Metabolic Dysregulation in HIV: T-Cell Aging Beyond Chronological Age

Marissa Flores-Santamaria[1], Gooya Banaei[1], Gloria Nieto [3], Patricia Echeverría [2,3], Anna Bonjoch [2,3], Antoni Jou [2,3], Guillem Sirera [3], Ana Martínez [3], Cristina Miranda [3], Ana Gervassi [1], Eugenia Negredo [2,3,4,5], Marta Massanella [1,4]

[1]IrsiCaixa, Badalona, Spain, [2]Department of Infectious Diseases, Hospital Germans Trias i Pujol, Badalona, Spain, [3]Fundació Lluita Contra les Infeccions, Badalona, Spain, [4]CIBER Infectious Diseases (CIBERINFEC), Institute of Health Carlos III (ISCIII), Madrid, Spain, [5]Universitat de Vic–UCC, Vic, Spain

mflores@irsicaixa.es
mmassanella@irsicaixa.es

256

BACKGROUND

- People with HIV on antiretroviral therapy (PWH_{ART}) experience premature immune aging driven by chronic immune activation and metabolic dysregulation. T-cell metabolic reprogramming may contribute to immunosenescence.
- This study evaluated age-related metabolic changes in T cells from PWH_{ART} compared with people without HIV (PWoH).

METHODS

- **MetabolHIV Study participants:** Cross-sectional study including PWH_{ART} and PWoH. N=90 (n=15 per age group).

vs n=90

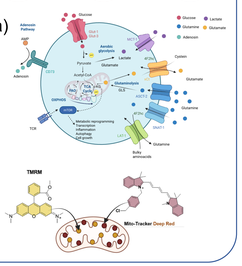
		PWH_{ART} (n)	PWoH (n)
Younger	18-35 years	15	15
Middle	40-55 years	15	15
Older	>60 years	15	15

- **Immunophenotyping** of metabolic parameters was performed by flow cytometry in cryopreserved PBMCs with overnight resting.



Panel 1: Nutrient markers expression (BD Fortessa)

GLUT1, GLUT3	Glucose
CD73	Adenosine
MCT1	Lactate/pyruvate
CD98, xCT, SNAT1	Amino acids



Panel 2: Mitochondrial parameters (BD LSR-II)

Mito-Tracker Deep Red	Mitochondrial mass (MM)
TMRM	Mitochondrial membrane potential (MMP)

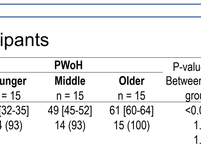


Table 1. Demographic characteristics of the participants

	PWH_{ART}			P-value K-w	PWoH			P-value K-W
	Younger n = 15	Middle n = 15	Older n = 15	Between HIV groups	Younger n = 15	Middle n = 15	Older n = 15	Between PWoH groups
Age, years, median [IQR]	33 [32-35]	48 [43-50]	61 [60-62]	<0.001	33 [32-35]	49 [45-52]	61 [60-64]	<0.001
Sex, male, n (%)	14 (93)	14 (93)	15 (100)	1.0	14 (93)	14 (93)	15 (100)	1.0
Ethnicity, n (%)				0.52				1.0
Caucasian	13 (87)	13 (87)	15 (100)		15 (100)	14 (93)	15 (100)	
Hispanic	2 (13)	2 (13)	0 (0)		0 (0)	1 (7)	0 (0)	
Time since diagnosis and ART initiation, months, median [IQR]	0.5 [0.3-1.2]	1.6 [0.4-3.4]	2.5 [0.8-7.7]	0.1	-	-	-	
Time on ART, years, median [IQR]	5 [4-8]	13 [7-14]	11 [7-14]	0.03	-	-	-	
CD4 T cell nadir, cells/µL, median [IQR]	418 [224-492]	270 [231-376]	291 [212-415]	0.37	-	-	-	
CD4 T cell nadir <350 cells/µl, n (%)	5 (33)	10 (67)	11 (73)	0.06	-	-	-	
VL <50 copies/mL, n (%)	15 (100)	15 (100)	15 (100)	1.0	-	-	-	

- Younger PWH_{ART} tended to have more comorbid conditions than their uninfected counterparts.
- The overall comorbidity burden increased with age across groups.

