Frequency and Demographic Characteristics of "Elite Controllers" among HIV-Infected Blood Donors

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Introduction

- Some HIV-infected individuals naturally suppress viremia below detection limits of viral load and blood screening nucleic acid amplification technology (NAT) assays. Such individuals are referred to as "Elite Controllers" (ECs).
- ECs are defined based on the following criteria:
  - Confirmed HIV-1 seropositive (exclude false positive serology and HIV-2 infections not detected by most NAT assays)
  - No detectable HIV RNA by sensitive viral load or qualitative NAT assays (limit of detection < 50 copies/mL) on multiple specimens for > 2 years.
  - Not on antiretrovirals.
- EC are under intense study to understand determinants of suppressed HIV replication that could guide development of vaccines and therapeutics.
- The proportion of individuals who become elite controllers is estimated at 1-5% but not well established.

Rationale / Objective

- Over the past decade HIV-1 NAT has been implemented by blood banks throughout the world in order to interdict pre-seroconversion window period donations (RNA+ / Ab-). Parallel NAT and serological screening allows discrimination of HIV antibody-positive donors into those who are viremic and ECs.
- We determined the rates of ECs in volunteer blood donors from five countries, and further characterized low level viremia and correlates of natural viral suppression in these donors.

Methods

- Routine HIV NAT (Gen-Probe/Chiron TMA; Roche PCR) and Ab screening (3rd gen assay) and confirmatory (Western blot, IFA, ImmunoComb, InnoLIPA) data were compiled from blood collection organizations.
  - US - 16-sample minipool (MP)-NAT
  - France - 8 or 24-sample MP-NAT
  - South Africa - individual donation (ID)-NAT
  - Australia - combination of 16-sample MP or ID-NAT
  - Germany - 96-donation MP-NAT with high-speed centrifugation (1hr at 48,000 X G) to concentrate virus prior to extraction.
- The analysis was restricted to allogeneic (volunteer) donors to exclude anti-retroviral treated autologous donors.
- Possible EC cases were evaluated by additional testing and follow-up, to exclude cases with false-positive (FP) serological results and HIV-2 infections (in France).
- ECs were further studied by high sensitivity viral load and replicate ID-NAT testing, and demographic characteristics of ECs were compared to those of HIV-viremic donors.

Results

Rates of HIV "Elite Controllers" in HIV Antibody-pos Blood Donors

Country	Period of screening	NAT (MP/ID) 50% LOD (cps/mL)	# Allogeneic donations screened	# (%) HIV Ab+ donors	# (%) ECs (Ab+ donors that tested NAT-Neg)
US	1/99-5/08	MP: ~222	62,044,407	1692 (0.0027)	58 (3.2)
France	7/01-12/07	MP: 50-75	16,400,000	226 (0.0014)	6 (2.6)
South Africa	10/05-9/07	ID: ~8.5	1,461,211	1705 (0.12)	12 (0.7)
Germany	2003-2007	MP: ~600	3,752,309	45 (0.0012)	1 (2.2)
Australia	6/00-9/08	MP: ~222	8,910,863	35 (0.0004)	0 (0.0)

HIV Viral Load in Blood Donors Classified as Elite Controllers

A. South African Donor Elite Controllers.

EC for 2 year period	S/CO on Prism	No. of Replicates Reactive	Follow-up Confirmed	Western Blot Pattern	Estimated Viral load Cps/mL	(95% CI)
2847074	85.35	0/33	No	p24, p31, gp120, gp41	<1	
2888634	67.76	3/10	No	p24, wk gp120, wk gp41	4.2	2.79-5.93
2916316	89.24	0/11	Yes	p24, p31, gp120, gp41	<1	
2972539	73.16	0/32	Yes	p24, wk gp120, gp41	<1	
2845047	69.84	7/14	No	p24, wk p31, gp120, gp41	8.3	5.91-11.83
2934818	87.07	8/9	No	p24, p31, gp120, gp41	43.97	27.94-84.99
2957480	31.13	4/11	Yes	p24, p31, gp120, gp41	5.05	3.43-7.07
18985235	139.63	6/31	No		2.79	1.71-4.04
19354914	132.18	11/40	Yes	GP160, GP120, p66, p55, p51 GP41, p31, p24, p17(W)	4.21	2.78-5.93
19836282*	100.6	0/2	Yes		<1	
20235369	148.47	4/7	No	All bands present	9.8	6.99-14.13

