrick P, Barco EA, Mallon PWG. Ageing with HIV. Healthcare (Basel) 2018;6. pii: E17. [Crossref]

2. May MT, Gompels M, Delpech V, et al. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count

and viral load response to antiretroviral therapy. AIDS 2014;28:1193-202. [Crossref]
3. Patterson S, Cescon A, Samji H, et al. Life expectancy of HIV-positive individuals on combination antiretroviral therapy in Canada. BMC Infect Dis 2015;15:274. [Crossref]
4. Antiretroviral Therapy Cohort Collaboration. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet HIV 2017;4:e349-56. [Crossref]
5. Egli A, Santer DM, O'Shea D, Tyrrell DL, Houghton M. The impact of the interferon-lambda family on the innate and adaptive immune response to viral infections. Emerg Microbes Infect 2014;3:e51. [Crossref]
6. Leung V, Gillis J, Raboud J, et al. Predictors of CD4:CD8 ratio normalization and its effect on health outcomes in the era of combination antiretroviral therapy. PLoS One 2013;8:e77665. [Crossref]
7. Tinago W, Coghlan E, Macken A, et al. Clinical, immunological and treatment-related factors associated with normalised CD4+/CD8+ T-cell ratio: effect of naive and memory T-cell subsets. PLoS One 2014;9:e97011. [Crossref]
8. McGettrick P, Tinago W, Lacey A, et al. Incremental association between CD4:CD8 ratio and incidence of non-AIDS events. In: CROI 2016; 22-26 February 2016; Boston, MA, USA.
9. Serrano-Villar S, Pérez-Elias MJ, Dronda F, et al. Increased risk of serious non-AIDS-related events in HIV-infected subjects on antiretroviral therapy associated with a low CD4/CD8 ratio. PLoS One 2014;9:e85798. [Crossref]
10. Mussini C, Lorenzini P, Cozzi-Lepri A, et al. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: an observational cohort study. Lancet HIV 2015;2:e98-106. [Crossref]
11. Serrano-Villar S, Sainz T, Lee SA, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. PLoS Pathog 2014;10:e1004078. [Crossref]
12. La Gruta NL, Rothwell WT, Cukalac T, et al. Primary CTL response magnitude in mice is determined by the extent of naive T cell recruitment and subsequent clonal expansion. J Clin Invest 2010;120:1885-94. [Crossref]
13. Booiman T, Wit FW, Girigorie AF, et al. Terminal differentiation of T cells is strongly associated with CMV infection and increased in HIV-positive individuals on ART and lifestyle matched controls. PLoS One 2017;12:e0183357. [Crossref]
14. O'Halloran JA, Dunne E, Gurwith M, et al. The effect of initiation of antiretroviral therapy on monocyte, endothelial and platelet function in HIV-1 infection. HIV Med 2015;16:608-19. [Crossref]
15. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 2008;5:e203. [Crossref]
16. Ford ES, Greenwald JH, Richterman AG, et al. Traditional risk factors and D-dimer predict incident cardiovascular disease events in chronic HIV infection. AIDS 2010;24:1509-17. [Crossref]
17. Serrano-Villar S, Zhou Y, Rodgers AJ, Moreno S. Different impact of raltegravir versus efavirenz on CD4/CD8 ratio recovery in HIV-infected patients. J Antimicrob Chemother 2017;72:235-9. [Crossref]
18. Mussini C, Lorenzini P, Cozzi-Lepri A, et al. Switching to dual/monotherapy determines an increase in CD8+ in HIV-infected individuals: an observational cohort study. BMC Med 2018;16:79. [Crossref]
19. Satchell CS, O'Halloran JA, Cotter AG, et al. Increased platelet reactivity in HIV-1-Infected patients receiving abacavir-containing antiretroviral therapy. J Infect Dis 2011;204:1202-10. [Crossref]
20. O'Halloran JA, Dunne E, Tinago W, Denieffe S, Kenny D, Mallon PWG. Switching from abacavir to tenofovir disoproxil fumarate is associated with rises in soluble glycoprotein VI, suggesting changes in platelet-collagen interactions. AIDS 2018;32:861-6. [Crossref]
21. McGinty T, Mallon PWG. Fractures and the gut microbiome. Curr Opin HIV AIDS 2018;13:28-37. [Crossref]
22. Dube MP, Chan ES, Lake Je, et al. A randomized, double-blind, placebo-controlled trial of the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin for reducing inflammation and immune activation in treated and suppressed HIV infection: ACTG5346. In: Antivir Ther 22(Suppl 1):A14; 2017.
23. Hsue P, Ribaudo HJ, Deeks SG, et al. Impact of low dose methotrexate on immune activation and endothelial function in treated HIV. In: CROI; 4-7 March 2018; Boston, MA, USA.
24. Obajemu AA, Rao N, Dilley KA, et al. IFN-lambda4 attenuates antiviral responses by enhancing negative regulation of IFN signaling. J Immunol 2017;199:3808-20. [Crossref]
25. Fan W, Xie S, Zhao X, et al. IFN-lambda4 desensitizes the response to IFN-alpha treatment in chronic hepatitis C through long-term induction of USP18. TJ Gen Virol 2016;97:2210-20. [Crossref]
26. Lazear HM, Nice TJ, Diamond MS. Interferon-lambda: immune functions at barrier surfaces and beyond. Immunity 2015;43:15-28. [Crossref]
27. Thorlund K, Horwitz MS, Fife BT, Lester R, Cameron DW. Landscape review of current HIV 'kick and kill' cure research - some kicking, not enough killing. BMC Infect Dis 2017;17:595. [Crossref]
28. Matsuda Y, Kobayashi-Ishihara M, Fujikawa D, Ishida T, Watanabe T, Yamagishi M. Epigenetic heterogeneity in HIV-1 latency establishment. Sci Rep 2015;5:7701. [Crossref]

Please cite this article as: McGettrick PMC, Alvarez Barco E, Kaminskiy G, Mallon PWG. The immune profile in HIV: A useful signature in future HIV research? GERMS. 2018;8(2):54-57. doi: 10.18683/germs.2018.1131.