

PHENOTYPIC AND METABOLIC FEATURES OF CD4 AND CD8 T CELLS OF AN ELITE CONTROLLER – A CASE REPORT

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Background: People living with HIV (PLHIV) who are capable of long-term viral suppression in the absence of antiretroviral therapy (ART) are defined as elite controllers (EC). Although there is evidence of phenotypic and functional alterations of T-lymphocytes in EC, neither the mechanisms of viral control, nor the necessity and timing of ART in this particular population have been elucidated.

Case presentation: We report the case of untreated HIV+ patient with undetectable viral load (VL), and preserved CD4 T cell absolute count (AC) and CD4/CD8 ratio since diagnosis in 2018. The detailed phenotype of EC CD4 and CD8 T cell pools including differentiation, effector, activation, immunosenescence and exhaustion markers was distinct from sex- and age-matched ART+PLHIV with immune recovery, and close to HIV(-) healthy controls (HC), except for a temporary increase of CD57+ CD8 T cells in 2023. The

only changing biomarkers were T cell mitochondrial mass (MM), slightly increased at the level of CD8 T cells in 2023, and drastically increased in both CD4 and CD8 T in 2025, together with the mitochondrial membrane potential (MMP), as compared to ART+PLHIV and HIV (-) HC.

Conclusions: CD4 and CD8 T cells of EC experience intensive oxidative stress and functional burden, possibly linked to the continuous effective HIV-specific immune response. CD4 and CD8 T cell MM may serve as a monitoring marker preceding the irreversible changes of immune profile and loss of viral control, and possibly predict the time for start of ART.

Key words: HIV, ART, elite controllers, mitochondrial mass, mitochondrial membrane potential

BACKGROUND

Human Immunodeficiency Virus (HIV) specifically binds CD4 antigens expressed mostly by the helper/inducer and regulatory T cell subset responsible for the orchestration of adaptive immune responses [1]. Immune response to HIV can only partially and temporarily control viral replication but is unable to eliminate HIV from the body. Therefore, untreated HIV infection leads to a gradual decline of CD4 AC, acquired immune deficiency syndrome, and fatal outcome. After the infection and the initial immune response, plasma HIV VL stabilizes at an individually specific level - the virological set point. The latter determines how long the gradual decline of CD4AC will last in the absence of ART. This progression usually occurs several years after the initial HIV infection [2]. Only few exceptional individuals are able to prevent HIV replication relying on their own immune system, in the absence of ART, and have become a focus of interest as a model for a potential functional therapeutic cure. HIV controllers are genetically and immunologically a rather heterogeneous population. Controller cohorts differ regarding the level of residual HIV viremia, duration of HIV control, level of immunological control, and the time to reach controller status [3]. Long-term non-progressors (LTNP) who comprise approximately 5% of all chronically HIV infected individuals maintain stable CD4 AC above 500 cell/ μ l, and stable low but detectable HIV VL for more than 7 years. EC are a further restricted population (about 0.3% of all HIV-infected), defined by stable CD4 AC (irrespective of the threshold), and persistently undetectable HIV VL (below 50 copies/

