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Research Paper

Role of APOBEC3H in the Viral Control of HIV Elite Controller Patients

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Abstract

Background APOBEC3H (A3H) gene presents variation at 2 positions (rs139297 and rs79323350) leading to a non-functional protein. So far, there is no information on the role played by A3H in spontaneous control of HIV. The aim of this study was to evaluate the A3H polymorphisms distribution in a well-characterized group of Elite Controller (EC) subjects.

Methods We analyzed the genotype distribution of two different SNPs (rs139297 and rs79323350) of A3H in 30 EC patients and compared with 11 non-controller (NC) HIV patients. Genotyping was performed by PCR, cloning and Sanger sequencing. Both polymorphisms were analyzed jointly in order to adequately attribute the active or inactive status of A3H protein.

Results EC subjects included in this study were able to maintain a long-term sustained spontaneous HIV-viral control and optimal CD4-T-cell counts; however, haplotypes leading to an active protein were very poorly represented in these patients. We found that the majority of EC subjects (23/30; 77%) presented allelic combinations leading to an inactive A3H protein, a frequency slightly lower than that observed for NC studied patients (10/11; 91%).

Conclusions The high prevalence of non-functional protein coding-genotypes in EC subjects seems to indicate that other innate restriction factors different from APOBEC3H could be implicated in the replication control exhibited by these subjects.

Key words: APOBEC3H polymorphisms; rs139297; rs79323350; HIV; elite controllers.

Introduction

The APOBEC3 (A3) protein family (apolipoprotein B mRNA-editing catalytic polypeptide 3) is a group of cellular restriction factors with intrinsic activity against HIV inducing modifications of nucleotide sequences into the viral genome [1,2]. The A3 family is composed of a group of seven genes in humans (A3A – A3H), four of them (A3G, A3D, A3F and A3H) with potent HIV

restriction ability [2].

In recent years, several studies have investigated the role of A3 members in HIV pathogenesis. A3G and A3F are the most studied members of A3 family; however, the influence of these A3 proteins on HIV disease progression and viral control remains uncertain [3-5]. The APOBEC3H (A3H) protein is the most polymorphic member of A3 family with seven described haplotypes (hap I-VII) which are composed of various combinations of polymorphisms that influence the protein stability and its activity against HIV [6]. Two A3H destabilizing polymorphisms: rs139297; exon 3 (R105G, change of arginine to glycine at position 105) and rs79323350; exon 2 (N15del, deletion of amino acid at position 15) can independently (only in homozygosis) cause an inactive A3H protein; while wild type alleles at both 15 and 105 positions lead to a stable protein with strong activity against HIV in vitro [6, 7].

Few studies have focused on the role of A3H polymorphisms in HIV disease progression or susceptibility to HIV infection [8-10]. We have previously evaluated the HIV mutation rates and its association with A3 activity in HIV patients with different levels of disease progression, and we found that most of these patients carried alleles leading to an inactive A3H protein, thus showing a genotype with poor contribution to HIV control [8]. Moreover, two recent studies have reported that the A3H genotypes containing the polymorphisms N15del and 105G leading to an inactive A3H protein were associated with susceptibility to HIV infection and disease progression in an Indian [9] and in a Japanese [10] HIV-infected population.

Interestingly, the activity of some members of the A3 family has been associated with the ability of the Elite controller (EC) subjects to spontaneously restrict viral replication [11, 12], but studies regarding A3H polymorphisms are still missing. Given the potent HIV restriction ability of the active A3H protein [2, 7, 13, 14], and the relative resistance of A3H protein to the HIV-1 Vif protein action [13-15], we hypothesized that the prevalence of A3H polymorphisms leading to an inactive protein may be very low in EC subjects. Therefore, in the present study we have analyzed the A3H polymorphisms distribution in a well-characterized group of EC subjects maintaining a long-term spontaneous control of HIV replication.

Materials and Methods

This is a cross-sectional study including two different groups of adult patients with chronic HIV infection and naïve to combined antiretroviral therapy (cART): one with detectable HIV-RNA viral load (non-controllers, NC, group), and another with complete viral suppression (Elite controllers, EC, group). A total of 41 patients were included: 11 belonging to NC group and 30 belonging to EC group.

The NC subjects were selected from the cohort of adults with HIV infection of the AIDS Research Network (CoRIS) [16, 17] and from Hospital La Fe (Valencia, Spain). CoRIS is an open, multicenter cohort of patients newly diagnosed with HIV infection at the hospital or treatment center, over 13 years of age, and naïve to antiretroviral treatment. All NC patients included were representative of this cohort of patients.

