Elite and viremic HIV-1 controllers in West Africa

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Background: Data on HIV-1 controllers in Africa are scarce. We report the proportion of HIV-1 controllers in a group of adults prospectively monitored with *frequent viral load* measurements as part of a clinical trial in West Africa.

Methods: For the Temprano trial, antiretroviral therapy (ART)-naive HIV-1 infected adults with no criteria for starting ART were randomized to start ART immediately or defer ART until the WHO starting criteria were met. Plasma viral load was measured every 6 months. The trial follow-up was 30 months. We considered all Temprano participants randomized to defer ART. Patients with all semestrial viral <2000 copies/ml and still off ART at month 30 were defined as HIV-1 controllers. Controllers with all viral loads <50 copies/ml were defined as elite controllers, the rest as viremic controllers.

Results: Of the 1023 HIV-1-infected adults randomized in the Temprano deferred-ART group, 18 (1.8%) met the criteria for classification as HIV controllers, of whom seven (0.7%) were elite controllers and 11 (1.1%) viremic controllers. The HIV-1 controllers had low peripheral blood mononuclear cell HIV-1 DNA and low inflammatory marker levels. They maintained high CD4$^+$ cell count and percentages and had a low morbidity rate.

Discussion: HIV controllers exist in Africa at a proportion close to that reported elsewhere. They represent a small fraction of all HIV-1-infected patients but raise important questions. Further studies should assess whether starting ART might represent more risk than benefit for some controllers, and where it does, how to identify these patients before they start ART.

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Introduction

Untreated HIV-1 infection leads to AIDS and death in the vast majority of patients. A minority of HIV-1-infected persons, known as long-term non-progressors, remain asymptomatic and maintain high $CD4^+$ cell count without the use of antiretroviral therapy (ART) [1−4]. A smaller group, known as HIV-1 controllers, control HIV-1 replication spontaneously and persistently without treatment [4−6]. Factors associated with control of the virus include a low reservoir level, a strong HIV-specific T-CD4 and T-CD8 cells immune response, the presence of alleles HLA-B*57 and HLA-B*27, and the presence of antiviral restriction factors, among several other immune or genetic factors [7−12].

Data on HIV-1 controllers in sub-Saharan Africa are scarce [13−15] and opportunities to record new data are getting fewer. In the past, many HIV-1-infected individuals living in sub-Saharan Africa had poor access to routine viral load monitoring before they were put on ART. Because ART is now recommended for all HIV-1-infected individuals irrespective of their $CD4^+$ cell count, data on monitored patients who are not on ART will not be recorded in future.

Here we describe the proportion of HIV-1 controllers identified in Côte d'Ivoire, West Africa, in a group of HIV-infected adults people who were followed without ART in the framework of a clinical trial from 2008 to 2015.

Methods

Patients and follow-up

Temprano ANRS 12136 was a 2 × 2 factorial plan randomized trial of early ART and isoniazid preventive therapy (IPT), the methods and results for which have been reported previously [16]. In summary, 2056 HIV-infected, ART-naive adults with no criteria for starting ART were randomized to start ART immediately (early-ART group) or defer starting until the WHO criteria for starting ART were met (deferred-ART group); to be given or not given 6 months of IPT. The $CD4^+$ cell count and HIV-1 plasma viral load (VL) were measured on enrollment and every 6 months thereafter. At the end of the trial, the HIV-1 DNA in the peripheral blood mononuclear cells (PBMCs) was measured in all patients and several plasma inflammatory markers were measured in the first 477 participants, using blood samples that had been taken on enrollment and frozen at −80°C [17,18].

The primary analysis showed that the participants randomized to early-ART had a lower risk of severe morbidity at 30 months [16]. The long-term follow-up analysis showed that participants randomized to IPT and those with low plasma soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble cluster of differentiation 14 (sCD14) at baseline had a lower risk of mortality [17,19].

Here, we report data from enrollment to month 30 for all trial participants with a baseline plasma HIV-1 RNA of <2000 copies/ml who were randomized to the deferred-ART group.

Definitions

We defined as HIV-1 controllers (HIC) patients still alive and off ART at month 30, who had at least three VLs measurents between baseline and month 30 and for whom all available VLs were below 2000 copies/ml. Controllers with every VL measurement below 50 copies/ml were defined as elite controllers, and the rest as viremic controllers. One blip interim value of above 50 copies/ml (EC) or above 2000 copies/ml (VL) occurring within a significant morbidity event was accepted [20]. All other patients were classified as progressors. In this report, we distinguish progressors who did not start ART (progressors-no ART) from those who started ART (progressors-ART) during trial follow-up.

