

Cross-clade recognition of Gag-p24 G_{PSHKARVL} epitope in HIV-1 infection



Castro E¹, Harari A¹, Cellerai C¹, Bart PA¹, Chave JP² and Pantaleo G¹.

¹Laboratory of AIDS Immunopathogenesis, Division of Immunology and Allergy and ²Division of Infectious Diseases, Lausanne University Hospital



Background

HIV-1 CD8 and CD4 T-cell epitopes databases rely on clade B sequences.

Most new infections arise in non-B and circulating recombinant forms epidemic's burden as Sub-Saharan Africa and Southern Asia. Therefore cross-clade epitopes are relevant tools in vaccine development.

Objective

To understand why a patient finds to control viral replication and show a non-progressive HIV infection evolution despite treatment interruption, we conducted a study that evaluates host genetics, virus autologous sequences and cellular immune specific responses to HIV during 1999 to 2005.

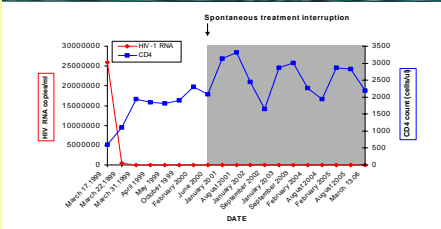
Patient and Clinical highlights

Clinical samples were obtained from a man, infected in Thailand and followed at our center since 1999 due to HIV primary infection. Viral load became undetectable soon after starting antiretroviral treatment (HAART). Thus, after spontaneous HAART interruption no rebound of viral load was seen. Additionally, CD4+ T-cell counts remained within normal values (Fig. 1) and the patient continued asymptomatic.

Fig. 1

A non-progressive HIV-1 infection despite treatment interruption.

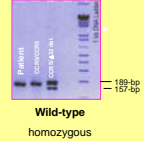
Evolution of CD4+ counts and HIV-1 viral loads



Host genetics

CCR5 genotype

PCR-based assay

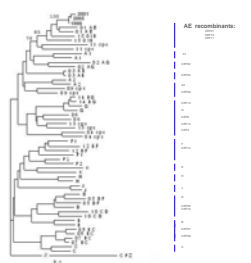


HLA Class I alleles
Sequencing-based typing
A*03010101 homozygous
B*070201, B*400102

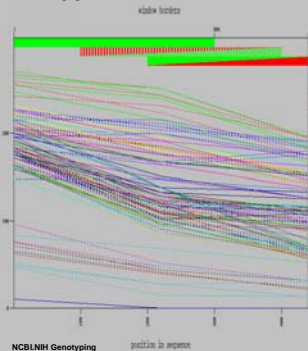
Host genetic factors not associated to disease protection.

Virus genotype

Neighbor-joining tree of gag 460bp alignment

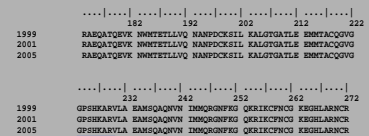


Baseline gag



AE recombinant genome according to phylogenetic analysis of gag, pol, env and nef partial sequences.

GAG p24 (223-231) alignment



Cellular Immune responses to HIV-1 clade B peptides

was analyzed with 28 pools consisting of 183 peptides known as CD8 and CD4 T-cell epitopes mainly described among HIV-1 subtype B infected individuals.

HIV Molecular Immunology Database, Los Alamos

Screening strategy

To measure overall pool responses

IFN- γ ELISpot

To confirm single peptide CD8+ T-cell responses
IFN- γ and IL-2 ICS

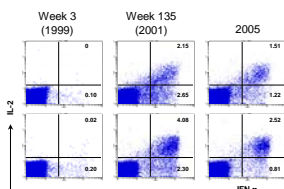
IFN- γ ELISpot Matrix

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
15	162	163	164	165	166	116	117	118	119	175	176	178	179	180
16	167	168	169	170	171	120	121	122	123	177	181	182	183	
17	172	173	174			123	124	125	126	184	185	186	187	
18	1	2	3	4	5	126	127	128	129	188	189	190	191	
19	6	7	8	9	10	128	130	131	132	192	193	194	195	
20	11	12	13	14	15	132	133	134	135	196	197	198	199	
21	16	17	18	19	20	135	136	137	138	200	201	202	203	
22	21	22	23	24	25	138	139	140	141	204	205	206	207	
23	26	27	28	29	30	141	142	143	144	208	209	210	211	
24	31	32	33	34	35	144	145	146	147	212	213	214	215	
25	36	37	38	39	40	147	148	149	150	216	217	218	219	
26	41	42	43	44	45	148	149	150	151	220	221	222	223	
27	46	47	48	49	50	149	150	151	152	224	225	226	227	
28	51	52	53	54	55	150	151	152	153	228	229	230	231	

Conserved motif:
A, C, D, CRF01_AE
CTL epitope HLA-B7 restricted in subtype B and C infections.
Goulder, 2000; Kiepiela, 2004

GAG 49 consensus peptide corresponds to G_{PSHKARVL} autologous sequence.

ICS screening of consensus vs autologous CD8+ T-cell Gag epitope



Gag consensus peptide (B7) GPGHKARVL
Gag autologous peptide (B7) GPSHKARVL

Conclusions and discussion

- No CD4+ T-cell responses to the matrix peptides were detected. Although weak responses to Gag were present at baseline when using "overlapping peptides".
- Among CD8+ T-cell responses a high magnitude response to gag GPGHKARVL epitope was present from early phase of infection as a monofunctional IFN- γ response shifting to a high magnitude polyfunctional IFN- γ +IL2 response at chronic phase of infection.
- We show that G_{PSHKARVL} Gag-p24 (223-231) is a CD8+ T-cell epitope in a HLA-B7 patient harboring a non-progressive HIV-1 AE recombinant infection.
- Specific CD8+ T-cell polyfunctional responses preserved in the absence of HAART could be a pathway to explain viral control and clinical outcome in this patient.
- Additionally, G_{PSHKARVL} motif conservation among different HIV-1 group M subtypes and CRFs, underlines its relevance for vaccine trial monitoring.
- CD4+ T-cell responses to the matrix peptides were detected. Although weak responses to Gag were present at baseline when using "overlapping peptides".

Acknowledgments

- Gonzalo Tapia, Laboratory of AIDS Immunopathogenesis, CHUV.
- Vaccinology Centre, Division of Immunology and Allergy, CHUV.
- NIH AIDS Research and Reference Reagent Program.
- Diagnosis Laboratory, Division of Immunology and Allergy, CHUV.