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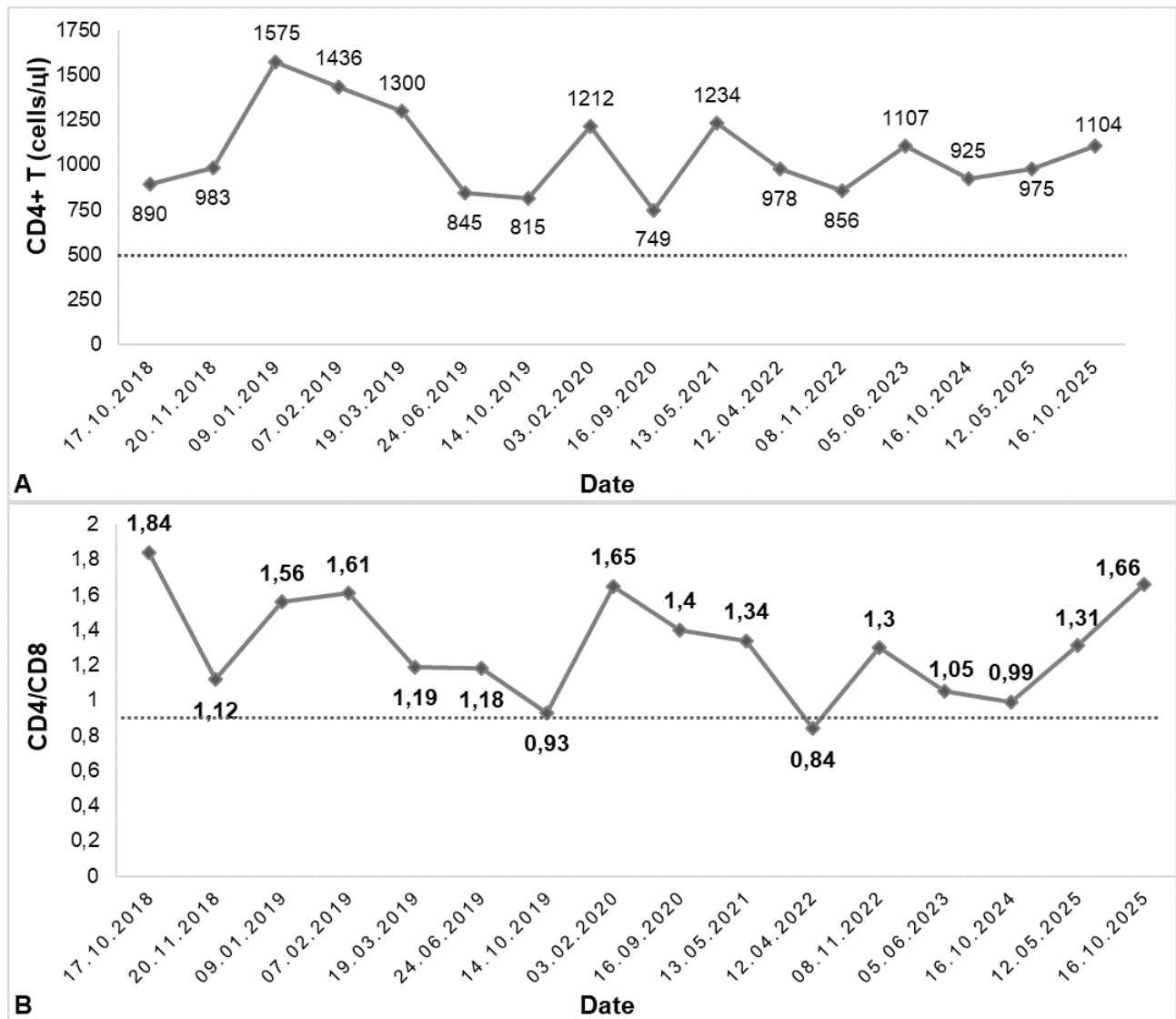


Fig.1. Dynamics of CD4AC (A) and CD4/CD8 ratio (B) of EC. Data from regular monitoring visits of EC are presented. Dotted lines correspond to the respective lower reference values for HIV (-) controls

ml) for more than 12 months [4, 5]. Some individuals showing both features of LTNP and VL control are defined as “elite LTNP” [6]. According to Genovese et al., long term controllers of HIV-1 infection progression are a heterogeneous group relying on different mechanisms of resistance [7]. The most widely accepted definition of an EC could be “an HIV-infected person followed-up for over 1 year, ART-naïve, with over 90% of his plasma HIV-RNA measurements below 50 copies/ml” [3].

The mechanisms of exceptional viral control comprise a number of virological, genetic, and immunity-related factors [8-11]. A relevant role of innate immunity in the long-term control of HIV has been proposed, including NKG2C-memory-like NK cells, CD16^{dim}CD56^{dim} NK subset and TCRγδ²⁺ cells. [10, 11]. As to adaptive immunity, ECs were character-

ized by increased CD4 naïve, Th1/17 and CD8 TEMRA cells, at the expense of Th17, Tfh cells and memory CD4 T [12]. However, the mechanisms controlling HIV replication in the absence of ART are still not fully established [13].

At the same time, an EC may eventually lose control on HIV infection, posing the problem of ART timing, and the requirement of routine virologic and immune monitoring. Although a number of studies have delineated cellular and soluble biomarkers possibly associated with loss of viral control, no marker has been accepted for routine laboratory application [11, 14-16].