Serological, immunological and virological assays

All participants in the Temprano trial were tested at least twice for HIV serology. Those who had a negative baseline plasma HIV-1 RNA were tested a third time, using different techniques. The tests were carried out following the recommendations in force in the national HIV program of Côte d'Ivoire (two different ELISA tests, one sensitive and one specific and discriminating for HIV-1 and HIV-2). People who were positive for HIV-2 alone were not included in the trial. People with a positive serology for HIV-1 alone, or for both HIV-1 and HIV2, were included. The latter represented 2.5% of all those included [16].

The $CD4^+$ percentage and absolute count (True Count technique on FACScan, Becton Dickinson) and plasma HIV-1 RNA (real-time polymerase-chain reaction assay, generic HIV viral load, Biocentric, threshold of detectability 50 copies/ml) were carried out in the CeDReS laboratory at the Treichville University Hospital in Côte d'Ivoire. PBMCs HIV-1 DNA (real-time PCR, Biocentric, Bandol, France) and inflammatory biomarkers (commercially available enzyme-linked immunosorbent assays) were carried out in France using techniques previously reported [17,18]. The technique was based on the amplification of the long terminal repeat (LTR) gene well adapted to HIV-1 non B sub-types and referring to the 8E5 cell line containing one HIV copy per cell (HIV DNA cell, Biocentric, Bandol, France). The threshold of the technique was five copies of HIV-1 DNA per PCR well. The HIV-1 DNA load was

expressed as a proportion of infected cells among the target cells. Results were expressed as the HIV-1 DNA $\log_{10}$ copy number per million PBMC.

Statistical analysis

This is a post-hoc analysis of the Temprano trial data. Continuous variables are described using medians and interquartile ranges (IQR). Categorical variables are described using numbers and percentages. We used Wilcoxon rank sum test to compare the distribution of each inflammatory biomarker at baseline between controllers (elite and viremic controllers in one group) and progressors (ART and no-ART in the other group).

The analysis was conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Funder, registration and ethics

The Temprano protocol was approved by the Côte d'Ivoire National Ethics Committee for Health Research. It was registered at ClinicalTrials.gov (NCT00495651). Informed consent was given prior to participation in the trial. The study sponsor (Agence Nationale de Recherches sur le Sida et les hépatites virales) played no part in the conduct of the study or interpretation of the data.

Results

From March 2008 to June 2012, 1023 patients were enrolled on the Temprano and randomly allocated to the deferred-ART group. Ninety one (9%) of them had a baseline plasma HIV-1 RNA below 2000 copies/ml. Of these 91 participants, 40 started ART before month 30, two were lost to follow-up while still off ART, and 49 were still in active follow-up, off ART, at month 30 (Fig. 1).

