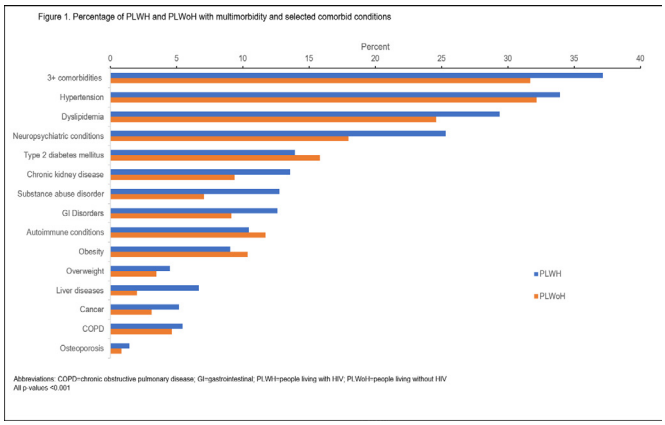


526 HIV DIFFERENTIALLY IMPACTS AGE-RELATED COMORBIDITY BURDEN AMONG US WOMEN AND MEN

Lauren F. Collins[1], Frank Palella[2], Cyra C. Mehta[1], JaNae Holloway[1], Valentina Stosor[2], Jordan Lake[3], Todd Brown[4], Kathryn Anastos[5], Seble Kassaye[6], Adaora Adimora[7], Mirjam-Colette Kempf[8], Susan L. Koletar[9], Phyllis Tien[10], Igho Ofotokun[1], Anandi N. Sheth[1]

[1]Emory University, Atlanta, GA, USA, [2]Northwestern University, Chicago, IL, USA, [3]University of Texas at Houston, Houston, TX, USA, [4]The Johns Hopkins University, Baltimore, MD, USA, [5]Albert Einstein College of Medicine, Bronx, NY, USA, [6]Georgetown University, Washington, DC, USA, [7]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [8]University of Alabama at Birmingham, Birmingham, AL, USA, [9]The Ohio State University, Columbus, OH, USA, [10]University of California San Francisco, San Francisco, CA, USA

Background: Age-related non-AIDS comorbidities (NACM) occur earlier and more frequently among people with HIV (PWH) than HIV-negative (HIV-) peers. HIV may also differentially impact the burden of NACM experienced by women vs men.

Methods: PWH and HIV- participants followed in the MACS/WIHS Combined Cohort Study (MWCCS) since 2008/2009 (when >80% of male/female participants used antiretroviral therapy) were included with outcomes measured up to 03/2019. Age, covariates, NACM prevalence, and NACM burden (total number out of 10) were summarized as of last observation. Unadjusted and adjusted (race, body mass index [BMI], smoking, drinking, crack/cocaine, socioeconomic status) linear regression models assessed the effects of HIV serostatus, age and sex on NACM burden.

Results: Women (2316 PWH, 922 HIV-) vs men (1452 PWH, 1239 HIV-) had a median age of 51 vs 58 years, median BMI of 30 vs 26 kg/m$_2$, 65% vs 25% were Black, and 78% vs 32% had income <150% of the federal poverty level, respectively. Overall, individual NACM prevalence ranged from 9-71%, and the distribution for women/men was: hypertension (68%/75%), psychiatric illness (55%/58%), dyslipidemia (41%/64%), liver (34%/38%), bone (42%/19%), lung (38%/10%) disease, diabetes (24%/17%), cardiovascular (15%/15%), kidney (14%/15%) disease, and cancer (7%/12%). Mean NACM burden was higher among women vs men (3.4 vs 3.2, p=0.015). In the unadjusted model, the estimated mean difference in NACM burden was significantly greater for women vs men in every age strata among PWH (all p<0.05): +0.33 (<40y), +0.37 (40-49y), +0.38 (50-59y), +0.66 (60-69y), +0.62 (≥70y); however, differed for women vs men by age strata among HIV- participants: +0.52 (<40y, p=0.01), -0.07 (40-49y, p=0.72), +0.88 (50-59y, p<0.01), +1.39 (60-69y, p<0.01), +0.33 (≥70y, p=0.46) [HIV*age*sex interaction, p<0.01]. In the adjusted model, findings were attenuated but HIV and age still significantly modified the estimated NACM burden by sex (HIV*age*sex interaction, p=0.038, Figure).

