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

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Abstract

Objectives—Several clinical trials have demonstrated that daily treatment of HIV-infected individuals with the antiherpes drug acyclovir slightly decreases HIV-1 viral load and slows disease progression. This study examines if this slowing in clinical progression is a direct cause of the decrease in viral load or an indirect effect of lower immune activation due to lower levels of herpetic reactivation.

Methods—Women who participated in a randomised clinical trial of daily acyclovir use (n=301) were monitored every 6 months for changes in immune activation. Soluble CD14 (sCD14), a marker for monocyte activation, and C-reactive protein (CRP), a marker for general immune activation, were measured by ELISA.

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Results—Initial levels of sCD14 and CRP were not predictive of HIV disease progression when controlling for initial CD4+ cell count and HIV viral load. sCD14 levels, but not CRP, decreased in the acyclovir treatment arm at a significantly faster rate than the placebo group, which was independent of changes in HIV viral load and CD4+ cell count in a multivariant mixed-effects model (p=0.039). However, the magnitude of this decrease was relatively small with a total estimated decrease of sCD14 of 15% of initial levels.

Conclusions—These data suggest that decreased monocyte activation may play a minor role in the ability of daily acyclovir use to slow HIV disease progression.

Introduction

Herpes simplex virus type 2 (HSV-2) has been shown to upregulate HIV-1 replication and is associated with increased HIV-1 viral load (VL).[1 2] Acyclovir treatment, which effectively blocks HSV replication, was shown to also significantly reduce HIV VL, as well as decrease the rate of disease progression in two separate randomised controlled trials.[3–5] This effect was most prominent in individuals with high HIV VLs.[3] It is unclear if the protective effect of acyclovir use in HIV disease progression is due to its direct effect of decreasing HIV replication or a secondary effect caused by decreased immune activation associated with less herpetic reactivation.[6–9]

A placebo-controlled trial of the use of valacyclovir, a derivative of acyclovir, in HIV-1/HSV-2 coinfected adults found that 18 weeks of treatment did not decrease cellular or inflammatory immune activation.[10] However, these individuals were on fully suppressive highly active antiretroviral therapy (HAART), which may have masked some of the effects of suppressing HSV replication. The same investigators performed a similar trial in HIV-uninfected women and found that 2-month valacyclovir treatment did not reduce cellular activation or levels of proinflammatory cytokines in the female genital tract.[11] In contrast to these smaller shorter studies, the randomised controlled trial of daily acyclovir use in Rakai district, Uganda, was performed over 2years on 440 participants, allowing for greater power to examine subtle and long-term changes in immune activation.[3]

C-reactive protein (CRP), a marker for general immune activation, has been shown to increase during HIV disease in this population.[12] Soluble CD14 (sCD14) is a marker for monocyte activation and has been shown to be predictive of HIV disease progression.[13 14] It is not fully understood how long-term acyclovir treatment may alter these markers. This study examined if acyclovir-induced changes in general immune activation account for a proportion of the protective effect seen in HIV disease progression or if it is due more to the direct effect of decreased HIV VL.

Materials and methods

Study population

Serum samples were collected at enrolment and every 6 months for 2years from all women who completed a randomised double-blinded placebo controlled trial of daily acyclovir (n=301). The recruitment, randomisation and detailed trial design were previously published.[3] Briefly, HIV-1/HSV-2 coinfected individuals from the Rakai Health Sciences

Program, Uganda, with a CD4+ cell count from 300–400 cells/μL were enrolled in a double-blind, individually randomised placebo-controlled trial of HSV-2 suppression to assess HIV disease progression. Participants were randomly assigned to receive placebo or 400 mg acyclovir tablets twice daily for 24 months. Individuals with AIDS defining illnesses or receiving HAART were excluded.

The primary outcome was defined as HIV-1 disease progression to a CD4 cell count <250 cells/μL or WHO stage IV at which time HAART was initiated. Serologic testing (HIV, HSV-2), CD4+ cell counts, physical examinations including clinical evaluation for genital ulcer disease, self-administered vaginal swabs and interviews to ascertain sociodemographic and behavioural characteristics were conducted at baseline. Participants were seen monthly for drug refill and adverse event review. All participants provided written informed consent, and the study was approved by the Uganda Virus Research Institute Science and Ethics Committee, the Uganda National Council for Science and Technology and the US National Institute of Allergy and Infectious Diseases Intramural Institutional Review Board.

All individuals were treated with acyclovir (intervention arm) or placebo (control arm). At enrolment and every 6 months, a general physical examination and repeat CD4 cell count and HIV VL testing were performed. Serum samples were stored at −80 until laboratory assays. Even individuals who reached the primary outcome of anti-retroviral therapy (ART) eligibility (CD4 cell count<250 cells/μL or WHO stage IV disease) continued to receive acyclovir or placebo for the first 24 months after enrolment.[3]

Laboratory assays

High sensitivity CRP (Genway Biotech; San Diego, California, USA) and sCD14 (R&D Systems; Minneapolis, Minnesota, USA) levels were measured on all available serum samples per manufacturer's recommendation. CD4 counts and HIV VLs were measured as previously reported.[3]

Statistical analyses

The distribution of baseline characteristics between trial arms were compared using χ^2 test for dichotomous and categorical variables and the Mann–Whitney U test for continuous variables. Longitudinal analyses of treatment outcome were right-censored at initiation of HAART for those women who started therapy. Univariate and multivariate HRs were calculated for baseline measurements previously shown to be associated with HIV disease progression (study arm, age, CD4 count, VL, sCD14, and CRP). The predictive value of CRP and sCD14 cut-offs on survival was estimated using Kaplan–Meier curves and Cox proportional hazard regression models, and the log-rank test was used to assess statistical significance. Mixed-effects models were used to examine time-varying CRP and sCD14 levels by study arm. Changes in sCD14 levels over time were also analysed with a model adjusted for longitudinal changes in HIV VL and CD4+ cell count. Stata V.13.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis (figure 1).

