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Interruption 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 continuous use of antiretroviral therapy (viral suppression [VS] arm) versus interrupted ART (drug conservation [DC] arm) in both HIV monoinfected and HIV/viral hepatitis co-infected individuals with a CD4+ >350 cells/µL (SMART Study Group; NEJM 2006).

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 (Tedaldi et al; CID 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; PLoS 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 manufacturers specifications. Alanine and aspartate aminotransferase 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 >72 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 (≤ or >75 ng/mL using a Kaplan-Meier plot

Table 1

Baseline characteristics

	HBV and/or HCV co-infected		HIV monoinfected	
	DC (n=347)	VS (n=328)	DC (n=347)	VS (n=327)
HBV+ n (%)	61 (17.6)	49 (14.9)	0	0
HCV+ n (%)	281 (81.0)	272 (82.9)	0	0
HBV+ and HCV+ n (%)	5 (1.4)	7 (2.1)	0	0
Female sex (%)	26.5	24.4	26.5	24.5
Black race (%)	48.7	48.2	33.1	35.2
History of alcohol abuse (%)	25.9	25.0	25.9	24.8
HIV-RNA ≤400 copies/mL(%)	67.6	60.4	65.1	69.4
Age (years)				
- Median	45	45	44	44
- IQR	40-51	41-50	40-51	40-50
Baseline CD4+ (cells/µL)				
- Median	599	566	567	599
- IQR	462-759	459-702	464-800	475-823

Figure 1

Changes in CD4+ and HIV-RNA during follow-up

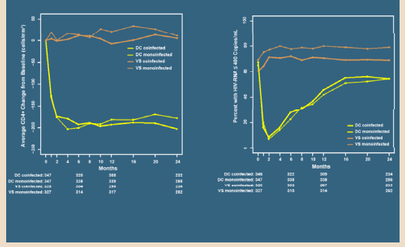
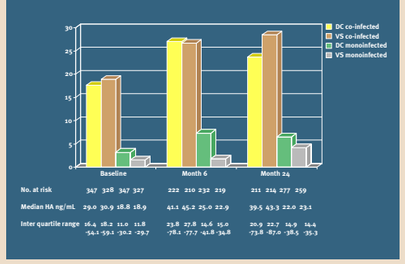


Figure 2

Percent with HA>75 ng/mL at baseline and follow-up



RESULTS

Baseline characteristics

Out of 5,472 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 was more likely to be of black race (48.4 vs. 34.1%) and less likely to be ART naïve (2.4 vs. 4.3%) and undergoing ART (79.3 vs. 85.8%) and had longer median time since initiation of ART (7 vs. 6 years). The median baseline CD4+ count was high for both co-infected and HIV monoinfected (580 vs. 583 cells/µL), **table 1**.

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 HIV-RNA and CD4+ during follow-up in co-infected and HIV monoinfected according to treatment arm. Among co-infected participants 52 (31 in DC, 21 in VS) died from non-AIDS causes, while 29 developed an opportunistic disease. 21 developed a major liver event (17 cirrhosis, 4 liver-related deaths)

HA levels at baseline and during follow-up

Median HA levels and percent with HA higher than the upper level of normal for co-infected and HIV monoinfected are shown in **figure 2**. By month 6 the DC group of co-infected participants, but not the HIV monoinfected controls, had a significant increase in median (IQR) HA compared to the VS, **figure 3**. However, this difference was not sustained at month 12 only co-infected) and 24 (data not shown).

HA as a predictor of development of clinical events

In co-infected participants, those with a baseline HA level >75 ng/mL and randomized to the DC arm had a cumulative risk of non-AIDS death of 37.3% after 48 months compared with only 7.3% in participants randomized to the VS arm irrespective of baseline HA level, **figure 4**. Similar trends, though less striking, were seen for liver-related outcomes. Baseline HA levels did not predict risk of opportunistic infections [data not shown].

The DC/VS hazard ratio (95% CI) for non-AIDS death in co-infected participants with a baseline HA level >75 ng/mL was [HR 3.8 (1.4-10.6, p=0.009], while for those with HA level ≤75 ng/mL it was [HR 0.9 (0.4-1.8), p=0.76]. P-value for interaction was 0.02. Only 16 monoinfected participants had a baseline HA >75 ng/mL, precluding an analysis of this group.

Association between HA and IL-6 and D-dimer

Co-infected participants with elevated baseline HA levels (>75 ng/mL) had significantly higher IL-6 and D-dimer levels than those with normal levels (<75 ng/mL), **table 2A** . Similar trends were also seen in the few HIV monoinfected individuals with elevated HA, **table 2B**.

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.

Figure 3

Percent with >1 standard deviation change (72 ng/mL) in median HA from baseline to Month 6

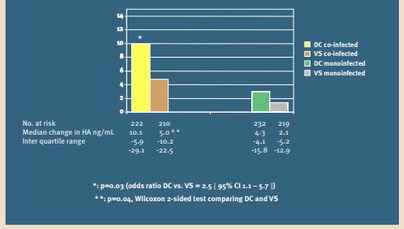


Figure 4

Risk of non-AIDS death in co-infected according to baseline HA and treatment arm

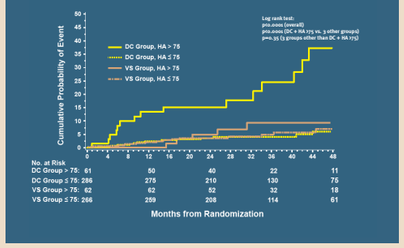


Table 2A&B

Baseline IL-6 and D-dimer according to baseline HA and coinfection status

Table 2A – Co-infected participants

	Baseline HA > 75		Baseline HA ≤ 75		
Baseline Marker	N	Median (IQR)	N	Median (IQR)	P-value*
IL-6	70	5.05 (2.85-9.89)	241	2.54 (1.69-3.92)	<0.0001
D-dimer	71	0.50 (0.22-1.17)	247	0.31 (0.17-0.57)	0.002

Table 2B – HIV monoinfected participants

	Baseline HA > 75		Baseline HA ≤ 75		
Baseline Marker	N	Median (IQR)	N	Median (IQR)	P-value*
IL-6	11	3.33 (1.37-4.62)	296	2.36 (1.47-3.69	0.46
D-dimer	12	0.41 (0.22-0.81)	306	0.30 (0.17-0.55)	0.22

*Wilcoxon rank sum test

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