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Plasma Levels of Complement Factor I and C4b Peptides Are Associated with HIV Suppression

Boyue Wu,[†,‡] Zhengyu Ouyang,[§] Christopher J. Lyon,[†,∥] Wei Zhang,[∥,⊥] Tori Clift,[∥] Christopher R. Bone,[∥] Boan Li,[#] Zhen Zhao,[¶] Jason T. Kimata,[○] Xu G. Yu,[§] and Ye Hu*[,†,∥,◆]

[†]Biodesign Center for Personalized Diagnostics, the Biodesign Institute, Arizona State University, 727 E. Tyler Street, Tempe, Arizona 85281, United States

[‡]College of Laboratory Medicine, Tianjin Medical University, 1 Guangdong Road, Tianjin 300203, China

[§]Ragon Institute of MGH, MIT and Harvard University, 400 Technology Square, Boston, Massachusetts 02139-3583, United States

[∥]Department of Nanomedicine, Houston Methodist Research Institute, 6670 Bertner Avenue, Houston, Texas 77030, United States

[⊥]Shengjing Hospital of China Medical University, 36 Sanhao Street, Heping District, Shenyang, Liaoning 110003, China

[#]Center for Clinical Laboratory, 302 Military Hospital of China, 100 Middle Section of West 4th Ring Road, Beijing 100038, China

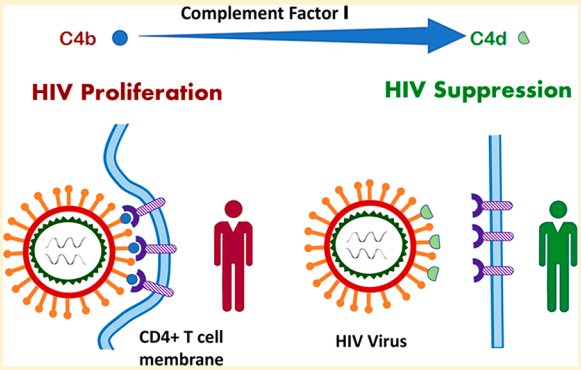
[¶]Department of Laboratory Medicine, Clinical Center, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892, United States

[○]Department of Molecular Virology and Microbiology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030, United States

[◆]School of Biological and Health Systems Engineering, Virginia G. Piper, Arizona State University, 727 E. Tyler Street, Tempe, Arizona 85281, United States

Supporting Information

ABSTRACT: Individuals who exhibit long-term HIV suppression and CD4 T-cell preservation without antiretroviral therapy are of great interest for HIV research. There is currently no robust method for rapid identification of these "HIV controller" subjects; however, HLA-B*57 (human leukocyte antigen (major histocompatibility complex), class I, B*57) genotype exhibits modest sensitivity for this phenotype. Complement C3b and C4b can influence HIV infection and replication, but studies have not examined their possible link to HIV controller status. We analyzed HLA-B*57 genotype and complement levels in HIV-positive patients receiving suppressive antiretroviral therapy, untreated HIV controllers, and HIV-negative subjects to identify factors associated with HIV controller status. Our results revealed that the plasma levels of three C4b-derived peptides and complement factor I outperformed all other assayed biomarkers for HIV controller identification, although we could not analyze the predictive value of biomarker combinations with the current sample size. We believe this rapid screening approach may prove useful for improved identification of HIV controllers.



KEYWORDS: *human immunodeficiency virus, complement factor I, complement C4b, elite controllers*

A small fraction of HIV-infected individuals exhibit long-term viral control and CD4 T-cell preservation in the absence of antiretroviral therapy.[1,2] These "HIV controllers" can be divided into viremic controllers (VCs; ~3.34% of HIV-positive patients), who have low but detectable viremia (usually <2000 HIV RNA copies/mL), and rare elite controllers (ECs; ~0.55%), who have undetectable viremia by conventional assays.[2−7] Recent work has shown that ECs harbor replication-competent viruses, strongly suggesting that host factors rather than defective viral infections contribute to HIV suppression.[2,10,8] Viral suppression mechanisms responsible for the EC phenotype are thus of great interest to researchers attempting to develop HIV vaccines and new anti-HIV therapy strategies. Several mechanisms, including host genetic factors, innate and adaptive immune responses, and viral attenuation,[9] have been proposed to explain the EC phenotype, but these efforts are hindered by the limited number of identified EC individuals available for study. Human leukocyte antigen (HLA)-B*57, which is involved in class-I-restricted adaptive immune responses, reportedly associates with controlled HIV replication and polyfunctional cytotoxic T cell responses in ECs,[11,12]