Results

There were 301 women who were enrolled in the trial and were eligible for this study (table 1). There were 148 women randomly assigned to the treatment arm and 153 to the placebo arm. There were no significant differences in baseline demographic, disease or immunological characteristics between the trial arms (table 1).

Higher baseline levels of sCD14 were found to be significantly associated with progression to HAART eligibility by Kaplan–Meier (log-rank test, p=0.037) and univariate survival analysis (HR=1.38, 95% CI 1.01 to 1.90) (table 2). Higher CRP levels were not predictive of disease progression in the Kaplan–Meier (log-rank test, p=0.77) or the survival analysis (HR=1.05, CI 0.77 to 1.43) (table 2). As expected, initial VL and baseline CD4+ cell count were predictive of disease progression (table 2). These were combined with age and study arm in a multivariate Cox analysis that found being randomised to the treatment arm (HR=0.67, CI 0.48 to 0.92) and higher baseline CD4 count (HR=0.47, CI 0.34 to 0.65) to be protective, whereas having a higher initial VL was predictive of a higher risk of disease progression (table 2). sCD14 was not significantly associated with disease progression in the adjusted model (table 2).

Longitudinal changes in sCD14 and CRP between study arms were analysed with a linear multieffects model. Levels of CRP increased significantly compared with baseline in both the treatment (0.002 $\log_{10}$ CRP/month, 95% CI −0.003 to 0.007) and the placebo (0.007 $\log_{10}$ CRP/month, 95% CI 0.002 to 0.011) arms, but were not significantly different (p=0.25). Conversely, levels of sCD14 decreased slightly, but at a significantly increased rate in the treated women (−0.003 $\log_{10}$ sCD14/month, 95% CI −0.005 to −0.002) compared with the placebo group (p=0.02), which did not experience a significant decrease in sCD14 (−0.001 $\log_{10}$ sCD14/month, 95% CI −0.002 to 0.001). This difference in sCD14 decrease by the treatment arm was independent of changes in HIV VL and CD4+ cell count (interaction coefficient=−0.003, 95% CI −0.005 to −0.000; p=0.039).

Discussion

Acyclovir is a potent inhibitor of HSV-2 replication and is highly effective in decreasing the severity and frequency of herpetic outbreaks.[6] It was also shown in two clinical trials to slow down HIV disease progression and decrease HIV VL.[3 4] It is possible that the effect of acyclovir on HIV disease progression is simply a direct effect of treatment lowering HIV VLs or an indirect effect of lower immune activation caused by decreased herpetic reactivation. To this later scenario, longitudinal levels of sCD14, a marker of monocyte activation, and CRP, a marker of global immune activation, were measured in a group of women who participated in a randomised trial of daily acyclovir use in Rakai district, Uganda.[3] These data demonstrated that although initial sCD14 was predictive of disease progression in a univariate analysis it was not a significant predictor when controlling for the treatment arm, VL and initial CD4 count. This multivariate analysis is somewhat contrary to a previous study of sCD14 levels and HIV disease progression in the Insight Smart study; however, that analysis was done on a much larger population and was not complicated by acyclovir treatment.[13]

Levels of CRP increased significantly in both study arms, but did not differ between study arms. Longitudinal increases in CRP were observed in a previous analysis of standard progressors in this population, and most likely are due to ongoing HIV replication and are not associated with HSV-2 reactivation status.[12]

Acyclovir decreased sCD14 levels significantly faster than in the placebo group. This effect was independent of changes in CD4+ cell count and VL. However, the decrease in sCD14 seen in the treatment group was small, with a total change in levels of 0.072 $\log_{10}$ (290 ng/mL) over the 2-year period, which is 15% of the mean sCD14 levels at baseline in the treatment group. Although these data support the hypothesis that decreased monocyte activation is at least in part contributing to the slower HIV disease progression, given the small overall effect over a 2-year period it is unlikely that this change is the driving force in this phenotype.

Two trials of valacyclovir did not observe a significant decrease in immune activation in HIV-infected or uninfected individuals using a variety of markers.[10 11] However, these trials were relatively short in comparison with this analysis, which, given the limited magnitude of the changes in monocyte activation, could be why they did not see an effect. Additionally, there was no difference in the change in overall immune activation as measured by CRP. Taken together, these data suggest that although one aspect of immune activation was slightly decreased with acyclovir use it is most likely not the major factor in slowing disease progression in this population. Given the initiatives to initiate ART earlier due to both the clinical benefit and the ability to prevent ongoing transmission it is most likely that the role of acyclovir as a pre-ART treatment for HIV is limited.

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Key messages

- Monocyte activation may contribute to the protective effect of the anti-HSV-2 (herpes simplex virus type) drug acyclovir on HIV disease progression, which is independent of viral load.
- The effect of acyclovir on HIV disease is limited as is the effect on monocyte activation.
- Current best practice is to initiate antiretroviral therapy early due to its clinical benefit and to prevent transmission, limiting acyclovir's effect as a treatment for HIV.

Table 1

Baseline characteristics by trial arm

Enrolment characteristics	Treatment		Placebo		p Value
	N	Per cent	N	Per cent	
Total	**148**	**100.0**	**153**	**100.0**	
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
<10000	53	36	54	35	
10000–49999	43	29	43	28	
50000–99999	13	9	16	10	
100000+	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

CRP, C-reactive protein.

Table 2

Rate and HR for ART eligibility by baseline covariates

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

Significant HR are shown in bold.

*Estimates for the adjusted HR include all variables listed in the table.

ART, antiretroviral therapy; CRT, C-reactive protein.