Conclusion: The prevalence and burden of NACM was high in the MWCCS among men and women with or at-risk for HIV, particularly for hypertension, psychiatric illness, dyslipidemia, liver, and bone disease. NACM burden was higher in women vs men, particularly among PWH, and the distribution of specific NACM prevalence differed by sex. Given HIV is associated with differential effects on age-related comorbidities by sex, HIV serostatus- and sex-specific strategies for NACM screening and prevention are needed.

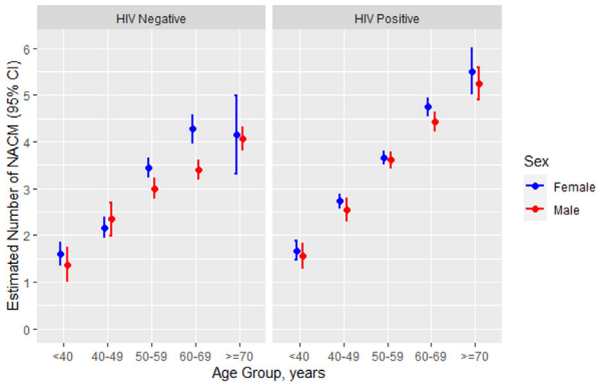


Figure. Estimated mean number of NACM among persons with HIV and HIV-negative participants in the MACS/WIHS Combined Cohort Study, stratified by sex and age group, adjusted for covariates (BMI, SES, crack/cocaine use, smoking status, alcohol use, race/ethnicity) (HIV*age*sex interaction term, *p*=0.038).

527 EFFECTS OF SWITCH FROM 3DR TO 2DR ON INFLAMMATORY BIOMARKERS

Sergio Serrano-Villar[1], María Rosa López-Huertas[2], Daniel Jiménez[1], Javier Martínez-Sanz[1], Raquel Ron[3], Luis Fernando López Cortés[4], José-Ramón Blanco[5], Victor Asensi[6], David Dalmau[7], Maria José Galindo[8], Santiago Moreno[1], for the Spanish AIDS Research Network (CORIS)

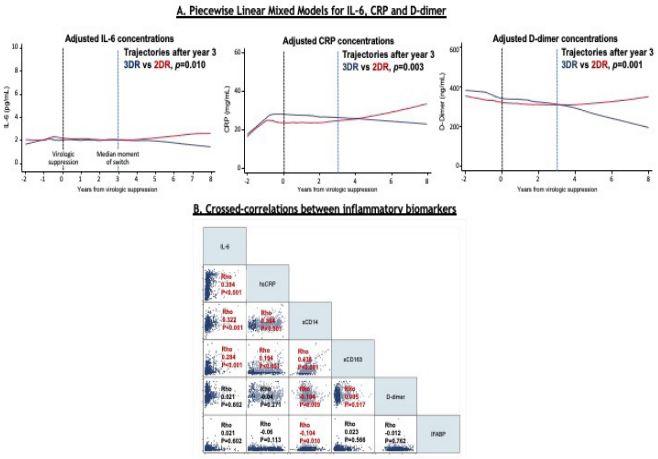
[1]Hospital Ramón y Cajal, Madrid, Spain, [2]Institute of Health Carlos III, Madrid, Spain, [3]UCL Great Ormond Street Institute of Child Health, London, UK, [4]Hospital Universitario Virgen del Rocio, Sevilla, Spain, [5]Hospital San Pedro, La Rioja, Spain, [6]Hospital Universitario Central de Asturias, Oviedo, Spain, [7]Hospital Universitari Mútua de Terrassa, Terrassa, Spain, [8]Hospital Clinic of Valencia, Valencia, Spain

Background: Because inflammation has been linked to HIV transcription in lymphoid tissues during ART-mediated viral suppression (VS), it is necessary to address the long-term effects of changing triple therapy (3DR) to 2-drug regimens (2DR) on plasma inflammatory markers.

