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Decay of Soluble CD30 and HIV-1 Plasma Viral Load during Early Highly Active Antiretroviral Therapy: A Short-Term Longitudinal Study

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Abstract

Background: Soluble CD30 (sCD30) has been suggested as a useful marker for estimating medium to long term viral suppression during antiretroviral therapy. High titres are also associated with hepatitis B and C virus (HBV/HCV) infections. It is unclear if sCD30 can be used to determine short term antiretroviral responses in individuals with only HIV infection and those co-infected with HBV or HCV.

Method: Plasma samples for baseline, days 7 and 28 from 18 individuals co-infected with HIV and HBV, 5 having anti-HCV, and controls with only HIV infection were obtained from a cohort of 138 HIV infected patients with baseline $CD4^+$ counts of ≤ 250 cells/μl. Clinical and demographic data was obtained from patient folders and sCD30 titres determined using the Human sCD30 ELISA (Bender MedSystems GmbH, Austria). HIV-1 plasma viral load was done with the COBAS Amplicor Monitor v1.5 tests (Roche Diagnostics).

Results: HIV-1 plasma viral loads differed significantly between the baselines, day 7 and day 28 plasma samples (Krystal Wallis H test, $p < 0.005$) but such a relationship did not exist for sCD30 titres. There was a positive but insignificant correlation between the two HIV-1 plasma viral load and sCD30 titres for all the three time points. sCD30 titres did not decline with any unique patterns for individuals infected with HIV infection with or without a particular kind of HBV infection, or with anti-HCV. There was a significant correlation between baseline $CD4^+$ and baseline sCD30 for patients with only HIV infection (Spearman's rho = 578, $p = 0.039$), but not those with HIV and HBV coinfection (Spearman's rho = 379, $p = 0.098$).

Conclusion: The results of this study suggest that it is unlikely that early sCD30 decline will significant correlate with HIV-1 plasma viral load decline during the first 28 days of ART.

Keywords: Soluble CD30; HIV-1; Plasma viral load, Short-term; Antiretroviral therapy

Background

The pathogenesis of human immunodeficiency virus type 1 (HIV-1) has been associated with changes in chemokine and cytokine profiles and infections have been associated with a shift from TH1 to TH2 cytokine profiles [1-3]. The tumour necrosis factor (TNF) receptor super family includes CD30, which is expressed on $CD4^+$ and CD8 T cell clones and produces TH2 cytokines [4,5]. The soluble form of this molecule, sCD30, is found in culture supernatants and in circulation [5,6]. Also, the activation of TH2-like cells is related to increased sCD30 levels [5].

sCD30 has been suggested as an independent predictor determining progression to AIDS [7], and has been shown to have a positive correlation with HIV-1 plasma viral load (HIV-1 pVL) during antiretroviral therapy (ART) in studies with both small and large sample sizes [8-10]. Since sCD30 decreases with decreasing HIV-1 pVL, it may be useful as an indicator for virological success during ART [8,10]. It is also known that early HIV-1 decay within one month of therapy can be predictive of long term outcomes [11-13]. However, it is unclear if sCD30 decline during the early stage of ART will be useful for predicting HIV-1 pVL suppression during this early phase of ART where immune reconstitution disease (IRD) and co-infections may be present [14].

In settings where hepatitis C virus (HCV) and / or hepatitis B virus (HBV) infections are common, the use of sCD30 to predict HIV-1 plasma viral load may be complicated as individuals with active HBV replication are more likely to have higher sCD30 levels than those who are HBsAg carriers [15]. Furthermore, in the treatment of chronic HCV infections, sCD30 has been reported to decrease with successful therapy [16,17]. Therefore during ART when HIV-1 pVL is being suppressed in HIV and HBV and/or HCV co-infection, high levels of sCD30 may persist from the replication of HBV and HCV.

With the high numbers of individuals being initiated on ART in developing countries where Enzyme Linked Immunosorbent assays (ELISA) are more common than HIV-1 pVL assays, it may be useful to use simple virological or immunological indicators to estimate successful ART. This will be especially beneficial since HIV-1 pVL decay after 6-7 days is useful in predicting long term outcomes [11,13], and long term follow-up may be problematic in developing countries. It is also unclear how the presence of sCD30 during short term ART may be affected by the presence or absence of other infecting agents.

