Introduction of Antiretroviral Therapy and Changes in Hyaluronic Acid as Marker of Liver Fibrosis Progression in SMART (Strategic Management of Antiretroviral Therapy) Viral Hepatitis Co-infected Participants and Matched Controls

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INTRODUCTION
The SMART study was a large randomized clinical trial that investigated the continuous use of antiretroviral therapy (triple suppression [VS] arm) versus interrupted ART (drug conservation [DC] arm) in both HIV monoinfected and HIV/viral hepatitis co-infected individuals (SMART Study Group, NEJM 2003). We have previously shown that co-infected individuals randomized to the DC arm had a much higher risk of death from any cause, but not opportunistic disease, than the HIV monoinfected individuals (Tateda et al., CJD 2008). This excess mortality was not due to any particular (including liver-related) cause. In another SMART substudy interleukin-6 (IL-6) and D-dimer were found to be strongly related to all-cause mortality in both co-infected and HIV monoinfected individuals (Kuller et al., Proc Med 2008).

OBJECTIVES
- To evaluate the impact of treatment interruptions on liver fibrosis progression in both HCV/HBV co-infected and HIV monoinfected using an indirect marker of liver fibrosis – hyaluronic acid (HA)
- Determine if baseline level and change in HA levels were associated with risk of opportunistic disease, non-AIDS death or major liver events

METHODS
Participants and study design
All participants positive at baseline for HCV-RNA (>615 IU/mL; denoted HCV+) and/or HBsAg (denoted HBV+) and with available plasma samples were included in the study.

HIV monoinfected controls
A control group of HIV monoinfected participants matched 1:1 on randomization date (+/-6 months), gender, age (+/-5 years), treatment group (DC vs. VS), history of alcohol abuse and number of follow-up plasma samples available (controls < cases), was included.

Hyaluronic acid
HA was measured in stored plasma samples at baseline and at month 6, 12 (co-infected only) and 24 during follow-up using a commercial enzyme linked binding protein assay (Corgenix, Colorado, USA) with a HA range in a healthy population between 0-75 ng/mL. Each HA level was measured in duplicate according to the manufacturer’s specifications. Baseline and asymptote amiphenasamine levels as well as liver biopsies were not routinely performed in the SMART study.

Statistical methods
- Wilcoxon rank sum test was used to compare median change in HA from baseline to month 6 and to compare baseline biomarker levels between DC and VS groups
- Logistic regression was used to model the odds of a 125 ng/mL (one standard deviation) change in HA from baseline to month 6
- Time to non-AIDS death for co-infected participants was compared between four groups according to treatment group and baseline HA (≤ 75 ng/mL or >72 ng/mL using a Kaplan-Meier plot

RESULTS
Baseline characteristics
Out of 2,540 participants enrolled in the SMART from January 2002 – January 2006, 675 were HBV+ or HCV+ and had specimens available for analysis. 110 (16.3%) were HBV+, 553 (81.9%) were HCV+ and 12 (1.8%) were both HBV+ and HCV+. Compared with the HIV monoinfected, the co-infected group had no more early mortality (0.4% vs. 3.4%), but a higher HA at baseline (median 45 ng/mL, IQR 40-51) and during follow-up (median 590 ng/mL, IQR 462-759) than the HIV monoinfected (median 30 ng/mL, IQR 25-50). The median baseline CD4+ count was high for both co-infected and HIV monoinfected (580 vs. 583 cells/μL, Table 2B).

Follow-up
The median follow-up was 33 months for the co-infected group and 35 months for the HIV monoinfected controls. Figure 1 shows the changes in HA levels and percent with HA higher than the upper level of normal for co-infected and HIV monoinfected according to treatment arm. Among co-infected participants 52 (20 ± 1) patients had no ART and 44 (20 ± 1) patients were ART naïve (p<0.0001).

Analysis of baseline HA and changes in HA levels for co-infected participants in SMART (Figure 2).

- Baseline HA was an independent predictor of time to development of non-AIDS death, but not opportunistic disease
- Co-infected participants randomized to the DC arm with a baseline HA level >75 ng/mL had a 37.5% risk of non-AIDS death compared to the VS (Figure 3).

SUMMARY
- Hepatitis co-infected participants had higher median plasma levels of HA at baseline and during follow-up than HIV monoinfected
- Interruption of ART was associated with a significant increase in HA levels at month 6 among co-infected participants randomized to the DC arm. This difference was not sustained at months 12 and 24.
- Baseline HA was an independent predictor of time to development of non-AIDS death, but not opportunistic disease
- Co-infected participants randomized to the DC arm with a baseline HA level >75 ng/mL had a 37.5% risk of non-AIDS death after 48 months, whereas the risk was only 5% for those with a baseline HA ≤75 ng/mL.

CONCLUSION
HA levels increases temporarily after ART is interrupted. Interruption of ART in chronic viral hepatitis co-infected persons is particularly dangerous if HA levels just prior to the interruption are elevated.