Poster 675

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IMMUNE IMPAIRMENTS IN HEALTHY ADOLESCENTS BORN OF HIV-INFECTED MOTHERS

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ABSTRACT

Background: Cell mediated immunity and T cell maturation are altered in HIV-uninfected newborns of HIV-infected mothers. We verified if these abnormalities are maintained years after intra-utero exposure to HIV and/or HIV antigens had ceased by studying healthy adolescents of HIV-infected mothers. Endogenous antivirals (APOBEC and TRIM proteins) were also assessed in all the adolescents.

Methods: Immunological analyses were performed in 15 seroreverter (SR) healthy adolescents (age range 11.3-19.9 years) born of HIV-infected mothers. Results were compared to those obtained in 20 healthy adolescents (HC) born of HIV-uninfected mothers (age range 12.3-19.3 years) and in 15 HIV-infected adolescents (HIV) born to HIV-infected mothers (age range 12.2-19.6 years). None of the SR or HIV was exposed in utero, at delivery, or neonatally to antiviral drugs. HCV coinfection was present in 8 SR and 7 HIV. CD4 counts and percentages were comparable at birth in SR and HIV, but were significanly reduced in HIV by month 12 after birth. Weight at birth and gestational age were comparable in the three groups examined. At the time of the study height, weight, and BMI were comparable between SR and HC; these parameters were reduced, albeit not significantly, in HIV-infected individuals.

Results: In SR B lymphocytes were augmented and NK cells were reduced compared to HC. Additionally in SR compared to HC: 1) CD4 EM (CCR7-/45RA-) were reduced whereas CD8 EM (CCR7-/45RA-) and TD (CCR7-/45RA+) lymphocytes were increased; 2) activated CD4 (25+) and CD8 (RO/38+) lymphocytes were increased; 3) double positive (3+/4+/8+/1a+) lymphocytes were increased. Finally, IFN mRNA was increased in SR, whereas APOBEC3G and 3F and TRIM mRNA were comparable in all groups of adolescents analysed.

Conclusions: Immune activation and a skewing of the maturative CD8 pathway favouring the most differentiated, perforin enriched cells is detected in seroverters healthy adolescent born of HIV-infected mothers. In contrast, the expression of the main endogenous antivirals is similar in all groups individuals analysed. These data suggest that in utero exposure to HIV and/or viral particles results in a long-lasting imprinting on the immune system. Alternatively, it could be speculated that an immune response that is naturally more prone to activation and to stronger effector mechanisms could be associated with the prevention of vertical HIV infection.

BACKGROUND

- Intrauterine exposure to HIV or its soluble factors occurs during pregnancies of HIV-infected mothers and could affect fetal immune maturation.
- Cell-mediated immunity and T-lymphocyte maturation are impaired in HIV-uninfected newborns of HIV-infected mothers (Blood, 96(12):3866-71; 2000).
- No data are available on the persistence of immune alterations in healthy adolescents born of HIV-infected mothers.

AIMS

To verify, in healthy adolescents of HIV-infected mothers. whether abnormalities in T cell maturation and function are maintained years after intra-utero exposure to HIV and/or HIV antigens has ceased.

MATERIALS and METHODS

- We enrolled in the study:
  - 15 seroreverter (SR) healthy adolescents born of HIV-infected mothers (age range 11.3-19.9 years)
  - 15 HIV-infected adolescents (HIV) born of HIV-infected mothers (age range 12.2-19.6 years)
  - 20 healthy adolescents (HC) born of HIV-unifected mothers (age range 12.3-19.3 years)
- The percentage of B, NK, CD4+, CD8+, CM, EM e TD T lymphocytes as well as of double positive cells was analysed.
- Endogenous antivirals (APOBEC and TRIM) and IFN-γ specific mRNA were also assessed in all the adolescents.