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In this study the trends in sCD30 levels were observed over 28 days for individuals with only HIV infection as compared to those with HIV and HBV co-infection or having anti-HCV from a previous study [18]. The primary goal was to ascertain the possible usefulness of sCD30 as an indicator for successful suppression of HIV-1 pVL during early ART. To our knowledge, no such study has ever been performed to address this issue.

Results

Hepatitis B and C markers

Of the 138 HIV infected patients screened for HBV and HCV markers from the previous study, 18 (13.0%) also had HBsAg and 5 (3.6%) anti-HCV. No patient was found to have both HBsAg and anti-HCV, but for those with HBV infection 10 (55.6%) had HBeAg while 8 (44.4%) had anti-HBe (Table 1). None of the 18 HIV infected patients co-infected with HBV had anti-HBc IgM. The details of the HIV infected patients with HBV co-infection or having anti-HCV, and the matched patients with only HIV are detailed in Table 1. The median/mean baseline (BL) $CD4^+$ (IQR) was 117.5 / 118.30 (132) for all patients.

HIV-1 quantitation

A total of 45, 30 and 22 HIV-1 pVL quantification results were available for baseline, day 7 and day 28 plasma samples respectively. HIV-1 pVL was done for all available BL and follow-up plasma samples of all cases and controls except KAF200 (Table 1). The mean (range) were 5.39 (3.52 to 6.45 log), 3.48 (2.60 to 5.24 log) and 2.76 (2.60 to 3.65 log) for BL, day 7 and day 28 samples respectively. A Wilcoxon Signed Ranks test showed that there was a statistically significant decline between BL and day 7 HIV-1 pVL (mean rank = 0.00), Z = -4.782, p = 000. A similar result was shown when comparing BL and day 28 HIV-1 pVL (mean rank = 0.00), Z = -4.107, p = 000.

Soluble CD30 analysis

A total of 30, 17 and 16 sCD30 quantitation results had CVs ≤ 15% for the BL, day 7 and day 28 plasma samples respectively. The mean (range) were 48.6 ng/ml (7.0 to 144.7 ng/ml), 45.8 ng/ml (14.8 to 107.3 ng/ml) and 48.8 ng/ml (12.1 to122.8 ng/ml) for baseline, day 7 and day 28 samples respectively. A Wilcoxon Signed Ranks test did not show a statistically significant difference between BL and day 7 sCD30 titres (mean rank = 6.38), Z = -1.695, p = 090. The result was not different when comparing BL and day 28 sCD30 titres (mean rank = 5.83), Z = -0.314, p = 754.

The presence or absence of HBV co-infection or anti-HCV in patients, the infectiousness of patients as determined by the presence or absence of HBeAg or anti-HBe, did not result in any statistically significant differences in sCD30 titres (Table 2). Even though positive Scatter plots with positive correlations were observed between BL HIV-1 pVL and BL sCD30 (r^2 = 0.017), day 7 HIV-1 pVL and day 7 sCD30 (r^2 = 0.132), and day 28 HIV-1 pVL and day sCD30 (r^2 = 0.052), these relationships were not statistically significant (Figure 1). Furthermore, there were not clear patterns of sCD30 decline even with significantly declining HIV-1 pVL within the first 28 days of ART (Figures 2 and 3).

There was no significant correlation between BL $CD4^+$ and BL sCD30 for all patients with available results (n = 30, Spearman's rho = .307, p = 0.098), and those with only HIV and HBV co-infection (n = 13, Spearman's rho = 379, p = 0.201). However, there was a significant correlation between BL $CD4^+$ and BL sCD30 for patients with only HIV infection n = 13, Spearman's rho = 578, p = 0.039).