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although HLA class I-restricted T-cell responses are not always required for long-term viral control.[13]

The complement system plays a major role in innate immunity and is composed of circulating proteins that interact in strictly regulated patterns via pathogen-triggered enzymatic cascades to promote inflammation and pathogen clearance. Complement proteins have important roles in the host response to HIV infection;[14,15] however, while the complement system plays a significant role in HIV neutralization and clearance, some complement factors can promote HIV interactions with target cells to enhance viral propagation.[16] HIV membrane proteins gp120 and gp41 are reported to directly interact with the membrane-bound complement proteins C3b and C4b[17,18] and are also targets for immunoglobulin and mannose-binding lectin, which can promote C4b membrane fixation.[16] HIV opsonization by complement factors enhances the infection of T-cells and monocyte/macrophages, while a blockade of complement receptor 1 (CR1), which binds both C3b and C4b,[19−21] inhibits infection. CR1 ligation is reported to promote HIV replication in $CD4^+$ T lymphocytes, increasing viral gene transcription, reverse transcriptase activity, and p24 release, and exhibits similar effects to regulate viral replication in $CD4^+$ T cells and monocytes/macrophages.[22] CR1 interacts with complement factor I (CFI), which plays a critical role in complement cascades by cleaving and inactivating C3b and C4b,[23,24] including HIV-bound C3b,[25] suggesting that CFI may attenuate HIV pathogenesis by inactivating HIV-conjugated C3b and C4b (Figure 1).

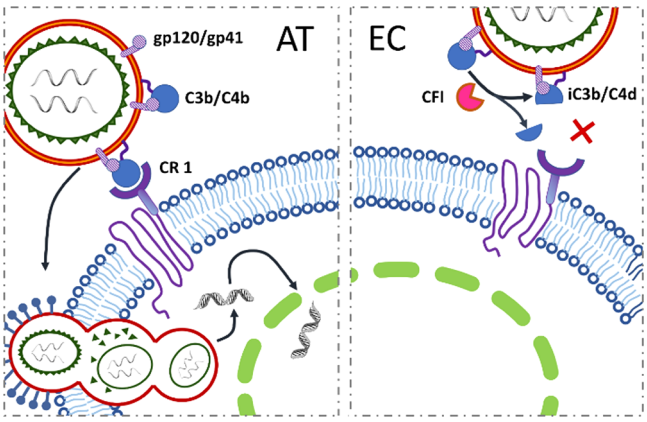

Figure 1. Model of CFI-mediated HIV regulation in AT and EC HIV patients. Left panel: Low CFI levels in AT patients allow C3b/C4b bound to HIV gp120/gp41 to interact with CR1 on the surface of $CD4^+$ T cells and other HIV targets, promoting HIV infection and replication. Right panel: High CFI levels in EC patients favor CFI-mediated cleavage of C3b/C4b to iC3b/C4d and C3b/C4b-derived peptides, blocking CR1-mediated HIV associations with target cells.

We hypothesized that elevated CFI activity, detectable by plasma C3b and C4b peptide levels, might be an important characteristic of EC patients. Results from our study to address this question revealed plasma CFI level was the best predictor of EC status, although three CFI-generated C4b peptides also had strong predictive value, and that both these factors had more predictive value than HLA-B*57 genotype.

RESULTS AND DISCUSSION

To evaluate parameters specific to our EC cohort, we enrolled three reference groups: (1) viremic controllers (VC), (2) patients receiving combined antiretroviral therapy (AT) who had undetectable viral loads when analyzed by commercial assays, and (3) HIV-negative (HN) subjects (Table 1). There were no significant differences in age or sex distribution among these populations, although the HN subject group tended to be younger and have fewer males. There were no differences in $CD4^+$ T-cell counts or time since diagnosis in any of the HIV-infected groups. HLA typing found that HLA-B*57, an HIV-protective allele associated with increased Gag-specific $CD8^+$ T cell frequency, was enriched in the EC vs AT and HN groups and exhibited allelic frequencies consistent with previous data.[13] The VC group, however, had an intermediate HLA-B*57 frequency that did not differ from any of the other groups. HLA-B*B7 expression is also linked to the frequency and quality of HIV-responsive $CD8^+$ T cells, but the study from which our samples were drawn did not analyze these parameters.