The 49 patients still off ART and alive at month 30 had a total of 211 plasma HIV-1 RNA cell measurements (median 5.0, IQR 4.0–5.0) and 212 CD4$^+$ cell count (median 5.0, IQR 4.0–5.0) measurements between month 6 and month 30, which corresponds to 86.1% and 86.5% of the 245 semestrial plasma HIV-1 RNA and CD4$^+$ cell count measurements scheduled in the protocol between month 6 and month 30. Based on the above definition, seven patients (0.7%) were classified as elite controllers, 11 (1.1%) as viremic controllers, 31 (3.0%) as progressors-no ART and 40 (3.9%) as progressors-ART (Fig. 1). The four groups were similar in age, sex and CD4$^+$ cell count or percentage distribution at baseline. The elite and viremic controllers had lower baseline HIV-1 DNA values than participants in the progressor groups. The percentage of participants with a baseline HIV-1 RNA <50 copies/ml was 64% in viremic controllers, 48% in progressors-no ART and 17% in progressor-ARTs
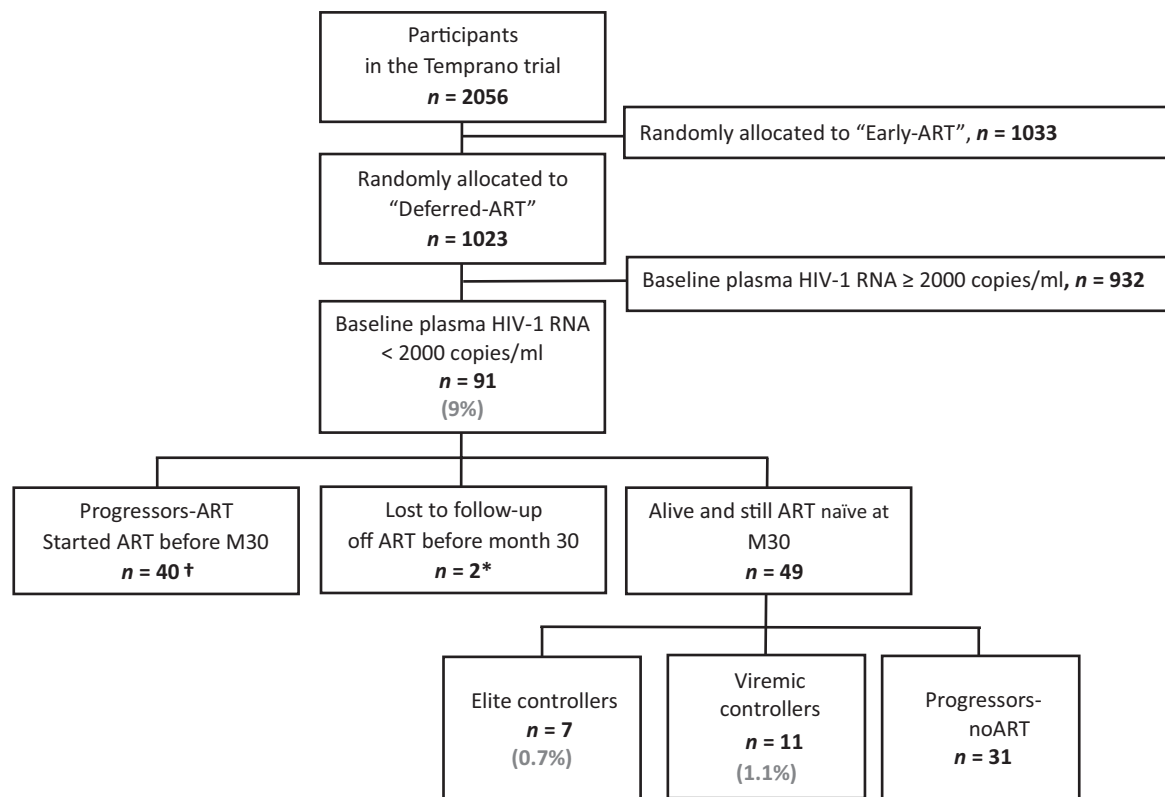

Fig. 1. Flow chart. *These two patients were lost to follow-up while still off ART and after only one viral load measurement. †These 40 patients started ART before the end of the trial. ART, antiretroviral therapy.

(Table 1). The majority of participants in all groups were women (Table 1).

Table 2 shows all recorded CD4$^+$ cell counts and plasma HIV-1 RNA values for participants who matched the definition for elite or viremic controller. Two elite controllers (EC1 and EC7) had a single VL blip above 50 copies/ml, and one viremic controller (VC4) had a single interim VL of above 2000 copies/ml during a documented malaria episode. Of the 30 CD4$^+$ cell count measured for the elite controllers over the entire follow-up, two (6.7%) were below 350 cells/μl 3 (10.0%) were between 350 and 399 cells/μl and 25 (83.3%) were 500 cells/μl or higher. Of the 50 CD4$^+$ cell counts measured for the viremic controllers over the entire follow-up, three (6.0%) were below 350 cells/μl, 19 (38.0%) were between 350 and 499 cells/μl and 28 (56.0%) were 500 cells/μl or higher. Of the 89 patients in the four groups, 43 patients participated in the sub-study of immunoinflammatory markers, including two elite controllers, five viremic controllers, 23 progressors–ART and 13 progressors-no ART. Figure 2 shows the values for all groups. The level of interleukin-1 receptor antagonist, sCD14, ultra-sensitive C-reactive protein, IL-6, D-dimer was significantly lower in controllers compared to progressors. The difference between both groups did not reach significance for IP10, CD163 and sVCAM.