EC subjects maintained a long-term spontaneous control of HIV replication, stable CD4 counts during the whole follow-up period, and were selected from the cohort of HIV controllers of the Spanish AIDS Research Network (ECRIS), launched in 2013. ECRIS is an open, multicentre cohort of HIV controller patients whose data come from the Spanish Long Term Non-Progressors (LTNP) cohort and the Spanish AIDS Research Network (CoRIS) cohort [16,17], and different clinical centres in Spain. An HIV-infected patient was considered as EC when having at least three consecutive plasma HIV viral load determinations with no more than 50 HIV-RNA copies/ml during at least 12 months of follow-up, in the absence of cART. All EC patients included were representative of this cohort of patients.

Only subjects meeting the inclusion criteria for each group (described above), with regular immunovirological (CD4 counts and plasma HIV-RNA load) follow-up, and with cryopreserved cellular samples available for A3H genotyping were included in the study. To participate in the study, written informed consent was obtained from all individuals, and the study protocol was evaluated and approved by the Hospital Ethical Committee in accordance with the World Medical Association Declaration of Helsinki.

Cell Samples

Samples from both groups of patients were kindly provided by the HIV Biobank integrated in the Spanish AIDS Research Network (RIS) [18]. Samples were processed following standard procedures and frozen immediately upon reception. Genomic DNA was extracted from cryopreserved PBMCs using the Speedtools tissue DNA extraction kit (Biotools B&M Labs S.A, Spain) following manufacturer's instructions. For some samples, genomic RNA was extracted from a second aliquot of cryopreserved PBMCs using the GeneJET RNA purification kit (Thermo Scientific) following manufacturer's instructions.

Genotyping of A3H polymorphisms

In order to adequately attribute the active or inactive status of A3H protein, both rs79323350 (N15del) and rs139297 (R105G) A3H polymorphisms were analyzed jointly. Firstly, PCR was performed on DNA samples from all patients to amplify exon 3 of A3H using primers 5′-CATGGGACTGGACGAAACG CA-3′ (A3H105F) and 5′-TGGGATCCACACAGAAG CCGCA-3′ (A3H105R). PCRs were performed with Phusion DNA polymerase (Thermo Scientific) using the following program: 2 min at 98°C, 30 cycles of 5 s at 98°C, 30 s at 67°C, and 30 s at 72°C, and a final extension of 10 min at 72°C. The resulting PCR was directly Sanger sequenced to ascertain the presence of arginine or glycine codons at residue 105 (SNP rs139297). Secondly, only for subjects homozygous or heterozygous for an arginine at position 105 (indicating a potentially active haplotype), PCR was performed to amplify A3H exon 2 using primers 5′-GTGGCTTGAGCCTGGGGTGA-3′ (A3H15F) and 5′-CAGAGAGCCCGTGTGGCACC-3′ (A3H15R) and the same conditions as above. The PCR product was then cloned using Clone Jet PCR Cloning Kit (Thermo Scientific) following manufacturer's instructions, and 5 clones per patient were analyzed for the presence of a deletion at amino acid position 15 (SNP rs79323350). The homozygous genotype for this deletion is indicative of an unstable A3H genotype. For those samples that were heterozygous for both analyzed polymorphisms, haplotypes were defined as follows. Genomic RNA was subjected to reverse transcription with Accuscript according to manufacturer's instructions (Agilent Technologies). A primary PCR partially covering both A3H exons 2 and 3 was performed using primers 5′-CGATGGCTCTGTTAAC AGCC-3′ (Exon2F) and A3H105R and the same conditions as above but with an annealing temperature of 65ºC. Secondary amplification was done by nested PCR using the internal primers 5′-CAGCCGAAACATTCCGCTTAC-3′ (A3H_exons2-3F) and 5′- CTTCTGCTGGGGCTTGCAC-3′ (A3H_exons2-3R) under the same conditions as above but with an annealing temperature of 67°C. PCR products were then cloned as mentioned above and one clone per patient was sequenced to determine the haplotype.

The main characteristics of the study population are expressed as median [interquartile range] (SPSS software version 15 (SPSS Inc., Chicago, IL, USA)).

