Depleted DHEA-S reserves are associated with early mortality after ART initiation in HIV/TB co-infected patients in Botswana

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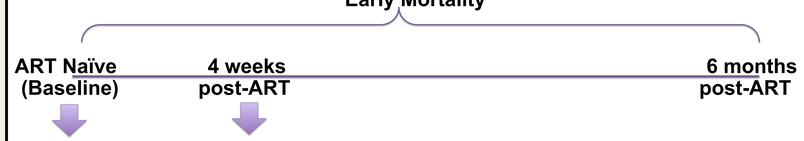
Background

Changes in levels of adrenal hormones observed in HIV-infection and TB disease may affect disease progression and outcome.[1,2,3] Of interest is dehydroepiandrosterone-sulfate (DHEA-S), which forms the reserve for the active form, DHEA.[4] DHEA-S is converted to DHEA and has been shown to enhance *Mycobacterium tuberculosis* (MTB)-specific Th1 responses following *in vitro* stimulation of peripheral blood mononuclear cells (PBMCs) isolated from HIV/TB co-infected patients.[2,4] We have demonstrated that poor immunologic recovery and elevated immune activation, despite virologic suppression, is associated with early mortality post-ART initiation in advanced HIV/TB.[5] **We therefore hypothesized that low pre-ART (baseline) DHEA-S levels are associated with early mortality after ART initiation in advanced HIV/TB. In addition, we explored the relationship between baseline DHEA-S and sex, as well as DHEA-S levels and immune parameters.**

Methods

Study design: Prospective cohort study of ART-naïve, HIV-infected adults with CD4 counts <125 and active pulmonary TB at enrollment.

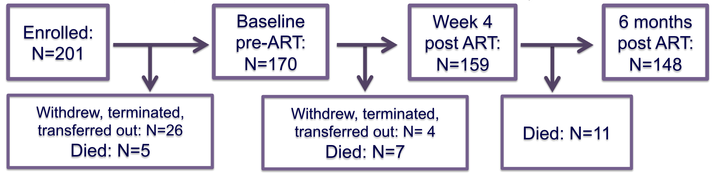


1. HIV- plasma viral load and CD4 counts.
2. Plasma for: DHEA-S, DHEA, cortisol, IL-6, and sCD14.
3. MTB-specific cellular immune response using fresh PBMCs by Purified Protein Derivative (PPD) stimulation and IFN-γ ELISPOT.
4. Death during follow up for 6 months post-ART initiation.

Continuous and categorical variables were compared using chi-square and rank-sum tests. Multivariable analysis was performed using logistic regression.

Results

Figure 1. Flow chart of patient enrollment and follow up in study.



Results

Table 1. Baseline characteristics of cohort.

Variables	Overall	Died	Survived	P value
Patients with baseline CD4 counts, N	**170**	**18 (11)**	**152 (89)**	
Female sex, n (%)	74 (44)	12 (67)	62 (41)	0.04
Age, mean (range in years)	37 (22-73)	39 (27-56)	36 (22-73)	0.31
ATT to ART initiation interval, median days (IQR)	28 (20-47)	29 (20-49)	28 (19-47)	0.81
NVP-based ART, n (%)	24 (14)	6 (33)	18 (12)	0.01
BMI, median (IQR)	19 (17-22)	19 (18-25)	19 (17-22)	0.55
Viral load, median copies/ml*10^4 (IQR)	34 (11-100)	49 (26-78)	33 (8.9-100)	0.31
CD4 counts, median cells/μl (IQR)	60 (31-90)	35 (14-66)	62 (32-93)	0.02
PPD-specific response, median SFU/10^6 PBMCs (IQR); n*	248 (18-918); 130	67.5 (35-371); 12	266 (13-927); 118	0.40
IL-6, median pg/ml (IQR); n*	8.1 (4.5-17.2); 132	12.0 (6.3-40.6); 18	7.7 (4.3-16.4); 114	0.14
sCD14, median ug/ml (IQR); n*	3.5 (2.6-4.4); 88	3.9 (2.6-4.6); 8	3.4 (2.6-4.2); 80	0.54

IQR= interquartile range; ATT= anti-tubercular therapy; NVP= nevirapine based ART regimen. *PPD-specific responses, IL-6, and sCD14 levels were quantitated in a subset of patients.

Figure 2. Comparison of baseline DHEA-S (A), DHEA (B), and cortisol (C) levels between survivors and deaths.

