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Elevated CD8 T-cell counts and virological failure in HIV-infected patients after combination antiretroviral therapy

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Abstract

Elevated CD8 counts with combination antiretroviral therapy (cART) initiation may be an early warning indicator for future treatment failure. Thus, we investigated whether elevated CD8 counts were associated with virological failure (VF) in the first 4 years of cART in Asian HIV-infected patients in a multicenter regional cohort.

We included patients from the TREAT Asia HIV Observational Database (TAHOD). Patients were included in the analysis if they started cART between 1996 and 2013 with at least one CD8 measurement within 6 months prior to cART initiation and at least one CD8 and viral load (VL) measurement beyond 6 months after starting cART. We defined VF as VL ≥ 400 copies/mL after 6 months on cART. Elevated CD8 was defined as CD8 ≥ 1200 cells/μL. Time to VF was modeled using Cox regression analysis, stratified by site.

In total, 2475 patients from 19 sites were included in this analysis, of whom 665 (27%) experienced VF in the first 4 years of cART. The overall rate of VF was 12.95 per 100 person-years. In the multivariate model, the most recent elevated CD8 was significantly associated with a greater hazard of VF (HR = 1.35, 95% CI 1.14–1.61; $P = 0.001$). However, the sensitivity analysis showed that time-lagged CD8 measured at least 6 months prior to our virological endpoint was not statistically significant ($P = 0.420$).

This study indicates that the relationship between the most recent CD8 count and VF was possibly due to the CD8 cells reacting to the increase in VL rather than causing the VL increase itself. However, CD8 levels may be a useful indicator for VF in HIV-infected patients after starting cART.

Abbreviations: cART = combination antiretroviral therapy, CI = confidence interval, HR = hazard ratio, IQR = interquartile range, LOCF = last observation carried forward, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse

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1. Introduction

Survival in HIV-infected individuals has improved since the introduction of combination antiretroviral therapy (cART).[1,2] However, there continue to be individuals for whom cART fails to suppress HIV to undetectable viral load (VL) levels.[3] According to previous studies, cumulative rates of virological failure (VF) after 2 years from initial suppression ranged from 20% to 40%.[4–7] Numerous predictors, such as younger age, African–American ethnicity, poor adherence to medication, missed visits, lower baseline CD4 counts, and higher baseline HIV RNA levels, have been associated with VF.[6–13]

Recently, some studies have reported that elevated total CD8 counts may be a potential predictor of VF.[14,15] Interestingly, a study reported that initial or serial elevated CD8 counts while on cART or an increase in CD8 counts from cART initiation may be early warning indicators of future treatment failure.[15] Also, because monitoring of CD8 counts with CD4 T cells is done in most countries, including in resource-limited settings, whether CD8 counts could be used an alternative marker of VF is important to know in terms of potential financial savings. However, these issues remain unresolved.

Thus, we investigated whether elevated CD8 counts were associated with increased risk of VF in the first 4 years of cART in Asian HIV-infected patients.

2. Methods

We analyzed data from the Therapeutics, Research, Education and AIDS Training in Asia (TREAT Asia) HIV Observational Database (TAHOD).[16] TAHOD is a multicenter, prospective, observational cohort study that was initiated in 2003 to assess HIV treatment outcomes in the Asia-Pacific region.[16] Patients were included in the analysis if they started cART between 1996 and 2013 with at least one CD8 measurement within 6 months prior to cART initiation and at least one CD8 and VL measurements beyond 6 months after starting cART. The analysis dataset included follow-up data collected until September 2013. We defined VF as VL $\geq$ 400 copies/mL after 6 months on cART. Elevated CD8 was defined as CD8 $\geq$ 1200 cells/μL.[15,17]

Time to VF was modeled using Cox regression analysis, stratified by site. The risk analysis period began at 6 months from the start of cART and was censored at the last available VL test. CD8 counts while on cART were analyzed as a time-updated covariate lagged to the next visit. Missing CD8 observations were filled in using last observation carried forward methods (LOCF) for up to 18 months. The covariate was then coded as "unknown" after 18 months until the next measurement. Other clinical characteristics adjusted in the model were age, sex, mode of HIV exposure, pre-cART VL, CD4 and CD8, prior mono or dual therapy, initial cART regimen, hepatitis B and C coinfection, CDC disease stage, and prior TB diagnosis. Due to potential collinearity between CD4 and CD8, we did not include pre-cART CD4 and pre-cART CD8 variables in the same model. The regression models were fitted using a backward stepwise selection process. Variables significant in the univariate model at $P < 0.10$ were chosen for inclusion in the multivariate model. Variables with $P < 0.05$ in the final multivariate model were considered statistically significant. Sensitivity analyses were performed by lagging CD8 counts for 6 months as well as measuring the effects of the changes in CD8 from pre-cART values on VF.

