Cenicriviroc Decreases sCD14 and LBP Levels Without Affecting Gut Permeability

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Background

- Cenicriviroc (CVC), a potent oral, once-daily CCR2/CCR5 antagonist, blocks HIV entry through CCR5 blockade and inhibits monocyte trafficking through CCR2.
- Monocyte recruitment promotes atherosclerosis, hepatic fibrosis and other end-organ diseases in HIV infection.[1,2]
- Soluble CD14 (sCD14) is a marker of monocyte activation, and is thought to be induced by lipopolysaccharide (LPS).[3] sCD14 predicts mortality in HIV infection.[4]
- In a completed randomized, double-blind study of 48 weeks of CVC or efavirenz (EFV) with tenofovir/emtricitabine (TDF/FTC) (Study 652-2-202; NCT01338883), sCD14 levels significantly decreased with 100mg or 200mg of CVC independent of HIV-1 RNA changes but increased in the EFV arm.
- We aimed to determine whether decreases in this monocyte activation marker with CVC were attributable to decreased intestinal permeability and microbial translocation.

Methods

- In 652-2-202, 135 men and 8 women were enrolled
  - Age 35±11 years
  - 46 Black, 35 Hispanic, 53 White, 9 Other
  - Median CD4 T cell count 385 cells/mm^3
  - Median HIV1 RNA 4.57 $\log_{10}$ copies/ml
  - Randomized 2:2:1 to CVC 100mg, 200mg or EFV
- Intestinal fatty acid binding protein (I-FABP), zonulin, flagellin and lipopolysaccharide binding protein (LBP) were measured by ELISA on stored plasma.
- TDF/FTC with 100mg or 200mg of CVC arms were pooled (N=115) and compared to the arm who received TDF/FTC with EFV 600mg (N=28).
- Fresh PBMCs from a healthy donor were incubated for 48 hours with varying CVC or EFV amounts with or without LPS (100 ng/ml).
- Median values were compared between groups by the Mann-Whitney *U* test and longitudinal within-group comparisons by Wilcoxon matched-pairs signed rank test. Pearson correlation coefficients were calculated.

Results

- Plasma I-FABP(Fig. 1A, F) and flagellin (Fig. 1C, H) levels increased after 48 weeks of TDF/FTC with CVC or EFV.
- LBP (Fig. 1D, I) levels decreased in both groups after 48 weeks of TDF/FTC with CVC or EFV.
- sCD14 (Fig. 1E, J) levels decreased in CVC group after 12 weeks.
- Zonulin (Fig. 1B, G) levels did not change significantly in either group.
- sCD14 shedding did not increase from PBMCs incubated with CVC with or without LPS, but increasing concentrations of EFV incubated with LPS in vitro resulted in increased sCD14 shedding (Fig. 2).

