AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 26, Number 4, 2010

DOI: 10.1089/aid.2009.0101

The Relationship Between Antibody to R7V and Progression of HIV Type 1 Infection

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Abstract

The presence of antibody to R7V (anti-R7VAb), a seven-amino acid sequence derived from β_2-microglobulin incorporated into HIV-1 virions from the surface of infected cells, has been proposed as an early marker of nonprogressive HIV-1 infection. The present study was undertaken because no prospective studies have tested this hypothesis. Stored samples collected prospectively from 361 HIV-1 seroconverting men in the Multicenter AIDS Cohort Study (0.44–1.53 years after seroconversion) were assayed for the presence or absence of anti-R7VAb, using a standardized ELISA. Using Cox proportional hazards models, crude and adjusted relative hazards (RH) were determined for the following outcomes: (a) clinically defined AIDS, (b) clinically defined AIDS or CD4 T cell count of <200 cells/μl, and (c) death. A total of 143 (39.6%) men had early anti-R7VAb and 218 (60.4%) did not; 192 (53.2%) developed AIDS. At the visit tested, men with anti-R7VAb had significantly lower CD4 T cell counts and higher plasma HIV-1 viral loads than those without antibody. After adjustment for CD4 T cell count, HIV-1 viral load, CCR5 polymorphism, and use of combined antiretroviral therapy, the presence of anti-R7VAb was associated with a higher risk of progression for all outcomes, but not significantly so. Absence of anti-R7VAb was significantly associated with expression of HLA-B*5701 and -B*2705, two alleles associated with slower progression of HIV-1 disease. The early presence of anti-R7VAb in HIV-1 seroconverters was not associated with slower progression of HIV-1 disease.

Introduction

Progression of HIV-1 infection is highly variable, with time from infection to AIDS ranging from less than 1 year to 20 years or more in the absence of effective therapy, and with rare people controlling the infection for long periods of time with little or no immune deterioration.[1] Host as well as viral factors have been associated with slower disease progression, such as genetic polymorphisms,[2–6] viral mutations,[7,8] and early host immune responses, both humoral[9–11] and cellular.[12,13] People who control viral replication to very low levels also have stronger CD8 T cell cytotoxic function than those who do not exert such control.[14] However, much if not most of the basis for slower progression of HIV-1 disease remains unexplained. The identification of early predictive markers of slow or nonprogression might assist in a better understanding of HIV-1 disease pathogenesis and management of HIV-1-infected patients.

It has been proposed that the presence of antibody to R7V (anti-R7VAb), a seven amino acid sequence (RTPKIQV), early in HIV-1 infection is associated with nonprogressive HIV-1 infection.[15–17] R7V is derived from β_2-microglobulin (β_2m), a highly conserved cellular protein that is incorporated into HIV-1 virions as they bud off the surface of infected cells, and was found in all HIV-1 isolates tested.[18] R7V is exposed on the surface of the virions and theoretically would offer an attractive basis for a protective immune response because it does not vary among HIV-1-infected individuals, in contrast to the viral envelope itself, which is notoriously variable. The hypothesis that anti-R7VAb is protective against HIV-1 disease progression has been supported by small cross-sectional studies.[15,16] based on the use of a qualitative assay that has been standardized to classify samples as containing or not containing antibody to R7V.[19] However, longitudinal studies to test this hypothesis have not been done. Therefore, we employed prospectively collected samples from the

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Multicenter AIDS Cohort Study (MACS), which has followed HIV-1-infected and -uninfected men since 1984, to determine whether individuals who have anti-R7VAb early in HIV-1 infection by this assay have a lower likelihood of progressing to AIDS than those who lack such antibodies.

