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Inflammatory Chemokine Profiles of Four Female Cameroonian HIV Elite Controllers

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ABSTRACT

Background: Antiretroviral therapy (ART) enables people infected with the Human immunodeficiency type 1 virus (HIV) to control viral replication and maintain undetectable plasma levels of the virus. However elite controllers are a unique subpopulation of HIV infected people capable of durable natural suppression of HIV without ART. Although elite controllers (ECS) are extremely rare they hold great potential in increasing our understanding about immune mechanisms and correlates of protection necessary for an efficient vaccine or functional cure of HIV. Cameroon has some of the most diversified HIV strains globally but no ECS have been described within this region. We present here four Cameroonian female HIV controllers from the CIRCB AFRODEC cohort of CRFO.2AG infected people.

Methods: We monitored four members of the CIRCB AFRODEC cohort who maintained persistent suppression of viral load (HIV RNA <50 copies/ml) during eight years without ART. A comparative analysis of plasma levels of five inflammatory

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chemokines including CXCL10/IP-10, Monocyte chemotactic protein-1 (MCP-1), MIG/CXCL9, RANTES/CCL5 and IL8 was made for the four elite controllers alongside with uninfected controls.

Results: Elite controller one (EC1) was diagnosed at 29 year old in 2003 after the husband died of HIV infection. Elite controller two (EC2) was diagnosed at 23 years old in 1995 while elite controller three (EC3) and four (EC4) were both diagnosed at 28 years in 2008 respectively. In contrast to the other three elite controllers EC2 had elevated plasma levels of IP-10 and MIG which was associated with decreasing helper CD4+ counts. ECI had at least three-fold more plasma levels of RANTES than the other elite controllers and a durable CD4/CD8 ratio higher than 2 throughout the study. Low plasma levels of CXCL10/IP-10, MCP-1, MIG/CXCL9 and IL-8 were associated with elite control of HIV-1 infection. This is in contrast with RANTES/CCL5 where higher plasma levels correlated with the best elite controller profile (ECI).

Conclusion: The inflammatory chemokine profiles of the elite controllers were heterogeneous probably reflecting underlying differences which can ultimately impact disease progression. This report highlights the need to monitor inflammatory chemokines and other plasma biomarkers in elite controllers as additional strategies toward predicting clinical outcomes in the long term management of elite controllers.

Keywords: Elite controllers, HIV, Inflammatory chemokines, Antiretroviral therapy, Viremia suppression

Abbreviations: ART: Antiretroviral Therapy; Abs.: Absolute; EC: Elite Controller; ECS: Elite Controllers; HIV: Human Immunodeficiency Virus Type 1; MCP-1: Monocyte Chemotactic Protein-1; IFN-γ: Interferon-Gamma; MIG: Monokine Induced by Gamma Interferon; CCR5: C-C Chemokine Receptor Type 5; CIRCB: Chantal Biya International Reference Center for Research on the Prevention and Management of HIV/AIDS; AFRODEC: African Dendritic Cell Targeted Vaccine Cohort; IP-10: IFN-γ-Inducible Protein 10; RANTES/CCL5: Regulated upon Activation Normal T-Cell Expressed and Secreted

BACKGROUND

Successful ART permits infected people to control HIV replication to an undetectable level and maintain normal helper CD4 T cells counts (>500 cells/ mm^3). Following the advent of 'test and treat' an increasing number of HIV infected people are entering ART [1-3]. However a unique minute fraction of HIV infected individuals referred to elite controllers is capable of spontaneous control of HIV without ART [4]. Due to their ability to resist HIV mediated disease progression and maintain persistent HIV viremia suppression current treatment guidelines do not clarify if ECS should be given ART [5]. As these individuals maintain ART independent undetectable viral load (plasma HIV RNA <50 copies/ml) there is confusion on initiating ART for this subset the reason being that the ultimate outcome of treatment would be undetectable viral load (plasma HIV RNA <50 copies/ml) and normal helper CD4 T cell values which they naturally achieve without ART.