We describe a case of an EC with undetectable HIV VL who maintained stable CD4AC and CD4/CD8 ratio since diagnosis in 2018. As compared to ART+ PLHIV with successful viral suppression and restored CD4AC

and CD4/CD8 ratio, the detailed T cell immunophenotype of EC revealed neither evidence of chronic immune inflammation, nor a tendency towards immune exhaustion or senescence. At the same time, a significant increase of both CD8 and CD4 T cell mitochondrial mass (MM) and mitochondrial membrane potential (MMP) were registered as probable first signs of intensive oxidative stress and functional exhaustion.

Case presentation

A 48 years old male was diagnosed with HIV infection at the National Center of Infectious and Parasitic Diseases, Sofia, after successive positive results in a rapid test, ELISA and Western blot (11.09.2018), confirmed by a second blood sample on 29.09.2018. He was registered at the Infectious Diseases Clinic at the University Hospital „Georgi Stranski , Pleven in October 2018, and was followed for 7 years thereafter. His HIV VL was <40 copies/ml at registration (17.10.2018) and has remained undetectable since then (last determination on 16.10.2025).

CD4 AC was within the reference range for HIV (-) controls at all test points, mean (min-max) 1041 (749 -1575) cells/μL (Fig.1A). The same was valid for the CD4/CD8 ratio: 1.3 (0.84 -1.84). Only once (on 12.04.2022), a suboptimal value of 0.84 was registered due to an increased CD8 AC (1164 cells/μL),

Fig.1B.

Based on the undetectable HIV VL and steady CD4 AC, the patient was defined as a long-term EC. ART was not recommended, and control examinations and laboratory monitoring were performed at 6-month intervals. The complete blood count (CBC) and basic biochemical parameters, including CRP, blood glucose, total cholesterol, triglycerides (TG) creatinine, urea, AST, ALT did not show important deviations from the accepted reference ranges during the follow-up (Table 1). Importantly, CRP never exceeded 2,9 mg/L. The tests for co-infections (HBsAg, anti-HCV, HAV and HEV antibodies, and *C. albicans* in faeces) were consistently negative.

In 2023 and 2025, a detailed phenotyping analysis of EC’s T cell pool was performed, including the shares of naïve (N, CD45RA+CCR7+), central memory (CM, CD45RA-CCR7+), effector-memory (EM, CD45RA-CCR7-) and terminal effector (CD45RA+CCR7-) CD4 and CD8 T, EM1 (CD27+CD28+), EM2 (CD27+CD28-) and EM3 (CD27-CD28-) CD8 T, exhausted/senescent (TIGIT+/CD57+) CD8 T, regulatory (CD25^{hi}CD127^{low}) CD4 T (Treg) as well as the number of CD38 molecules (CD38 antibody-binding sites, ABS) on CD4 and CD8 T cell as an indicator of chronic activation. EC phenotype was compared to age- and sex-matched HIV+ART+ patients with undetectable HIV VL and

Table 1. Basic laboratory parameters of EC in 2023 and 2025

Parameter	Unit	EC			Reference range
		2023	2025	min-max for all tests	
Hb	g/l	152	162	145-166	135 - 175
Er	x10 ¹² /L	5,09	5,67	4.7-5.7	4.2 - 6.2
Hct	L/L	0,45	0,485	0.41-0.48	0.37 - 0.55
Leu	g/L	6,5	7,5	5.9 - 8.3	3.5 - 10.5
Neut	%	50	55,4	48 - 69	44 -76
Ly	%	41	36,9	33 - 44	20 - 40
Mo	%	9	7,7	6-11%	3 - 13
Plt	x10 ⁹ /L	246	259	241-337	130 - 440
CRP	<10.0 mg/L	1,28	1,13	0.7-2.74	<5
Total Cholesterol	(mmol/L)	6,2	6,58	5.8-6.6	3.5-5.2
TG	(mmol/L)	1,62	1,74	1.4-3.7	0.3-1.7
ALT	U/L	26	27	24-46	<50
AST	U/L	16	18,36	15-21	<50
Glucose	mmol/L	5,95	6,0	4.8-6.5	3.6 - 6.1
Creatinine	μmol/l	91	94	85-99	62 - 106
Urea	mmol/L	6,3	5,32	4.7-8.1	2.14 - 7.14