Ethics approval was obtained from institutional review boards at each of the participating clinical sites, the data management and analysis center, and the coordinating center. All data management and statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC) and STATA software version 12.1 (STATA Corp., College Station, TX).

3. Results

In total, 2475 patients from 19 sites in China, including Hong Kong SAR, India, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam were included in this analysis. Of the 2475 patients, 665 (27%) experienced VF in the first 4 years of cART (Table 1). Most patients were males (78.8%) with heterosexual HIV exposure (54.9%). More than half (64.2%) initiated cART with nucleoside reverse transcriptase inhibitors (NRTIs) and non-NRTI (NNRTI) combinations. The median CD8 count prior to cART initiation was 752 cells/μL (interquartile range [IQR] 480–1089). At the time of VF, the mean VL was 82,558 copies/mL and the median was 3500 copies/mL (IQR 786–42,100 copies/mL). Additionally, there were 196/665 patients (29%) with VL 400–1000 copies/mL, 209 (31%) with VL 1001–10,000 copies/mL, 160 (24%) with VL 10,001–100,000 copies/mL, and 100 (15%) with VL > 100,000 copies/mL. However, there was no increasing trend in the proportion of patients with CD8 elevation across these VL groups ($P = 0.357$).

Table 2 shows the Cox regression analysis for time to first VF in the first 4 years on cART. The overall rate of failure was 12.95 per 100 person-years. In the univariate analysis, variables that were significant at $P < 0.10$ were time-updated CD8 counts ($P < 0.001$), age ($P = 0.005$), mode of HIV exposure ($P < 0.001$), pre-cART CD4 count ($P < 0.001$), prior mono/dual therapy ($P < 0.001$), initial cART regimen ($P < 0.001$), CDC disease stage at cART initiation ($P < 0.001$), and prior tuberculosis diagnosis ($P < 0.001$). In the final multivariate model, factors significantly associated with greater hazards of VF were elevated CD8 of $\geq$ 1200 cells/μL after cART initiation versus CD8 < 1200 cells/μL (hazard ratio [HR] = 1.35, 95% confidence interval [CI] = 1.14–1.61; $P = 0.001$), injecting drug use compared with heterosexual HIV exposure (HR = 1.74, 95% CI = 1.19–2.54; $P = 0.005$), having prior mono/dual therapy compared to initiating with cART (HR = 2.43, 95% CI = 2.01–2.95; $P < 0.001$), and being on a protease inhibitor (PI)-based regimen (HR = 1.37, 95% CI = 1.12–1.67; $P = 0.002$) and other treatment combinations (HR = 1.60, 95% CI = 1.13–2.27; $P = 0.008$) compared with NRTI+NNRTI combinations. Variables that showed a protective effect for VF were older age groups of 31 to 40 years (HR = 0.74, 95% CI = 0.61–0.90; $P = 0.002$), 41 to 50 years (HR = 0.66, 95% CI = 0.53–0.83; $P < 0.001$), 51 years

Table 1
Patient characteristics.

