Sevelamer Does Not Decrease Plasma LPS or sCD14 but Does Decrease Soluble Tissue Factor and LDL

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I. Introduction

- Intestinal barrier damage in HIV infection permits translocation of microbial products from the intestinal lumen into the circulation
- High plasma lipopolysaccharide (LPS) levels in HIV infection are associated with immune activation, which is associated with disease progression and all-cause mortality in HIV infection
- Sevelamer is an orally administered, non-absorbable polymer that binds phosphate and is administered to dialysis patients
- In a longitudinal study of hemodialysis patients, sevelamer decreased LPS levels by 80%, CRP by 78%, LDL by 23% after 6 months (Stinghen, Blood Purif, 2010)
- Sevelamer is well-tolerated with minimal side effects in healthy volunteers and dialysis patients

- **Hypothesis: Sevelamer, an LPS-binding compound, will reduce plasma LPS levels and LPS-associated monocyte and T cell activation in HIV-infected subjects**

II. Methods

- Single arm study enrolling 40 subjects:
  - Male or female subjects ≥ 18 years with chronic HIV infection
  - CD4+ T-cell count ≥ 400 cells/mm^3
  - HIV RNA > 50 copies/mL
  - No ART for 24 weeks before study entry
- Intervention:
  - 8 weeks of sevelamer carbonate 1600mg three times daily
  - 8 weeks of follow-up
- Statistical analysis: As-treated analysis
  - Anticipated 32 evaluable subjects for primary endpoint determination
  - 80% power to demonstrate a significant reduction in sCD14 or LPS from baseline to week 8
  - Statistical significance was tested using a two-sided alpha = 0.05 sign test with no adjustment for multiple testing

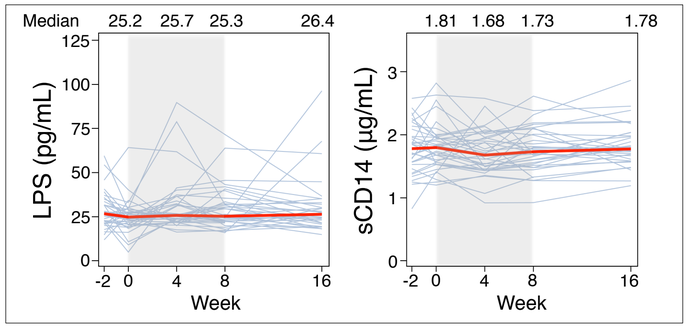
III. Results

Table 1. Baseline characteristics.

Characteristic		Total (N=40)	Included in Primary Analysis? Yes (N=36)	No (N=4)	*P*
Age (years)	**Median (Q1, Q3)**	44 (34, 51)	44 (35, 51)	33 (23, 45)	.27
	10%, 90%	28, 55	30, 56	19, 51	
Race/Ethnicity	**White Non-Hispanic**	10 (25%)	10 (28%)	0 (0%)	.46
	Black Non-Hispanic	24 (60%)	21 (58%)	3 (75%)	
	Hispanic	6 (15%)	5 (14%)	1 (25%)	
Sex	**Male**	29 (73%)	26 (72%)	3 (75%)	1.00
	Female	11 (28%)	10 (28%)	1 (25%)	
HIV-1 RNA (log_{10} copies/mL)	**Median (Q1, Q3)**	3.58 (2.94, 4.17)	3.58 (2.95, 4.02)	3.07 (1.72, 4.36)	.59
	10%, 90%	2.20, 4.52	2.48, 4.60	1.59, 4.44	
CD4 T-cell count (cells/mm^3)	**Median (Q1, Q3)**	580 (494, 716)	585 (494, 716)	556 (470, 806)	.85
	10%, 90%	418, 1,044	424, 1,045	396, 1,044	

Four subjects were excluded from the analyses: 1 began ART at week 7, and 3 missed key study visits. Baseline characteristics of 36 subjects who were analyzed did not differ markedly from these 4 subjects.

Figure 1. Effects of sevelamer on circulating LPS and soluble CD14 levels



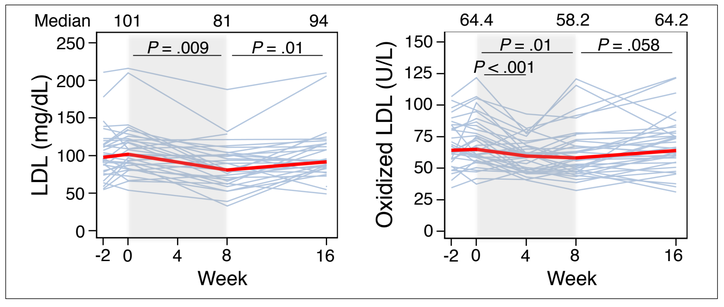
Sevelamer had no significant effect on LPS or sCD14 levels and no effect on endotoxin core antibody or LPS binding protein levels. Gray indicates treatment period. Red indicates median levels.