Materials and Methods

Study participants and samples

To address the above hypothesis, we studied men with incident HIV-1 infection (HIV-1 seroconverters) in the MACS, a prospective, observational study of the natural and treated histories of HIV-1 infection among men who have sex with men in the United States.[20,21] In all, 6972 men were recruited in three enrollments (4954 in 1984–1985, 668 in 1987–1991, and 1350 in 2001–2003) at centers located in Baltimore, MD, Chicago, IL, Los Angeles, CA, and Pittsburgh, PA. Participants returned every 6 months for detailed interviews, physical examinations, quality-of-life assessments, and collection of blood for laboratory testing and storage. In some cases, men who had recently seroconverted to HIV-1 were followed at 3- rather than 6-month intervals. Serum and plasma were stored at -80°C until used. Positive enzyme-linked immunosorbent assays (ELISAs) with confirmatory Western blot tests were used to determine HIV-1 seropositivity. HIV-1 RNA levels were determined using fresh or frozen serum or plasma and the Roche Ultrasensitive RNA PCR assay (Roche Molecular Systems, Branchburg, NJ), with a detection limit of 50 copies/ml, or Roche standard assay, with a detection limit of 400 copies/ml. T cell subset levels were quantified by each MACS center using standardized flow cytometry.[22]

The present study was conducted in accordance with an FDA-approved protocol for the registration of a kit for the standardized qualitative assay of anti-R7Vab.[19] The study population consisted of all HIV-1 seroconverters in the MACS who met the following criteria: (a) the interval between the last HIV-1-seronegative and first -seropositive study visit was 1 year or less; (b) follow-up information was available beyond 2 years after the time of seroconversion (defined as the midpoint between these two study visits); and (c) a CD4 T cell count and a specimen of serum or plasma were available at the second, third, or fourth study visit after seroconversion. There were 361 men who met these criteria. The samples tested consisted of serum ($n = 321$, 89%) or plasma ($n = 40$, 11%) obtained at the second through fourth seropositive visits, corresponding to approximately 0.44–1.53 years after estimated time of seroconversion. The visit selected for testing was the latest visit within 1 year following the first HIV-1-seropositive visit. Three outcomes were assessed: (1) clinically defined AIDS (1993 CDC definition[23] except that CD4 T cell count <200 cells/μl by itself was not considered AIDS), (2) clinically defined AIDS or CD4 T cell count of <200 cells/μl, and (3) death. CD4 T cell counts were by definition available at the time the test sample was obtained. CCR5 genotype (wild type or heterozygous) was available for 346 men based on testing performed at Dr. Stephen O'Brien's laboratory at the National Cancer Institute,[24] and viral load determinations were available for 333 men. HLA typing was performed by Dr. Mary Carrington's laboratory at the National Cancer Institute.[25] Use of highly active antiretroviral therapy (HAART) was defined according to the DHHS/Kaiser Panel guidelines (http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL05042006050.pdf), and summarized at each visit. The date of HAART initiation was defined as the midpoint between the last visit without report of HAART use and the first visit at which HAART use was reported.

Assay for anti-R7VAb

Specimens to be tested for anti-R7VAb were shipped on dry ice from the MACS repository to SeraCare Life Sciences (Gaithersburg, MD), who performed the tests according to the manufacturer's protocol for the ELISA kit [IVAGEN SA Bernis, France, licensed by URRMA R&D (Aubagne, France)]. The assay is an indirect noncompetitive enzyme immunoassay with the R7V peptide covalently linked to the microplate wells. The immobilized peptide captures the anti-R7VAb from the diluted sample, which is then revealed by the sequential addition of peroxidase-conjugated antihuman IgG and 3,3′,5,5′-tetramethylbenzidine substrate, reading of absorbance at 450 nm, and determination of the optical density for each microwell. Prior to testing of the samples for this study, staff at SeraCare were trained in the use of the test kit and reporting of the data. The 361 samples were tested in 10 independent runs using a single lot of the anti-ELISA kit provided directly to SeraCare by IVAGEN; each sample was blindly tested in one duplicate pair under code, and was reported as either "positive" or "negative" according to whether the ratio of the average of the duplicate optical densities for that sample to that of an internal calibrator was greater than or less than 1.3. This cutoff value was specified before the testing was performed. Coefficients of variation for optical densities for the internal negative and positive controls were $\pm 5\%$. For the duplicate measurements on the study samples themselves, the intraclass correlation was very high at 0.94, and the concordance of the replicates as both positive or negative was also very high at 92.3% [$\kappa = 0.8354$ (95% CI = 0.78, 0.89)].