	Total (N=) 2475	No VF (N=) 1810	VF (N=) 665	*P
Age, y				
Median age (IQR)	36 (30–43)	36 (31–43)	35 (29–42)	
≤30	649 (26.2)	450 (24.9)	199 (29.9)	0.059
31-40	1035 (41.8)	765 (42.3)	270 (40.6)	
41-50	519 (21.0)	395 (21.8)	124 (18.6)	
51+	272 (11.0)	200 (11.0)	72 (10.8)	
Sex				
Male	1951 (78.8)	1411 (78.0)	540 (81.2)	0.080
Female	524 (21.2)	399 (22.0)	125 (18.8)	
Mode of HIV exposure				
Heterosexual contact	1360 (54.9)	980 (54.1)	380 (57.1)	0.119
Homosexual contact	795 (32.1)	605 (33.4)	190 (28.6)	
Injecting drug use	109 (4.4)	75 (4.1)	34 (5.1)	
Other/unknown	211 (8.5)	150 (8.3)	61 (9.2)	
Pre-cART viral load (copies/mL)				
Median $\log_{10}$ VL (IQR)	4.88 (4.27–5.38)	4.88 (4.29–5.37)	4.89 (4.20–5.38)	
≤10,000	361 (14.6)	251 (13.9)	110 (16.5)	0.291
10,001–100,000	773 (31.2)	570 (31.5)	203 (30.5)	
>100,000	814 (32.9)	580 (32.0)	234 (35.2)	
Not tested	527 (21.3)	409 (22.6)	118 (17.7)	
Pre-cART CD4 (cells/μL)				
Median CD4 (IQR)	144 (44–244)	156 (51–247)	115 (32–222)	
≤50	667 (26.9)	451 (24.9)	216 (32.5)	<0.001
51-100	318 (12.8)	222 (12.3)	96 (14.4)	
101-200	599 (24.2)	441 (24.4)	158 (23.8)	
201+	889 (35.9)	694 (38.3)	195 (29.3)	
Not tested	2 (0.1)	2 (0.1)	0 (0.0)	
Pre-cART CD8 (cells/μL)				
Median CD8 (IQR)	752 (480–1089)	757 (487–1102)	739 (467–1054)	
≤600	906 (36.6)	658 (36.4)	248 (37.3)	0.617
601-1199	1083 (43.8)	788 (43.5)	295 (44.4)	
≥1200	486 (19.6)	364 (20.1)	122 (18.3)	
Prior mono/dual therapy				
No	2096 (84.7)	1635 (90.3)	461 (69.3)	<0.001
Yes	379 (15.3)	175 (9.7)	204 (30.7)	
Initial cART regimen				
NRTI+NNRTI	1590 (64.2)	1226 (67.7)	364 (54.7)	<0.001
NRTI+PI	783 (31.6)	523 (28.9)	260 (39.1)	
Other	102 (4.1)	61 (3.4)	41 (6.2)	
Hepatitis B coinfection				
Negative	1782 (72.0)	1306 (72.2)	476 (71.6)	0.300
Positive	213 (8.6)	149 (8.2)	64 (9.6)	
Not tested	480 (19.4)	355 (19.6)	125 (18.8)	
Hepatitis C coinfection				
Negative	1826 (73.8)	1334 (73.7)	492 (74.0)	>0.999
Positive	167 (6.7)	122 (6.7)	45 (6.8)	
Not tested	482 (19.5)	354 (19.6)	128 (19.2)	
CDC stage				
A	1392 (56.2)	1078 (59.6)	314 (47.2)	<0.001
B	237 (9.6)	176 (9.7)	61 (9.2)	
C	846 (34.2)	556 (30.7)	290 (43.6)	
Previous TB diagnosis				
No	2183 (88.2)	1625 (89.8)	558 (83.9)	<0.001
Yes	292 (11.8)	185 (10.2)	107 (16.1)	

cART=combination antiretroviral therapy, CDC=centers for disease control, HIV=human immunodeficiency virus, IQR=interquartile range, NNRTI=non-nucleoside reverse transcriptase inhibitor, NRTI=nucleoside reverse transcriptase inhibitor, PI=protease inhibitor, TB=tuberculosis, VF=virological failure.
* P-values are χ^2 test of proportions excluding "not tested" values.

and above (HR=0.71, 95% CI=0.54–0.94; P=0.017), compared with age ≤ 30 years, and pre-cART CD4 counts > 200 cells/μL (HR=0.68, 95% CI=0.55–0.83; P < 0.001) versus CD4 ≤ 50 cells/μL.

To determine whether elevated CD8 caused subsequent VF or whether the association seen in Table 2 was the result of CD8 levels increasing due to VF, we performed a sensitivity analysis by lagging CD8 counts for 6 months. The lagging meant that VF

Table 2

Time to virological failure.