Results

Study population

Table 1 summarizes the main characteristics of the 41 subjects enrolled in this study. All NC subjects tested were European Caucasian and showed relative conserved CD4 T-cells counts during the follow-up (530 [380-634] cells/μL). The median HIV-RNA load was 24760 [15849-94607] copies/mL and the median age was 35 [25-49] years. Most NC patients were male (10 out of 11). All 30 EC subjects evaluated had a long-term follow-up (median 12 [7-12] years). Their plasma viral loads remained undetectable (<50 copies HIV-RNA/mL) without antiviral therapy, and showed optimal CD4 T-cells counts during the follow-up (803 [706-988] cells/μL). The median age was 34 [30-40] years. Thirteen (43%) were male and 17 (57%) were female. The majority of individuals tested were European Caucasian (83%, 25/30) and the remaining patients were Latin American (3/30) or of unknown origin (2/30).

A3H polymorphisms

Since an inactive form of A3H protein is assumed when the mutated variant is in homozygosis in at least one of two polymorphisms rs79323350 (N15del) and rs139297 (R105G) independently of the other, we first evaluated the rs 139297 variant (R105G) in exon 3 of A3H. Our results showed that 53% (16/30) of EC and 64% (7/11) of NC patients were homozygous for the 105G variation (G/G) leading to an inactive A3H protein (**Table 2**) without differences between groups of patients (Chi-squared test p=0.8)**.** For the rest of the patients, which carried at least one potentially active A3H allele, we evaluated the rs79323350 variant (N15del) in exon 2 of A3H**.** We found that 5/14 (36%) EC patients and 1 out of 4 (25%) NC patients were wild-type homozygous for N15 allele (N15/N15) and thus carried at least one active A3H allele. None of the EC patients were homozygous for the N15 deletion (N15del/N15del); in contrast, 75% (3/4) of NC patients were (**Table 2**). Finally, while 9 out of 14 (64%) EC subjects were heterozygous for the N15del variation (N15/N15del), none of NC patients were. Seven out of these nine EC patients were also heterozygous for R105G variation (R/G) and haplotype analyses showed that both mutations never fell within the same haplotype, thus leading to an inactive A3H protein (**Table 2**). This result is consistent with previous studies showing that these loci encoding the two destabilizing proteins (R105G and N15del) were rarely found on the same chromosome [6].

Overall, our data from both studied polymorphisms (R105G and N15del) showed that the majority of both EC (23/30, 77%) and NC (10/11, 91%) patients presented allelic combinations of the two evaluated polymorphisms leading to an inactive A3H protein (**Table 2**).

Table 1. Clinical and epidemiological characteristics of study populations.

Patient Code	Region of Origin	Sex[a]	Age[b] (years)	Length of HIV diagnosis (years)	Length of Follow-up[c] (years)	HIV-RNA load (copies/mL) Median [IQR]	Nº of HIV-RNA blips[d]	CD4 count (cells/µL) Median [IQR][e]
EC-1	Europe	F	31	24	13.48	< 50	0	941 [887 - 1026]
EC-2	Europe	F	35	4	2.88	< 50	2	1125 [1032 - 1176]
EC-3	Europe	F	40	20	11.88	< 50	4	987 [944 - 1099]
EC-4	Europe	M	43	12	9.88	< 50	3	830 [563 - 946]
EC-5	Europe	F	22	14	12.56	< 50	5	725 [658 - 824]
EC-6	Europe	F	32	24	12.88	< 50	0	945 [851 - 1050]
EC-7	Europe	M	33	15	11.80	< 50	0	804 [770 - 837]
EC-8	Europe	F	24	18	12.48	< 50	1	1171 [1016 - 1342]
EC-9	Europe	F	46	13	1.64	< 50	0	1386 [1139 - 1604]
EC-10	Europe	F	26	20	12.00	< 50	3	733 [329 - 774]
EC-11	Europe	F	36	20	12.80	< 50	1	1109 [874 - 1213]
EC-12	Europe	F	32	23	9.24	< 50	2	956 [855 - 1125]
EC-13	Europe	M	21	14	10.64	< 50	1	555 [458 - 637]
EC-14	Europe	M	28	18	13.24	< 50	2	516 [472 - 574]
EC-15	Europe	F	40	18	12.48	< 50	5	776 [697 - 943]
EC-16	Europe	F	38	25	12.24	< 50	1	801 [700 - 885]
EC-17	ND	M	37	23	12.56	< 50	2	676 [541 - 960]
EC-18	LA	F	24	6	4.88	< 50	0	1290 [1122 - 1388]
EC-19	Europe	M	46	5	4.08	< 50	2	626 [351 - 885]
EC-20	Europe	M	42	16	5.56	< 50	0	716 [613 - 887]
EC-21	Europe	F	42	11	12.16	< 50	0	480 [407 - 578]
EC-22	LA	F	27	17	10.88	< 50	1	872 [766 - 1113]
EC-23	Europe	M	41	21	11.40	< 50	0	859 [675 - 950]
EC-24	Europe	M	43	21	6.72	< 50	1	674 [503 - 828]
EC-25	Europe	M	34	24	11.88	< 50	4	523 [482 - 644]
EC-26	Europe	M	30	22	11.48	< 50	3	720 [636 - 958]
EC-27	Europe	M	35	21	9.88	< 50	1	989 [939 - 1149]
EC-28	Europe	F	34	17	12.40	< 50	1	792 [666 - 967]
EC-29	LA	F	32	6	4.72	< 50	0	1463 [1406 - 1865]
EC-30	ND	M	34	8	5.24	< 50	2	762 [560 - 1050]
NC-3	Europe	M	22	1.78	1.78	211622 [60738 - 395936]	NA	380 [330 - 519]
NC-4	Europe	M	26	2.49	2.49	26824 [17064 - 74553]	NA	707 [537 - 762]
NC-5	Europe	M	37	2.24	2.24	115556 [67095 - 164576]	NA	413 [315 - 460]
NC-6	Europe	M	42	3.10	3.10	74579 [23460 - 129395]	NA	379 [307 - 651]
NC-7	Europe	M	54	1.63	1.63	94607 [53113 - 144196]	NA	535 [341 - 847]
NC-8	Europe	M	25	1.30	1.30	24760	NA	338 [290 -349]
NC-9	Europe	M	35	1.84	1.84	9692 [6705 - 12153]	NA	936 [767 - 1064]
NC-11	Europe	M	52	2.89	2.89	8413 [6901 - 11876]	NA	530 [480 - 689]
NC-14	Europe	M	31	3.50	3.50	17799 [9583 - 23499]	NA	579 [470 - 660]
NC-15	Europe	M	25	3.26	3.26	15849 [14219 - 71265]	NA	446 [399 - 573]
NC-16	Europe	F	49	20.64	20.64	19300 [11600 - 27100]	NA	634 [537 - 878]