Statistical analysis

Analyses were performed by the MACS data coordinating center. Cox proportional hazards models were used to determine crude and adjusted relative hazards (RH) and 95% confidence intervals (CI). Two models were used. The first model examined the association of the presence of anti-R7VAb with all three study outcomes, with adjustment for HAART use and the CD4 T cell count at the visit at which anti-R7VAb were measured. This model included data from all 361 eligible study participants, so as to minimize selection within the cohort. In the second model, we further adjusted for CCR5 gene polymorphisms and for plasma HIV-1 RNA level; 333 men had complete data for these variables, which had been determined in other substudies. For each of the three outcomes evaluated, individuals contributed time from the date of seroconversion to the event or, if they did not have the event, to the last date of contact. For time to <200 CD4 T cells/μl, if all values were 200 cells/μl or greater the participant contributed time to the last date at which the CD4 T cell count was determined. The date of analysis was July 1, 2007 and individuals without an event by that date were censored as event free as of July 2007. Use of HAART was treated as a time-dependent covariate in the analysis. All other covariates were fixed as of the time the anti-R7VAb was assessed. Statistical analyses were performed with SAS software 9.1 (Cary, NC). The statistical significance of differences between the

anti-R7VAb-negative and -positive donors for concurrent immunologic and virologic parameters was assessed by the Wilcoxon nonparametric test. The distributions of HLA types by the presence or absence of anti-R7VAb were compared by Fisher's exact test for each of the 61 Class I alleles present in the study population, using the Bonferroni correction for multiple comparisons. Thus, the cutoff for statistical significance was $0.05/61 = 0.0082$. Homozygous men were counted only once.

Results

Among the 361 samples tested, 143 (39.6%) were positive for anti-R7VAb and 218 (60.4%) were negative. The donors of the positive and negative samples did not differ by race, CCR5 heterozygosity, or distribution of sampled visits relative to seroconversion, but did differ by MACS center (Table 1). In almost all cases, the study visit tested was the second or third seropositive visit, corresponding to 0.44–1.53 years after the estimated date of seroconversion. Those who were positive for anti-R7VAb at the visit tested had significantly lower CD4 T cell counts and higher plasma HIV-1 viral loads than those who were antibody negative (Table 1). This difference was unlikely to be due to the differing prevalence of acute HIV-1 infection, because the earliest visit sampled was the second one after seroconversion. Moreover, the two donor groups had almost identical distributions of visits studied relative to serconversion, times from seroconversion to the visit studied,

Table 1. Characteristics of Study Population (HIV-1 Seroconverters from the MACS) by Anti-R7V Antibody (R7VAb) Status

	Negative for anti-R7VAb (n = 218)		*Positive for anti-R7VAb (n = 143)*		*Overall (n = 361)*		
	N	%	N	%	N	%	p *Value*[a]
Race							0.49[b]
White	190	87.2	119	83.2	309	85.6	
Black	15	6.9	11	7.7	26	7.2	
Other[c]	13	6.0	13	9.1	26	7.2	
MACS center							0.001[b]
Baltimore, MD	63	28.9	21	14.7	84	23.3	
Chicago, IL	53	24.3	25	17.5	78	21.6	
Pittsburgh, PA	45	20.6	41	28.7	86	23.8	
Los Angeles, CA	57	26.1	56	39.2	113	31.3	
CCR5 32 genotype							0.32[b]
Homozygous wild type	171	78.4	118	82.5	289	80.1	
Heterozygous 32	39	17.9	20	14.0	59	16.3	
Missing	8	3.7	5	3.5	13	3.6	
Test visit relative to first HIV-1-seropositive visit							1.0[d]
+1	100	45.9	65	45.5	165	45.7	
+2	114	52.3	75	52.4	189	52.4	
+3	4	1.8	3	2.1	7	1.9	
	N	**Median (IQR)[e]**	*N*	**Median (IQR)**	*N*	**Median (IQR)**	p value[f]
Year of seroconversion (SC)	218	1986.4 (1985.2, 1990.0)	143	1987.5 (1985.6, 1990.5)	361	1986.8 (1985.3, 1990.2)	0.05
Age at SC (years)	218	33.8 (29.2, 40.1)	143	34.9 (29.9, 40.5)	361	34.5 (29.4, 40.2)	0.48
CD4 T cell count (cells/μl)[g]	218	628 (505, 880)	143	518 (388, 701)	361	595 (459, 802)	<0.0001
HIV-1 RNA (copies/ml)[g]	210	18,475 (4735, 46,074)	136	42,916 (16,092, 102,268)	346	26,634 (7,903, 61,544)	<0.0001
HIV-1 RNA setpoint (copies/ml)[h]	197	18,007 (6138, 46,625)	134	38,703 (13,638, 81,672)	331	25,107 (8,001, 62,936)	<0.0001
Time from HIV-1 seroconversion to test sample (years)	218	1.09 (0.83, 1.21)	143	1.08 (0.83, 1.21)	361	1.08 (0.83, 1.21)	0.44
Time from first HIV-1-positive visit to test sample (years)	218	0.82 (0.56, 0.96)	143	0.82 (0.56, 0.96)	361	0.82 (0.56, 0.96)	0.74