Total	No. of patients	Follow up, y	No. of VF	Rate (/100 pys)	Univariate HR	95% CI	P	Multivariate HR	95% CI	P
	2475	5134	665	12.95						
Pre-cART CD8 (cells/μL)							0.898			
≤600	906	1932.61	248	12.83	1					
601–1199	1083	2204.13	295	13.38	1.03	(0.87, 1.23)	0.701			
≥1200	486	997.24	122	12.23	0.97	(0.78, 1.21)	0.796			
CD8 counts after cART initiation[*] (cells/μL)										
<1200	–	3744.41	429	11.46	1			1		
≥1200	–	1193.99	189	15.83	1.37	(1.15, 1.63)	<0.001	1.35	(1.14, 1.61)	0.001[†]
Unknown	–	195.58	47	24.03						
Age, y							0.005			0.001[†]
≤30	649	1312	199	15.17	1			1		
31–40	1035	2158.71	270	12.51	0.81	(0.67, 0.97)	0.024	0.74	(0.61, 0.90)	0.002[†]
41–50	519	1099.51	124	11.28	0.70	(0.56, 0.88)	0.002	0.66	(0.53, 0.83)	<0.001[†]
51+	272	563.61	72	12.77	0.75	(0.57, 0.99)	0.040	0.71	(0.54, 0.94)	0.017[†]
Sex										
Male	1951	4009.45	540	13.47	1			1		
Female	524	1124.53	125	11.12	0.97	(0.79, 1.19)	0.763	0.92	(0.74, 1.15)	0.488
Mode of HIV exposure							<0.001			0.006[†]
Heterosexual contact	1360	2884.78	380	13.17	1			1		
Homosexual contact	795	1656.65	190	11.47	0.71	(0.58, 0.87)	0.001	0.83	(0.67, 1.03)	0.091
Injecting drug use	109	167.32	34	20.32	1.47	(1.01, 2.15)	0.042	1.74	(1.19, 2.54)	0.005[†]
Other/unknown	211	425.22	61	14.35	0.90	(0.67, 1.20)	0.476	0.99	(0.74, 1.33)	0.961
Pre-cART viral load (copies/mL)							0.511			0.723
≤10,000	361	729.83	110	15.07	1			1		
10,001–100,000	773	1659.07	203	12.24	0.79	(0.63, 1.00)	0.053	0.92	(0.72, 1.17)	0.497
>100,000	814	1639.52	234	14.27	0.88	(0.70, 1.11)	0.275	0.98	(0.76, 1.26)	0.868
Not tested	527	1105.56	118	10.67						
Pre-cART CD4 (cells/μL)							<0.001			<0.001[†]
≤50	667	1310.91	216	16.48	1			1		
51–100	318	663.21	96	14.48	0.89	(0.70, 1.14)	0.353	0.91	(0.71, 1.17)	0.462
101–200	599	1268.87	158	12.45	0.78	(0.63, 0.96)	0.019	0.84	(0.68, 1.03)	0.100
>200	889	1884.67	195	10.35	0.64	(0.52, 0.78)	<0.001	0.68	(0.55, 0.83)	<0.001[†]
Not tested	2	6.32	0	0.00						
Prior mono/dual therapy										
No	2096	4434.6	461	10.40	1			1		
Yes	379	699.38	204	29.17	2.7	(2.27, 3.22)	<0.001	2.43	(2.01, 2.95)	<0.001[†]
Initial cART Regimen							<0.001			0.002[†]
NRTI+NNRTI	1590	3259.55	364	11.17	1			1		
NRTI+PI	783	1676.38	260	15.51	1.85	(1.53, 2.25)	<0.001	1.37	(1.12, 1.67)	0.002[†]
Other	102	198.06	41	20.70	2.33	(1.66, 3.28)	<0.001	1.60	(1.13, 2.27)	0.008[†]
Hepatitis B coinfection										
Negative	1782	3693.95	476	12.89	1			1		
Positive	213	441.25	64	14.50	1.09	(0.83, 1.42)	0.535	1.06	(0.81, 1.39)	0.657
Not tested	480	998.78	125	12.52						
Hepatitis C coinfection										
Negative	1826	3846.39	492	12.79	1			1		
Positive	167	305.21	45	14.74	1.21	(0.88, 1.65)	0.239	1.11	(0.78, 1.56)	0.567
Not tested	482	982.38	128	13.03						
CDC Stage							<0.001			0.352
A	1392	2849.29	314	11.02	1			1		
B	237	570.27	61	10.70	1.09	(0.81, 1.46)	0.580	0.91	(0.67, 1.22)	0.521
C	846	1714.42	290	16.92	1.49	(1.26, 1.76)	<0.001	1.11	(0.90, 1.35)	0.326
Previous TB diagnosis										
No	2183	4542.4	558	12.28	1			1		
Yes	292	591.58	107	18.09	1.47	(1.18, 1.82)	<0.001	1.21	(0.97, 1.52)	0.091