ARVs™	Visits	Co-infected						HIV infection only				
		KAF	Hep	Gender	Age	Stage	$CD4^+$	KAF	Gender	Age	Stage	$CD4^+$
d4T + 3TC + NVP	0, 7, 28	**151**	B^e	F	41	3	24	**075**	F	32	3	14
d4T + 3TC + NVP	0, 7	**083**	B	F	43	3	180	**124**	F	26	4	138
d4T + 3TC + NVP	0, 7	**092**	B	F	35	3	233	**023**	F	35	3	175
d4T + 3TC + NVP	0, -, 28	**028**	B^e	F	35	3	15	**130**	F	35	4	32
d4T + 3TC + EFV	0, 7, 28	**090**	B	M	34	3	216	**033**	M	50	3	132
CBV + NVP	0, 7, 28	**056**	B^e	F	27	3	137	**081**	F	31	3	190
CBV + NVP	0, 7, 28	**071**	B	F	26	2	224	**078**	F	32	3	250
CBV + NVP	0, -, 28	**120**	B^e	M	39	4	39	**104**	F	28	3	56
CBV + NVP	0, 7	**026**	B	F	38	3	124	**149**	F	28	2	238
CBV + NVP	0, 7	**115**	B^e	F	39	3	55	**074**	F	30	4	1
CBV + EFV	0, 7, 28	**031**	B	F	54	3	203	**137**	M	52	4	157
CBV + EFV	0, 7, 28	**061**	B^e	M	39	3	81	**010**	M	45	3	94
CBV + EFV	0, 7, 28	**077**	B^e	M	43	3	136	**064**	M	46	3	179
CBV + EFV	0, -, 28	**041**	B^e	F	34	3	151	**121**	M	44	3	101
-	0	**156**	B^e	F	26	2	168	**037**	M	41	3	232
-	0	**011**	B	M	34	3	1	**095**	M	56	3	90
-	0	**109**	B^e	M	33	3	44	**019**	F	39	3	17
-	0	**200**	B	M	49	3	195	**133**	F	36	3	118
d4T + 3TC + EFV	0, 7, 28	**034**	C	F	44	3	94	**044**	M	42	3	50
d4T + 3TC + EFV	0, 7	**005**	C	M	39	3	117	**069**	F	48	3	116
CBV + NVP	0, 7	**079**	C	F	40	3	81	**059**	F	38	3	27
CBV + EFV	0, 7	**045#**	C	F	45	3	250	**072**	F	44	3	178
-	0	**066**	C	F	35	3	86	**024**	F	37	3	27

KAF, patients ID; Cases, individuals infected with HIV and HBV or having anti-HCV; Controls, those infected with only HIV; Stage, WHO clinical stage; ARVs, antiretroviral drugs used for HAART; Visits, the number of plasma samples available for HIV-1 pVL testing (0 = pre-HAART, 7 and 28 = 7 and 28 days after HAART; Hep, hepatitis B or C status; B, co-infection with HBV; B^e, presence of HBeAg; C, having anti-HCV; CD4 time code, the time (months) between the dates of the last $CD4^+$ determination and initiating HAART.

Table 1: Immunological, demographic and clinical details patients.

Groups*	Mean Rank	χ^2 (2)	p
Baseline			
HIV only (n = 13)	12.73		
HIV and HBV (n = 13)	17.15	2.424 (2)	.298
HIV and anti-HCV (n = 4)	19.13		
HIV only (n = 13)	12.73		
eAg (n = 8)	15.38	3.273 (3)	.351
anti-HBe (n = 5)	20.00		
anti-HCV (n = 4)	19.13		
Day 7			
HIV only (n = 8)	9.69		
HIV and HBV (n = 7)	7.36	1.597 (2)	.450
HIV and anti-HCV (n = 2)	12.00		
HIV only (n = 8)	9.69		
eAg (n = 3)	4.00	3.920 (3)	.270
anti-HBe (n = 4)	9.88		
anti-HCV (n = 2)	12.00		
Day 28			
HIV only (n = 8)	7.50		
HIV and HBV (n = 7)	8.71	2.231 (2)	.328
HIV and anti-HCV (n = 1)	15.00		
HIV only (n = 8)	7.50		
eAg (n = 5)	10.00	3.507 (3)	.320
anti-HBe (n = 2)	5.00		
anti-HCV (n = 1)	15.00		

*HIV only, with HIV infection alone; HBV and anti-HCV, HIV and HBV infection or with anti-HCV; HIV and HBV, HIV with HBV co-infection; anti-HCV, HIV infection with anti-HCV; HBeAg, HIV and HBV infections with HBeAg; Anti-HBe, HIV and HBV infections with anti-HBe.