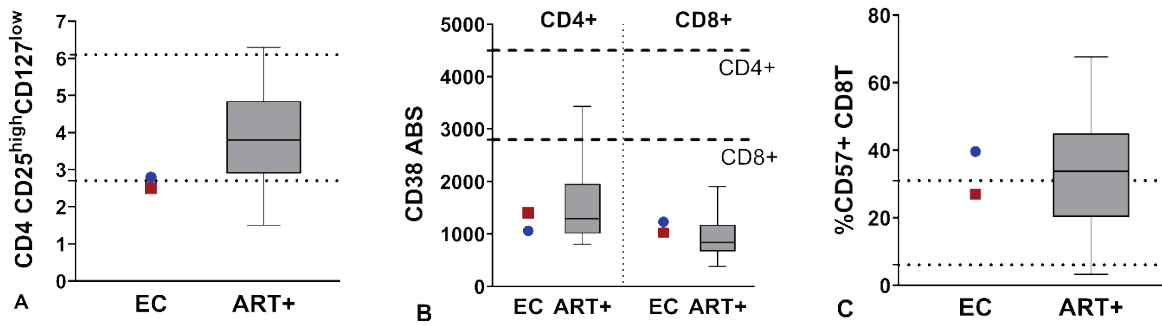


Fig.2 Chronic T cell activation and senescence markers in EC: the share of Treg (A); the number of CD38 molecules (ABS) on CD4 and CD8 T (B), and the expression of CD57 on CD8 T cells (D) were determined in 2023 (blue circle) and 2025 (red square) in comparison to ART+HIV (mean, min-max; box-and whiskers). Dotted lines correspond to Treg and CD57+CD8 reference ranges for HIV (-) HC. Thick lines correspond to the upper limit for CD38ABS on CD4 and CD8 T cells of HIV (-) HC, as designated.

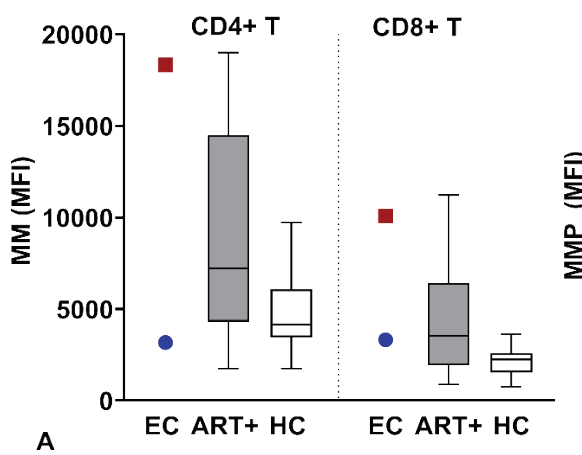


Fig.3 Dynamics of EM CD8 T cell pool. The co-expression of TIGIT and CD57 exhaustion markers in 2023 (blue) and 2025 (red) was analyzed within EM1 (A), EM2 (B) and EM3 (C) CD8 T cell subsets.

CD4 AC > 500 (n=39) (age 45 (34 – 51)), as well as to HIV- healthy controls (n=33) (46 (38 – 53)). (Table 2 and Fig.2).

The shares of naïve CD4 and CD8 T of EC were consistently higher as compared to ART+PLHIV: 55% and 46% vs. 34% (25.3% – 41.78%); 37% and 31% vs 24% (17.63% – 33.7%), and within the reference ranges for HIV (-) HC, (25% - 61%) and (25% -70%), respectively. Regulatory T cells (Treg) were consistently lower as compared to ART+PLHIV, 2.8% and 2.5% vs. (2.5% – 4.7%), and comparable to HIV (-) HC: (2.7% – 6.1%), Fig.2A. The measured CD38ABS on CD4 and CD8 T cells of EC, as well as those of ART+PLHIV: 1066, 1417 and 1291 (1002 -1957); 1230, 963 and 836 (666 -1174), were within the reference ranges for HIV (-) HC: (600 – 4500) and (510 – 2800) respectively, indicating absence of on-going immune activation (Fig.2B, C). Noteworthy, in 2023 the share of CD57+ CD8 T was significantly increased (39.6%), and similar to ART+PLHIV (20% – 45%) but two years later it has returned within the HIV (-) HC reference range (29% vs. 6% - 31%), Fig.2D.

