Cholesterol Efflux in Newly Diagnosed HIV and Effects of Antiretroviral Therapy

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Background

HDL cholesterol efflux capacity (HCEC) relates inversely to incident cardiovascular events in the general population.[1] Previous studies suggest that HCEC is decreased in HIV[2] and data on effects of antiretroviral therapy (ART) on HCEC are conflicting.[3,4,5] Here, we compare HCEC in ART-naïve, newly diagnosed HIV+ subjects versus that in matched HIV- controls. We further test effects of newly initiated elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) on HCEC. Within the HIV+ cohort, we assess relationships between ART-induced changes in metabolic/immune parameters and HCEC.

Methods

Baseline data from 10 ART-naive HIV+ subjects and 12 prospectively matched HIV- controls were analyzed. In the HIV+ cohort, findings before and 6 months after E/C/F/TDF therapy were also assessed. The primary outcome was HCEC, as measured by the ability of J774 mouse macrophages under low-level LXR stimulation to efflux cholesterol to apo-B depleted sera from participants.

Results

In the ART-naive HIV+ group, HIV diagnosis was established within 0.73±0.62 years, median age was 29 years, and median HDL level was 40 mg/dl. CD4 count was 440±143 cells/mm^3 and median viral load was 32,000 copies/mL. There were no statistically significant differences in age or HDL levels in the HIV+ versus HIV- group. None of the study participants were on a statin. HCEC was significantly lower in the HIV+ group (1.3% HIV+ vs. 5.8% HIV-, p<0.0001). In the HIV+ group, as expected, 6 months of E/C/F/TDF resulted in a rise in CD4 and suppression of viral load.

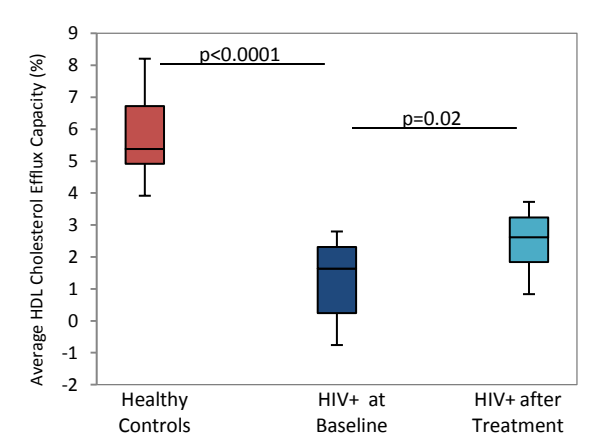
Results Continued

Table 1. Demographic Characteristics of Non-HIV-Infected and HIV-Infected ART-Naïve Subjects

	Non-HIV (n=12)	HIV+ (n=10)	P-Value
TRADITIONAL RISK PARAMETERS			
Race White Black Asian Other	 92% (11/12) 8% (1/12) 0% (0/12) 0% (0/12)	 70% (7/10) 10% (1/10) 10% (1/10) 10% (1/10)	0.32
Age (years)	48 (27, 51)	29 (26, 43)	0.29
BMI (kg/m^2)	26.2 ± 2.9	25.7 .± 4.0	0.77
Total Cholesterol (mg/dL)	175 ± 32	157 ± 30	0.13
LDL Cholesterol (mg/dL)	102 ± 24	95 ± 27	0.29
HDL Cholesterol (mg/dL)	52 (45,64)	40 (36, 47)	0.07
Triglycerides (mg/dL)	89 .± 34	83 .± 29	0.74
Total/ HDL Cholesterol Ratio	3.3 .± 0.7	3.7 .± 1.0	0.37
10-year ASCVD Risk Score*(%)	1.8 (0.7, 5.3)	2.1 (0.9, 3.8)	1.00
Current HTN	17% (2/12)	20% (2/10)	0.84
Current Smoker	25% (3/12)	50% (5/10)	0.22
Current Hepatitis C	0% (0/12)	10% (1/10)	0.20
Family History of Premature CHD**	9% (1/11)	0% (0/9)	0.27
HIV-SPECIFIC PARAMETERS			
Years since HIV Diagnosis	--	0.73 ± 0.62	--
CD4+ T cell count (cells/mm^3)	--	440 ± 143	--
Log VL	--	4.4 ± 0.7	--

*For study participants with age <40, age was imputed in order to calculate ASCVD Risk Score
** Family history was unknown for one study participant due to subject being adopted

Figure 1: HDL Cholesterol Efflux Capacity among Newly-Diagnosed ART-Naïve HIV+ Subjects Before and after 6 Months of E/C/F/TDF Therapy and among Healthy Controls



Results Continued

E/C/F/TDF significantly increased HCEC (mean Δ 1.1%, p=0.02), although not to the level seen in controls. With E/C/F/TDF, there were trends towards an increase in HDL levels (p=0.06) and decrease in levels of the monokine CXCL10 (p=0.09).
ART-induced changes in HCEC related inversely to ART-induced changes in CD14-CD16+ (non-classical) monocytes (R^2 = 0. 51, p= 0.047) and in CXCL10 (R^2 = 0.47, p=0.03). Among the whole group, in multivariate modeling, HIV status and HDL levels remained significantly, independently related to HCEC (R^2 = 0.84, p for overall model <0.0001, p for HIV status <0.0001, p for HDL = 0.01).

Conclusions

Our data suggest benefits of E/C/F/TDF on HCEC, a CVD risk surrogate linked to events. Moreover, among newly diagnosed HIV+ individuals with preserved CD4, we show a relationship between ART-induced dampening of immune activation and ART-induced improvement in HCEC. Further work is needed to characterize whether ongoing HDL dysfunction contributes to CVD risk even among ART-treated HIV+ individuals.

References

1. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med.* Dec 18 2014;371(25):2383-2393.
2. Mujawar Z, Rose H, Morrow MP, et al. Human immunodeficiency virus impairs reverse cholesterol transport from macrophages. *PLoS Biol.* Oct 2006;4(11):e365.3
3. Rose H, Hoy J, Woolley I, et al. HIV infection and high density lipoprotein metabolism. *Atherosclerosis.* Jul 2008;199(1):79-86.
4. Lo J, Rosenberg ES, Fitzgerald ML, et al. High-density lipoprotein-mediated cholesterol efflux capacity is improved by treatment with antiretroviral therapy in acute human immunodeficiency virus infection. *Open Forum Infect Dis.* Dec 2014;1(3):ofu108.
5. El Khoury P, Ghislain M, Villard EF, et al. Plasma cholesterol efflux capacity from human THP-1 macrophages is reduced in HIV-infected patients: impact of HAART. *J Lipid Res.* Mar 2015;56(3):692-702.

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