[a] *p* values refer to differences between anti-R7Ab-negative and -positive men.
[b] By Chi-square test.
[c] For anti-R7V antibody-negative group, 12 Hispanic and 1 Asian or Pacific Islander; for anti-R7V antibody-positive group, 11 Hispanic, 1 Asian or Pacific Islander, and 1 other.
[d] By Fisher's exact test.
[e] Interquartile range.
[f] By Wilcoxon test.
[g] Values at visit at which anti-R7VAb was measured.
[h] Before HAART; defined as the average of pre-HAART HIV RNA values obtained from 12 to 24.5 months following the date of seroconversion, excluding the first seropositive visit if it fell within this interval.

and times from the first HIV-1-positive visit to the visit studied (Table 1). Thus, very soon after becoming HIV-1 infected those with anti-R7VAb showed more evidence of disease progression than those without this antibody.

Overall, the follow-up period spanned from 1984 to 2007, including calendar time prior to the availability of HAART and time when HAART was used extensively. This represented 3924 person-years of follow-up, comprised of 5779 person-visits including 1983 (34.2%) at which use of HAART was reported. The overall median times to AIDS and death for the 361 seroconverters were 9.9 and 13.6 years, respectively. Among the 192 (53.2%) men who developed AIDS, the mean time from seroconversion to AIDS was 7.0 (95% CI 6.49, 7.41) years. For the 182 men who died, the mean time from seroconversion to death was 8.6 (95% CI 8.06, 9.16) years.

Table 2 shows the results of survival analyses of the data, based on the three study outcomes evaluated. Model 1 included the presence of anti-R7VAb (yes/no), HAART use (yes/no), and CD4 T cell count at the visit at which anti-R7VAb was assessed. As expected, HAART use and a higher CD4 T cell count were significantly associated with reduced hazards for all outcomes. In this model, the presence of anti-R7VAb was associated with a significantly higher relative hazard (RH) of all outcomes. (The results were almost unchanged if this analysis was restricted to the 333 men included in Model 2.) In Model 2, CCR5 genotype and HIV-1 plasma RNA (viral load) were added to the analysis. Viral load was highly significant for all outcomes; CD4 T cell count and HAART use remained significant (except for CD4 T cell count and the outcome of death). After these adjustments, the presence of anti-R7VAb was still associated with more rapid progression to each outcome (i.e., RH >1), but the effects were attenuated and no longer statistically significant. The association of the presence of anti-R7VAb with the outcome of having either AIDS or a CD4 T cell count <200 cells/μl (RH $=1.31$) was of borderline significance ($p=0.071$). These results were not changed by restricting the analyses to data collected before 1996, when HAART use by the cohort began, or by logarithmic or square-root transformation of the CD4 T cell count.

Class I HLA types were available for all but 12 men. Two HLA-B alleles were significantly associated with the absence of anti-R7VAb after correction for multiple comparisons: B*5701 was present in 21/212 men without antibody but 0/137 with it ($p=2.8\times10^{-5}$); the corresponding numbers for B*2705 were 18/212 and 1/137 ($p=0.0012$). One B allele was associated with presence of anti-R7V antibody: B*4201 was present only in men with antibody (5/137), which was of borderline significance after Bonferroni correction ($p=0.0089$). There were no significant associations with Class 1 A or C alleles.

