Decreased monocyte activation with daily acyclovir use in HIV-1/HSV-2 co-infected women

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Background:

- **Acyclovir treatment significantly reduces HIV viral load (0.25-0.5 log) and decreases the rate of HIV disease progression.[1, 2]**
- **Is the protective effect of acyclovir on HIV disease progression due to:**
  1) Direct effects of decreasing HIV replication?
  2) Decreased immune activation associated with less herpetic reactivation?
- **A pilot placebo-controlled trial of Valacyclovir in HIV-1/HSV-2 co-infected adults demonstrated that 18-weeks of treatment did not decrease cellular or inflammatory immune activation.[3]** Limitation: Individuals were on fully suppressive HAART, which may have masked some of the effects of suppressing HSV replication.
- **Similar trial in HIV-uninfected women found that a two-month HSV-2 treatment regimen did not reduce cellular activation or levels of pro-inflammatory cytokines in the female genital tract.[4]** Limitation: Short-period of HSV-2 suppressive therapy.

Study Objective:

To determine the long-term effect of HSV-2 suppression on systemic immune activation in HSV-2/HIV co-infected individuals, and to examine its role in HIV disease progression.

Methods:

- **Double-blind, randomized placebo-controlled trial of acyclovir in HIV-1/HSV-2 co-infected individuals (N=301) from the Rakai Health Sciences Program, Uganda.**
  - Randomly assigned placebo or 400mg acyclovir twice daily for 24 months.
  - CD4+ cell count of 300-400 cells/μL was required at enrollment.
  - Individuals with AIDS defining illnesses or receiving ART were excluded.
  - Disease progression defined as CD4+ cell count <250 cells/uL or WHO stage IV, at which point ART was initiated.
- **Serum samples were collected at enrollment and every six months for 24 months.**
- **Immune activation markers measured on serum samples:**
  - High sensitivity CRP (Genway Biotech; San Diego, CA)
  - sCD14 (R&D Systems; Minneapolis, MN)
- **Statistical Analysis:**
  - Cox proportional hazard regression models, Kaplan-Meier survival curves and log-rank test to assess baseline associations and the predictive value of CRP and sCD14 levels with HIV disease progression (ART eligibility).
  - Mixed-effects models to determine change in time-varying CRP and sCD14 levels by study arm (right-censored individuals post-ART initiation).

Results:

Table 1. Baseline characteristics by study arm.

Enrolment characteristics	Treatment		Placebo		p-value*
	N	*%*	*N*	*%*	
Total	148	100	153	100	
Age (years)					0.980
20-29	37	25	36	24	
30-39	65	44	66	43	
40-49	31	21	35	23	
50+	15	10	16	10	
CD4+ T cell count					0.564
300-349	69	47	66	43	
350-399	79	53	87	57	
HIV Viral load categories					0.973
<10,000	53	36	54	35	
10,000-49,999	43	29	43	28	
50,000-99,999	13	9	16	10	
≥100,000	39	26	40	26	
Log_{10} HIV Viral load					
Median (IQR)	4.33	(3.77,5.03)	4.39	(3.66,5.04)	0.880
sCD14					0.300
<Median	79	53	72	47	
≥Median	69	47	81	53	
Log_{10} sCD14					
Median (IQR)	3.31	(3.20-3.45)	3.34	(3.20-3.43)	0.816
CRP					0.084
<Median	82	55	69	45	
≥Median	66	45	84	55	
Log_{10} CRP					
Median (IQR)	0.99	(0.40-3.30)	1.32	(0.46-3.86)	0.329

P-values determined by Chi-squared and Mann-Whitney U tests for categorical and continuous variables, respectively.

Results:

Figure 1. Cumulative probability of ART eligibility by baseline sCD14 and CRP levels.