Global P-values for age, pretreatment CD8, CD4, and viral load are tests for trend. Other P-values are tests for heterogeneity excluding not tested values.

Non-significant factors were presented in the multivariate model adjusted for significant predictors, with the exception of pre-cART CD8 due to potential collinearity with the pre-cART CD4 variable.

cART = combination antiretroviral therapy, CDC = Centers for Disease Control, CI = confidence interval, HR = hazard ratio, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, pys = person-years, TB = tuberculosis, VF = virological failure.

[*] Time-updated covariate where each patient can contribute follow-up time in more than one category.

[†] P-values represent significant covariates in the final model.

could not be associated with CD8 measurements taken less than 6 months prior to the failure date, thus minimizing the possibility of capturing the increase in CD8 as a response to VF. Table 3(i) shows the univariate and the adjusted HRs for the lagged CD8 variable. There was no evidence to suggest that having an elevated CD8 count at least 6 months prior was associated with VF in either the univariate (HR = 1.07, 95% CI = 0.90–1.28; P = 0.420) or the adjusted (HR = 1.08, 95% CI = 0.91–1.29; P = 0.389) model. This indicates that the relationship between CD8 and VF observed in Table 2 was possibly due to the CD8 cells responding to the increase in VL rather than causing the VL increase itself. When absolute CD8 count was replaced by changes in CD8 from pre-cART values (Table 3[ii]), the increase in CD8 was borderline significant in the univariate model (HR = 1.18, 95% CI = 1.00–1.40; P = 0.056), but was not associated with VF in the adjusted model (HR = 1.01, 95% CI = 0.84–1.22; P = 0.909).

4. Discussion

In this study, we found that the most recent elevated CD8 count after cART was significantly associated with VF, but there was no association between elevated CD8 counts measured at least 6 months prior and the subsequent virological outcome. This suggests that the CD8 levels may be considered not as a predicting factor of VF but a potential indicator for VF in HIV-infected patients after starting cART.

The relationship between CD8 response and HIV outcomes is not fully understood. CD8 response can be measured through HIV-specific CD8, CD8 activation, and total CD8 counts.[15] Among them, HIV-specific CD8 have an important role in the control of viremia,[18] increasing in response to ongoing HIV replication [19] and have been associated with poor outcomes.[20,21] Activation of CD8 subsets may accelerate immune dysfunction. The expression of CD38 on CD8 has been linked to HIV disease progression.[22–24] One cross-sectional study showed that elevated levels of CD8 CD38 were found in HIV-infected patients with VF after cART.[14] However, it lacked sufficient sensitivity and specificity to replace viral load testing in assessing the efficacy of ART.

Additionally, some studies have demonstrated elevation of total CD8 counts in untreated HIV infection [25–27] and showed significant associations between elevated baseline total CD8 counts and progression to AIDS.[28,29] Moreover, a retrospective cohort study recently reported that an increase in CD8 counts from cART initiation was significantly associated with treatment failure.[15] This suggests that elevated CD8 counts after cART

may be useful as a predictor of VF. Krantz et al[15] explained these associations by the adverse effects of a hyperdynamic immune response or low-level viremia associated with increased risk of VF.