For the 40 patients who started ART before month 30, a total of 103 plasma HIV-1 RNA measurements (median 2.0, IQR 2.0−4.0) and 103 CD4$^+$ cell measurements (median 2.0, IQR 2.0−4.0) were carried out between month 6 and starting ART. Of these 40 patients, 31 started ART because they reached at least one clinical or immunological starting criterion from those listed in the WHO guidelines at the time, and nine because they were pregnant. Before they started ART, 22 patients had less than three semestrial VL measurements and 18 patients had three or more. Among the latter, the pre-ART viral loads were all below 2000 copies/ml in three patients. The other 15 all had one or more viral loads of above 2000 copies/ml.

Discussion

Several definitions have been proposed for classifying individuals as HIV controllers [3,4,21,22]. For this study the US definition was used, in which patients not on ART monitored for at least one year are defined as elite controllers if at least three consecutive HIV-1 RNA tests are below 50 copies/ml; and as viremic controllers if at least three consecutive plasma HIV-1 RNA tests are

Table 1. HIV-1 infected adults randomized in the deferred ART group of Temprano with a plasma HIV-1 RNA below 2000 copies/ml (N = 89^a).

	Did not start ART before 30 months			Started ART before 30 months
	Elite controllers n = 7	Viremic controllers n = 11	Progressors no ART n = 31	Progressors ART n = 40
Baseline				
Age, years, median (IQR)	34 (27–49)	35 (32–44)	36 (31–42)	34 (30–42)
Sex, female, n (%)	6 (85.7)	10 (90.9)	26 (83.9)	38 (95.0)
WHO clinical stage 1 or 2, n (%)	7 (100)	11 (100)	29 (93.5)	37 (92.5)
Body mass index (kg/m^2), median (IQR)	24.0 (21.4–26.6)	25.0 (22.8–29.7)	24.3 (21.8–26.9)	22.9 (21.0–26.0)
Hemoglobin (g/l), median (IQR)	128 (116–131)	118 (110- 124)	114 (107–127)	109 (99–117)
Positive HBs antigen, n (%)	0 (0)	1 (9.1)	2 (6.5)	3 (7.5)
CD4$^+$ cell count/μl, median (IQR)	595 (508–685)	514 (471–611)	556 (476–668)	451 (336–521)
CD4$^+$ percentage, median (IQR)	31.2 (21.7–35.4)	28.2 (22.8–32.3)	25.5 (23.0–28.5)	21.5 (18.6–25.9)
Plasma HIV-1 RNA, n (%)				
<50 copies/ml	7 (100)	7 (63.6)	15 (48.4)	7 (17.5)
50–2000 copies/ml	0	4 (36.4)	16 (51.6)	33 (82.5)
HIV-1 DNA, log$_{10}$ copies/10^6 PBMC, median (IQR)	0.0 (0.0–1.3)	1.6 (1.4–1.7)	2.1 (1.9–2.5)	2.4 (2.0–2.7)
Follow-up				
Received isoniazid Preventive therapy, n (%)	3 (42.9)	6 (54.5)	11 (35.5)	23 (57.5)
Delta CD4$^+$ cell count M0 to M30, median (IQR)	−38 (−166; +62)	+38 (−1; +85)	−71 (−143; +83)	+103 (+34; +245)
Serious adverse event (SAE), n (%)				
Patients with at least one SAE	0 (0)	1 (9.1)	1 (3.2)	4 (10.0)
Number of SAE	0	1^b	1^c	5^d

ART, antiretroviral therapy; IQR, interquartile range; PBMC, peripheral blood mononuclear cells.
^{a}The two patients lost to follow-up while still off ART are not included in this table.
^{b}Pyelonephritis in a patient with decompensated diabetes.
^{c}Pelvic carcinosis, n = 1.
^{d}Pulmonary tuberculosis, n = 3; pyelonephritis, n = 1; profound lymph-node tuberculosis, n = 1.

Table 2. Baseline characteristics and CD4$^+$ and HIV-1 viral load values over time in elite controllers and viremic controllers.

