Published in final edited form as:

HIV Med. 2011 October ; 12(9): 580–581. doi:10.1111/j.1468-1293.2011.00920.x.

HIV Antiretroviral Therapy Reduces Circulating Surfactant Protein-D Levels

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Keywords

Human immunodeficiency virus; Highly active antiretroviral therapy; Surfactant protein D; Biological markers; Lung diseases

Untreated HIV infection is associated with abnormal lung inflammation, even when CD4+ counts are relatively well preserved. Compared to patients without HIV infection, patients with HIV infection demonstrate increases in CD8+ T cells in bronchoalveolar lavage (BAL) fluid¹ that normalize within 6 months of antiretroviral therapy (ART) initiation². BAL allows direct sampling of lung inflammatory cells, but requires an invasive procedure and specialized personnel to perform. Therefore, we investigated the effects of ART on a non-invasive blood marker of lung inflammation, surfactant protein D (SP-D).

Study participants were required to have HIV infection and not have taken ART for at least 3 months prior to enrollment. Exclusion criteria included age <18 or >65 years, pregnancy, concurrent self-limited bacterial infection, and active illicit drug or alcohol use. The protocol was registered at ClinicalTrials.gov (NCT 00783614) and approved by the local ethics committee.

Plasma was collected at baseline, then again at month 3 and month 5 following ART initiation. Plasma SP-D levels were determined using a commercially available sandwich ELISA assay (BioVendor, Candler, NC). Paired differences in SP-D were compared from baseline to month 3 and baseline to month 5. Statistical analyses were performed using STATA 9 (College Station, TX)

Stored specimens from 15 patients were available: 12 and 13 had plasma specimens at month 3 and 5, respectively, to characterize changes from baseline.

Mean age was 37 years, 80% were male, and 33% were Caucasian. Baseline median CD4+ cell count was 320 cells/mm³, increased to 412 cells/mm³ at month 3 (p=0.01 vs. baseline) and was 466 cells/mm³ at month 5 (p=0.007 vs. baseline). Median baseline viral load was 17,970 copies/mL and was fully suppressed at <75 copies/mL among all participants at month 3 and at month 5 visits (both p<0.001 vs. baseline). Eleven participants started a protease inhibitor and 4 participants started a non-nucleoside reverse transcriptase inhibitor;

all participants started nucleoside reverse transcriptase inhibitors. No patients had known lung disease.

Median baseline SP-D was 64.1 ng/mL (interquartile range 49.2 – 73.6 ng/mL). Smoking is known to increase blood SP-D levels³, and our sample of smokers (n=9, 60%) had a higher baseline median SP-D level compared to non-smokers that was not statistically significant (64.3 ng/mL vs. 53.2 ng/mL, respectively, p=0.19). At month 3, there was a non-significant reduction in median SP-D level to 51.6 ng/mL (p=0.10) and at month 5, the reduction became significant to a median SP-D level of 47.3 ng/mL (p=0.01) (Figure). A random effects regression model test for trend showed a slope of -2.7 ng/mL change in SP-D per month (p=0.009).

We have demonstrated for the first time that ART initiation and suppression of HIV replication appears to be associated with a reduction in blood SP-D levels. Studies in non-HIV populations have suggested a relationship between SP-D blood levels and mortality in pulmonary fibrosis⁴, lung function in cystic fibrosis⁵, and respiratory health status in chronic obstructive pulmonary disease⁶. Thus, while our study was a small pilot study, we believe our study provides rationale for expanding research into pulmonary outcomes among patients with HIV infection.

The ongoing Strategic Timing of AntiRetroviral Therapy (START) trial will evaluate early (CD4+ cell counts >500 cells/mm³) vs. deferred ART initiation in randomized fashion. Lung function, respiratory health status, and respiratory medication use will be ascertained in a subset of 1000 participants (ClinicalTrials.gov NCT00867048). Such studies are required to better understand HIV-specific consequences for pulmonary disease, and whether treatment with ART will improve pulmonary outcomes.

Acknowledgments

Study supported by National Institutes of Health grant K12 RR023247 (to JVB).

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Figure.

Boxplots of paired plasma surfactant protein D (SP-D) comparisons from baseline to 3 months after ART initiation (n=12), and baseline to 5 months after ART initiation (n=13). p-values derived using Wilcoxon signed rank testing. Random effects regression model test for trend p=0.009.