

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Role of Normalized T-Cell Subsets in Predicting Comorbidities in a Large Cohort of Geriatric HIV-infected Patient

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1655086> since 2018-10-29T17:41:03Z

Published version:

DOI:10.1097/QAI.0000000000001496

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

Role of Normalized T-Cell Subsets in Predicting Comorbidities in a Large Cohort of Geriatric HIV-infected Patient

Calcagno A^{1*}, Piconi S^{2*}, Focà E³, Nozza S⁴, Carli F⁵, Montrucchio C¹, Cattelan AM⁶, Orofino G⁷, Celesia BM⁸, Morena V⁹, De Socio GV¹⁰, Guaraldi G⁵ for the GEPPPO (GEriatric Patients living with HIV/AIDS: a Prospective Multidimensional cOhort) Study Group

1 Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino;

2 1st Division of Infectious Diseases Unit, University of Milano, Ospedale L. Sacco, Milano;

3 Department of Infectious and Tropical Diseases, University of Brescia

4 Department of Infectious Diseases, San Raffaele Scientific Institute, Milano;

5 University of Modena and Reggio Emilia, Department of Mother, Child and Adult Medicine and Surgical Science, Infectious Diseases Clinic, Modena;

6 Unit of Infectious Diseases, Department of Internal Medicine, Azienda Ospedaliero-Universitaria di Padova, Padova;

7 Unit of Infectious Diseases, "Divisione A", OspedaleAmedeo di Savoia, ASLTO2, Torino;

8 Department of Clinical and Molecular Biomedicine, Division of Infectious Diseases, University of Catania, ARNAS Garibaldi, Catania;

9 3rd Division of Infectious Diseases, University of Milano, Ospedale L. Sacco, Milano;

10 Department of Infectious Diseases, Azienda Ospedaliero-Universitaria di Perugia, Perugia;

Formattato: Italiano

*These two authors equally contributed to the study.

Running Head: Immunity and aging in HIV

Type of article: Concise Communication

Word count: 1751 (abstract 252)

Funding: This work was supported by internal funding.

Corresponding Author:

Andrea Calcagno,
Unit of Infectious Diseases,
Department of Medical Sciences, University of Torino
c/o Ospedale Amedeo di Savoia,
C.so Svizzera 164
10159, Torino, Italy
+390114393884, fax +390114393818
andrea.calcagno@unito.it

Formattato: Italiano

Abstract

Background: Adults aging with HIV are at greater risk for several comorbidities. The CD4+ cell count and CD4+/CD8+ ratio often fail to normalize in elderly patients despite prolonged antiretroviral therapy; this has been associated with concomitant diseases and poor prognosis.

Methods: A cross-sectional analysis in antiretroviral-treated HIV-positive patients aged ≥ 65 years. Aim of the study was to describe the predictors of normalized T cell subsets ("nT", CD4+/CD8+ ratio ≥ 1 and CD4+ ≥ 500 cells/uL) in a cohort of geriatric HIV-positive patients and its association with HIV-associated non-AIDS conditions (HANA).

Results: 1092 patients were included: nT was observed in 340 patients (31.1%). Multivariate binary logistic analysis showed that plasma HIV RNA < 50 copies/mL ($p=0.004$), female gender ($p=0.002$) and nadir CD4+ cell count ($p<0.001$) were independent predictors of nT. Age and gender-adjusted prevalence of hypertension ($p=0.037$), lipid abnormalities ($p=0.040$) and multimorbidity (MM, $p=0.034$) was higher in subjects with nT while chronic obstructive pulmonary disease (COPD) and cancer were lower (respectively $p=0.028$ and $p=0.005$). Multivariate analysis showed that HIV duration was an independent predictor of several comorbidities while nT was protective for cancer and COPD. HIV duration and nT were simultaneously predictors of MM.

Conclusions: Normalized T cell subsets were observed in approximately one third of geriatric HIV-positive subjects and they were predicted by female gender and immunovirological features. HANA conditions were more prevalent in patients with longer HIV duration while nT represented a protective factor for cancer and COPD.

Key words: CD4/CD8 ratio; aging; multimorbidity; non AIDS co-morbidities, COPD.