Table 2: sCD30 levels in HIV infected patients with and without HBV infection or anti-HCV.

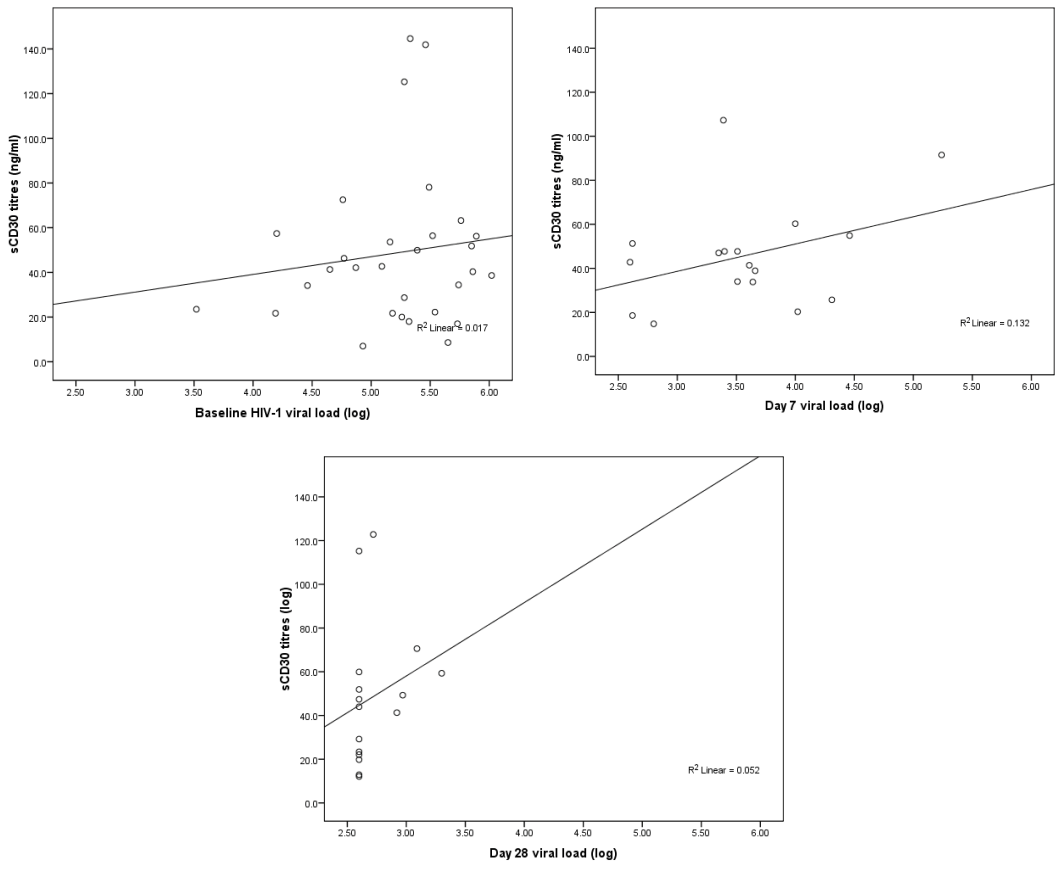

Figure 1: Scatter diagrams showing the correlation between sCD30 titres and HIV-1 plasma viral load. (**Top Left**) Correlation between baseline samples (p = 0.630, N = 30); (**Top Right**) Correlation between day 7 samples (p = 650, N = 17); (**Bottom**) Correlation day 28 samples (p = 069, N = 16).