Binding of C3b and C4b to HIV may increase viral infection by promoting HIV interaction with CR1 proteins on the surface of $CD4^+$ T cells and other HIV targets,[17,18,23] while CR1 ligation on monocytes and $CD4^+$ T cells may promote viral replication.[22] CFI-mediated cleavage of C3b and C4b would block these interactions and attenuate HIV disease outcomes. We thus hypothesized that elevated plasma levels of CFI or its C3b and C4b peptides might differentiate EC cases from other HIV-positive groups. Plasma CFI levels were higher in EC and VC subjects than AT or HN subjects (Figure 2A) but did not differ between EC and VC or AT and HN subjects, suggesting that chronically elevated CFI activity may represent a novel mechanism for HIV suppression.

Consistent with previously reported data,[26] plasma levels of complement C3 and C4 did not differ among the patient groups (Figure 2B,C), but MS analysis of nanotrap-enriched peptides identified three predicted C4b fragments (m/z 1626.88, 1739.94, and 1896.04) associated with CFI activity[27] that were higher in EC than AT and HN subjects (Figure 2D). All three C4b peptides contained the C4b N-terminus generated by CFI-mediated excision of C4d from C4b and revealed serial C-terminal deletions (Table S1, Figures S1−S3). However, despite the high abundance of C3 in circulation, we could not conclusively identify any nanotrap-enriched C3b peptides in these samples, since all candidate peptides were present at concentrations too low for peptide sequencing. Plasma CFI and C4b peptide levels did not differ between individuals with HLA-B*57-positive and -negative genotypes in any of the study groups (Figure S4), suggesting that these factors do not interact and may thus have independent predictive value for EC cases.

Plasma CFI concentration did not correlate with C4 level or HLA-B*57 genotype but strongly correlated with all three C4b peptides (Figure 3A). Receiver operating characteristic (ROC) analyses found that CFI and C4b peptide level and HLA-B*57 genotype data could distinguish EC from AT patients. ROC area under the curve (AUC) values for these factors revealed that CFI level had the greatest EC vs AT discriminatory power, followed by single or composite C4b peptide level and then HLA-B*57 genotype (Figure 3B−D). ROC analyses performed with combinations of CFI, C4b peptide, and HLA-B*57 genotype data did not, however, reveal significant predictive

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Table 1. Clinical Characteristics of EC, VC, AT, and HN Groups[a]

characteristic	EC	VC	AT	HN	*p* value
n	48	45	35	34	
male, no. (%)	39 (81.3)	35 (77.8)	26 (74.3)	19 (55.9)	NS
age, mean (SD)	60 (14.7)	53 (10)	57 (9)	42 (12)	NS
years HIV-infected, mean (SD)	18 (16)	14 (9)	17 (6)	N/A	NS
$CD4^+$ T cells/μL, mean (SD)	1004 (356)	761 (288)	756 (260)	N/A	NS
HIV copies/mL, mean (SD)	39 (20)	197 (221)	29 (15)	N/A	<0.001[b]
HLA-B*57+ genotype, no. (%)	23 (48)	15 (33)	4 (11)	8 (24)	<0.05[c]

[a]Group differences were analyzed by one-way ANOVA with a Kruskal–Wallis post-test for comparisons between each subgroup, where $p < 0.05$ was considered significant. HLA-B*57 differences between EC or VC and AT + HN groups were analyzed in independent chi-square tests. NS: not significant. [b]VC vs EC, AT. [c]EC vs AT, HN.