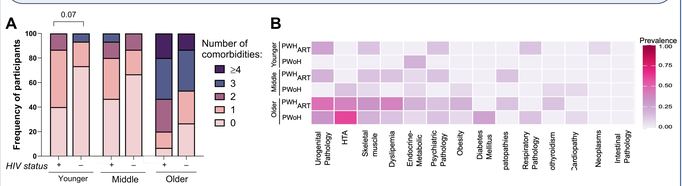
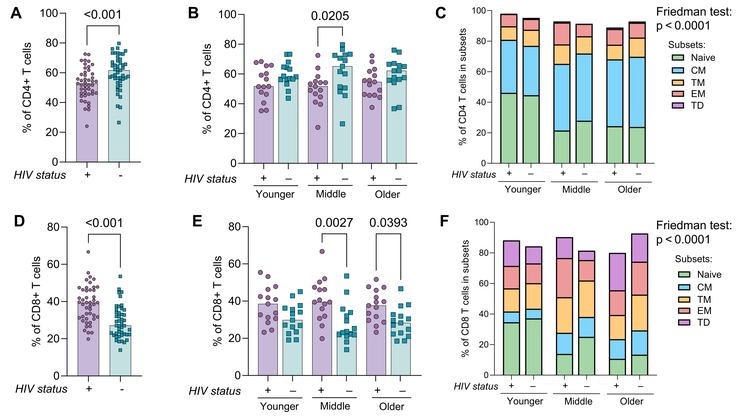


Fig 1. Comorbidity patterns by age and HIV status. (**A**) Number of comorbid conditions. (**B**) Prevalence of specific comorbidities.

HIV and aging exert combined impacts on T-cell metabolism, driving CD73 loss, transporter imbalance, and mitochondrial stress, especially in CD8 memory cells

RESULTS



- PWH_{ART} showed lower CD4 and higher CD8 T-cell frequencies.
- Age effects were modest, most evident in middle-aged and older adults.
- Subset distributions were similar between groups, with aging shifting cells from naïve toward CM subsets.

Fig 2. T-cell frequencies and subset distributions by HIV status and age. CD4 and CD8 T-cell frequencies (**A & D**) by HIV status, (**B & E**) across age groups, (**C & F**) subsets distribution.

- PWH_{ART} displayed broad dysregulation of nutrient transporters (CD73, GLUT3, MCT1, CD98, SNAT1), affecting multiple CD4 and CD8 T-cell subsets.
- Aging drove consistent declines in CD73 and age-dependent changes in GLUT3, MCT1, and CD98 across CD4 and CD8 memory T-cell subsets.