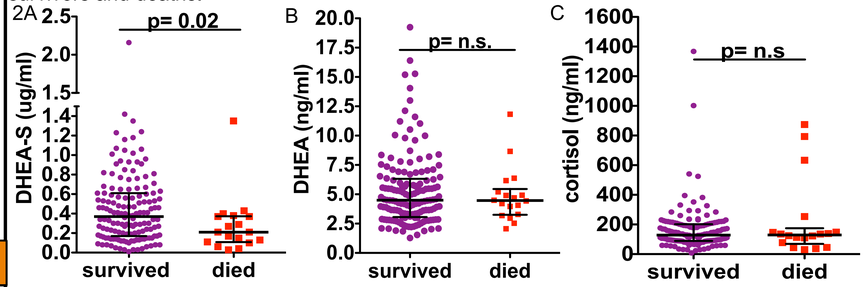


Table 2. Spearman correlation between baseline DHEA-S and immunologic parameters.

	Baseline		Week 4		Change from 0-4 weeks	
Immunologic parameter:	**Rho**	**P**	**Rho**	**P**	**Rho**	**P**
CD4 Count	0.06	0.43	0.05	0.54	0.04	0.58
TB-specific response	0.04	0.58	0.05	0.61	-0.10	0.24
IL-6	-0.08	0.34	-0.24	0.007	-0.17	0.06
sCD14	-0.33	0.002	-0.34	0.001	-0.007	0.90

Rho=spearman correlation coefficient; P= p value indicating significance level of the correlation.

Results

As levels of DHEA-S vary in men and women and DHEA has been shown to have sex-specific health effects[6,7], we explored gender differences in baseline DHEA-S levels and its association with early mortality.

Figure 3. Baseline DHEA-S levels stratified by sex (A). Comparison of baseline DHEA-S between women (B) and men (C) who survived and died.

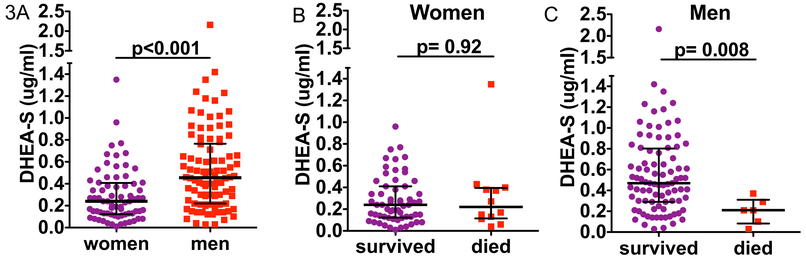


Table 3. Relationship between baseline DHEA-S and odds of early mortality.

Baseline DHEA-S: each 0.1ug/ml increase	Unadjusted OR (95% CI); P value	Adjusted OR (95% CI); P value
Overall cohort	0.82 (0.66 - 0.01); 0.06	0.87 (0.69 - 1.1); 0.28
Female	1.05 (0.83 - 1.34); 0.64	1.07 (0.83 - 1.4); 0.60
Male	0.54 (0.3 - 0.95); 0.03	0.50 (0.27 - 0.94); 0.03

Factors associated with death at a P value of ≤0.2 (Table 1) were considered as potential confounders and included in the multivariable logistic regression model to calculate adjusted Odds Ratios (OR) and 95% confidence intervals (CI). Baseline CD4, female sex, NVP regimen, and IL-6 were included in the final models. Protective effect of DHEA-S was not entirely independent of baseline CD4 count for the overall cohort.

Conclusions

Low baseline DHEA-S levels were associated with early mortality in unadjusted analyses. Baseline DHEA-S levels were:

1. inversely correlated with sCD14 levels, but did not correlate with immune recovery.
2. lower in women, but had a protective effect only in men. In men, every 0.1ug/ml increment in DHEA-S was independently associated with 46% decrease in odds of early mortality. A protective association of DHEA-S in men, but not women, has been shown for cardiovascular disease and depression.[6,7]

Reduced DHEA-S reserves persisted at week 4 post-ART initiation, while cortisol (p=0.011) and IL-6 (p=0.004) levels increased in deaths vs. survivors (data not shown).

More studies are needed to evaluate the therapeutic potential of DHEA or its synthetic derivatives in advance HIV/TB co-infected men and women.[2,8]

References: [1]Bottasso et al. Neuroimmunomodulation, 2009; [2]Quiroga et al. PLoS ONE, 2011; [3]Mayo et al. Arch Intern Med, 2002; [4]Krobath et al. J Clin Pharmacol, 1999; [5]Ravimohan et al. JID, 2013; [6]Hsu et al. Exp Gerontol. 2012; [7]Michikawa T et al. Am J Geriatr Psychiatry, 2013 ; [8] Hernandez-Pando et al. JID, 2005. **Acknowledgements**: NIAID- R01 AI80337 (Bisson, Weissman) and the patients who agreed to be part of this study.