Methods: Nested study in the Spanish AIDS Research Network (CoRIS). We selected HIV-infected ART-naive patients initiating 3DR from 2004 to 2017 who achieved VS in the first 48 weeks of ART and either remained on 3DR during their entire follow-up or were switched to 2DR (3TC+bPI; 3TC+DTG; DTG+RPV) after at least 48 weeks of suppressive ART. 180 subjects were selected based on plasma availability and longer follow-up. We assessed the trajectories of inflammation markers (IL-6, hsCRP), macrophage activation (sCD163), monocyte activation (sCD14), coagulation (D-dimer) and markers of intestinal damage (IFABP) during VS using multivariate piecewise mixed models.

Results: We analyzed 619 plasma samples from 148 subjects (3DR, N=90; 2DR, N=58), mean age 38 (SD 10) years, 87% men, 67% MSM, mean CD4 nadir 278 (SD 185) cells/uL, median duration of VS 4.3 (3-6.2) years. Median time from ART initiation to censoring was 4.6 (3.2-6.2) years. Median time from VS to 2DR was 3.4 (1.8-5.2) years. Subjects with 3DR experienced a slow decline of IL6, CRP, sCD14, sCD163 and D-dimers over time (figure A). In contrast, compared to 3DR, switching to 2DR was associated with increases in IL-6 (p=0.01), CRP (p=0.003) and D-dimer (p=0.001) after year 3 from VS, after adjusting for covariates. Compared to 3DR, 2DR was associated with higher risk of CRP quartile increase (aOR 3.3, 95%CI 1.1-10) and D-dimer quartile increase (aOR 3.7, 95%CI 1.1-13). The adjusted biomarker trajectories did not reveal a distinct pattern according to the type of 2DR used. We also studied cross-correlations among the biomarkers, and found sCD14 and sCD163 to be more highly correlated (figure B, Rho 0.438, P<0.0001).

Conclusion: In this observational study in virally suppressed individuals, maintaining 3DR was associated with a more favourable long-term anti-inflammatory profile than switching to 2DR. The potential clinical implications of these findings on the development of non-AIDS events deserve further investigation.



528 SOLUBLE IMMUNE COSTIMULATORY MOLECULES ARE PREDICTIVE OF NON-AIDS EVENTS

Thomas A. Premeaux[1], Carlee B. Moser[2], Ashley McKhann[2], Stephen Yeung[1], Alina Pang[1], Micheal Corley[1], Alan Landay[3], Sara Gianella[4], Lishomwa Ndhlovu[1]
[1]Weill Cornell Medicine, New York, NY, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]Rush University Medical Center, Chicago, IL, USA, [4]University of California San Diego, San Diego, CA, USA

Background: Despite suppressive antiretroviral therapy (ART), people with HIV (PWH) experience an increased risk of morbidity and mortality, in part due to chronic inflammation and immune dysfunction. Immune co-stimulatory molecules exist in soluble forms at normal physiological conditions and many are elevated in cancer, HIV infection, and other inflammatory diseases, suggesting they could serve as promising early predictive biomarkers of adverse outcomes in PWH. We aimed to identify relationships between plasma levels of soluble immune co-stimulatory molecules with the incidence of non-AIDS events (NAEs) utilizing a nested case-control study from the AIDS Clinical Trials Group ALLRT cohort.