Patient	Sex	Age	Baseline HIV-1 DNA [a]	Baseline HIV-1 RNA [b]	M6 HIV-1 RNA [b]	M12 HIV-1 RNA [b]	M18 HIV-1 RNA [b]	M24 HIV-1 RNA [b]	M30 HIV-1 RNA [b]	Baseline CD4$^+$ cell count [c] (%)	M6 CD4$^+$ cell count [c] (%)	M12 CD4$^+$ cell count [c] (%)	M18 CD4$^+$ cell count [c] (%)	M24 CD4$^+$ cell count [c] (%)	M30 CD4$^+$ cell count [c] (%)
EC 1	F	34	46	0	0	0	125	0	0	592 (35%)	426 (38%)	598 (37%)	619 (40%)	536 (37%)	528 (31%)
EC 2	F	35	17	0	0	0	Missing	0	0	508 (24%)	517 (28%)	735 (32%)	Missing	1153 (27%)	342 (16%)
EC 3	M	26	22	0	0	0	0	0	0	612 (31%)	624 (40%)	661 (32%)	773 (38%)	565 (45%)	674 (42%)
EC 4	F	30	0	0	0	0	Missing	Missing	0	599 (22%)	498 (23%)	290 (21%)	Missing	Missing	359 (20%)
EC 5	F	27	0	0	0	0	0	Missing	Missing	502 (39%)	802 (41%)	595 (45%)	553 (50%)	Missing	Missing
EC6	F	49	0	0	0	188	0	0	0	782 (34%)	740 (35%)	807 (32%)	1096 (28%)	929 (31%)	771 (30%)
EC 7	F	53	0	0	0	0	0	0	0	685 (22%)	787 (26%)	639 (23%)	918 (25%)	761 (24%)	748 (26%)
VC 1	F	30	27	0	0	0	0	324	Missing	1456 (30%)	1307 (33%)	1392 (30%)	1148 (37%)	522 (41%)	Missing
VC 2	F	48	43	0	0	0	0	997	0	611 (41%)	578 (37%)	798 (41%)	470 (42%)	464 (42%)	497 (34%)
VC 3	F	44	0	0	0	0	1371	0	0	471 (24%)	530 (28%)	557 (26%)	495 (24%)	473 (23%)	589 (33%)
VC 4	F	24	217	0	499	0	23324	1317	215	547 (21%)	445 (21%)	565 (28%)	357 (30%)	575 (25%)	524 (25%)
VC 5	F	35	35	786	1022	0	0	708	Missing	514 (32%)	321 (31%)	383 (35%)	282 (26%)	435 (39%)	Missing
VC 6	F	35	40	1452	715	1654	869	493	0	504 (23%)	592 (29%)	683 (27%)	666 (26%)	563 (26%)	505 (25%)
VC 7	F	36	Missing	1449	619	0	1030	0	417	309 (34%)	470 (30%)	420 (28%)	403 (28%)	479 (29%)	347 (30%)
VC 8	F	32	152	0	0	353	Missing	901	0	578 (27%)	732 (25%)	557 (27%)	Missing	514 (25%)	674 (27%)
VC 9	M	44	40	0	0	0	0	455	413	354 (22%)	378 (24%)	373 (22%)	452 (27%)	438 (27%)	353 (28%)
VC 10	F	51	20	0	0	0	2066	715	371	502 (29%)	667 (38%)	540 (36%)	479 (30%)	547 (35%)	578 (35%)
VC 11	F	34	49	1377	Missing	Missing	1388	749	453	702 (28%)	Missing	Missing	669 (33%)	512 (29%)	787 (29%)

