OBJECTIVES: The use of thymidine NRTI (tNRTI) drugs for treatment of HIV, specifically stavudine and zidovudine, increases the risk of developing lipoatrophy – a pathology of the adipose tissue involving reduction in mitochondrial (mt) DNA copy numbers per adipocyte, tissue fibrosis and increased adipocyte death. Adipose tissue pathology in other settings represents a significant risk for cardiovascular health.

METHODS: To elucidate the pathogenesis of lipoatrophy, we have quantified proportional fat loss by DEXA-measured leg fat percentage normalized by body mass index (BMI), adipocyte tissue mtDNA by qPCR, adipose tissue macrophages by histological evaluation and adipokine expression (including IL-6, IL-8, TNF-α, MCP-1, HGF, resistin and adiponectin in fat and plasma samples) by lincoplex and luminex technology. Adipose tissue biopsies were obtained from consenting study participants from the West Australian observational HIV cohort, including samples from NRTI-treated patients (stavudine n=37, zidovudine n=65 and abacavir n=45) and ART-naïve patients (n=50).

RESULTS: Significant mtDNA depletion in subcutaneous fat was specifically associated with tNRTI treatment (P≤0.0001), with a more pronounced effect of stavudine > zidovudine (P<0.05). Values for abacavir NRTI therapy were comparable with ART-naïve samples (P=0.2). Adipocyte mtDNA depletion occurred relatively early (within 6 months) on tNRTI therapy and then equilibrated to a drug-specific level, whereas limb fat loss occurred more slowly over 1–3 years. During tNRTI therapy, nadir leg fat percentage/BMI correlated with increases in the number of adipose tissue macrophages (P<0.0001), as well as decreases in plasma adiponectin (P<0.05). Plasma adiponectin also correlated negatively with tissue protein expression of IL-6, IL-8, MCP-1 and HGF (P<0.05). Examining paired tissue samples from 15 individuals pre- and post-tNRTI switching, we found partial normalization of mtDNA, in that values were still significantly lower than ART-naïve individuals (P=0.01 after 1–6 months and P=0.05
after 8 months), but were also significantly increased from pre-switch levels ($P \leq 0.01$). Upon switching from thymidines, increases in adipocyte mtDNA correlated with decreases in adipose tissue inflammatory-related proteins leptin, MCP-1, HGF, resistin, PAI, IL-6 and IL-8 ($P=0.005$). We found poor correlations between the same analyte in plasma versus tissue measured at similar time points, with the exception of MCP-1 and IL-8 ($r \geq 0.5$ for both). Individuals with more severe lipoatrophy, as assessed by nadir leg fat percentage/BMI, showed less reduction in tissue expression of IL-6, IL-8, MCP-1 and HGF after switching from tNRTI treatment.

**CONCLUSIONS:** The study demonstrates that lipoatrophy shares a number of histopathological features with obesity, including adipose tissue inflammation and macrophage infiltration, although in this case adipocyte-specific mt toxicity appears to be a primary pathogenic mechanism. Those with most severe pathology appear to show the poorest recovery.

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