Methods: Study participants were evaluated at baseline (pre-ART; 66 cases, 97 controls), 1 year post-ART (112 cases, 211 controls), and immediately preceding an event (89 cases, 163 controls). NAEs (cases) include myocardial infarction (MI)/stroke, malignancy, serious bacterial infection, and non-accidental death. Matched controls had an event-free follow-up equal or greater than that of the relevant case. All participants were virally suppressed on ART at year 1 and matched for age (within 10 years, median 45 years), sex (84% male), pre-ART CD4+ T cell count (within 50 cells/mm$_3$, median 213 cells/mm$_3$), ART regimen at 1 year, and parent study. Soluble co-stimulatory molecules CD27, CD28, CD40, GITR, GITRL, HVEM, BTLA, and ICOS were measured by Luminex. Conditional logistic regression analysis assessed associations of co-stimulatory molecules and events, adjusting for pertinent covariates at each timepoint; noteworthy associations used a threshold of an effect size (OR per one IQR) ≥1.5.

Results: Higher levels of CD27 were associated with increased risk of NAEs at each time point: baseline [unadjusted odds ratio (OR) per 1 IQR =2.1, p=0.008], year 1 (OR=1.6, p=0.001), pre-event (OR=2.1, p<0.001). Higher levels CD40 was associated with increased risk of NAEs at baseline (OR=1.8, p=0.019) and pre-event (OR=1.7, p=0.008). These associations remained after adjustments for HIV RNA levels and CD4 counts. Furthermore, examining specific NAEs, higher CD27 was associated with both increased risk of death and MI/stroke at multiple time points (OR= 2.9-5.3) and CD40 associated with malignancy at baseline and pre-event (OR=2.3-2.4).

Conclusion: Soluble CD27 and CD40 are predictive of NAEs and may inform interventional studies aimed to reduce morbidity and mortality in PWH on suppressive ART.

Table 1: Unadjusted and Adjusted Conditional Logistic Regression Models for Associations between Co-stimulating Molecules and non-AIDS events at Three Time-points.

Biomarker	Baseline (pre-ART) N=163		Year 1 (post-ART) N=323		Pre-Event N=252	
	Unadjusted OR (95% CI) per one IQR; p-value*	Range of Adjusted OR per one IQR	Unadjusted OR (95% CI) per one IQR; p-value*	Range of Adjusted OR per one IQR	Unadjusted OR (95% CI) per one IQR; p-value*	Range of Adjusted OR per one IQR
CD27	**2.1 (1.2, 3.6); p=0.01**	1.9 – 2.3	**1.6 (1.2, 2.2); p=0.001**	1.6 – 1.7	**2.1 (1.4, 3.3); p<0.001**	1.9 – 2.3
CD28	1.3 (0.8, 2.1); p=0.30	1.1 – 1.3	1.0 (0.7, 1.3); p=0.93	0.9 – 1.0	1.4 (0.9, 2.1); p=0.11	1.2-1.4
CD40	**1.8 (1.1, 2.8); p=0.02**	1.5 – 1.8	1.2 (0.9, 1.6); p=0.27	1.1 – 1.2	**1.7 (1.2, 2.5); p=0.01**	1.4 – 1.7
GITR	1.2 (0.8, 1.9); p=0.33	1.2 – 1.3	0.9 (0.7, 1.2); p=0.51	0.8 – 0.9	1.3 (0.9, 1.7); p=0.15	1.1 – 1.3
GITRL	1.4 (0.9, 2.1); p=0.16	1.3 – 1.4	1.1 (0.8, 1.4)1; p=0.69	1.0 – 1.1	**1.6 (1.0, 2.4); p= 0.03**	1.3 – 1.6
HVEM	1.3 (0.9, 2.0); p=0.20	1.0 – 1.3	1.1 (0.9, 1.4); p=0.48	1.0 – 1.1	1.4 (1.0, 1.9); p=0.09	1.2 – 1.4
BTLA	1.3 (0.8, 2.1); p=0.23	1.2 – 1.4	1.0 (0.7, 1.3); p=0.88	0.9 – 1.0	1.4 (0.9, 2.0); p=0.11	1.2 – 1.4
ICOS	1.4 (0.9, 2.2); p=0.16	1.3 – 1.4	1.0 (0.7, 1.3); p=0.85	0.9 – 1.0	1.3 (0.9, 1.9); p=0.13	1.2 – 1.3