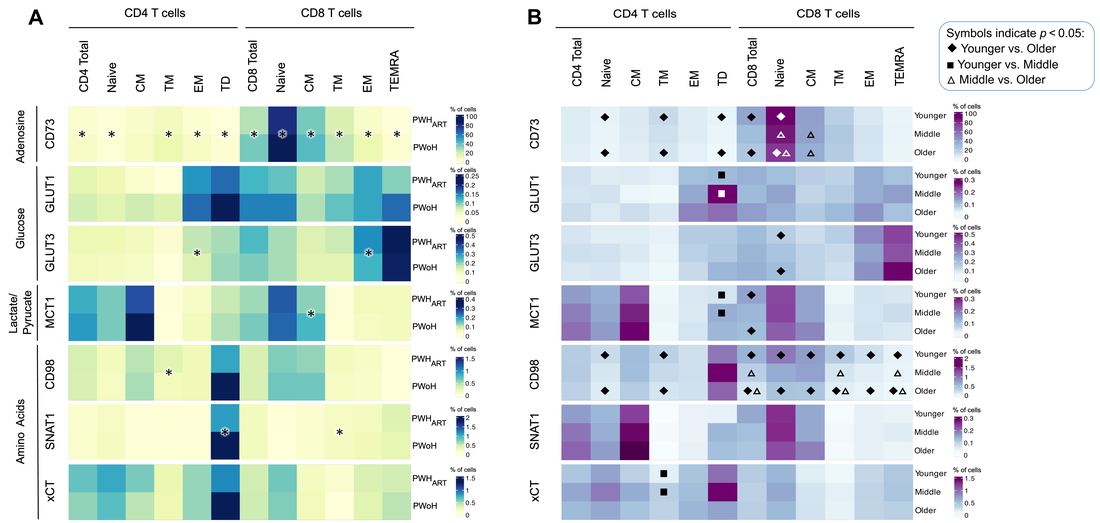


Fig 3. Metabolic Marker Expression Across T-cell Subsets. (**A**) Differences by HIV status (PWH_{ART} vs PWoH). (**B**) Age-related differences across younger, middle-aged, and older groups.

- Younger PWH_{ART} showed reduced CD73 expression in EM CD4 and in CM, EM, and TM CD8 T-cell subsets, with significant differences or strong trends across groups.

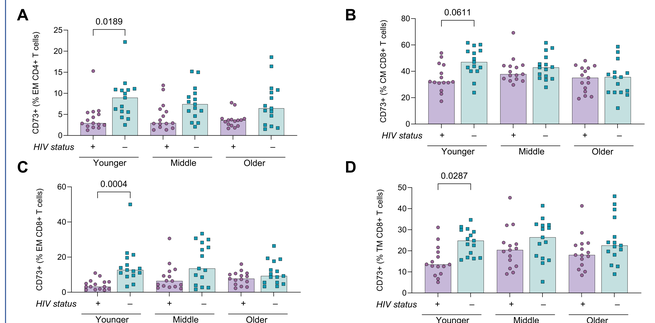


Fig 4. CD73 expression in memory T cells by HIV status and age. (**A**) EM CD4, (**B**) CM CD8, (**C**) EM CD8, (**D**) TM CD8.

- PWH_{ART} showed higher mitochondrial membrane potential (MMP), especially in differentiated CD8 subsets (TM, EM, TD).
- Mitochondrial mass showed no significant differences.

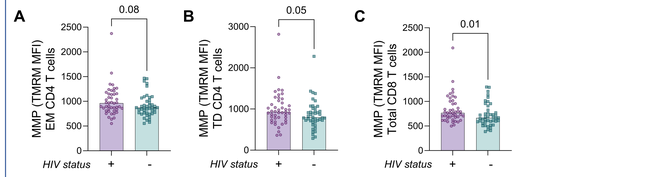


Fig 5. MMP in T-cell subsets by HIV status.(A) EM CD4, (**B**) TD CD4, (**C**) Total CD8, (**D**) TM CD8, (**E**) EM CD8, (**F**) TD CD8, (**G**) EM CD8 MMP/MM

CONCLUSIONS

- PWH_{ART} show persistent immune and metabolic imbalance, with reduced CD73 and altered GLUT3/MCT1/CD98 across CD4 and CD8 subsets.
- Aging adds additional metabolic shifts, including progressive loss of CD73 and age-dependent changes in key transporters.
- Increased mitochondrial activation in PWH_{ART}, particularly in differentiated CD8 T cells, supporting accelerated immune aging.

Acknowledgements: This research was funded by PID2020-114929RA from Spanish Ministry of Science and Innovation (MCIN) and State Research Agency (AEI). M. Flores was granted with PRE2021-099939/MCIN/AEI/10.13039/501100011033. M. Massanella was granted with RYC2020-028934-I/AEI/10.13039/501100011033 from MCIN/AEI and the European Social Fund "investing in your future".