Table 2. Effects of sevelamer on markers of inflammation

	Baseline	Wk 8 On sevelamer	Wk 16 8 wks off sevelamer	Wk 8 vs Baseline *P*	Wk 16 vs Wk 8 *P*
IL-6 (pg/mL)	1.65 (1.23, 2.20)	1.71 (1.27, 2.31)	1.68 (1.20, 3.08)	.87	.39
CRP (ng/mL)	1768 (883, 4029)	2199 (708, 4249)	2353 (834, 4077)	.62	.39
IL-1β (pg/mL)	0.23 (0.14, 0.32)	0.26 (0.12, 0.35)	0.24 (0.08, 0.33)	.38	.70
IP-10 (pg/mL)	278 (198, 463)	287 (168, 412)	343 (201, 4356)	.24	.06
sCD163 (ng/mL)	1006 (690, 1352)	968 (735, 1236)	991 (638, 1398)	.87	.86
Fetuin A (mg/mL)	0.88 (0.46, 1.34)	0.55 (0.22, 0.98)	0.66 (0.30, 1.16)	.41	.61

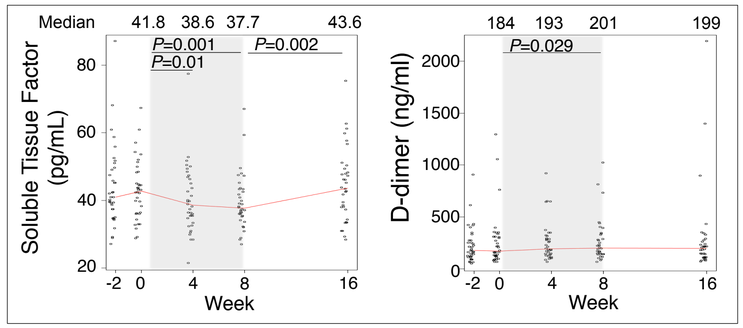
Sevelamer had no significant effect on markers of inflammation and cardiovascular disease. Median (Q1, Q3) values are reported.

Figure 2. Effect of sevelamer on lipids



LDL and oxLDL cholesterol levels decreased during sevelamer treatment and increased after treatment cessation. Gray indicates treatment period. Red indicates median levels.

Figure 3. Effect of sevelamer on soluble TF and D-dimer levels



Soluble tissue factor decreased with sevelamer treatment and increased after treatment cessation whereas D-dimer increased minimally during sevelamer treatment. Gray indicates treatment period. Red indicates median levels.

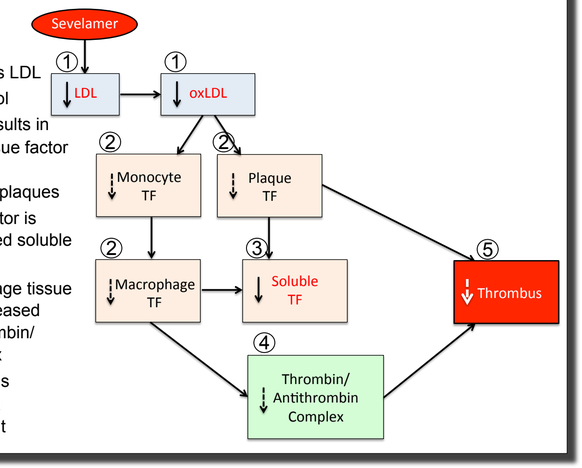
Safety
- Well-tolerated
- No significant change in CD4 T-cell counts
- No significant change in HIV RNA levels
- No significant change in phosphate levels

IV. Conclusions

- In patients not on ART, 8 weeks of sevelamer did not decrease microbial translocation or inflammation markers, possibly due to:
  - Ongoing intestinal damage by viral replication
  - Impaired LPS clearance due to defective phagocytosis, decreased endotoxin core antibody levels, hepatic dysfunction
  - Alteratively, low levels of microbial translocation in this relatively healthy population may have precluded a significant effect
- However, 8 weeks of sevelamer carbonate decreased LDL and oxLDL levels with a comparable effect to statins

Proposed Model:

1. Sevelamer decreases LDL and oxLDL cholesterol
2. Decreased oxLDL results in decrease surface tissue factor on monocytes and macrophages and in plaques
3. Decreased tissue factor is reflected by decreased soluble tissue factor
4. Decreased macrophage tissue factor results in decreased formation of the thrombin/ antithrombin complex
5. Thrombus formation is decreased, yielding a cardiovascular benefit



References

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