To further characterize the differentiation of the CD8 T cell effector pool, we analyzed the co-expression of CD28 and CD27 co-stimulatory molecules, together with exhaustion and senescence-related TIGIT and CD57. As shown in Table 2 and Fig.3, between 2023 and 2025 the share of EM3 (CD27-CD28-) significantly decreased at the expense of the less differentiated EM1 and EM2 stages. Thus, in 2025 EM1 (69%), EM2 (8.3%) and EM3(21%) CD8 T cells of EC fell within the ranges for HIV(-) controls, (53%-84%); (3.1%-10.7%), and (9% - 33.5%), respectively.

The decrease of CD57 observed between 2023 and 2025 was mostly at the expense of terminally differ-

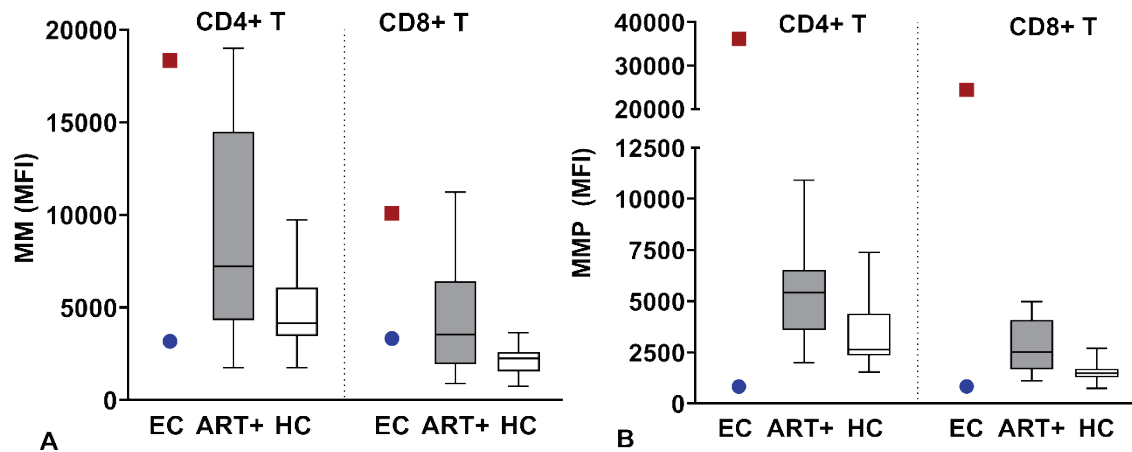


Fig.4 Significant increase of CD4 and CD8 T cell MM (A) of EC between 2023 and 2025 accompanied by an increase of MMP (B). MM and MMP of CD4 and CD T cells were determined in 2023 (blue circle) and 2025 (red square) according to the mean intensity of fluorescence (MFI) in comparison to ART+PLHIV (box and whiskers, gray) and HIV (-) HC (box-and-whiskers, open)

entiated (CD57+TIGIT-) EM3, Fig.3C. Also, the intermediate EM2 which is supposed to contain HIV-specific effector cells, was repopulated with functional TIGIT-CD57-/CD57+ cells (Fig.3B).

It is well established that mitochondrial dysfunction precedes T cell exhaustion. Both MM and MMP are closely related to the functional state of mitochondria. Increased MM is a sign of mitochondrial disruption, while hyperpolarization is associated with lymphocyte activation and imminent apoptotic events. To measure MM and MMP, freshly isolated peripheral blood mononuclear cells (PBMC) were stained with CD45, CD3 and CD8 mAb, followed by Mitotracker Green FM (ThermoFisher) and Mitotracker Red FM (ThermoFisher) as previously described [17]. In 2023, EC CD4 T MM was comparable to HIV(-) HC: MFI 3175 vs. 4163 (3462-6073). Although CD8 T MM slightly exceeded the upper level for HIV(-) HC, it was within the range for ART+ PLHIV with undetectable HIV VL: 3323 vs. 2252(1541-2583) vs. 3541(1926-6443). At the same time, CD4 and CD8 MMP were low as compared to both HIV(-) HC and ART+PLHIV (**Fig.4 A,B and Table 2**).