However, in our study, the relationship between CD8 counts and VF may be due to the CD8 cells responding to, rather than causing, the VL increase. Possible explanations for these findings include the overstimulation of CD8 immune responses against increased circulating HIV or subsequent CD8 compensation, known as "blind T-cell homeostasis," with decreased CD4 in VF.[30] Leonard et al[30] hypothesized that in T cell loss, both CD4 and CD8 will be produced until the absolute T-cell count is normal. This suggests that the selective loss of CD4 will induce the production of both CD4 and CD8 with the result that T-cell counts will return to normal, but there would be a persistent CD8 elevation and CD4 decrease.[30]

On the other hand, these findings suggest that using CD8 levels may be a potential indicator for VF in HIV-infected patients after starting cART. If CD8 levels could be used as a marker of VF, they could supplement more expensive and technologically complex VL testing. In addition, as current flow cytometer access is greater in resource-limited settings than PCR, this could facilitate more active monitoring in patient care settings. Further studies would be needed to determine the clinical and economic outcome of using CD8 levels as an indicator for VF after cART. Also, because another situation to suspect VF is CD4 count drop or failure to increase, comparing CD4 with CD8 values in terms of association with VF could be needed.

Our study limitations are primarily related to the potential for bias in our patient sampling and data. Participating cohort study sites are primarily tertiary-care referral centers, which could impact the acuity of patients as well as the level of laboratory monitoring conducted. In addition, not all TAHOD sites performed routine CD8 or VL testing, and levels of data completeness varied by both site and country. Our findings should be interpreted in these contexts, and may not necessarily apply to the broader patient populations in the Asia-Pacific. Secondly, we defined elevated CD8 as ≥ 1200 cells/μL. Although this value is the upper limit of normal, according to clinical laboratory reference values, it is based on values from Western populations.

In conclusion, our study indicates that the observed relationship between CD8 counts and VF in our cohort may have been due to CD8 cell responses to increases in VL rather than causing the increases themselves. The potential utility of CD8 levels in monitoring for VF could make it an adjunct to VL testing in the future.

Table 3

Sensitivity analyses: (i) CD8 counts lagged for 6 months, and (ii) CD8 counts replaced by changes in CD8 from pre-cART values.

	Univariate			Multivariate*		
	HR	95% CI	P	HR	95% CI	P
(i) CD8 counts lagged for 6 months† (cells/μL)						
<1200	1			1		
≥1200	1.07	(0.90, 1.28)	0.420	1.08	(0.91, 1.29)	0.389
(ii) Changes in CD8 from pre-cART values†						
Decrease or stay the same	1			1		
Increase	1.18	(1.00, 1.40)	0.056	1.01	(0.84, 1.22)	0.909
Unknown						

cART = combination antiretroviral therapy, HR = hazard ratio, CI = confidence interval.
* Adjusted for other significant predictors.
† Time-updated covariates.

References

[1] Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. JAMA 2006;296:827–43.

[2] Abaasa AM, Todd J, Ekoru K, et al. Good adherence to HAART and improved survival in a community HIV/AIDS treatment and care programme: the experience of The AIDS Support Organization (TASO), Kampala, Uganda. BMC Health Serv Res 2008;8:241.

[3] Sabin CA, Smith CJ, et al. Collaboration of Observational HIVERES-GResponse to combination antiretroviral therapy: variation by age. AIDS 2008;22:1463–73.

[4] Le Moing V, Chene G, Carrieri MP, et al. Predictors of virological rebound in HIV-1-infected patients initiating a protease inhibitor-containing regimen. AIDS 2002;16:21–9.

[5] Mocroft A, Ruiz L, Reiss P, et al. Virological rebound after suppression on highly active antiretroviral therapy. AIDS 2003;17:1741–51.

[6] Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. Lancet 1999;353:863–8.

[7] Phillips AN, Staszewski S, Weber R, et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. JAMA 2001;286:2560–7.

[8] Deeks SG, Hecht FM, Swanson M, et al. HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: response to both initial and salvage therapy. AIDS 1999;13:F35–43.

[9] Hartzell JD, Spooner K, Howard R, et al. Race and mental health diagnosis are risk factors for highly active antiretroviral therapy failure in a military cohort despite equal access to care. J Acquir Immune Defic Syndr 2007;44:411–6.

[10] Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. Ann Intern Med 1999;131:81–7.

[11] Mocroft A, Gill MJ, Davidson W, et al. Predictors of a viral response and subsequent virological treatment failure in patients with HIV starting a protease inhibitor. AIDS 1998;12:2161–7.