Introduction

The introduction of combination Antiretroviral Treatment (cART) profoundly changed the life expectancy of HIV-positive patients. By transforming a deadly infection into a chronic disease the number of elderly patients increased significantly: models estimate that the proportion of patients aged 60 years or older will increase from 8% to 39% in 2030.⁽¹⁾ Aging with HIV is seldom healthy and patients have to face the inevitable passage of time with additional burdens.⁽²⁾⁽³⁾⁽⁴⁾ HIV-infected patients age with several years of immune deficiency, chronic inflammation, co-infections and drug-associated toxicities: the longer the infection the higher the prevalence of comorbid conditions. The aging immune system faces several changes (including the reduction in CD4-T cell reserves, in naïve T cell anliad telomere shortening) that eventually lead to immune senescence and low grade inflammation (the so-called inflammaging).⁽⁵⁾⁽⁶⁾ In HIV-uninfected subjects the ratio between CD4+ and CD8+ T lymphocytes (CD4+/CD8+ ratio) represents a marker of T-cell function and an “inverted” value (<1) has been identified as a predictor of unfavourable outcomes in elderly individuals.⁽⁷⁾ In 85-90% of virologically suppressed cART-treated patients the CD4+/CD8+ ratio fails to normalize: low nadir CD4+ cell counts and advanced age have been identified as risk factors for incomplete immunological recovery.⁽⁸⁾ Several pieces of evidence confirm that a persistently low CD4+/CD8+ ratio during effective cART is associated with increased innate and adaptive immune activation, an immunosenescent phenotype and higher risk of morbidity/mortality in this group of individuals.⁽⁹⁾⁽¹⁰⁾ Aim of this study was to describe the predictors of normalized T cell subsets (“n-T” *i.e.* CD4+/CD8+ ratio ≥ 1 and CD4+ cell count ≥ 500 /uL) and its association with HIV-associated non AIDS conditions (HANA) in a cohort of HIV-positive patients above the age of 65.

Formattato: Inglese americano

Formattato: Inglese (Regno Unito)

Methods

The GEPPPO cohort (GEriatric Patients living with HIV/AIDS: a Prospective Multidimensional cOhort) is a multi-centric ongoing study in HIV-positive geriatric patients (≥ 65 years old) enrolled in ten Italian institutions. This study is a cross-sectional analysis of the entire GEPPPO cohort (n=1679) at initial visit (performed between June 2015 and May 2016) including patients with available CD4+ and CD8+ T-cell count. Inclusion criteria were: age older than 65 years, confirmed HIV-positivity, being on cART (combination AntiRetroviral Treatment) for at least 6 months. Ethics Committee approval was obtained from Research Ethics Board of each individual centers belonging to the GEPPPO cohort. All participants provided written consent at their initial clinical visit.

Study endpoints were the prevalence and the predictors of nT; secondary endpoint was the association of nT with comorbidities, multimorbidity (MM) and polypharmacy (PP). MM was defined as the presence of 3 or more HANA while PP as the regular consumption of 5 or more drugs beyond ARVs as previously described.⁽¹⁰⁾ Duration of HIV infection was calculated as the time between HIV diagnosis and last study visit. This variable was stratified into <10, 10-20 and >20 years duration groups. Laboratory results were included if within 6 months of the study visit.

Data are expressed as number (prevalence) or average (\pm standard deviation). Multivariate binary logistic regression was used for obtaining age and gender-adjusted associations between nT and HANA conditions. Stepwise multivariate binary logistic regression models were tested using clinically relevant and significant variable at bivariate parametric analysis ($p < 0.10$).

Results

A total of 1092 patients were included: their clinical and epidemiological features are described in Table 1 (and stratified by gender in supplementary Table). Their median age was 71.3 years (± 4.9 , range 65-91). nT was observed in 340 patients (31.1%); patients not presenting nT (nnT) were more likely to be male ($p = 0.01$), with lower nadir and current CD4+ cell count, higher CD8+ cell count and not virologically suppressed. No other statistically significant difference emerged between the two groups. No association between the number of ARV drugs (triple vs. dual vs. mono therapies) or the features of third drugs [protease inhibitors (PIs) vs. non nucleoside reverse transcriptase inhibitors (NNRTIs) vs. integrase strand transfer inhibitors (INSTIs)] and the prevalence of nT was observed. When we stratified patients for HIV duration we observed that 305 subjects (28.3%) were infected for >20 years, 511 (47.4%) between 10 and 20 years while 261 (24.2%) for <10 years. Current CD4+ cell count was higher in patients with longer infection [655 (>20 years) vs. 631 (10-20 years) vs. 579 (<10 years), ANOVA $p = 0.005$]; nadir CD4+ cell count was lower in those with HIV duration between 10 and 20 years [197 cells/uL ± 165 vs. 225 cells/uL ± 171 (<10 years) and 244 cells/uL ± 202 (>20 years), ANOVA $p = 0.002$]. CD4+/CD8+ ratio did not differ among HIV duration strata. The prevalence of nT was not higher in subjects with longer HIV duration [31.4% (<10) vs. 32.1% (10-20) vs. 29.8% (>20), $p = 0.796$]. At multivariate binary logistic analysis (including HIV duration and age) only plasma HIV RNA <50 copies/mL ($p = 0.004$, Beta 3.77, 95%CI 1.53-9.26), female gender ($p = 0.002$, Beta 1.75, 95%CI 1.22-2.51) and nadir CD4+ cell count (per 100 cells/uL increase $p < 0.001$, Beta 1.50, 95%CI 1.36-1.66) were independent predictors of nT.