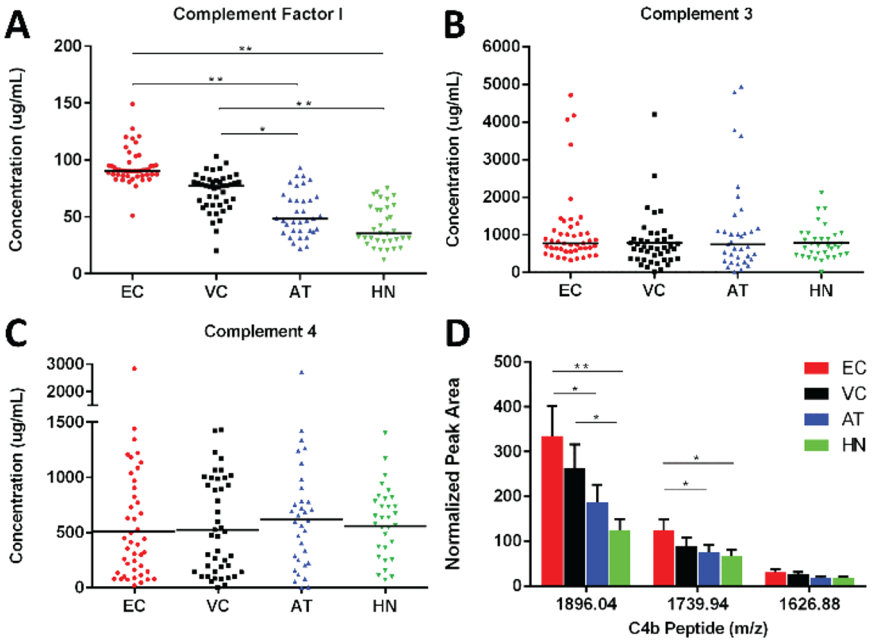

Figure 2. Plasma levels of CFI, C3, C4, and C4b-derived peptides in EC, VC, AT, and HN patients. Plasma concentrations of CFI (A), C3 (B), and C4 (C) as quantified by ELISA. (D) Relative C4b peptide (m/z 1896.04, 1739.94, and 1626.88) signal measured by Nanotrap-coupled MALDI-TOF-MS. Error bars indicate the standard error of the mean. EC, $n = 48$; VC, $n = 45$; AT, $n = 35$; HN, $n = 34$. *$p < 0.05$, **$p < 0.01$ by one-way ANOVA with a Kruskal-Wallis post-test for comparisons between each subgroup.

differences at the current sample size, and it is thus not possible to examine potential independent contributions of these factors.

ROC analysis found that an 80.39 μg/mL CFI concentration best distinguished EC cases from HN + AT cases and exhibited 95.8% (46/48) diagnostic sensitivity for EC cases and 94.9% (75/79) specificity for excluding HN + AT cases. A relative peak area of 197.3% for the m/z 1896.04 C4b peptide best distinguished these groups, and there was 87.5% (42/48) sensitivity and 88.6% (70/79) sensitivity for EC diagnosis. HLA-B*57-positivity exhibited 47.9% (23/48) sensitivity and 84.8% (67/79) specificity. Further studies are required to validate these values and to determine the utility of these markers differentiating EC subjects from the general HIV-affected population.

We did not detect C3b peptide fragments in these groups, and the reasons for this are unclear. On the basis of the literature, we would expect both C3b and C4b to modify HIV virions and that CFI would cleave both proteins efficiently to release detectable C3b and C4b fragments into the circulation. Our failure to detect C3b-derived peptides could have several explanations. C3b and C4b may not similarly modify HIV, or CFI may have differential activity for C3b and C4b due to their different cofactor requirements. The C3b and C4b cleavage products may be subject to differential degradation rates or subject to differential enrichment on our nanotrap platform. We did not examine whether the EC and control groups exhibited differential plasma expression of CFI regulatory factors, or protease activities, which could influence the relative stability of CFI-derived peptides of C3b and C4b due to material limitations. Future studies are required to address these questions and to determine whether C3b and C4b play distinct or complementary roles in regulating HIV pathogenesis via interaction with CR1, since this point has important implications for our proposed EC mechanism.

We cannot rule out the possibility that other serum proteases could cleave C4b, or potentially C4, to generate the C4b peptides we observe, since some pathogen-derived proteases cleave complement proteins to block complement activity. The possibility that an exogenous or cryptic endogenous protease activity is responsible for the C4b peptide increases observed in EC subjects appears very unlikely, however, since it would imply robust systemic action in these nonimmunocompromised subjects. It also appears unlikely that these fragments result