[12] Paredes R, Mocroft A, Kirk O, et al. Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study. Arch Intern Med 2000;160:1123–32.

[13] Weintrob AC, Grandits GA, Agan BK, et al. Virologic response differences between African Americans and European Americans initiating highly active antiretroviral therapy with equal access to care. J Acquir Immune Defic Syndr 2009;52:574–80.

[14] Steel A, John L, Shamji MH, et al. CD38 expression on CD8 T cells has a weak association with CD4 T-cell recovery and is a poor marker of viral replication in HIV-1-infected patients on antiretroviral therapy. HIV Med 2008;9:118–25.

[15] Krantz EM, Hullsiek KH, Okulicz JF, et al. Elevated CD8 counts during HAART are associated with HIV virologic treatment failure. J Acquir Immune Defic Syndr 2011;57:396–403.

[16] Zhou J, Kumarasamy N, Ditangco R, et al. The TREAT Asia HIV Observational Database: baseline and retrospective data. J Acquir Immune Defic Syndr 2005;38:174–9.

[17] Wolfe WH, Miner JC, Michalek JE. Immunological parameters in current and former US Air Force personnel. Vaccine 1993;11:545–7.

[18] Ogg GS, Jin X, Bonhoeffer S, et al. Quantitation of HIV-1-specific cytotoxic T lymphocytes and plasma load of viral RNA. Science 1998;279:2103–6.

[19] Keoshkerian E, Ashton LJ, Smith DG, et al. Effector HIV-specific cytotoxic T-lymphocyte activity in long-term nonprogressors: associations with viral replication and progression. J Med Virol 2003;71:483–91.

[20] Macias J, Leal M, Delgado J, et al. Usefulness of route of transmission, absolute CD8+ T-cell counts, and levels of serum tumor necrosis factor alpha as predictors of survival of HIV-1-infected patients with very low CD4+T-cell counts. Eur J Clin Microbiol Infect Dis 2001;20:253–9.

[21] Bonnet F, Thiebaut R, Chene G, et al. Determinants of clinical progression in antiretroviral-naive HIV-infected patients starting highly active antiretroviral therapy. Aquitaine Cohort, France, 1996-2002. HIV Med 2005;6:198–205.

[22] Bofill M, Mocroft A, Lipman M, et al. Increased numbers of primed activated CD8+CD38+CD45RO+ T cells predict the decline of CD4+ T cells in HIV-1-infected patients. AIDS 1996;10:827–34.

[23] Giorgi JV, Liu Z, Hultin LE, et al. Elevated levels of CD38+ CD8+ T cells in HIV infection add to the prognostic value of low CD4+ T cell levels: results of 6 years of follow-up. The Los Angeles Center, Multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr 1993;6: 904–12.

[24] Liu Z, Cumberland WG, Hultin LE, et al. Elevated CD38 antigen expression on CD8+ T cells is a stronger marker for the risk of chronic HIV disease progression to AIDS and death in the Multicenter AIDS Cohort Study than CD4+ cell count, soluble immune activation markers, or combinations of HLA-DR and CD38 expression. J Acquir Immune Defic Syndr Hum Retrovirol 1997;16:83–92.

[25] Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: causes and consequences. J Pathol 2008;214:231–41.

[26] Hazenberg MD, Otto SA, van Benthem BH, et al. Persistent immune activation in HIV-1 infection is associated with progression to AIDS. AIDS 2003;17:1881–8.

[27] Appay V, Almeida JR, Sauce D, et al. Accelerated immune senescence and HIV-1 infection. Exp Gerontol 2007;42:432–7.

[28] Anderson RE, Shiboski SC, Royce R, et al. CD8+ T lymphocytes and progression to AIDS in HIV-infected men: some observations. AIDS 1991;5:213–5.

[29] Phillips AN, Sabin CA, Elford J, et al. CD8 lymphocyte counts and serum immunoglobulin A levels early in HIV infection as predictors of CD4 lymphocyte depletion during 8 years of follow-up. AIDS 1993;7:975–80.

[30] Adleman LM, Wofsy D. T-cell homeostasis: implications in HIV infection. J Acquir Immune Defic Syndr 1993;6:144–52.