In this regard persistent ECS are proposed both as a model of functional cure and a potential source of correlates of immune protection for the development of a vaccine against HIV [5,6]. In regions of intense concurrent infectious diseases like sub Saharan Africa little is known about long term ART naïve suppression of HIV replication. Several factors including genetic [7], immunological [8] and virological [9] have been associated with elite control of HIV. Prominent amongst these factors are host immune responses which are necessary in controlling HIV replication [10-12]. In addition host immune responses in suppressing viral replication might also dampen the persistent inflammation associated with HIV infection. Thus measuring systemic biomarkers of inflammation such as chemokines in ECS could identify factors relevant to elite control or disease progression which could be used in the long term management of HIV in ECS.

However ECS is a heterogeneous population as a result of variations in several characteristics related to disease progression [13,14]. Well over 28% of ECS for reasons unknown are reported to lose virological control over time and eventually progressing in disease [15]. The mechanisms causing accelerated disease progression in some ECS is not known. Nevertheless, generalized inflammation and trafficking of activated immune cells to sites of infection are known to exacerbate disease progression. HIV immune activation induces expression of inflammatory chemokines IP-10, MCP-1, MIG and ITAC which direct cellular immune responses to sites of infection [16]. Enhanced expression of chemokine receptors on lymphocytes (e.g. CXCR3 [17] increases the transit of immune cells to sites of infection.

To investigate the impact of inflammatory chemokines on elite control of HIV we measured plasma levels of IP-10, MIG, MCP-1, RANTES/CCL5 and IL-8 in 16 control HIV negative participants and four ECS from the CIRCB AFRODEC cohort. Our hypothesis is that lower levels of plasma inflammatory chemokine could be relevant in persistent EC of HIV infection. Thus, describing distinct inflammatory chemokines profiles in relation to EC of HIV can determine factors that would be necessary for predicting ECS and optimizing relevant biomarkers which can be used in the long term management of HIV in general. Understanding these factors should also provide vital

information for the design of future vaccines or the pursuit of a functional cure of HIV.

METHODS

Study population

All participants of this study were adult participants of the CIRCB AFRODEC cohort [35-37]. Participants were 21 to 65 years old and samples were collected as part of the CIRCB AFRODEC (African HIV-1 dendritic cell targeted vaccine) study. During the course of eight years 766 members of CIRCB AFRODEC cohort were monitored in CIRCB CIRCB (Ethics Protocol numbers: CIRCB/14-11DROS631-1112 and 2014/10/499/CE/CNERSH/SP). In addition to people who did not provide consent, participants who had been diagnosed with Hepatitis B virus, Hepatitis C virus, Dengue virus, Mycobacterium tuberculosis, or malaria were excluded from the study. Absolute numbers of helper CD4+ T-cells for HIV-1 positive participants were determined in fresh whole blood by BD multi-test CD3/CD8/CD45/CD4 and TruCount tubes (BD Biosciences, San Jose, USA) according to the manufacturer's instructions. Plasma HIV-1 viral load was determined on the m2000rt machine using the Abbott Real-Time HIV-1 Assay protocol.

Plasma sample collection and processing

About 4 ml of blood was collected into plastic Vacuum blood spray-coated K2EDTA tubes called Vacutest (Vacutestkirma, Italy). Subsequently, samples were transported to the Vaccinology laboratory of Chantal BIYA International Reference Centre (CIRCB) for storage and analysis. All samples were stored at room temperature and processed within 4 hours of collection. To obtain plasma, samples were centrifuged at 2,000 rpm for 10 min at 4°C. The plasma fraction was harvested sterile under the hood, aliquoted in small single-use volumes and stored at -20°C until use.

Chemokine plasma levels assays

Measurements of IP-10/IP-10/CXCL10, MIG, MCP-1/CCL2, RANTES/CCL5 and IL-8 in the plasma samples were conducted using cytometric bead assay (CBA) (BD Biosciences, USA) according to manufacturer's instructions. The data were collected using a BD Canto II flow cytometer (BD Biosciences, USA) and the results were analyzed in FCAP Array software (Soft Flow).

HIV infection and CD4 T-cell enumeration

Confirmation of HIV status was done as described for the CIRCB AFRODEC cohort using the Cameroon's national algorithm for the diagnosis of HIV infection as previously reported for the CIRCB AFRODEC cohort [35-37].