*noteworthy results are bold

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio

Adjustments were done individually for the following covariates: i.) HIV-disease measure (Baseline: log-10 HIV RNA level, Post-Baseline: CD4 cell count); ii.) Time updated chronic Hepatitis B/C status; iii.) Time updated smoking status; iv.) Baseline injection drug use; v.) Time updated waist-to-hip ratio; vi.) Time updated diabetes status; vii.) Time updated hypertension status; viii.) Time updated use of antihypertensive or lipid lowering medications; and ix.) Time updated family history of myocardial infarction

529 PLASMA GALECTIN-9 AS A PREDICTOR OF NON-AIDS EVENTS DURING SUPPRESSIVE ART

Thomas A. Premeaux[1], Carlee B. Moser[2], Ashley McKhann[2], Martin Hoenigl[3], Michael M. Lederman[4], Alan Landay[5], Sara Gianella[3], Lishomwa Ndhlovu[1]
[1]Weill Cornell Medicine, New York, NY, USA, [2]Harvard TH Chan School of Public Health, Boston, MA, USA, [3]University of California San Diego, San Diego, CA, USA, [4]Case Western Reserve University, Cleveland, OH, USA, [5]Rush University Medical Center, Chicago, IL, USA

Background: People with HIV (PWH) on antiretroviral therapy (ART) still experience an increased risk of morbidity and mortality, which is partly driven by chronic inflammation. We previously demonstrated that soluble galectin-9 (Gal-9), a pleiotropic glycan-binding immunomodulatory protein, is elevated in PWH on ART and associated with markers of HIV persistence, neurological complications and indices of morbidity and mortality in HIV infection. Here, we aimed to identify relationships between Gal-9 and the occurrence of non-AIDS events (NAEs) in PWH on suppressive ART, utilizing a nested case-control study from the AIDS Clinical Trials Group ALLRT cohort.

Methods: Study participants were evaluated at baseline (pre-ART; 66 cases, 97 controls), 1 year post-ART (112 cases, 211 controls), and immediately preceding an event (89 cases, 162 controls). NAEs (cases) include myocardial infarction/stroke, malignancy, serious bacterial infection, and non-accidental death. Matched controls had an event-free follow-up equal or greater than that of the relevant case. All participants were virally suppressed by ART by year 1 and matched for age (within 10 years, median 45 years), sex (84% male), pre-ART CD4+ T cell count (within 50 cells/mm$_3$, median 213 cells/mm$_3$), ART regimen at 1 year, and parent study. Gal-9 levels in plasma were assessed by ELISA. Conditional logistic regression analysis assessed associations of Gal-9 with NAEs. Spearman correlations assessed associations between biomarkers among the controls.

Results: Higher plasma levels of Gal-9 were associated with increased risk of NAEs at year 1 and pre-event (unadjusted OR per 1 IQR (95% CI) = 1.4 (1.0, 1.9), p=0.04 and OR=1.6 (1.0, 2.3), p=0.03). Association at year 1 remained significant with adjustment for CD4 count. Higher levels of Gal-9 were associated with specific NAEs, MI/stroke (OR= 1.9) and death (OR=2.8) at year 1 and malignancy (OR=1.8) pre-event. Gal-9 also correlated with markers previously assessed to be predictive of NAEs, including sTNFR-I, sTNFR-II, and suPAR, at each timepoint (all r≥0.45, p<0.0001).

Conclusion: Elevated plasma Gal-9 levels are predictive of NAEs; due to the pleiotropic nature of Gal-9 it may be an ideal target for intervention to help attenuate chronic immune activation and, as a result, lessen the risk of morbidity during suppressive ART.