%, percentage; EC, elite controller; M0, month 0 (baseline); M6, month 6; VC, viremic controller.
[a]Copies per 10^6 peripheral blood mononuclear cells.
[b]Copies per milliliter.
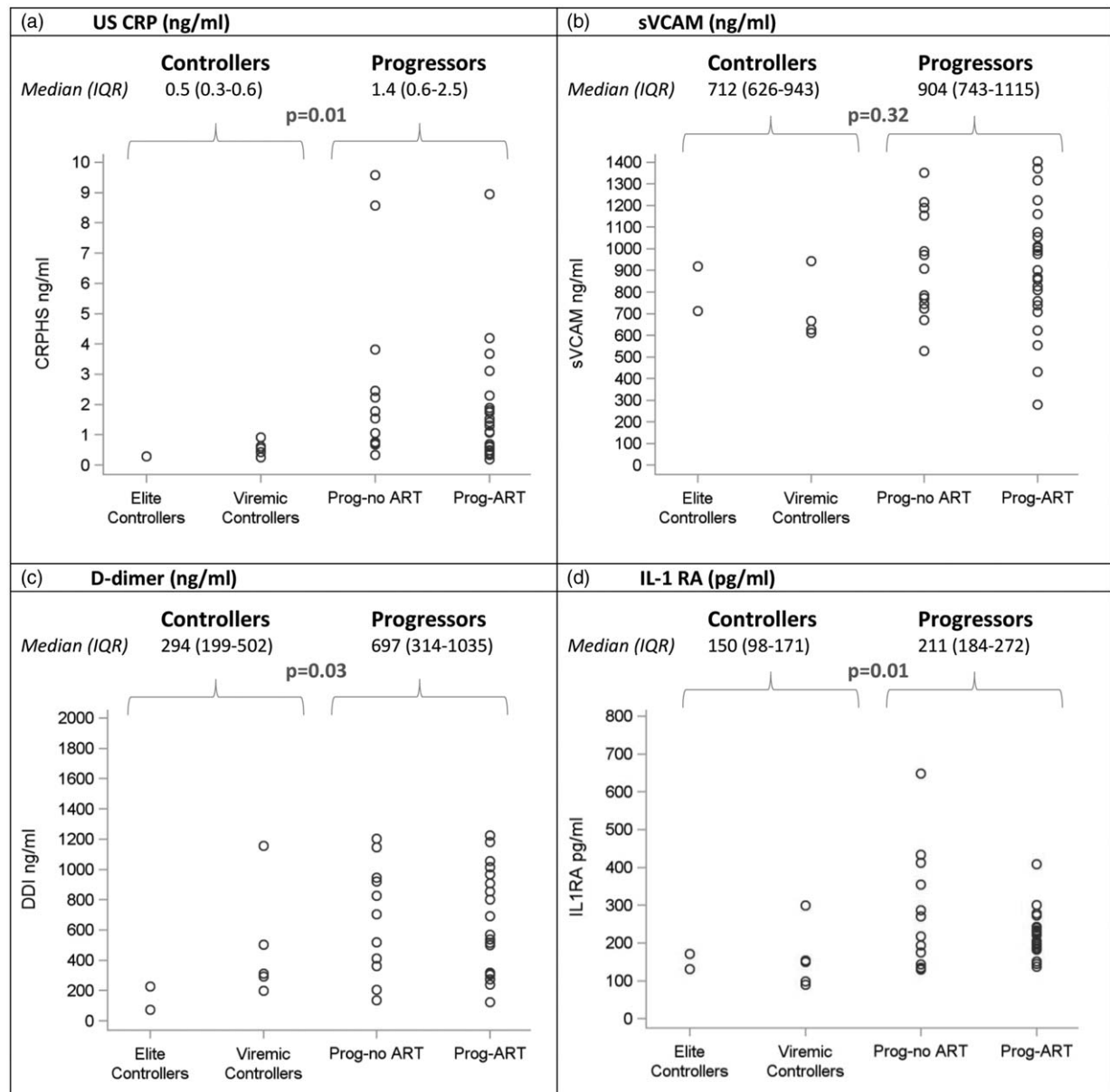[c]Per cubic millimeter.

Fig. 2. Baseline biomarker levels in elite controllers, viremic controllers and progressors. Each boxplot display the minimum, first quartile (Q1), median, third quartile (Q3), and maximum value of the marker. Dots below and above the minimum and maximum values are outliers. Interferon gamma-induced protein 10 and D-dimer. (a) US CRP (ng/ml). (b) sVCAM (ng/ml). (c) D-dimer (ng/ml). (d) IL-1 RA (pg/ml). (e) CD163 (ng/ml). (f) sCD14 (ng/ml). (g) IL 6 (pg/ml). (h) IP 10 (pg/ml). (i) HIV-1 DNA (log_{10} copies/10^6 PBMC). CD163, cluster of differentiation 163; DNA, deoxyribonucleic acid; IL-1-RA, interleukin-1 receptor antagonist; IL-6, interleukin-6; PBMC, peripheral blood mononuclear cells; prog-ART, progressors-ART; prog-no ART, progressors-no ART; sCD14, soluble cluster of differentiation 14; sVCAM-1, soluble vascular cell adhesion molecule-1; US CRP, ultra-sensitive C-reactive protein.

below 2000 copies/ml, with some above 50 copies/ml [6,7].