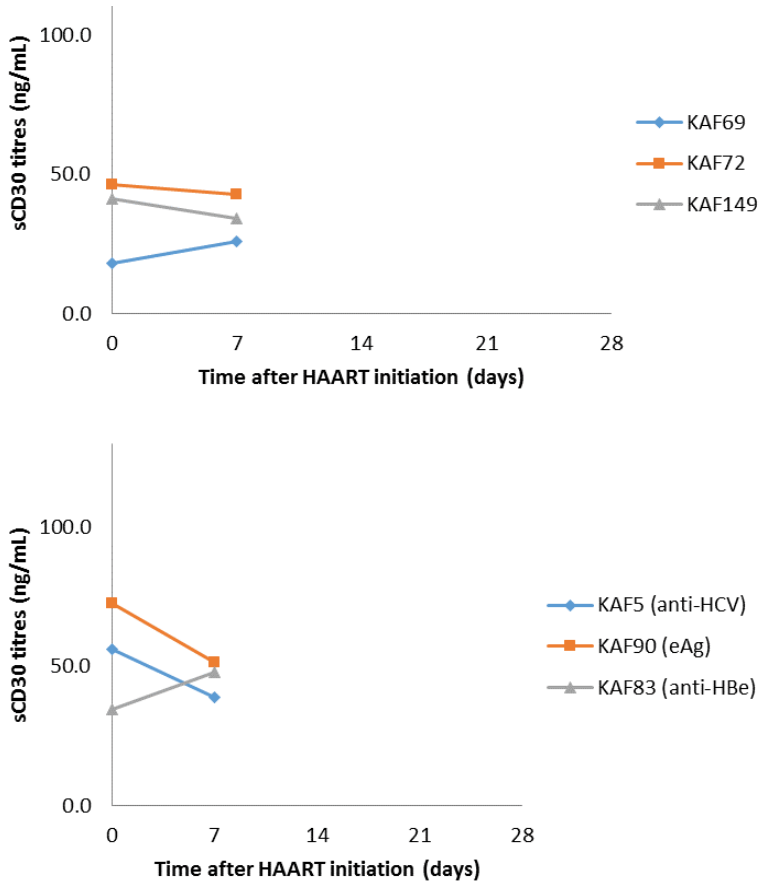

Figure 2: Changes in sCD30 titres during the first 7 days after initiation of ART. (**Top**) Changes during the first 7 days in patients with only HIV infection; (**Bottom**) Changes during the first 7 days in patients with HBV co-infection with HBeAg (eAg) or anti-HBe, and anti-HCV.

Discussion

It has been shown that sCD30 levels are higher in HIV drug naïve individuals than in those on ART, and to have a strong positive correlation between sCD30 and HIV-1 pVL has been observed after medium to long term ART [8,10]. Also, active and chronic HBV infections and HCV related diseases have been associated with elevated sCD30 [15,19]. Therefore it was hypothesized that the TH2→TH1 environment that may be created by ART may be distorted because of the presence of HBV or HCV co-infection. Thus, a drastic decrease in HIV-1 pVL should correspond to a corresponding decrease in sCD30 in individuals with only HIV infections. On the other hand, the co-infection with HBV or the presence of anti-HCV which may reflect co-infection, will maintain elevated sCD30 levels even after a decline in HIV-1 pVL.

The observed results especially showing the patterns of change in sCD30 even after a decline in HIV-1 pVL for all patients does not suggest that sCD30 will be useful for estimating success in suppressing HIV-1 pVL during early ART. One of the most likely explanations for the changes in the sCD30 titres over the first 28 days of ART may be the presence of IRD since during early ART there is activation of some opportunistic infections [20]. It must be noted that the decline patterns of both HIV mono-infected and co-infected individuals did not suggest any influence by the HBV. However, the significant correlation between HIV infected individuals without HBV or HCV co-infection and BL $CD4^+$ seems to suggest that the presence of HBV may play a role in determining BL levels of sCD30 which diminishes during ART. Since the presence of HBeAg has been shown to result in more severe immune suppression in the patients used in this study [18], it may be responsible for the lack of correlation between BL sCD30 and BL CD4+ in the HIV and HBV co-infected patients.

The results of this study therefore suggest that even in HIV infected individuals without HBV or possible HCV co-infections; there was no clear pattern of the sCD30 decline during ART while HIV-1 pVL declined significantly especially after 6-7 days of ART which is critical in determining long term outcomes [11,13]. The fact that no specific group or patients based on the nature and type of infection had differences in sCD30 titres even when considering only BL plasma samples suggests that IRDs are strongly responsible for the observed differences. However, this may only be prominent in individuals who had only HIV infection which reflected in a significant and positive correlation between BL $CD4^+$ and sCD30. Thus, in these patients, the titres of sCD30 found in plasma were higher in those with higher $CD4^+$ counts. This is further supported by the low levels of $CD4^+$ counts of patients generally initiating ART. The phenomenon where TH1 / TH2 cytokine profiles are modulated by opportunistic infections (OIs) in