PATIENTS and CONTROLS: CLINICAL CHARACTERIZATION

						AT BIRTH				AT EVALUATION					Actual ARV
patient ID	age (years)	HIV infection	HCV infection	weight at birth (gr)	gestational age	CD4 count	% CD4	HIV EIA	p24	HIV RNA (cp/ml)	HIV DNA	WEIGHT	HEIGHT	BMI	(months of treatment)
SR 1	19,9	neg	neg	3100	37	2434	54	pos	ND	< 50	neg	67	175	22	NA
SR 2	18,5	neg	pos	1200	32	1656	40	pos	neg	< 50	neg	59	188	17	NA
SR 3	16,8	neg	neg	2640	39	3300	51	pos	neg	< 50	neg	62	169	22	NA
SR 4	15,8	neg	pos	2800	39+4	4658	66	pos	neg	< 50	neg	62	162	24	NA
SR 5	14,4	neg	neg	2100	34	3500	56	pos	neg	< 50	neg	60	168	21	NA
SR 6	14,3	neg	neg	3200	38+2	3256	48	pos	neg	< 50	neg	46	162	18	NA
SR 7	14,3	neg	neg	1750	38+4	2283	60	pos	neg	< 50	neg	43	160	17	NA
SR 8	14,2	neg	neg	2490	36+2	1338	41	pos	neg	< 50	neg	77	172	26	NA
SR 9	14,1	neg	neg	3030	39+4	1512	40	pos	neg	< 50	neg	65	169	23	NA
SR 10	13,5	neg	neg	1990	37+4	2800	54	pos	neg	< 50	neg	49	161	19	NA
SR 11	13,1	neg	neg	3240	41	6775	58	pos	neg	< 50	neg	52	158	21	NA
SR 12	10,0	neg	neg	3420	39	4346	49	pos	neg	< 50	neg	32	135	17	NA
SR 13	7,3	neg	neg	3000	39	3157	40	pos	neg	< 50	neg	25	122	16	NA
SR 14	10,9	neg	neg	2720	39+2	7231	64	pos	neg	< 50	neg	66	141	33	NA
SR 15	13,6	neg	neg	2870	40+5	2566	48	pos	neg	< 50	neg	48	158	19	NA
HIV 1	19,6	pos	neg	3000	40	2800	54	pos	ND	98	ND	53	167	19	3TC+TDF+EFV (26ms)
HIV 2	19,1	pos	neg	3700	40	3200	48	pos	ND	155	ND	59	164	22	3TC+TDF+EFV (19ms)
HIV 3	17,5	pos	pos	3470	40	4100	62	pos	neg	< 50	ND	57	177	18	3TC+TDF+EFV (20ms)
HIV 4	16,2	pos	neg	2500	38	3200	54	pos	neg	< 50	ND	60	153	26	3TC+AZT+EFV (74ms)
HIV 5	15,3	pos	neg	3400	39	2900	50	pos	neg	< 50	ND	67	170	23	3TC+TDF+EFV (28ms)
HIV 6	15,4	pos	neg	2730	37	2100	45	pos	pos	< 50	ND	49	158	19	3TC+TDF+EFV (28ms)
HIV 7	11,3	pos	neg	2950	36	2400	48	pos	pos	< 50	ND	40	146	18	3TC+TDF+EFV (20ms)
HIV 8	13,9	pos	pos	2950	41+4	1467	48	pos	neg	< 50	ND	58	158	23	3TC+TDF+EFV (27ms)
HIV 9	13,2	pos	pos	3040	39+5	1837	48	pos	neg	< 50	ND	33	144	16	3TC+TDF+EFV (26ms)
HIV 10	12,7	pos	neg	3650	36	5300	60	pos	neg	< 50	ND	58	154	24	3TC+TDF+EFV (19ms)
HIV 11	10,0	pos	neg	2750	38	3475	59	pos	neg	< 50	ND	28	134	16	3TC+TDF+EFV (20ms)
HIV 12	7,2	pos	neg	3200	39	4200	42	pos	neg	56	ND	30	133	17	3TC+TDF+EFV (26ms)
HIV 13	11,2	pos	neg	3450	39	6500	62	pos	neg	< 50	ND	45	156	18	3TC+TDF+EFV (18ms)
HIV 14	17,1	pos	neg	3150	40	2500	45	pos	neg	< 50	ND	57	147	26	3TC+TDF+EFV (20ms)
HIV 15	16,3	pos	neg	3460	40+2	3676	59	pos	pos	24365	ND	63	166	23	no treatment