RESULTS

Clinical findings

We followed a cohort of 766 HIV infected people, median age 32 years at enrollment in CIRCB from 2011 to 2018. Twenty one participants (2.7%) were identified as viremic controllers and 4 (0.52%) as ECS (EC1, EC2, EC3 and EC4). ECS members of CIRCB AFRODEC have a median antiretroviral therapy (ART) naïve period of 14 years.

EC1 is a 44 year old woman who was first diagnosed at the age of 29 years old after the husband who had already been on ART died of HIV infection in 2003. She was confirmed as being infected with group M virus by central Pasteur of Cameroon. The viral load after diagnosis was undetectable and has remained suppressed till the date of this report. The helper CD4+ T cell count at diagnosis in 2003 was 1445 cells/mm^3 with CD4:CD8 ratio of 3.2 and has remained above 900 cells/mm^3 throughout the follow up **(Figures 1A-1C)**.

EC2 is a 46 years old woman who was first diagnosed at the age of 23 years old in 1995 also with a group M virus. She is a mother of six children all HIV negative and born when she was already infected with the virus. The husband has remained seronegative since 1995. In spite the fact that her helper CD4+ T cells count remained below 500 cells/mm^3 **(Figures 1A-1C)** she maintained undetectable viral load till 2017. Sudden detectable plasma virus was observed in 2017 with peak viral load (VL) of 3185 RNA copies/ml in 2017 and remained detectable in 2018 (peak VL 11207 copies/ml) when she opted to enter ART.

EC3 is a 37 year old woman who was first diagnosed at the age of 28 years in 2008. She had a child in 2010 whom together with the father are HIV negative. Her helper CD4 T cell count at diagnosis was 984 cells/mm^3 with CD4:CD8 ratio of 1.35. Viral load has remained undetectable till date with no dramatic changes in helper CD4+ T cell counts.

EC4 is also a 37 years old woman first diagnosed at the age of 28 years in 2008. Her helper CD4+ T cell count at diagnosis was 516 cells/mm^3 with CD4:Cd8 ratio of 0.93 but has steadily increased over the years to 774 cells/mm^3 and CD4:CD8 ratio of 1.34. VL has remained undetectable throughout the follow up period.

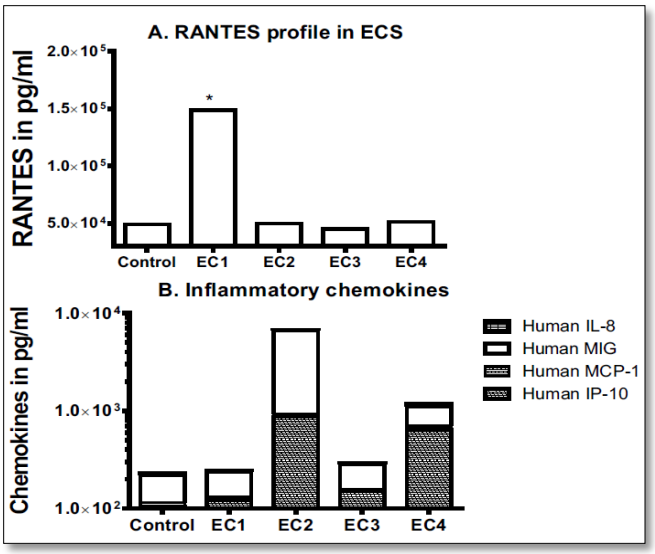

Figure 1. Longitudinal measurements of CD4 and CD8 T cells of the elite controllers. Measurements of CD4 **(A)**, CD8 **(B)** and CD4:CD8 ratio **(C)** for all ECS during a period of eight years is presented. Yearly values for each EC are indicated from 2011 to 2018.