Two years later, while no significant changes were observed in most phenotypic subsets a striking increase was noted for both CD4 and CD8 T cell MM: (MFI) 18340 vs. 3175 and 10068 vs. 3323, respectively. At that point, the MMP of both subsets has also increased to extreme values as compared to ART+PLHIV and HIV(-)HC: 36132 vs. 5430 (3600-6534) vs. 2634 (2352-4388), and 24454 vs. 2527 (1675-4080)

vs. 1477 (1280-1691). Therefore, despite the steady CD4 AC, CD4/CD8 ratio, and undetectable HIV VL, EC T cells likely experienced importantly increased metabolic demands probably reflecting intensive viral stimulation, and preceding apoptosis.

DISCUSSION

EC represent the closest natural model to functional cure of HIV infection, offering an opportunity to study the features of protective HIV immunity, as well as to unravel early biomarkers predicting loss of HIV immune control.

A recent study highlighted multiple relevant trajectories among ECs: progress to immune deficiency despite undetectable viral loads (nonviremic progressors); loss of viral and immunologic control in 5 or more years; or rebound in HIV viremia followed by spontaneous viral resuppression (recontrollers) [18]. Due to this heterogeneity, there is no current consensus whether preventive treatment should be started and when. [19]. Therefore, early and reliable predictive markers of viral reactivation and imminent immune control failure are needed.

To this end, we performed detailed phenotypic analysis of an EC T lymphocyte pool and mitochondria at two time points in the settings of over 7 years undetectable HIV VL and stable CD4AC, and propose that the earliest biomarkers predicting loss of control are associated with mitochondrial function.

Not unexpectedly, the detailed immunophenotypic profile of EC resembled much more to a HIV (-) HC,

Table 2. Immunophenotypic analysis* of T cell subsets of EC in 2023 and 2025 in comparison to ART+PLHIV and HIV (-) HC

Subsets	Unit	Phenotype	EC 2023	EC 2025	ART+HIV+ (IQR)	HIV(-)HC (IQR)
CD8 T cells						
N	%	CD45RA+CCR7+	37	31	17 - 30	25 - 70
CM	%	CD45RA-CCR7+	5	8	6 - 18	5 - 14
EM	%	CD45RA-CCR7-	27	24	28 - 46	11 - 29
TEMRA	%	CD45RA+CCR7-	32	36	17 - 31	13 - 47
EM1	%	CD27+CD28+	47	69	38 - 62	53 - 84
EM2	%	CD27+CD28-	2	8	3.2- 9.1	3.1 - 10.7
EM3	%	CD27-CD28-	45	21	29 - 55	9 - 34
Senescent	%	CD57+	39.6	27	20 - 45	6 - 31
Exhausted	%	TIGIT+	43.9	42.5	43 - 61	32 - 56
Activated	ABS	CD38+	1230	963	666 - 1174	510 - 2800
MM	MFI	-	3323	10068	1926 - 6443	1541 - 2583
MMP	MFI	-	-	24454	1675 - 4080	1280 -1691
CD4 T cells						
N	%	CD45RA+CCR7+	55	46	24.7 - 41.5	25 - 61
CM	%	CD45RA-CCR7+	25	27	31.7 - 47.6	33 - 44
EM	%	CD45RA-CCR7-	13	19	13.7 - 24.6	18 - 30
TEMRA	%	CD45RA+CCR7-	7	8	2.1 - 8.8	1.6 - 4
EM1	%	CD27+CD28+	76	88	73 - 87	73 - 90
EM2	%	CD27-CD28+CD4+	14	5	6.6 - 10.4	2.4 -10.4
EM3	%	CD27-CD28-CD4+	10	6	3.5 - 17.2	2.2 - 17.3
Senescent	%	CD57+CD4	6	4	2.1 - 7.4	3.1 - 11.8
Exhausted	%	TIGIT+CD4	18	17	18.7 - 30.5	17.4 - 27.2
Regulatory	%	CD25 ^{hi} CD127	2.80	2,50	2.5 - 4.7	2.7 - 6.1
Activated	ABS	CD38+	1066	1417	1002 -1957	600 - 4500
MM	MFI	-	3175	18340	4304 -14504	3462 - 6073
MMP	MFI	-	-	36132	3600 - 6534	2352- 4388