The prevalence of specific HANA conditions, MM and PP is described in table 1. The prevalence of hypertension [172 (69.1%) vs. 336 (61.7%), $p=0.037$], lipid abnormalities [189 (75%) vs. 370 (68%), $p=0.040$] and MM [105 (55.6%) vs. 202 (46.7%), $p=0.034$] were significantly higher (age and gender-adjusted) in subjects with nT compared to nnT patients. Conversely the prevalence of COPD [8 (3.4%) vs. 43 (8.5%), $p=0.028$] and cancer [35 (15.5%) vs. 27 (25.2%), $p=0.005$] were significantly lower in nT patients (Table 1). When stratified for HIV duration the prevalence of HANA conditions was higher in patients with more than 20 years of infection: such a difference was statistically significant for bone disease (39.8% vs. 27.6% vs. 2.6%, $p=0.001$), cardiovascular disease (25.7% vs. 18% vs. 16.7%, $p=0.048$), lipid abnormalities (74.6% vs. 74.4% vs. 59.8%, $p<0.001$), diabetes (39.9% vs. 28.2% vs. 20%, $p<0.001$), cirrhosis (11.7% vs. 4.5% vs. 1%, $p<0.001$), COPD (11.1% vs. 4.6% vs. 6.4%, $p=0.015$) and multimorbidity (65.3% vs. 48.6% vs. 34.2%, $p<0.001$).

To explore whether nT was associated with HANA conditions or MM independently of HIV duration bi-variate (Fig.1) and multivariate binary logistic regression analysis were carried out. After correcting for age, gender, body mass index and n-T, HIV duration was an independent predictor of chronic kidney impairment, bone disease, lipid abnormalities, hypertension, diabetes and cirrhosis. n-T was independently protective for cancer and COPD. HIV duration and n-T were simultaneous predictors of multimorbidity.

Discussion

We observed that approximately one third (31.1%) of geriatric HIV-positive patients obtained normalized T cell subsets; female gender, a higher pre-cART CD4+ cell count and control of plasma viral load were associated with such immunological goal. The nT prevalence is not different from what observed in other studies where it ranged from 19 to 26% in younger subjects; using a 0.7 threshold this further increased to 37%.(8)(11) While CD4+ cell count nadir has been linked to nT in almost all studies, other predictors have been variably associated, such as treatment with non-nucleoside reverse transcriptase inhibitors, age and negative cytomegalovirus IgG serological results.(12)(13) Male and female seem to suffer the same age-related changes in the immune system; however males usually display a more rapid immune senescence and more commonly an inverted CD4+/CD8+ ratio.(14)(15) In our analysis female subjects, despite being only 17.5% of the cohort, had a significantly higher prevalence of nT than males (39.3% vs. 29.4%; $p=0.010$) and of normalized CD8+ cell percentage (73.3% vs. 60.6%, $p=0.001$). Our initial hypothesis was that the age of HIV acquisition might be a determinant for insufficient T cell normalization as it is relevant for the prevalence of several comorbidities.(9) We observed no effect of longer HIV

duration on the probability of reaching normalized T cell subsets, though our results may be biased by a lower CD4+ cell count at nadir in the intermediate HIV duration range. The strongest predictor of a nT was the presence of controlled plasma HIV viral load. Persistent low level viremia has been associated with microbial translocation and inflammation.(16) Furthermore lifelong cumulative HIV viremia has been associated with the CD4+/CD8+ ratio recovery in a cohort of patients followed since primary infection and persistent low level viremia (measured as viremia-copy-years) has been associated with a high risk of all-cause mortality in HIV-infected patients.(17)(18) These pieces of evidence highlight the need for optimal viral control (potentially including other chronic infections such as cytomegalovirus) to improve the function of a senescent immune system.