EC, elite controller; NC, non-controller; ND, no data; NA, not applicable; LA, Latin America; [a]F, Female and M, Male; [b]Age at inclusion as EC or NC; [c]Length of follow-up maintaining EC or NC status; [d]All elite controller subjects maintained undetectable HIV RNA load, but some of them experienced a few blips throughout the follow-up; [e]Median [interquartile range] of all CD4 counts available during the follow-up period.

Discussion

Elite controllers (EC) are a particular group of HIV infected patients who show spontaneous control of viral replication [19]. The mechanisms underlying this spontaneous viral control are poorly understood [20, 21], although this may be critical to the development of strategies aimed to a functional cure of HIV infection. This is the first study showing the frequency of A3H polymorphisms in a group of HIV elite controller subjects. Surprisingly, our results show that most of EC patients presented allelic combinations of the two evaluated polymorphisms leading to an inactive A3H protein, similar to non-controller patients. This suggests that A3H is not involved in the viral control observed in EC subjects. Also, the frequencies of both studied polymorphisms (R105G and N15 del) in our EC patients were similar to those of healthy European Caucasian individuals in which 63% of evaluated individuals carried inactive A3H protein coding-genotypes [14].

All these results seem to indicate a loss of the antiviral activity of A3H protein, as shown by OhAinle et al., who found evidence that although recent human ancestors encoded a highly potent antiviral version of A3H gene, inactive A3H alleles are present in the majority of human populations, and only a small proportion of humans still encode an active allele of A3H. In that study, it was emphasized that the loss of the antiviral activity of A3H protein in recent human evolution should have important consequences for susceptibility to retroviral infections

[6]. Our study confirms this loss of activity in A3H protein, at least in European Caucasian population, since haplotypes leading to an active protein ("antiviral haplotype") were very poorly represented in both EC and NC patients.

Table 2. A3H genotypes in HIV elite controller and HIV progressor subjects.