		AT EVALUATION		
patient ID	age (years)	WEIGHT	HEIGHT	BMI
HC 1	15,1	55	162	21
HC 2	17,6	70	175	23
HC 3	12,3	38	145	18
HC 4	15,1	56	168	20
HC 5	18	54	166	20
HC 6	15,5	60	171	21
HC 7	12,7	44	156	18
HC 8	18	52	167	19
HC 9	13,1	45	156	18
HC 10	17,6	52	164	19
HC 11	17,1	53	165	19
HC 12	19,3	55	168	19
HC 13	16	54	163	20
HC 14	17,2	52	165	19
HC 15	13,7	48	158	19
HC 16	16,6	62	173	21
HC 17	14,4	53	160	21
HC 18	15,9	54	162	21
HC 19	15,9	60	173	20
HC 20	16,3	55	163	21

RESULTS

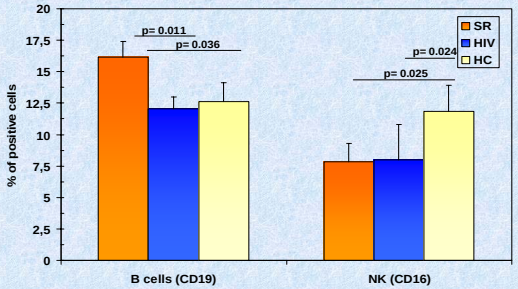

Figure 1. Percentage of B (CD19+) and Natural Killer (CD16+) cells in SR, HIV and HC adolescents. Mean values and S.E. are shown.

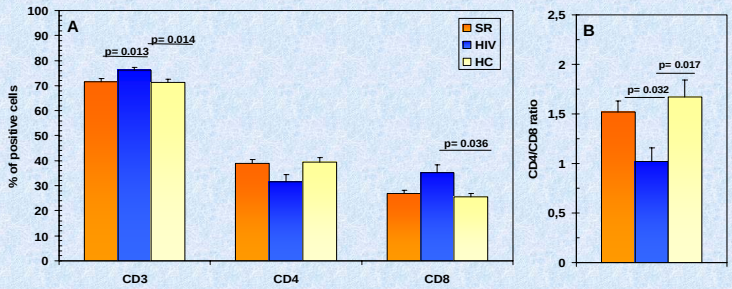

Figure 2. Percentage of total (CD3+), CD4+ and CD8+ T cells (panel A) and CD4/CD8 ratio (panel B) in SR, HIV and HC adolescents. Mean values and S.E. are shown.

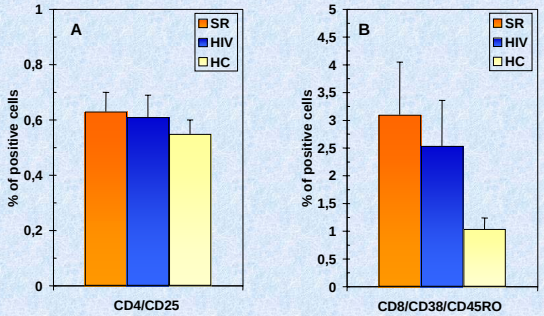

Figure 3. Activation Markers. Percentage of activated CD4 (CD25+) (panel A) and CD8 (CD38+/CD45RA+) (panel B) T cells) in SR, HIV and HC adolescents. Mean values and S.E. are shown.

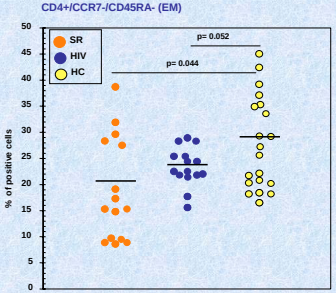

Figure 4. Effector Memory CD4 T cells (CCR7-/CD45RA-) in SR, HIV and HC adolescents. Mean values are indicated by horizontal lines.