*The following mAbs were used in the multicolor flow cytometry panel: anti-h CD3 AmCyan (cat# 339186), anti-h CD4 (PE cat# 565999), anti-h CD25 (APC-Cy7 cat# 557753), anti-hCD45RA (FITC cat# 555488), anti-h CCR7 (PE-Cy cat# 560765), anti-h CD38 (PE cat# 2117530), anti-h CD8 (APC cat# 340659), anti-h CD27 (AF700 cat# 356416), anti-h CD127 (PcpCy5.5 cat# 353220), anti-h CD8 (V450, cat# E-AB-F1110Q), anti-h CD57 (FITC cat# E-AV-F-1067C), anti-h CD45 (FITC cat# 2522025), anti-h CD45 (PerCP cat# E-AB-F1137F), anti-h CD28 (APC cat#377610), anti-h TIGIT (BV421 cat#2463550). T-lymphocyte activation was evaluated by the number of CD38 molecules expressed on CD4+ and CD8+ T cells (CD38 antibody-binding sites, ABS) that were quantified using the Quantibrite PE CD38 calibration flow cytometry kit (cat# 340495, BD Bioscience) according to manufacturer’s instructions. Samples were analysed using fresh whole blood.

Abbreviations

- AC – absolute count
- ART – antiretroviral therapy
- CBC - complete blood count
- EC – elite controller
- LTNP – long term non-progressors
- MFI - mean fluorescent intensity
- MM – mitochondrial mass
- MMP – mitochondrial membrane potential
- PLHIV – people living with HIV
- PMNC – peripheral blood mononuclear cells
- TG - triglycerides
- Treg – T regulatory cells
- VL – viral load

than to successfully treated HIV+ patients. At the same time, the CD4 and CD8 T cell pools of EC were distinguished by the prevalence of naïve over CM T, and increased TEMRA subset, especially among CD8 T. This particular differentiation profile implies a robust antiviral response, driving a constant repopulation with recent thymic emigrants, and their quick differentiation to the terminal effector stage. A low proliferation of naïve T-cells combined with high proliferation of terminally differentiated effector T-cells has been already associated with a better virus control [11]. Recent deep immunophenotyping studies confirmed a number of specific T cell homeostasis alterations in EC including increased shares of naïve and CM CD4 T, as well as functional effector CD8 T cells as biomarkers of potent anti-HIV response [15]. Although in 2015, Bansal et al. concluded that elite controllers with preserved CD4T cells (EC) can control HIV-driven activation and CD4 percentage could be employed to determine the need for ART, further studies proposed that a “normal” CD4 count does not guarantee immune control [16].

The typical immunophenotypic changes in ART+ PLHIV with restored CD4 AC are a complex result of previous HIV-driven damage, ART-specific side effects plus on-going low level immune activation. Therefore, activation, exhaustion and senescence markers have been largely employed to characterize immune damage and/or restoration of the T cell pool. The effective inflammation control in EC has been previously demonstrated by similar levels of CD38/HLA-DR, CD57/CD28 defined T cell subpopulations, and PD-1 expression in EC and HIV (-) HC [16, 20]. Further on, inefficient viral control has been associated with an increase of CD8 T-cell activation and exhaustion including the presence of PD-1-expressing CD8+ T cells [9], a change from Th1 to Th2 cytokine profile [21], low Gag-specific T-cell polyfunctionality, and high proinflammatory cytokine levels [14]. In our EC case, effective inflammation control was associated with absence of CD38 ABS elevation in the absence of Treg increase.

Interestingly, a significant but transient increase of the terminally differentiated CD57+ CD8 T cell subset was registered which did not precede any deterioration of CD4AC or HIVVL increase. In fact, our observation corroborates with other authors’ data defining CD57 rather as a marker of increased cytotoxicity than of T cell senescence and imminent apoptosis [22]. We

have already proposed [17] that increased CD57+ CD8 T subset could notify a microbial or non-infectious stimulation, driving the terminal differentiation of a limited number of clones, and not necessarily - a loss of HIV control. In support, the expression of TIGIT by CD8 and CD4 T cell pool of EC did not increase between 2023 and 2025, while TIGIT expression was shown to correlate with HIV disease progression, even in PLHIV with antiretroviral control [24].