Patient Code	Exon 3	Exon 2*	A3H protein**
	A3H genotype (rs139297)	A3H genotype (rs79323350)	
EC-1	G/G	-	Inactive
EC-2	R/G	N15/N15del	Inactive
EC-3	R/G	N15/N15	Active
EC-4	G/G	-	Inactive
EC-5	G/G	-	Inactive
EC-6	G/G	-	Inactive
EC-7	R/G	N15/N15del	Inactive
EC-8	G/G	-	Inactive
EC-9	G/G	-	Inactive
EC-10	R/R	N15/N15del	Active
EC-11	G/G	-	Inactive
EC-12	G/G	-	Inactive
EC-13	G/G	-	Inactive
EC-14	R/R	N15/N15del	Active
EC-15	G/G	-	Inactive
EC-16	R/G	N15/N15del	Inactive
EC-17	R/G	N15/N15del	Inactive
EC-18	R/G	N15/N15	Active
EC-19	R/G	N15/N15	Active
EC-20	G/G	-	Inactive
EC-21	G/G	-	Inactive
EC-22	G/G	-	Inactive
EC-23	G/G	-	Inactive
EC-24	R/G	N15/N15	Active
EC-25	R/G	N15/N15del	Inactive
EC-26	G/G	-	Inactive
EC-27	R/G	N15/N15del	Inactive
EC-28	R/G	N15/N15del	Inactive
EC-29	G/G	-	Inactive
EC-30	R/R	N15/N15	Active
NC-3	G/G	-	Inactive
NC-4	G/G	-	Inactive
NC-5	G/G	-	Inactive
NC-6	G/G	-	Inactive
NC-7	R/R	N15del/ N15del	Inactive
NC-8	R/R	N15del/ N15del	Inactive
NC-9	G/G	-	Inactive
NC-11	G/G	-	Inactive
NC-14	G/G	-	Inactive
NC-15	R/G	N15/N15	Active
NC-16	R/R	N15del/ N15del	Inactive

* SNP rs79323350 in exon 2 was genotyped only in EC and NC subjects carrying R/G or R/R genotypes at SNP rs139297 in exon 3. ** Haplotype analyses were done for patients showing both variants in heterozygosis to define A3H status.

Interestingly, two recent studies evaluating the two polymorphisms rs79323350 (N15del) and rs139297 (R105G) have reported that A3H genotypes containing the variants leading to an inactive A3H protein were associated with susceptibility to HIV infection and disease progression in an Indian [9] and in a Japanese [10] HIV-infected populations. Since the frequency of the active A3H allele varies globally [6,14], results shown in Indian and Japanese subjects could indicate that some populations still retain the A3H antiviral activity, as suggested by OhAinle et al. [6], in contrast to the European Caucasian population (mainly Spanish) that we have studied.

The role of APOBEC3 protein family in HIV infection control may be distinct for the different members of the family. Indeed, previous studies have shown a protective role in viral replication levels in typical progressor patients as well as in long-term non-progresors for A3G [3, 22] and for A3F [3], and a role for A3H in susceptibility to HIV infection [9,10]. Moreover, RNA levels of A3D and A3C members increased in EC patients compared with ART-suppressed patients [11], and elevated hypermutation levels in the HIV genome associated to the activity of A3G were observed in HIV-patients naïve for antiretroviral treatment [8] and in EC patients [12].

Given that EC subjects included in this study are able to maintain a long-term sustained spontaneous HIV viral control and optimal CD4 T-cell counts in the absence of active A3H genotypes, restriction factors other than A3H, or the combined activity of some others members of A3 family, should be implicated in HIV replication control exhibited by EC subjects. Further studies in larger cohorts are needed to elucidate the actual contribution of different members of APOBEC3 to spontaneous control of HIV infection having into account the potential differences among human populations.

Abbreviations

APOBEC3 (A3): apolipoprotein B mRNA-editing catalytic polypeptide 3; A3H: APOBEC3H; cART: combined antiretroviral therapy; DNA: deoxyribonucleic acid; EC: elite controller; Hap: haplotype; HIV: human immunodeficiency virus; LTNP: Long Term Non-Progressors; NC: non-controller; PBMC: peripheral blood mononuclear cells; RNA: ribonucleic acid; SNP: single nucleotide polymorphism.

Supplementary Material

Text S1. Clinical Centers and research groups which contribute to ECRIS.
http://www.medsci.org/v15p0095s1.pdf

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Authorship

NR, JMB, JMC, and RS conceived and designed the experiments; JH, JMC, and CR performed the experiments; NR, JMB, and JMC wrote the manuscript; NR, JMB, and JMC analyzed and interpreted the data; AL, ER, RP, and MG were in charge of resources and data curation.

Competing Interests

The authors have declared that no competing interest exists.