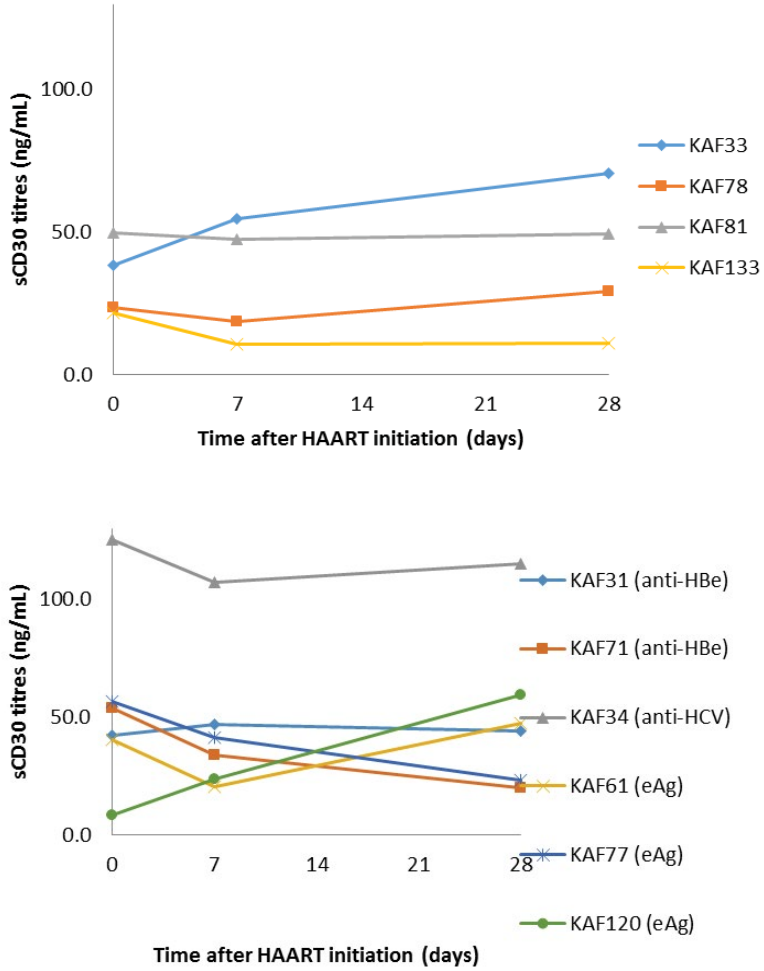

Figure 3: Changes during the first 28 days in patients with only HIV infection; (**Top**) Changes during the first 28 days in patients with only HIV infection; (**Bottom**) Changes during the first 28 days in patients with HBV co-infection with HBeAg (eAg) or anti-HBe, and anti-HCV.

HIV infection has been confirmed [21]. It is therefore possible that with higher $CD4^+$ counts at BL, the decline of HIV-1 pVL will have a positive correlation with sCD30 decline.

The use of sCD30 as a marker for early responses to ART will therefore be problematic and will not correspond to HIV-1 pVL decay. This may be due to the confounders which this study may not have addressed. In some instances decline of sCD30 was gradual and consistent suggesting that the results may not have been affected by the half-life of sCD30. It was essential that a rigid criterion for accepting variations between sCD30 runs was established. This created some gaps in the data used for analysis but results from similar studies with both small and large sample sizes have shown similar results [8,10].

Conclusion

Although the decline in the numbers of follow-up samples is a notable limitation of this study, the data trends and other studies strongly suggest that in HIV infected individuals with or without HBV co-infection or having anti-HCV, sCD30 decline during early ART does not reflect plasma HIV-1 viral load suppression.

Methods

Patient population and blood processing

The study was performed at the Fever's Unit of the Korle Bu Teaching Hospital (FU), Accra, Ghana. Treatment naïve HIV-infected persons with a baseline CD4 count ≤ 250 cells/µl with and without HBV infection and the presence of anti-HCV and were about to initiate ART were eligible. The study population was obtained from a cross-section of 138 individuals who were enrolled from a previous study [18]. Blood samples were obtained at BL, day 7 and 28 after ART. The study was approved by the University of Ghana Medical School Ethics and Protocol Review Committee and informed consent was obtained from patients before being enrolled in the study.

