MITOCHONDRIAL HAPLOGROUPS, ANTIRETROVIRAL DRUGS, AND DIABETES RISK AMONG MEN WITH HIV

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BACKGROUND

- People with HIV (PWH) have a higher prevalence of diabetes mellitus (DM) compared to epidemiological comparable people without HIV
- Mitochondrial DNA (mtDNA) haplogroups represent the major branch points on the phylogenetic tree. Variation in mitochondrial haplogroups have been associated with aging-related complex diseases in the general population.
- We previously observed that African mtDNA haplogroups (L2 and L3) were associated with the risk of DM among women with HIV. .
- It is unclear to what extent this association is influenced by antiretroviral (ART) exposure.
- Our objective was to assess the association between mtDNA haplogroup and DM risk in men with African and European descent. We further evaluated the interaction between mtDNA haplogroup and D drug exposures in DM risk.

METHODS

- We included men without DM who had fasting glucose (FG) data available at baseline from the Multicenter AIDS Cohort Study (MACS).
- DM was defined by fasting glucose ≥ 126 mg/dL, the use of DM medication, a DM diagnosis, or hemoglobin A1c ≥ 6.5%.
- Self-reported time-varying exposure to mitochondrial-toxic ART (D-drugs; stavudine, zalcitabine, and didanosine) were obtained at 6-monthly visits.
- Haplogroups were determined from genotyping data using HaploGrep.
- We used multivariable Cox regression to examine the race-stratified association between common European (UK, JT) or African haplogroups (L2, L3) and hazard of DM over time. We further examined the association with and without D-drug exposure, as well as with a statistical interaction term.
- Models were controlled for principal components of genetic ancestry, age, BMI, HCV or HBV infection, and smoking.

Mitochondrial haplogroup *L3* increases the risk of incident diabetes in African-ancestry men with HIV. Exposure to mitochondrial-toxic ART further accentuates this risk.

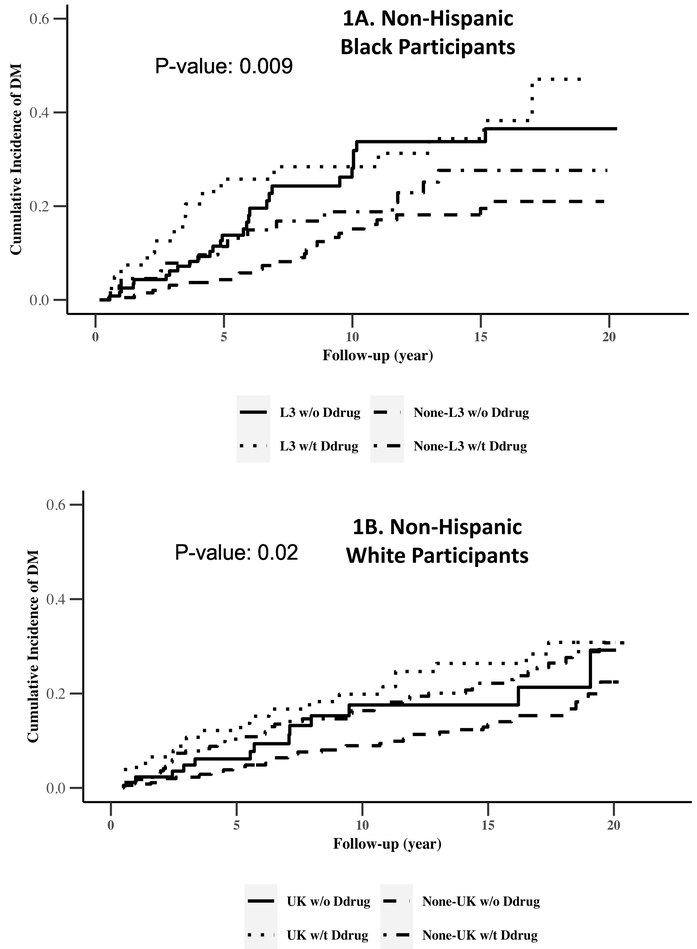
RESULTS

- Participants characteristics
  - Total: 2598 men (1249 men HIV, 1349 men without HIV), Median age: 44 years (IQR, 37, 50)
  - Non-Hispanic black: 667, non-Hispanic White: 1616
- Among PWH of African descent, Haplogroup L3 was associated with increased hazard of incident DM (HR: 1.92, 95% CI 1.2, 3.1), independent of covariates and D-drug exposures. D-drug exposure was independently associated with incident DM (HR: 2.8, 95%CI 1.5, 5.3). Men with haplogroup L3 and exposure to D-drugs took the shortest time to develop DM (median: 3.5 years), while men without L3 and D-drug exposures took the longest time to develop DM (median: 7 years; Figure 1A).
- No association between European haplogroup (UK or JT) and DM risk was observed. PWH with European haplogroup UK and exposure to D-drug had a significantly shorter time to incident DM, compared to other groups (**Figure 1B**).
- We did not observe association between mtDNA haplogroup and DM risk in men without HIV.

CONCLUSIONS

- A common mitochondrial DNA haplogroup L3 increases the risk of incident DM in African-ancestry men with HIV. This association was accentuated by exposure to mitochondrial-toxic ART, but was seen in all men having this haplogroup.
- Among men with European haplogroup, we observed strong association between D drug exposures and DM risk

Figure. Time to incident diabetes mellitus by mitochondrial DNA haplogroups and D-drug antiretroviral therapy exposures in the Multicenter AIDS Cohort Study (MACS).



ADDITIONAL KEY INFORMATION

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MWCCS MACS/WIHS COMBINED COHORT STUDY

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