VL estimated using replicate dHIV TMA and probit analysis

B. French Donor Elite Controllers.

	Gender / Age	BD Category	Risk Factor	NAT	S/CO on Prism	No. of Replicates Reactive on Pool	No. of Replicates Reactive on Single	Follow-up Confirmed	WB Pattern	Viral load Cps/mL
1-2002	F/51	FTBD	?	TMA x 8	88/91	2/5	2/2	No	All bands present	27 [1]
2-2004	F/62	RBD	Hetero	TMA x 8	8	0/1	3/6	Yes (1 month)	p24, p31, p55, p68, gp160	33 [1]
3-2004	M/43	FTBD	MSM	Roche x24	160	0/1	1/1	Yes (16 days)	All bands present	13 [1]
4-2004	M/47	FTBD	Hetero	TMA x 8	83	0/1	1/1	no	GP160, GP120, GP41, p24, p17(W)	11 [1]
5-2005	M/36	FTBD	Africa	Roche x24	pos	0/2	0/2	no	GP160, GP120, p24, p17(W)	< 50 [2]
6-2006	F/25	FTBD	Hetero	TMA x 8	pos	0/2	0/2	Yes (3 months)	All bands present	Neg [1]

VL: 1) Monitor HIV Roche US Method ; or 2) Quantiplex bDNA Bayer

C. US (ARC) Donor Elite Controllers.

- 65 ECs (MP-NAT-neg / Ab-confirmed pos) were tested by PCR at National Genetics Institute (NGI) : 17 (26%) had detectable RNA. (most below 100 c/mL quantitation limit).
- 8 of the NGI PCR-negative ECs were tested by 8-10 replicate dHIV TMAs: 7 (87%) had detectable RNA.
- 24 WB-pos donations that met criteria of probable FP WBs (low S/C; weak band patterns without p31, negative NGI PCR) were also tested in parallel by 10 replicate dHIV TMA: all 24 tested negative X 10, corroborating FP classifications and specificity of replicate TMA testing.

Demographic Correlates of "Elite Controller" among HIV Seropositive Donors

A. Rate of Elite Controllers by Gender.

US (Clade B)	Female	Male	Total
No Ab+ Donors	412	1091	1503
No Elite controllers	25	28	53
%	5.5%	2.5%	3.3%

SA (Clade B)	Female	Male	Total
No Ab+ Donors	907	826	1734
No Elite controllers	8	3	11
%	0.88%	0.36%	0.63%

France	Female	Male	Total
No Ab+ donors	61	162	223
No Elite controllers	3	3	6
%	4.9%	1.8%	2.7%

B. Ethnic Breakdown of Elite Controllers - South Africa.

	Asian	Coloured	Black	White	Total
No of Donations	126187	65085	104979	1163430	1464477 *
No of Ab+ donations	63	121	1349	188	1734 **
	0.05%	0.19%	1.3%	0.016%	0.12%
No of Elite controllers	0	1	7	3	11
	0.00%	0.83%	0.52%	1.60%	0.63%

* 4796 unknown race; ** 13 unknown race

C. Age Breakdown of Elite Controllers - South Africa.

	< 20	20-25	26-30	31-40	41-50	51-60	61-70	Total
No of Donations	221346	190732	129112	311984	298775	280434	85015	1464477 *
No of Ab+ donations	185	336	368	528	239	69	9	1734
	0.11%	0.18%	0.29%	0.17%	0.08%	0.02%	0.01%	0.12%
No of Elite controllers	0	3	2	3	1	2	0	11
	0.00%	89%	0.54%	0.57%	0.42%	2.9%	0.00%	0.63%

* 2912 unknown age

D. Rate of Elite Controllers by Geographic Origin - France.

	France	Overseas French Territories	Sub-Saharan Africa	Others / Unknown	Total
Ab+ Donors	160	23	13	27	223
No Elite controllers (%)	5 (3.1%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	6 (2.7%)

Conclusions

- Parallel screening of blood donors using HIV NAT and antibody assays provides the first systematic estimate for the frequency of ECs among newly diagnosed, asymptomatic HIV-infected persons (0.7 - 3.2%).
- The higher rates of ECs among HIV-1 infected donors in the US, France, and Germany relative to South Africa, probably reflects use of MP-NAT in these countries and ID-NAT in South Africa.
- Additional ID-NAT testing of EC donors detected very low-level plasma viremia in the large majority of cases evaluated.
- The rates of EC are similar among demographic subgroups, except for ~2-fold higher rate in females in 3 countries, indicating similar immunopathogenesis in these divergent clade settings and a possible role of gender on control of HIV viremia.
- Detection of very low-level viremia in EC donors, and published studies documenting viral isolation from ECs, indicates that NAT screening cannot replace HIV Ab screening, even when using very sensitive ID-NAT.

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