Discussion

In contrast to previous cross-sectional studies, the present longitudinal study found no evidence of an association between antibody to R7V early in infection and slower progression of HIV-1 infection. At the earliest visit studied, which was about 0.4–1.5 years after seroconversion, those with anti-R7VAb already had more advanced HIV-1 infection than those without this antibody, as evidenced by lower CD4 T cell counts and higher plasma viral loads. Moreover, after adjusting for this difference there was still no evidence of a protective association of anti-R7VAb with slower progression of HIV-1 infection, in that relative hazards for disease outcomes remained greater than 1 (though not significantly so). Taken together, these data provide strong evidence that the early presence of anti-R7VAb, as measured by the standardized assay used in this study, was not associated with future slower progression of HIV-1 disease in the MACS cohort of HIV-1 seroconverters. Thus, the anti-R7VAb test as currently configured, i.e., yielding a qualitative output of presence or absence of antibody, when used either as a stand-alone test or in combination with CD4 T cell count and viral load in the early stages of HIV-1 infection, did not provide complementary data to predict a favorable progression of HIV-1 disease. Indeed, the presence of anti-R7VAb had, if anything, a negative prognostic import.

The discrepancy between the present study and the previous cross-sectional studies is likely explained by two aspects of the present study: its prospective design and the use of samples from donors with known durations of HIV infection. In the cross-sectional studies, many donors, especially those with slow disease progression, were studied after many years

Table 2. Relative Hazards and 95% Confidence Intervals (CI) for Times to Clinical AIDS, AIDS or Low CD4 T Count, and Death among MACS HIV-1 Seroconverters

	AIDS		*AIDS or CD4 <200*		*Death*	
	RH	*95% CI*	*RH*	*95% CI*	*RH*	*95% CI*
Model 1 ($n=361$)						
Presence of anti-R7V antibody	1.44	(1.08, 1.94)	1.72	(1.31, 2.25)	1.54	(1.14, 2.08)
HAART use	0.31	(0.19, 0.51)	0.14	(0.07, 0.26)	0.34	(0.22, 0.52)
CD4 T cell count (per change of 50 cells/μl)[a]	0.96	(0.93, 0.99)	0.96	(0.93, 0.99)	0.97	(0.95, 1.00)
Model 2 ($n=333$)[b]						
Presence of anti-R7V antibody	1.07	(0.78, 1.46)	1.31	(0.98, 1.75)	1.23	(0.89, 1.70)
HAART use	0.28	(0.17, 0.47)	0.12	(0.06, 0.24)	0.29	(0.18, 0.45)
CCR5 32	0.85	(0.55, 1.31)	0.86	(0.58, 1.25)	0.60	(0.37, 0.98)
CD4 T cell count (per change of 50 cells/μl)[a]	0.97	(0.94, 1.00)	0.97	(0.94, 0.99)	0.99	(0.96, 1.02)
Log_{10} HIV-1 RNA (per increase of one log)[a]	2.08	(1.63, 2.64)	1.79	(1.44, 2.22)	1.77	(1.39, 2.24)

[a]Values at visit at which anti-R7VAb was measured.
[b]Model 2 excludes participants with no CCR5 32 information or with no HIV-1 RNA information at study visit.

of being HIV infected. If, for example, people acquire or lose anti-R7VAb over the course of HIV infection, this would confound cross-sectional studies based on people at different stages of disease. Also, cross-sectional studies often do not include the most rapid disease progressors, who, according to the results of the present study, might have included many people with anti-R7VAb. This may have happened in two recent cross-sectional studies interpreted to suggest the disappearance of anti-R7VAb over the course of HIV infection.[26,27] The present study avoided these issues by studying groups of men whose durations of infection were almost identical and short, i.e., soon after seroconversion and prior to disease progression. The reasons why some men expressed anti-R7VAb and others did not are unknown. Possible explanations could include variations in levels of expression of the R7V epitope, processing of the epitope during incorporation into virions, or host reactivity to the epitope; also some men might have had levels of antibody that were below the threshold of detection of the assay used. Further research will be needed to clarify this question.

Because R7V and β_2m are part of the MHC class I molecule, we asked whether Class I polymorphisms might be related to generation of anti-R7VAb. Two associations that were significant after a conservative correction for multiple comparisons were found: B*2705 and B*5701 were present almost exclusively in men who did not have detectable anti-R7VAb. Interestingly, both of these alleles are associated with slower progression of HIV disease.[4] Further studies will be needed to clarify this inverse relationship between these alleles and anti-R7VAb, but the fact that protective alleles were associated with the absence of anti-R7VAb is consistent with the lack of protective effect of this antibody in this study.