In this study we also observed a very high prevalence of comorbidities; almost half of the included patients fulfilled the multimorbidity criteria. This is in line with the observed and projected data in HIV-positive subjects and shows a higher prevalence than in age-matched negative individuals.(10)(1) In younger HIV-positive subjects the association of an inverted CD4+/CD8+ ratio with several comorbidities has been reported. Nonetheless data in elderly individuals are limited and affected by a relevant survival bias. In our study we observed a significantly higher prevalence of multimorbidity, independently from traditional risk factors, in individuals with normalized T cell subsets; these surprising results might be explained by several years of cART-associated toxicities (and confirmed by the higher prevalence in patients with longer HIV duration) and they may represent a survivor effect where other factors (including health conditions, body mass index and genetics) have affected the outcome of major cardiovascular disorders. On the other hand normalized T cell subsets were protective for COPD and non-AIDS cancers independently from the duration of HIV infection and antiretroviral treatment. Both diseases, COPD and non AIDS-cancer, require immune vigilance and it seems reasonable that a normalized T cell count might be associated with a lower prevalence of such conditions. Recent evidence confirms our results since low CD4/CD8 ratio has been associated with non AIDS-defining cancers in patient on cART and a ratio <0.5 could identify patients who require a more intensive strategy for cancer prevention and screening.(19) Other data, also, showed that HIV suppression normalizes peripheral and lung immunity in smokers reducing the risk of COPD.(20) The association between a normalized CD4+/CD8+ ratio and a lower prevalence of comorbidities and cancers is still uncertain: the reduction in PD1 expression on CD8+ cells in patients with high CD4+/CD8+ ratios may determine a better immunological effectiveness as well as an improved response to vaccines.(9)(21)

We should acknowledge a few limitations of this study: the cross-sectional design, the lack of cytomegalovirus serology and titer, the lack of specific T cell subpopulations. The single-point

evaluation and the lack of blood pressure measurements in all patients warrant caution in interpreting the observed association with hypertension.

In conclusion 31.1% of geriatric HIV-positive subjects have normalized T cell subsets; higher CD4+ nadir, female gender and plasma HIV RNA undetectability were independently associated with this endpoint. n-T was independently associated with hypertension and protective for cancer and COPD. HANA conditions were more common in patients with more than 20 years of infection that represents an independent predictor of chronic kidney impairment, bone disease, lipid abnormalities, hypertension, diabetes and cirrhosis. Both HIV duration and nT were simultaneous predictors of MM. According to these results the normalization of T-cell subset is uncommon in geriatric HIV-positive patients but it is protective for certain comorbidities. Beside earlier cART initiation specific strategies for improving the immune system in elderly HIV-positive subjects are needed.

References

1. Smit M, Brinkman K, Geerlings S, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. *Lancet Infect Dis*. 2015 Jul;15(7):810–8.
2. Calcagno A, Nozza S, Muss C, et al. Ageing with HIV: a multidisciplinary review. *Infection*. 2015 Oct;43(5):509–22.
3. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2011 Dec;53(11):1120–6.
4. Hogg RS, Eyawo O, Collins AB, et al. Health-adjusted life expectancy in HIV-positive and HIV-negative men and women in British Columbia, Canada: a population-based observational cohort study. *Lancet HIV*. 2017 Mar 2;
5. Rickabaugh TM, Kilpatrick RD, Hultin LE, et al. The dual impact of HIV-1 infection and aging on naïve CD4 T-cells: additive and distinct patterns of impairment. *PLoS One*. 2011 Jan 26;6(1):e16459.
6. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014 Jun;69 Suppl 1:S4–9.
7. Strindhall J, Nilsson B-O, Löfgren S, et al. No Immune Risk Profile among individuals who reach 100 years of age: findings from the Swedish NONA immune longitudinal study. *Exp Gerontol*. 2007 Aug;42(8):753–61.
8. Castilho JL, Shepherd BE, Koethe J, et al. CD4+/CD8+ ratio, age, and risk of serious noncommunicable diseases in HIV-infected adults on antiretroviral therapy. *AIDS Lond Engl*. 2016 Mar 27;30(6):899–908.