To our knowledge, this is the first prospective estimate of the proportion of HIV controllers in Western Africa. In this cohort with semestrial viral load monitoring and a mean of six viral load measurements per person, 1.8% of 1023 adults were classified as HIV-1 controllers, including

0.7% of elite controllers and 1.1% of viremic controllers. These rates are higher than those recently estimated in Uganda and Ethiopia [14,15], and within the range of those found in other continents [4,6,14,15,23]. Unlike studies in Europe or North America, the HIV-1 controllers in our study and those in the Ugandan and Ethiopian studies were mostly female, which is consistent with HIV epidemic characteristics in sub-Saharan Africa.
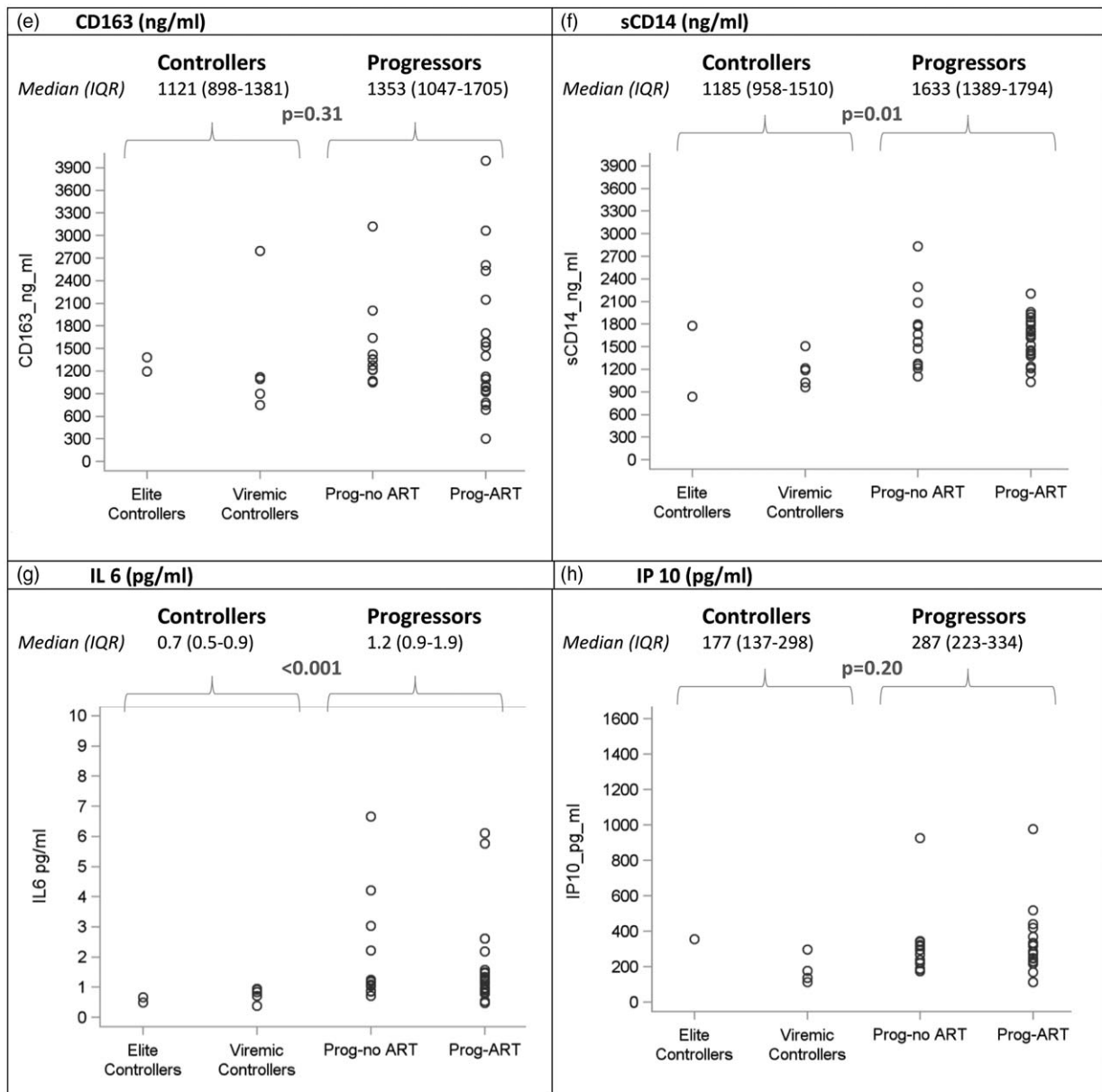
Fig. 2. (Continued).