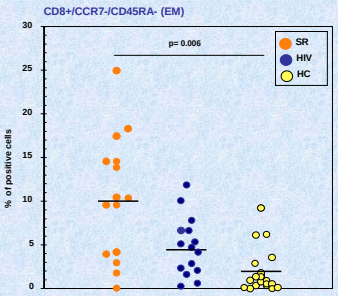

Figure 5. Effector Memory CD8 T cells (CCR7-/CD45RA-) in SR, HIV and HC adolescents. Mean values are indicated by horizontal lines.

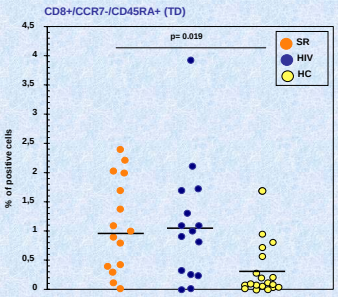

Figure 6. Terminally Differntiated CD8 T cells (CCR7-/CD45RA+-) in SR, HIV and HC adolescents. Mean values are indicated by horizontal lines.

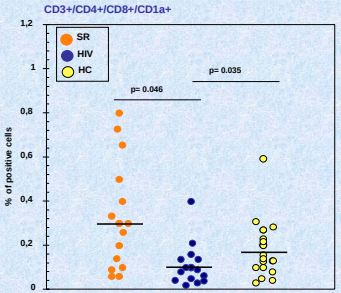

Figure 7. Double positive T cells (CD3+/CD4+/CD8+/CD1a+) in SR, HIV and HC adolescents. Mean values are indicated by horizontal lines.

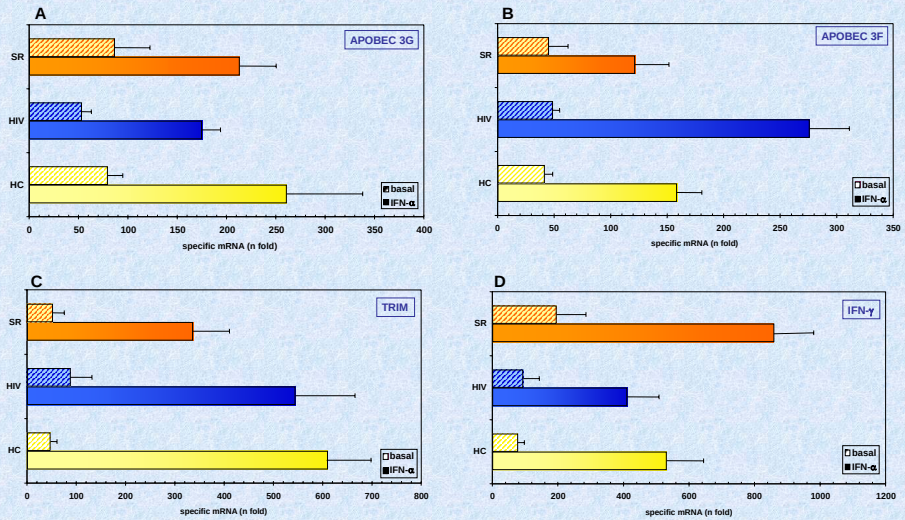

Figure 8. APOBEC 3G (panel A), APOBEC 3F (panel B), TRIM (panel C) and IFN-γ (panel D) specific mRNA in SR, HIV and HC adolescents. Mean values and S.E. are shown.

CONCLUSIONS

- Immune activation and a skewing of the maturative CD8 pathway favoring the most differentiated, perforin enriched cells is detected in seroreverters healthy adolescents born of HIV-infected mothers.
- The expression of the main endogenous antivirals is similar in all groups of individuals analysed.
- In utero exposure to HIV and/or antigens results in a long-lasting imprinting on the immune system.
- An immune response that is naturally more prone to activation and to stronger effector mechanisms could be associated with prevention of vertical HIV infection.