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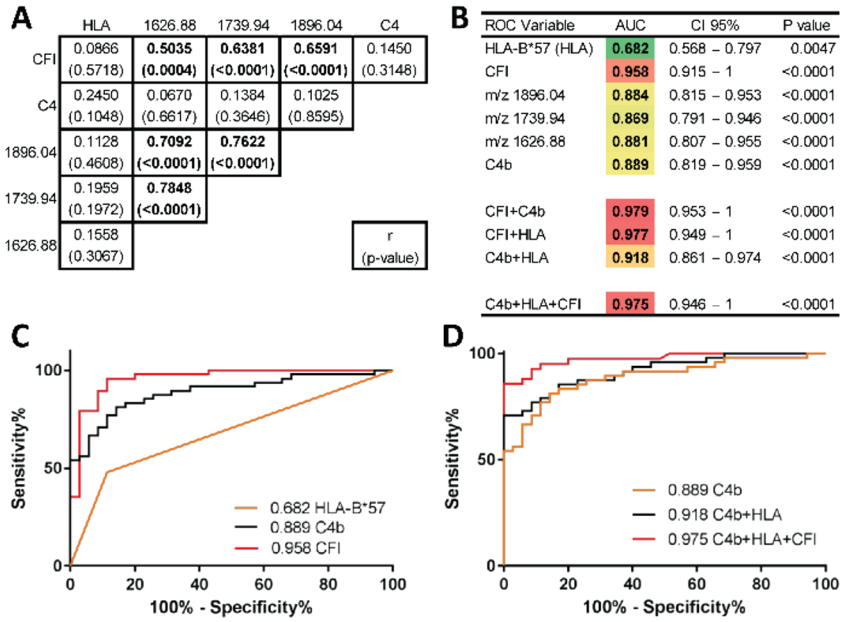

Figure 3. Correlation and receiver operating characteristic (ROC) analyses of plasma factors. (A) Spearman correlations among plasma CFI, C4, HLA, and C4b peptide levels. (B) ROC area under the curve (AUC) values, 95% confidence intervals, and *p* values for discrimination between EC and AT cases for each of the analyzed factors and a composite factor (C4b) derived from the plasma level of three C4b peptides. ROC graphs indicating the relative performance of candidate single-factor (C) and multifactor (D) ROC analyses. C4b represents a composite value formed by all of C4b peptides.

from CFI activity on C4, since CFI does not have significant activity on C3 and C4 and must recognize C3b and C4b in the context of specific cofactors to exhibit robust protease activity.[30] However, while CFI appears to generate the N-terminal cleavage site of the C3b peptides, it is not clear what protease(s) generate their C-termini.

Our results indicate that plasma levels of CFI and its products have strong potential as quantitative biomarkers for rapid identification of EC cases currently defined by their long-term control of HIV viremia in the absence of antiretroviral treatment. Rapid screening for rare EC patients is highly desirable, since this group is of intense interest in studies examining mechanisms for durable viral control but is difficult to identify, which severely restricts the size of EC populations available for different studies. Although limited by its observational nature and small sample size, our data suggest that complement factors play key roles in maintaining the EC phenotype and form the basis for future functional analysis of CFI activity in durable HIV control.

METHODS

Study Population. EC and VC subjects who maintained characteristic viral loads (EC: <75 HIV-RNA copies/mL, n = 48; VC: <2000 copies/mL, n = 45) for ≥1 year in the absence of antiretroviral treatment, combined antiretroviral therapy-treated HIV patients with suppressed viremia (AT; <75 copies/mL, n = 35), and HIV seronegative individuals (HN, n = 34) were recruited for this study. The Institutional Review Board of Massachusetts General Hospital/Partners Healthcare approved this study. and all subjects gave written informed consent. Study cohorts were matched for age, gender, viral subtype (clade B), years since HIV diagnosis, $CD4^+$ T-cell counts, viral hepatitis coinfection status (not shown), and patient ancestry (not shown) to avoid confounding data. Table 1 presents the clinical characteristics of the four cohorts. HLA class I typing was performed by sequence-specific PCR, using standard procedures. Commercial ELISA kits were used to measure CFI (ab195460, Abcam, San Francisco, CA), C3 (HC3KT, Molecular Innovations, Novi, MI), and C4 (SEA888Hu, CloudClone, Houston, TX) levels in human plasma.