Inflammatory chemokine profiles

ECS has been suggested to possess unique inflammatory signatures which could be relevant in the natural control of HIV-1 [18,19]. RANTES/CCL5 levels in EC2, EC3 and EC4 were comparable with HIV negative controls in contrast to EC1 with at least a threefold higher plasma levels of CCL5 **(Figure 2A)**. Whereas IP-10 was comparatively higher in all the ECS than the HIV negative controls; EC2 and EC4 had additionally higher levels of IP-10 than the remaining ECS **(Figure 2B)**. In addition to maintaining an undetectable viral load EC1 also showed sustained higher helper CD4 T cells counts (>900 cells/mm^3), very low CD8 T cells (<500 cells/mm^3 and a CD4:CD8 ratio greater than 2.7 throughout the follow up period **(Figures 1A-1C)**. EC2 with the worst helper CD4 T cell profile also had CD4:CD8 T cell ratio around 0.3 and CD8 T cell values above 1000 cells/mm^3 throughout the follow up period. Taken together with respect to clinical and plasma inflammatory chemokines profiles ECS are heterogeneous population. Nevertheless pour CD4 T cells counts and a low CD:CD8 ratio could be an indication of ultimate worst outcomes in ECS.

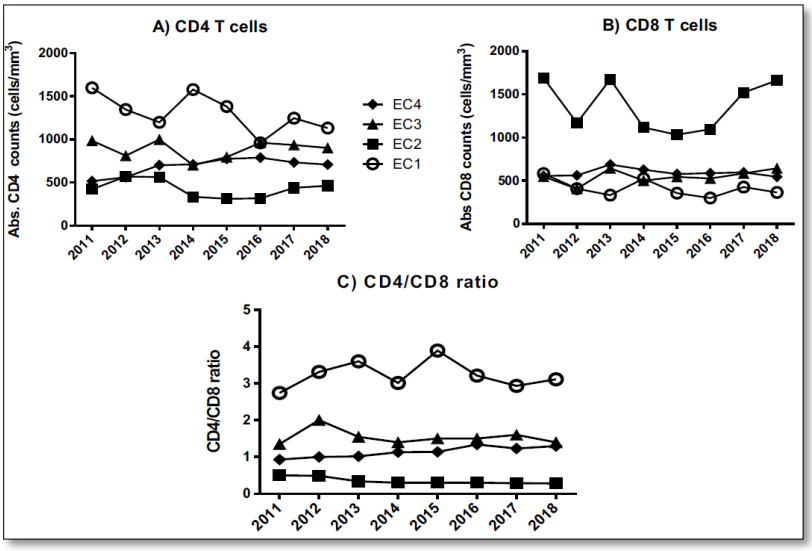

Figure 2. HIV Elite controller characterization. In **(A)** plasma concentrations of RANTES/CCL5 in the eighth year for EC1, EC2, EC3 and EC4 together with the mean plasma RANTES/CCL5 of five HIV negative individuals as control. Plasma level of RANTES/CCL5 for EC1 was three fold higher than the other ECS and the control group. In **(B)** plasma chemokine levels for EC1, EC2, EC3, EC4 and the control group, respectively.

DISCUSSION

During the last eight years we identified and monitored four Cameroonian women from the CIRCB AFRODEC cohort with sustained spontaneous ART independent control of HIV. From 2010 to 2018 all ECS had at least one viral load estimation performed every year and except for EC2 viral load in all elite controllers (EC1, EC3 and EC4) remained undetectable without ART for the duration of follow up. Even though these ECS were enrolled in the CIRCB AFODEC cohort just eight years ago their cumulative clinical history shows that they have been able to maintain persistent ART independent suppression of HIV for at least 10 years. In addition findings from this study like previous reports demonstrate that our ECS were actually a heterogeneous population [20-22]. Following the advent of 'test and treat' in Sub Saharan Africa an increasing number of HIV infected people are entering ART. However there are no clear cut guidelines on initiating and evaluating ART effectiveness in ECS. Just about every HIV clade circulates in Cameroon, so these ECS could potentially yield important and unique insights into HIV control in the absence of treatment. This makes it necessary to pursue a continuous assessment of this unique minute fraction of HIV infected people for the identification of predictive biomarkers [5,6,14,23] which could become essential in the long term management of the infection in ECS.