Whole blood from patients was obtained using vacutainer K2 EDTA tubes and samples transported to the laboratory on ice packs or kept at +2 to +8°C. Blood was centrifuged within 6 hours after collection at 4500 RPM for 20 minutes using the EBA 20 table-top centrifuge (Hettich Zentrifugen, Tuttlingen, Germany) and plasma kept in aliquots of approximately 600 µl at -85°C during long term storage. Clinical assessments including $CD4^+$ count determination and HIV

disease staging were performed before study entry as part of standard routine clinical procedures at the FU. Clinical data was obtained from patient folders after initiation of therapy. The four drug regimens being used were d4T, 3TC and EFV or NVP, and CBV (d4T and 3TC) with EFV or NVP. After initial screening for HBsAg and anti-HCV, matched individuals for all HIV patients with HBV co-infection or with anti-HCV were chosen based on a baseline CD4+ > or < 100 cells/µl and the type of ARV regimen.

Hepatitis B viral markers

Plasma from BL samples were screened for HBsAg using a third generation ELISA, Surase B 96 (TMB), General Biologicals Corp, Hsin Chu, Taiwan, and the Core HBsAg rapid test, Core Diagnostics, Birmingham, UK. All HBsAg positives were also screened for HBeAg / anti-HBe and anti-HBc IgM (antibodies to hepatitis B core antigen) with the EASE BN-96 (TMB) and ANTICORASE MB-96 (TMB) kits respectively (General Biologicals, Taiwan). Hepatitis C antibodies (anti-HCV) were detected with SP-Nanbase C-96, also from General Biologicals Corporation, Taiwan, and the Foresight HCV Antibody EIA (ACON Laboratories Inc.), was used for supplemental testing.

HIV-1 RNA quantitation

HIV-1 pVL determination was done with the COBAS Amplicor Monitor v1.5 tests and the COBAS Amplicor analyzer (Roche Diagnostics GmbH, Mannheim, Germany). HIV-1 RNA levels were mainly determined in duplicates for all available baseline, day 7 and day 28 plasma samples to reduce errors inherent within the Amplicor Monitor v1.5 assay. Since the lower limits of the standard monitor assay was 400 copies/ml any viral load value < 400 copies/ml was considered as 400 copies/ml. To ensure that marginal differences did not affect viral load analysis, all plasma samples were frozen in aliquots to avoid multiple freeze-thaws, and new frozen plasma vials at -85°C were mainly used in determining viral loads.

Soluble CD30 quantitation

Soluble CD30 (sCD30) was detected in plasma using the Human sCD30 ELISA (Bender MedSystems GmbH, Austria) for all available baseline, day 7 and day 28 plasma samples for co-infected individuals and their matched controls according to manufacturer's instructions. Tests were performed in duplicate with 100 µl of diluted standards and the same volume of sample diluent added to blank wells. The plates was then read at 450 nm using the MULTISKAN Microplate reader. The Auditable Data Analysis and Management System for ELISA (ADAMSEL-v1.1) were used to fit the Human sCD30 concentration standard curve and to estimate sample concentrations. Some samples that had duplicates with CV > 15% were re-run in singletons, and the CV calculated between that sample and the previous two duplicate concentrations. The two with the least CV ≤ 15% were accepted as the concentration of sCD30 for that sample. All duplicates with CVs of > 15% and for which further testing could not be done were excluded from the final analysis.

Analysis of data

The Krustal Wallis H test was used to determine sCD30 titre differences in HIV-1 infected patients alone, those with HBV co-infection, anti-HCV and HBeAg / anti-HBe profiles. Scatter plots were used to examine the correlation between sCD30 titres and plasma HIV-1 viral load at specific time points and the Kendall's tau_b non-parametric test used to estimate the significance of the correlation. Finally, the Wilcoxon Signed Ranks Test was used to perform a pairwise comparison between baseline, day 7 and day 28 HIV-1 plasma viral loads and sCD30 titres. The SPSS Version 17 software (SPSS Inc., Chicago, Illinois) for statistical analysis.

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