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Characterization of age-associated gut microbial dysbiosis and plasma metabolite alterations in people living with HIV (PLWH)

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Background: HIV-1 infection and aging are independently associated with gut microbial dysbiosis and neurocognitive impairment. However, the interactive effects of HIV-infection and aging on the development of specific pathogenic features of gut microbial dysbiosis and consequent metabolic abnormalities associated with neurocognitive dysfunction remain largely undetermined and were examined in the present study. **Methods:** PLWH participants (n=31) were enrolled from the HIV Care Clinic, UofL Medical Center. Fecal specimens, plasma, and demographic characteristics including age (50-70) were obtained. We performed metagenomic analysis of fecal microbiome employing 16S rRNA gene sequencing using the Illumina MiSeq platform and targeted metabolomics analysis of plasma employing direct injection mass spectrometry with a reverse-phase LC-MS/MS. Statistical analyses included the non-parametric Mann Whitney test and Spearman correlations. **Results:** Metagenomics analysis showed that gut dysbiosis associated with aging in PLWH is characterized by a significant reduction of the *Firmicutes/Bacteroidetes* (F/B) ratio and beneficial butyrate-producing family *Lachnospiraceae* and *Veillonellaceae* ($r>0.38$, $p=0.05$). Notably, the butyrate-producing families as a collective were significantly reduced ($p=0.02$) in the>60 age group. Further, metabolomics analysis of plasma showed that correspondent with a decrease in butyrate-producing bacteria, increasing age was associated with a significant decrease in butyric acid ($r=-0.41$, $p=0.04$) along with a decrease in i) serotonin ($r=-0.42$, $p=0.04$), ii) primary conjugated bile acids- glycocholic acid (GCA; $r=-0.46$, $p=0.02$) and glycochenodeoxycholic acid (GCDA; $r=-0.45$, $p=0.03$), iii) glutamate ($r=-0.43$, $p=0.03$) and glutamate to glutamine ratio (Glu/Gln, $r=-0.50$, $p=0.01$). **Conclusions:** Aging in PLWH is marked by loss of butyrate-producing bacteria (microbial dysbiosis) and is associated with pathogenic alterations in plasma metabolites that are linked with neurocognitive impairment.