Amongst the 4 ECS described in this study only one individual (EC2) demonstrated loss of elite control capability approximately 21 years after the initial diagnosis. This is similar with previous reports where disease progression in ECS has been described [14,24-28]. Interestingly EC2 neither transmitted the virus to her six HIV negative children born after haven been tested HIV positive nor to her husband who remained negative in spite of repeated exposure. The loss of elite control capability in EC2 was accompanied by a significant increase in both MIG and IP-10 ($p=0.05$) relative to the other ECS. IP-10 and MIG are inflammatory chemokines which are known to bind on CXCR3 on TH1 cells thereby mobilizing leukocytes to inflammatory sites. Both chemokines have previously been associated with HIV mediated immune activation and disease progression [29,30]. The ultimate emergence of detectable plasma HIV RNA levels during the last two years in EC2 was preceded by persistent progressive helper CD4+ T-cell loss over several years. This loss of natural suppression of HIV has been reported to occur in well over 28% of ECS [13,15,28].

In contrast EC1 maintained plasma levels of several inflammatory chemokines including CXCL10/IP-10, MCP-1, MIG/CXCL9 and Il-8 at values comparable with HIV-negative individuals. In addition she also showed higher (normal) helper CD4+ T-cells counts and a CD4:CD8 ratios greater than 2.7 throughout the follow up period. Such low levels of MIG and IP-10 have also previously been associated with elite control of HIV [31]. In addition EC1 plasma levels of RANTES/CCL5 were also comparatively higher (threefold) than for the other ECS and the HIV negative controls. RANTES/CCL5 is a ligand for CCR5 a major co-receptor for HIV which is capable of blocking HIV infection. High levels of RANTES in plasma have been demonstrated to be protective against HIV infection and disease progression [32,33]. This implies that a combination of several factors would probably be necessary to defined durable elite control of HIV. On the other hand some biomarkers such as unusual high plasma levels of IP-10 and MIG in conjunction with a progressive decline in CD4 T cell levels could constitute early warning indicators of loss of elite control capability.

CONCLUSION

In conclusion we have shown that a differential expression of some inflammatory chemokines including IP-10, MIG and RANTES could be relevant in predicting the long term outcome of elite control of HIV infection. All ECS had higher levels of IP-10 when compared to HIV negative individuals. Elevated plasma IP-10 levels during HIV infection have been suggested to be predictive of earlier decline in the helper CD4 T cell count [34]. In this regard elevated plasma IP-10 and MIG levels in association with low levels of RANTES/CCL5 might be considered as predictors of poor outcomes in ECS. On the other hand high levels of RANTES/CCL5 together with sustained high CD4 T cell counts and a CD4:CD8 ratio above 2.7 was associated with better outcomes in ECS. Our findings are useful because these biomarkers could potentially be useful in the long term management of elite control of HIV infection in sub Saharan Africa.

DECLARATIONS

Ethics approval and consent to participate

This study received ethical approval from the Cameroon National Ethics Committee for Human Health Research (Reference numbers CIRCB/14-11/DROS631-1112 and 2014/10/499/CE/CNERSH/SP) and the CIRCB institutional review board (protocol number 14-11). All participants provided written informed consent. Data were processed using specific identifiers for privacy and confidentiality purposes. Clinical data generated during the course of this study was provided free of charge to all participants.

Consent for publication

EC1, EC2, EC3 and EC4 provided written informed consent for the publication of this manuscript.

Availability of data and materials

Information regarding data referring to the CIRCB AFRODEC cohort used in this manuscript is part of the data bank of the Chantal Biya international Reference center for research on the prevention and management of HIV/AIDS; it

is not possible to obtain them by URL. All data are fully available without restriction. Data are available from the CIRCB Institutional Data Access/Ethics Committee for researchers who meet the criteria for access to confidential data. All requests for Data should be addressed to the director General of CIRCB reachable by the following address:

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Never the less all supporting datasets relevant to the conclusions of this case report have been included within the article (five figures).

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

Conceived and designed the experiments: GWN, LNN and NNN.

Performed the experiments: LNN, NNN, AAN, GA, JLS, MSS, SM, ASO, RSK, GOC, ABW, AG, RG.

Technical assistance: RG, AG, CGP, SM, GOC, MIO, ASO, LK, COE, ABW.

Analyzed the data: GWN, LNN, NNN and AAA.

Wrote the paper: LNN, GWN and ABW. The final manuscript was read and approved by all Authors.

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