DRAFT Neuropathy CROI 2011 Abstract

Abstract Title Impact of Nucleoside Backbone and Predictors of Change over 24 Weeks in Distal Leg Epidermal Nerve Fiber Density following Initiation of Potent Antiretroviral Therapy

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Background: Quantification of epidermal nerve fiber density (ENFD) is a validated predictor of small unmyelinated nerve fiber damage. We assessed week 0-24 change in distal leg ENFD within SEARCH 003, a 150 n antiretroviral (ARV) clinical trial in Bangkok, Thailand evaluating the mitochondrial toxicity potential of 3 different ARV regimens differing by nucleoside backbone [stavudine (d4T, 30 mg bid) vs zidovudine (ZDV) vs tenofovir (TDF)].

Methods: Four mm proximal thigh and distal leg skin punch biopsies were obtained at week 0 and week 24. Peripheral blood mononuclear cell (PBMC) oxidative phosphorylation (OXPHOS) complex I and complex IV protein and activity levels and monocyte (CD14+) HIV DNA levels were assessed in cryopreserved batched specimens. Statistical methods included ANOVA and multiple regression.

Results: Matched proximal thigh and distal leg ENFD values from week 0 (entry) and week 24 were available in 114 subjects with mean [SD] age at entry of 35.2 [7.7] yrs, CD4 count of 159 [92] cells/mm^3, and mean $\log_{10}$ HIV RNA of 4.9 [0.7] copies/ml. All subjects were free of neuropathy at baseline. At week 24, 85.9% had $\log_{10}$ HIV RNA <1.7 copies/ml and all remained free of clinical neuropathy. Substantial variation in distal leg ENFD change over 24 weeks was seen however, with median ENFD value (fibers/mm) of -1.66 [interquartile range: 9, min: -16.85, max: 36.73]. No difference in week 0-24 ENFD change was observed by nucleoside backbone (p=0.56). By multiple regression (estimated coefficient, p-value), baseline values of distal leg ENFD (-0.43, p<0.001), monocyte HIV DNA (-0.04, p=0.032), and PBMC OXPHOS complex I protein levels (-0.50, p=0.004) were significant predictors of ENFD change and baseline PBMC OXPHOS complex I activity showed marginal significance 0.28, p=0.070). Baseline CD4 count was a predictor on univariate analysis but its effect was reduced and no longer significant when baseline distal leg ENFD was added to the model.

Conclusions: Both deterioration and improvement in distal leg ENFD are seen over 24 weeks following initiation of potent ARV therapy. Use of d4T at a dose of 30 mg bid in

this population is not associated with poorer ENFD change compared to use of ZDV or TDF. Baseline distal leg ENFD, monocyte HIV DNA, and PBMC mitochondrial function as assessed by complex I OXPHOS protein/activity levels are more important predictors of improvement or deterioration in ENFD than choice of nucleoside backbone.