References

1. Harris RS, Dudley JP. APOBECs and virus restriction. Virology. 2015; 479-480: 131-45.
2. Hultquist JF, Lengyel JA, Refsland EW, et al. Human and rhesus APOBEC3D, APOBEC3F, APOBEC3G, and APOBEC3H demonstrate a conserved capacity to restrict Vif-deficient HIV-1. J Virol. 2011; 85: 11220-34.
3. Kourteva Y, De Pasquale M, Allos T, et al. APOBEC3G expression and hypermutation are inversely associated with human immunodeficiency virus type 1 (HIV-1) burden in vivo. Virology. 2012; 430: 1-9.
4. Amoêdo ND, Afonso AO, Cunha SM, et al. Expression of APOBEC3G/3F and G-to-A hypermutation levels in HIV-1-infected children with different profiles of disease progression. PLoS One. 2011; 6: e24118.
5. Cho SJ, Drechsler H, Burke RC, et al. APOBEC3F and APOBEC3G mRNA levels do not correlate with human immunodeficiency virus type 1 plasma viremia or CD4+ T-cell count. J Virol. 2006; 80: 2069-72.
6. OhAinle M, Kerns JA, Li MM, et al. Antiretroelement activity of APOBEC3H was lost twice in recent human evolution. Cell Host Microbe. 2008; 4: 249-59.
7. Refsland EW, Hultquist JF, Luengas EM, et al. Natural polymorphisms in human APOBEC3H and HIV-1 Vif combine in primary T lymphocytes to affect viral G-to-A mutation levels and infectivity. PLoS Genet. 2014; 10: e1004761.
8. Cuevas JM, Geller R, Garijo R, et al. Extremely High Mutation Rate of HIV-1 In Vivo. PLoS Biol. 2015; 13: e1002251.
9. Naruse TK, Sakurai D, Ohtani H, et al. APOBEC3H polymorphisms and susceptibility to HIV-1 infection in an Indian population. J Hum Genet. 2016; 61: 263-5.
10. Sakurai D, Iwatani Y, Ohtani H, et al. APOBEC3H polymorphisms associated with the susceptibility to HIV-1 infection and AIDS progression in Japanese. Immunogenetics. 2015; 67: 253-7.
11. Abdel-Mohsen M, Raposo RA, Deng X, et al. Expression profile of host restriction factors in HIV-1 elite controllers. Retrovirology. 2013; 10: 106.
12. Eyzaguirre LM, Charurat M, Redfield RR, et al. Elevated hypermutation levels in HIV-1 natural viral suppressors. Virology. 2013; 443: 306-12.
13. Dang Y, Siew LM, Wang X, et al. Human cytidine deaminase APOBEC3H restricts HIV-1 replication. J Biol Chem. 2008; 283: 11606-14.
14. Wang X, Abudu A, Son S, et al. Analysis of human APOBEC3H haplotypes and anti-human immunodeficiency virus type 1 activity. J Virol. 2011; 85: 3142-52.
15. Harari A, Ooms M, Mulder LC, et al. Polymorphisms and splice variants influence the antiretroviral activity of human APOBEC3H. J Virol. 2009; 83: 295-303.
16. Caro-Murillo AM, Castilla J, Pérez-Hoyos S, et al. [Spanish cohort of naïve HIV-infected patients (CoRIS): rationale, organization and initial results] In spanish. Enferm Infecc Microbiol Clin. 2007; 25: 23-31.
17. Sobrino-Vegas P, Gutiérrez F, Berenguer J, et al. [The Cohort of the Spanish HIV Research Network (CoRIS) and its associated biobank; organizational issues, main findings and losses to follow-up] In spanish. Enferm Infecc Microbiol Clin. 2011; 29 (9): 645-53.
18. García-Merino I, de Las Cuevas N, Jiménez JL, et al. Spanish HIV BioBank. The Spanish HIV BioBank: a model of cooperative HIV research. Retrovirology. 2009; 6: 27.
19. Lambotte O, Boufassa F, Madec Y, et al. HIV controllers: a homogeneous group of HIV-1-infected patients with spontaneous control of viral replication. Clin Infect Dis. 2005; 41: 1053-6.
20. Autran B, Descours B, Avettand-Fenoel V, et al. Elite controllers as a model of functional cure. Curr Opin HIV AIDS. 2011; 6: 181-7.
21. Shasha D, Walker BD. Lessons to be learned from natural control of HIV - future directions, therapeutic, and preventive Implications. Front Immunol. 2013; 4: 162.
22. Jin X, Brooks A, Chen H, et al. APOBEC3G/CEM15 (hA3G) mRNA levels associate inversely with human immunodeficiency virus viremia. J Virol. 2005; 79: 11513-6.