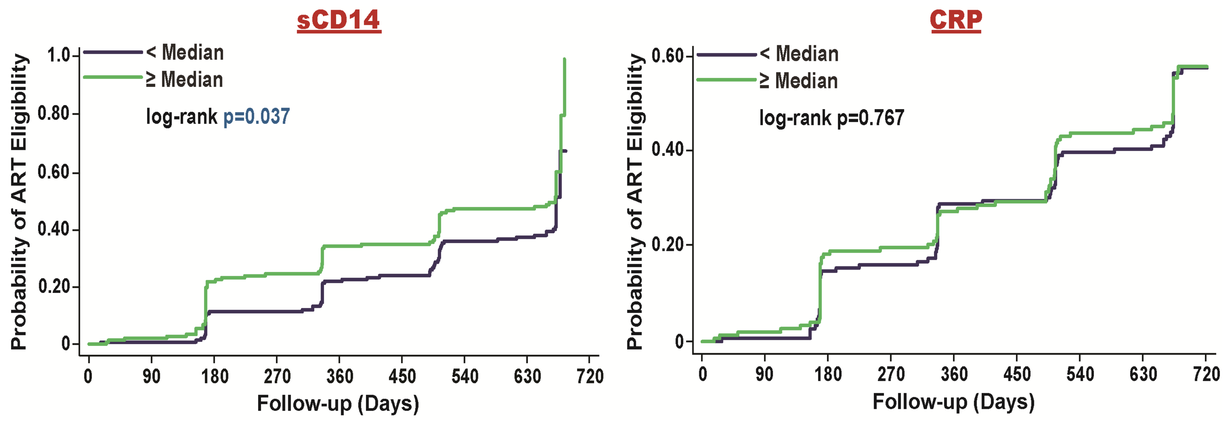


Table 2. Rate and hazard ratio of ART eligibility by baseline covariates.

	N	Eligible/ person-years	Eligible per 100 person-years	Crude Hazard Ratio (95% CI)	Adj. Hazard Ratio* (95% CI)
Overall	301	156/ 428.4	36.4		
Study arm					
Placebo	153	85/205.7	41.3	1.0 (ref)	1.0 (ref)
Treatment	148	71/222.7	31.9	0.78 (0.57, 1.07)	0.67 (0.48, 0.92)
Age (years)					
20-29	73	42/103.1	40.7	1.0 (ref)	1.0 (ref)
30-39	131	68/185.0	36.8	0.92 (0.63, 1.36)	1.02 (0.69, 1.51)
40-49	66	34/97.1	35.0	0.89 (0.57, 1.40)	1.15 (0.73, 1.83)
50+	31	12/43.2	27.8	0.72 (0.38, 1.37)	0.91 (0.47, 1.74)
CD4+ T cell count					
300-349	135	89/174.9	50.9	1.0 (ref)	1.0 (ref)
350-499	166	67/253.5	26.4	0.50 (0.36, 0.69)	0.47 (0.34, 0.65)
Log_{10} HIV Viral load					
continuous	301	-	-	1.77 (1.47, 2.14)	1.80 (1.48, 2.20)
sCD14					
<Median	151	73/230.6	31.7	1.0 (ref)	1.0 (ref)
≥Median	150	83/197.8	42.0	1.38 (1.01, 1.90)	1.18 (0.85,1.63)
CRP					
<Median	151	78/218.7	35.7	1.0 (ref)	1.0 (ref)
≥Median	150	78/209.7	37.2	1.05 (0.77, 1.43)	0.95 (0.69, 1.31)

**Multivariate model adjusted for all covariates. Significant hazard ratios shown in blue (p<0.05).*

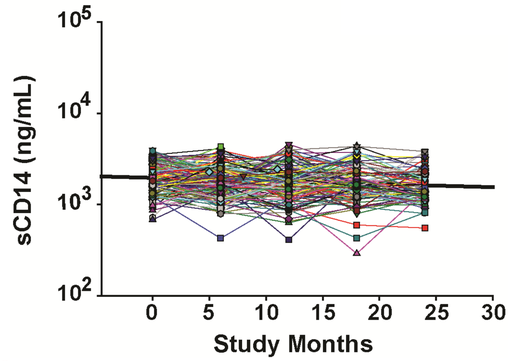
- **Higher baseline sCD14 levels were not associated with progression to ART eligibility after adjusting for co-variates.**
- **Higher baseline CRP levels were also not predictive of disease progression.**
- **CRP levels increased in both arms, and were not different (p=0.25).**
- **sCD14 levels decreased slightly in both arms, but at a significantly higher rate in the treated women compared to the placebo group, independent of viral load and CD4 count (p=0.039).**
- **The decrease in sCD14 levels in the treatment group was small with a total change in levels of 0.072 log_{10} (290 ng/mL) over 2 years, which is 15% of the mean sCD14 levels at baseline in the treatment group.**

Table 3. Long-term effects of acyclovir treatment on sCD14 and CRP levels.

	Coefficient log/month (95% CI)	p-value	Adj. Coefficient log/month* (95% CI)	p-value
sCD14	-0.003 (-0.005, -0.000)	0.02	-0.002 (-0.005,0.000)	0.039
CRP	-0.004 (-0.012, 0.003)	0.25	-	-

** Adjusted for time-varying HIV viral load and CD4 counts.*

Figure 2. Long-term effects of acyclovir treatment on sCD14 levels.



Conclusions:

- **sCD14 levels decreased faster in the acyclovir treated arm than in the placebo arm independent of viral load and CD4 count.**
- **These data support the hypothesis that decreased monocyte activation may contribute in part to the slower HIV disease progression observed during daily acyclovir treatment.**

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