Nanotrap Fractionation. Low-molecular-weight plasma peptides were enriched by incubation with mesoporous silica nanotraps[28,29] that exclude peptides >10 kDa and then subjected to matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) analysis. Briefly, individual wells on a nanotrap-coated 4-in. silicon wafer were incubated with 6 μL of human plasma for 30 min at 25 °C in a humidified chamber. The wells were then aspirated and washed three times with 10 μL of deionized water, and captured peptides were eluted by a 90 s incubation with 6 μL of a 0.1% trifluoroacetic acid/50% acetonitrile solution containing 10 nmol/L of aa18-39 of the human adrenocorticotropic hormone (ACTH) (2465.67 m/z, Sigma-Aldrich, St. Louis, MO) as an internal peptide standard.

Peptide Identification by HPLC-MS/MS. Peptide peaks were acquired using an UltiMate 3000 nanoLC system (Thermo Scientific) coupled to an Orbitrap Velos Pro instrument (Thermo Scientific). Nanotrap-enriched peptides from plasma samples were dried by vacuum centrifugation, suspended in buffer A (0.1% formic acid in water), and injected into the HPLC sample port. Peptides were then fractionated with a linear gradient of 2−37% buffer B (100% ACN and 0.1% formic acid) at a flow rate of 300 nL/min on an EASY-Spray C18 LC column (Thermo Scientific; 15 cm × 75 μm I.D. and 3 μm particle size). MS data were acquired using a data-dependent strategy selecting the fragmentation events based on the precursor abundance in the survey scan (275−1850 Th). The resolution of the survey scan was 120 000 at m/z 400 Th. MALDI data was analyzed with MarkerView (version 1.3, AB SCIEX Pte Ltd.), and ions that demonstrated a significant ≥2-

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fold difference in their mean relative peak areas between EC and other groups were subjected to tandem mass spectrum analysis to identify their peptide sequence and protein of origin. Low resolution collision-induced dissociation (CID) MS/MS spectra were acquired in rapid CID scan mode for the 15 most intense peaks from the survey scan, using a normalized collision energy of 35 for fragmentation and a 40 s dynamic exclusion and excluding early expiration. The isolation window for MS/MS fragmentation was set to 2 Th. The MS/MS spectra were searched against the human proteome in UniProt (released in March, 2017) using the Mascot Server (version 2.6, Matrix Science, London, UK) and the following parameters: non-enzyme digestion, precursor and product mass tolerances of 10 ppm and 0.8 Da, and cysteine carbamidomethylation and methionine oxidation as fixed and dynamic modifications.

Statistical Analysis. MALDI-TOF MS data was analyzed using FlexAnalysis software v1.33 (Bruker Daltonic, Billerica, MA), and mean area of selected monoisotopic peaks was determined from duplicates after normalization with an ACTH (18-39) internal standard peptide. Differences between groups were analyzed using unpaired t tests, with $p < 0.05$ differences considered statistically significant. Multivariable logistic regressions and receiver operating characteristic (ROC) and correlation analyses were performed using SPSS Statistics 19 (IBM, NY) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA). HLA-B*57 differences between EC or VC and AT + HN groups were analyzed in independent chi-square tests.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsinfecdis.7b00042.

Table S1, tandem mass spectrum matches of m/z 1896.04, 1739.94, and 1626.88; Figure S1, MALDI TOF MS spectrum from serum samples of all four study groups; Figure S2, MS/MS spectra of C4b peptide fragments; Figure S3, schematic of the cleavage events that release the C4b fragments detected in our assay; Figure S4, plasma levels of CFI and each C4b-derived peptide for HLA-B*57-positive and -negative subjects (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tyhu@asu.edu.

ORCID

Ye Hu: 0000-0001-7255-5409

Author Contributions

B.W. and Y.H. designed the research approach. B.W. performed the experiments. B.W., Z.O., and W.Z. analyzed the data. B.W., C.J.L., and Y.H. wrote the manuscript with help from T.C., C.R.B., B.L., Z.Z., and J.T.K. X.G.Y. contributed to study design and critically reviewed the study data and the manuscript. All authors approved the content of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AT, combined antiretroviral therapy patients with undetectable viremia; AUC, area under the curve; CFI, complement factor I; CR1, complement receptor 1; EC, elite controller; HLA-B*57, human leukocyte antigen (major histocompatibility complex), class I, B*57; HN, HIV-negative control; MALDI-TOF-MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; ROC, receiver operating characteristic; VC, viremic controller

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