9. 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 May;10(5):e1004078.
10. Guaraldi G, Zona S, Brothers TD, et al. Aging with HIV vs. HIV seroconversion at older age: a diverse population with distinct comorbidity profiles. *PLoS One.* 2015;10(4):e0118531.
11. Masiá M, Padilla S, Barber X, et al. Comparative Impact of Suppressive Antiretroviral Regimens on the CD4/CD8 T-Cell Ratio: A Cohort Study. *Medicine (Baltimore).* 2016 Mar;95(11):e3108.
12. 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 Mar;2(3):e98–106.
13. Poizot-Martin I, Allavena C, Duvivier C, et al. CMV⁺ Serostatus Associates Negatively with CD4:CD8 Ratio Normalization in Controlled HIV-Infected Patients on cART. *PLoS One.* 2016;11(11):e0165774.
14. Gubbels Bupp MR. Sex, the aging immune system, and chronic disease. *Cell Immunol.* 2015 Apr;294(2):102–10.
15. Strindhall J, Skog M, Ernerudh J, et al. The inverted CD4/CD8 ratio and associated parameters in 66-year-old individuals: the Swedish HEXA immune study. *Age Dordr Neth.* 2013 Jun;35(3):985–91.
16. Reus S, Portilla J, Sánchez-Payá J, et al. Low-level HIV viremia is associated with microbial translocation and inflammation. *J Acquir Immune Defic Syndr 1999.* 2013 Feb 1;62(2):129–34.
17. Seng R, Goujard C, Krastinova E, et al. Influence of lifelong cumulative HIV viremia on long-term recovery of CD4⁺ cell count and CD4⁺/CD8⁺ ratio among patients on combination antiretroviral therapy. *AIDS Lond Engl.* 2015 Mar 13;29(5):595–607.
18. Quiros-Roldan E, Raffetti E, Castelli F, et al. Low-level viraemia, measured as viraemia copy-years, as a prognostic factor for medium-long-term all-cause mortality: a MASTER cohort study. *J Antimicrob Chemother.* 2016 Dec;71(12):3519–27.
19. Hema MN, Ferry T, Dupon M, et al. Low CD4/CD8 Ratio Is Associated with Non AIDS-Defining Cancers in Patients on Antiretroviral Therapy: ANRS CO8 (Aproco/Copilote) Prospective Cohort Study. *PLoS One.* 2016;11(8):e0161594.
20. Popescu I, Drummond MB, Gama L, et al. HIV Suppression Restores the Lung Mucosal CD4⁺ T-Cell Viral Immune Response and Resolves CD8⁺ T-Cell Alveolitis in Patients at Risk for HIV-Associated Chronic Obstructive Pulmonary Disease. *J Infect Dis.* 2016 Nov 15;214(10):1520–30.
21. Avelino-Silva VI, Miyaji KT, Hunt PW, et al. CD4/CD8 Ratio and KT Ratio Predict Yellow Fever Vaccine Immunogenicity in HIV-Infected Patients. *PLoS Negl Trop Dis.* 2016 Dec;10(12):e0005219.

Compliance with Ethical Standards

Funding

This work has been possible thanks to an unconditional grant by ViiV Healthcare within the Ageing & Frailty Working Group.

Disclosures

AC received grants, travel grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. EF received travel grants or speakers honoraria from BMS, Gilead, Janssen-Cilag, MSD, Viiv Healthcare and consultancy fees from Gilead, Janssen-Cilag, Viiv Healthcare and BMS. SN received travel grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. DSGV received travel grants from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. AMC received grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. BMC received grants, travel grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. GG received grants, travel grants and speaker's honoraria from BMS, Gilead, Viiv, Janssen-Cilag and MSD. SP, FC, CM, GO and MV reported no potential conflict of interest.

The GEPPPO Study Group

Giovanni Di Perri¹, Stefano Bonora¹, Francesco Castelli³, Paola Magro³, Eugenia Quiros Roldan³, Antonella Castagna⁴, Andrea Poli⁴, Nadia Galizzi⁴, Marinello Serena⁶, Mariana Farenga⁷, Andrea Marino⁸, Bruno Cacopardo⁸, Gervasi Elena⁹, Massimo Galli⁹, Chiara Mussi¹¹.

¹¹*Centro di Valutazione e Ricerca Gerontologica, University of Modena and Reggio Emilia, University of Modena and Reggio Emilia, Modena.*