Mitochondria are essential for the intensive metabolism of immune cells. We and others have shown that both HIV-infection and ART contribute to mitochondrial damage, and therefore - to accelerated senescence in PLHIV [17, 24]. We reasoned that eventual loss of HIV control in EC would lead to vigorous viral replication, lymphocyte activation and, finally, exhaustion that might be preceded by signs of accelerated mitochondrial function.

A minor MM elevation only at the level of CD8 T cells in 2023 might be associated with a non-HIV-mediated activation, as commented for the transient CD57+CD8 elevation. However, the dramatic increase of MM in both CD4 and CD8 T, accompanied by MMP elevation deserves further close monitoring. Increased MM of CD4 and CD8 was reported as a sign of higher metabolic activity in virally stimulated immune cells of ART-naïve PLHIV [25]. Research data in EC reveal MM similar to HC and lower as compared to their ART+ counterparts [26], and viremic PLHW [24]. Data about loss of mitochondrial “fitness” in EC are limited. A study in EC reported increased MM as a sign of uncontrolled HIV infection [27]. In line with our results, a recent study demonstrated that unlike EC and HIV (-) HC, CD8 T cells from PLHIV, regardless of ART, are enriched in PD-1^{hi}EOMES^{hi}T-bet^{low}TIGIT⁺ exhausted CD8 T cells, also characterized by high expression of the glucose transporter, Glut-1, and impaired mitochondrial function. Consequently, mitochondrial antioxidant treatment was proposed for combined reconstitution therapies in HIV-1 infection [8].

MMP is essential for cellular respiration and ATP synthesis, and changes in MMP in the settings of HIV infection are associated with apoptosis. Chronic HIV infection leads to metabolic dysregulations of immune cells including mitochondrial damage, higher reactive oxygen species (ROS) production and reduction in glucose uptake [28-30]. In a previous study, we reported that elevated CD4 T cell MMP of PLHIV could further increase in the settings of ART, possi-

bly suggesting reactivation of HIV reservoirs [17]. In the case of EC, abrupt CD4 and CD8 MMP increase accompanied the increase of MM.

Studies in EC have demonstrated superior mitochondrial fitness as compared to ART-suppressed and HIV+ viremic individuals. In particular, the TCF1 transcription factor associated with the expansion capacity of HIV-specific CD8+ T-cells was overexpressed in HIV-specific CD8 T of EC, as compared to ART-suppressed and HIV+ viremic individuals [31, 32]. High TCF1 expression was shown to continuously maintain T cell mitochondrial fitness [33].

Indeed, most studies have linked mitochondrial disruption and reduced respiratory activity to MMP^{lo} / MM^{hi} phenotype [34, 35]. However, a recent study showed that just before activation-induced apoptosis, lymphocytes underwent hyperpolarization of mitochondrial membrane [36].

CONCLUSIONS

EC constitute a heterogeneous group with yet unpredictable loss of HIV VL, and undefined needs and timing of ART. In the settings of efficient anti-HIV immune response, more sensitive prognostic markers than CD4 AC are needed. In our case report phenotypic markers of CD4 and CD8 T cell differentiation, activation, exhaustion and senescence did not differentiate reliably between EC and HIV (-) HC. The registered significant increase of MM and MMP in the settings of undetectable HIV VL and stable immune parameters warrants further close monitoring. MM and MMP may be easily employed as biomarkers of mitochondrial fitness, sensing increased metabolic needs and predicting the loss of HIV control.

Limitations

Some limitations of this case report should be acknowledged. The stark increase of MM and MMP observed between 2023 and 2025 could be the only sign of undetected subclinical co-infection, an effect of developing metabolic syndrome (justified by the elevated cholesterol and triglyceride values) or other unknown factors. The speculation that elevated MM and MMP constitute a very early sign of viral reactivation, a follow-up monitoring would bring more clarity. Finally, the changes observed in a single EC may not be universal due to the presumably different mechanisms of viral control in this heterogeneous group of patients.

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