In our study, controllers had low reservoirs and low levels of inflammatory markers. They maintained high CD4+ cell count and percentages in the medium term, and had few episodes of severe morbidity. Whether HIV controllers with such a low risk profile should be considered as a group deserving specific guidelines for starting ART is a debatable issue. [26,27]

On the one hand, it is well known that a few controllers ultimately lose virologic control, increase their viral load, decrease their CD4+ cell count and develop HIV-related diseases [3,4,6,21,22,28–31]. There can be no doubt that controllers who are destined to subsequently lose

virologic control should start ART before the loss of control occurs. In addition, even if they maintain low plasma HIV-1 RNA levels and high CD4+ cell count in the long term, controllers may have residual viral replication, persistent immune activation and chronic inflammation. This may increase the risk of various diseases while they still apparently control replication [6,32–35].

On the other hand, an unknown percentage of elite controllers may never lose apparent virologic control or have deleterious residual viral replication if they stay off ART, and therefore may not derive any benefit from
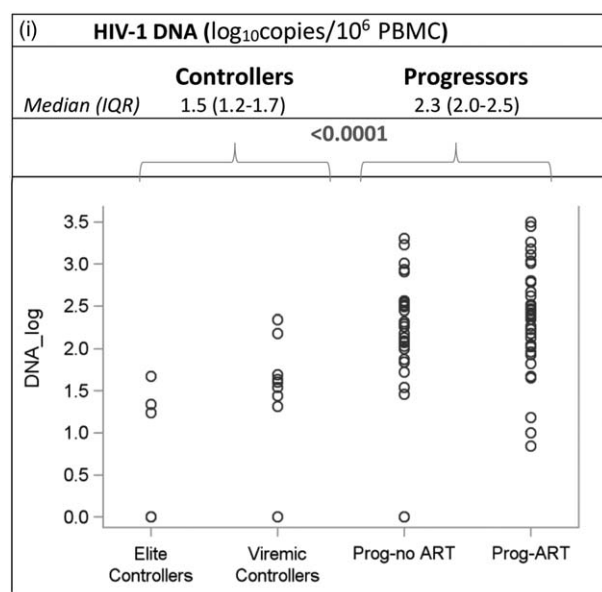
Fig. 2. (Continued).

ART. The fact that these people represent a small percentage of HIV-1 controllers and a tiny percentage of all HIV-1 patients does not remove the question of their individual care. The recommendation to treat all people infected with HIV is based on a favorable collective benefit/risk ratio. If this rule would disadvantage a small number of individuals with an unfavorable individual benefit/risk ratio, it is the responsibility of the healthcare system to identify these individuals and establish specific guidelines for them.

HIV sub-types were not analyzed in this study. In sub-Saharan Africa, a variety of HIV subtypes are in circulation, with a predominance of subtype C [24]. In Côte d'Ivoire, the predominant subtype is CRF02_AG [25]. The fact that there are apparently as many controllers in an African country with predominant subtype C as in other regions with predominant subtype B may suggests that the HIV subtype may not play a major role in HIV control.

Our data are descriptive, their strength being the estimation of the frequency of controllers in an African cohort well followed for 30 months with repeated measurements of viral load. They do not provide new information concerning the mechanism of HIV control. Further studies including human leucocyte antigen (HLA)-typing could provide new insight. Although HLA-B27/HLA-B57 are the main HLA-alleles associated with natural immunity against HIV-infection, there are other HLA-alleles with protective immunity [36], as well as alleles associated with HIV-disease progression [37]. Identifying new alleles associated with control or progression, and exploring the association of HIV-sub-type with certain HLA-type in different regions could be highly informative. In conclusion, this study provides prospective evidence that HIV controllers exist in West Africa at a proportion close to that previously reported in high-income countries. In accordance with the WHO 2015 guidelines, HIV controllers will now start ART immediately. This will have two consequences. First, it will not be known that they HIV controllers since the current definition is based on a number of measurements repeated over time for patients not on ART. Second, if it were shown that a sub-group of controllers incurred more risks than benefits from starting ART, there are currently no markers to identify people in this sub-group before they start ART. Further studies should try to confirm whether this sub-group exists, and if it does, identify markers indicating they need not start ART [38] and explore whether other tests, such as integration of intact proviruses in heterochromatin regions, may allow to identify such persons, even when treated with ART [39,40].

J.-B,N., D.G. and X.A. drafted the manuscript. All authors provided critical input into the manuscript.

Conflicts of interest

There are no conflicts of interest.

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