Figure 1

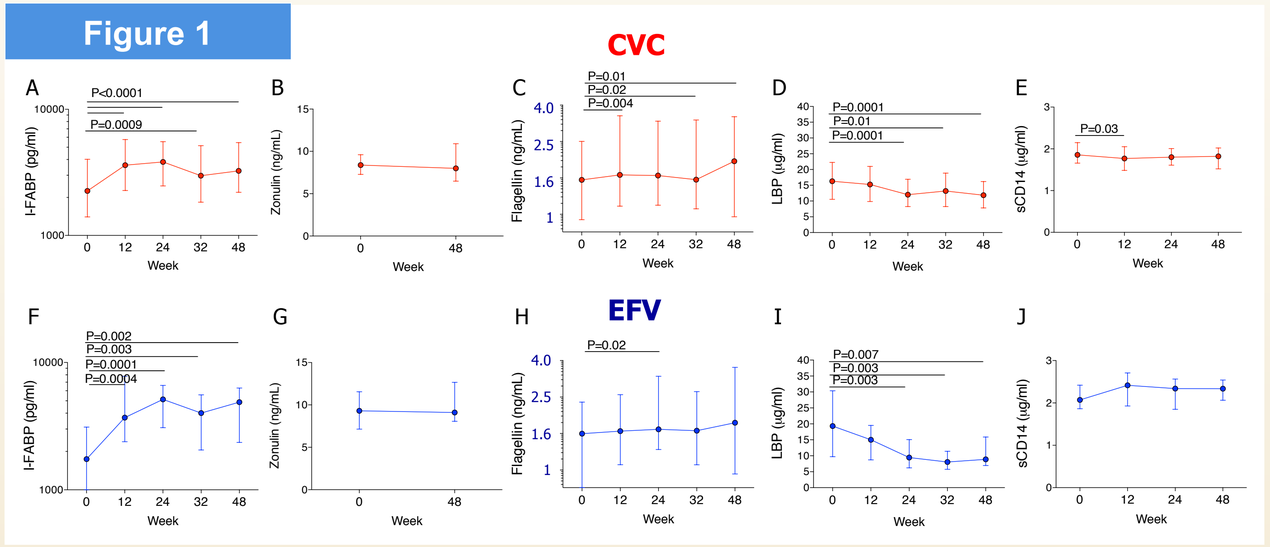


Figure 1. Plasma levels of markers of enterocyte turnover (I-FABP; A, F), tight junction integrity (zonulin; B, G), microbial translocation (flagellin; C, H), and LPS-induced responses (LBP and sCD14; D, E and I, J) in HIV-infected participants naïve to ART and treated with TDF/FTC + CVC or TDF/FTC + EFV.

Figure 2

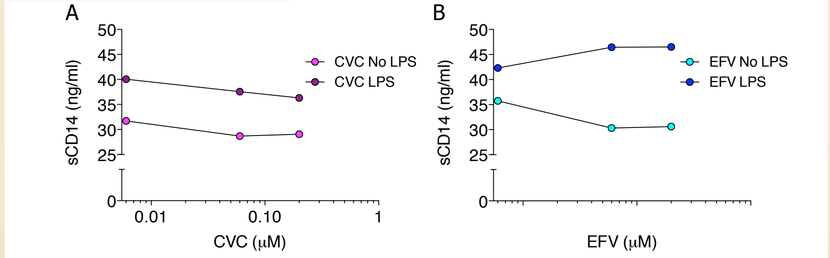


Figure 2. sCD14 shedding from PBMCs after 48-hour incubation with CVC (A) or EFV (B) with or without LPS. At higher concentrations of CVC and to a greater extent of EFV, substantial cell death was observed.

Figure 3

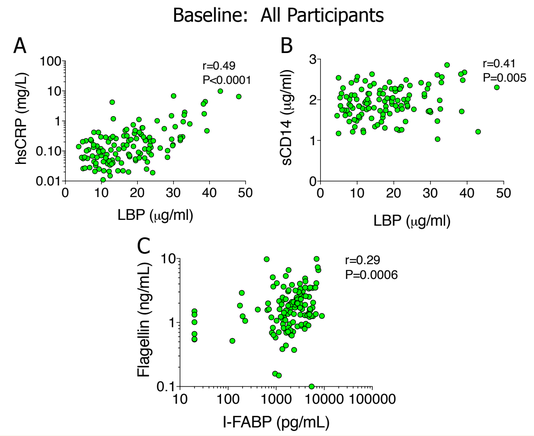


Figure 3. Baseline correlations of LBP, hsCRP, sCD14, I-FABP, and flagellin.

- Lower LBP levels were associated with lower hsCRP (Fig. 3A), sCD14 (Fig. 3B) and GGT at weeks 24 (r=0.33, P=0.002) and 48 (r=0.34, P=0.003) in CVC group.
- I-FABP correlates with flagellin at baseline only (Fig. 3C).

Conclusions

- The decrease in sCD14 levels reflecting a reduction in monocyte activation with CVC was not accompanied by decreased intestinal permeability (based on I-FABP and zonulin levels) or bacterial products (flagellin).
- In vitro, EFV augmented sCD14 increases with LPS stimulation whereas CVC had no additive effect and may even dampen LPS-induced monocyte activation, mirroring in vivo results.
- The decrease in LBP with CVC could reflect decreased LPS in the liver, but the consistent correlation with decreases in CRP suggests decreased activation of the acute phase response.
- Thus, CVC decreases sCD14 levels independently of changes in microbial translocation or gut integrity.

References

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