It remains possible that a more quantitative assay for anti-R7VAb might find a relationship between levels of this antibody and HIV-1 disease progression. The possibility also exists that the use of frozen, stored samples may have affected the results of the assays, but similar samples were also used in the cross-sectional studies that suggested a protective role for anti-R7VAb. It is also possible that other types of anti-R7VAb, such as those that can neutralize HIV,[18] which are not specifically measured by the assay used in this and the previous cross-sectional studies, would correlate better with slower HIV disease progression. However, our results suggest that the mere presence of antibodies directed against this epitope of the HIV-1 envelope is not of central importance in protection against the pathogenic effects of HIV-1 infection.

Acknowledgments

We thank Dr. J.C. Chermann from URRMA RetD for R7V expertise and assistance during the licensing process of the anti-R7V antibody kit, and Ms. Sandra Reynolds and Ms. Xiulong Li for assistance with data management and analysis. The MACS is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute and the National Heart, Lung and Blood Institute: UO1-AI35042, 5-MO1-RR-00722 (GCRC), UO1-AI35043, UO1-AI-37984, UO1-AI-35039, UO1-AI-35040, UO1-AI-37613, and UO1-AI-35041.

Principal contributions made by each of the authors to the article: Margolick: obtaining the test samples, analysis and design of the study, interpretation of the data, preparation of the manuscript. Da Costa Castro, Sanchez, Gemrot: preparation of the test kits used, training of the laboratory in the use of the kits, interpretation of the data, preparation of the manuscript. Phair: obtaining the test samples, design of the study, interpretation of the data, preparation of the manuscript. Jamieson: design of the study, interpretation of the data, preparation of the manuscript. Rinaldo: obtaining the test samples, design of the study, interpretation of the data, preparation of the manuscript. Jacobson: design of the study, analysis and interpretation of the data, preparation of the manuscript.

Author Disclosure Statement

No competing financial interests exist.

References

1. Deeks SG and Walker BD: Human immunodeficiency virus controllers: Mechanisms of durable virus control in the absence of antiretroviral therapy. Immunity 2007;27(3):406–416.
2. Hogan CM and Hammer SM: Host determinants in HIV infection and disease. Part 2: Genetic factors and implications for antiretroviral therapeutics. Ann Intern Med 2001;134(10): 978–996.
3. Ball TB, Ji H, Kimani J, McLaren P, Marlin C, Hill AV, *et al.*: Polymorphisms in IRF-1 associated with resistance to HIV-1 infection in highly exposed uninfected Kenyan sex workers. AIDS 2007;21(9):1091–1101.
4. Carrington M and O'Brien SJ: The influence of HLA genotype on AIDS. Annu Rev Med 2003;54:535–551.
5. Moore JP and Klasse PJ: HIV-1 pathogenesis: The complexities of the CCR5-CCL3L1 complex. Cell Host Microbe 2007; 2(5):281–283.
6. Reiche EM, Bonametti AM, Voltarelli JC, Morimoto HK, and Watanabe MA: Genetic polymorphisms in the chemokine and chemokine receptors: Impact on clinical course and therapy of the human immunodeficiency virus type 1 infection (HIV-1). Curr Med Chem 2007;4(12):1325–1334.
7. Lum JJ, Cohen OJ, Nie Z, Weaver JG, Gomez TS, Yao X-J, *et al.*: Vpr R77Q is associated with long-term nonprogressive HIV infection and impaired induction of apoptosis. J Clin Invest 2003;111:1547–1554.
8. Zhang L, Huang Y, Yuan H, Tuttleton S, and Ho DD: Genetic characterization of vif, vpr, and vpu sequences from long-term survivors of human immunodeficiency virus type 1 infection. Virology 1997;228:340–349.
9. Martinez V, Costagliola D, Bonduelle O, N'go N, Schnuriger A, Theodorou I, *et al.*: Combination of HIV-1-specific CD4 Th1 cell responses and IgG2 antibodies is the best predictor for persistence of long-term nonprogression. J Infect Dis 2005;191(12):2053–2063.
10. Rezza G, Fiorelli V, Dorrucci M, Ciccozzi M, Tripiciano A, Scoglio A, *et al.*: The presence of anti-Tat antibodies is predictive of long-term nonprogression to AIDS or severe immunodeficiency: Findings in a cohort of HIV-1 seroconverters. J Infect Dis 2005;191(8):1321–1324.
11. Farzadegan H, Chmiel JS, Odaka N, Ward L, Poggensee L, and Phair JP: Association of antibody to human immunodeficiency virus type 1 core protein (p24), CD4+ lymphocyte number, and AIDS-free time. J Infect Dis 1992;166:1217–1222.
12. Schmitz JE, Kuroda MJ, Santra S, Sasseville VG, Simon MA, Lifton MA, *et al.*: Control of viremia in simian immunodeficiency virus infection by $CD8^+$ lymphocytes. Science 1999; 283:857–860.

13. Margolick JB, Gange SJ, Detels R, O'Gorman MRG, Rinaldo C, and Lai S: Impact of inversion of the CD4/CD8 ratio on the natural history of HIV-1 infection. J Acquir Immun Defic Syndr 2006;42:620–626.
14. Saez-Cirion A, Lacabaratz C, Lambotte O, Versmisse P, Urrutia A, Boufassa F, *et al.*: HIV controllers exhibit potent CD8 T cell capacity to suppress HIV infection ex vivo and peculiar cytotoxic T lymphocyte activation phenotype. Proc Natl Acad Sci USA 2007;104(16):6776–6781.
15. Le Contel C, Galea P, Silvy F, Hirsh I, and Chermann JC: Identification of the B2m derived epitope responsible for neutralization of HIV isolates. Cell Pharmacol AIDS Sci 1996;3:68–73.
16. Galea P, Le Contel C, and Chermann JC: Identification of a biological marker of resistance to AIDS progression. Cell Pharmacol AIDS Sci 1996;3:311–316.
17. Haslin C and Chermann JC: Anti-R7V antibodies as therapeutics for HIV-infected patients in failure of HAART. Curr Opin Biotechnol 2002;13(6):621–624.
18. Galea P, Le Contel C, and Chermann JC: A novel epitope R7V common to all HIV-1 isolates is recognized by neutralizing IgG found in HIV-infected patients and immunized rabbits. Vaccine 1999;17(11–12):1454–1461.
19. Sanchez A, Gemrot F, and Da Costa Castro JM: Development and studies of the anti-R7V neutralizing antibody ELISA test: A new serological test for HIV seropositive patients. J Immunol Methods 2008;332(1–2):53–60.
20. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, and Rinaldo CR: The Multicenter AIDS Cohort Study: Rationale, organization, and selected characteristics of the participants. Am J Epidemiol 1987;126:310–318.
21. Dudley J, Jim S, Hoover D, Metz S, Thackerey R, and Chmiel J: The Multicenter AIDS Cohort Study: Retention after 9 1/2 years. Am J Epidemiol 1995;142:323–330.
22. Schenker EL, Hultin LE, Bauer KD, Ferbas J, Margolick JB, and Giorgi JV: Evaluation of a dual-color flow cytometry immunophenotyping panel in a multicenter quality assurance program. Cytometry 1993;14:307–317.
23. CDC: 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;41:1–19.
24. Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, *et al.*: Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. Science 1996;273(5283):1856–1862.
25. Liu C, Carrington M, Kaslow RA, Gao X, Rinaldo CR, Jacobson LP, *et al.*: Association of polymorphisms in HLA Class I and TAP genes with resistance to HIV-1 infection. J Infect Dis 2003;187:1404–1409.
26. Ergünay K, Altinbas A, Calik BN, Unal S, Us D, Karabulut E, *et al.*: [Investigation of anti-R7V antibodies in HIV-infected patients under highly active antiretroviral therapy]. Mikrobiyol Bul 2008;42(3):413–419.
27. Lafia E, Houeze M, Zannou M, Bigot A, Guedou F, Anagonou S, *et al.*: Anti-R7V antibodies prevalence in HIV-infected patients followed in the ambulatory care centre of a university hospital, Cotonou, Benin. 18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Barcelona, Spain, April, 2008.

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