MITOCHONDRIAL HAPLOGROUPS AND LEFT VENTRICULAR DYSFUNCTION IN PEOPLE LIVING WITH AND WITHOUT HIV

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BACKGROUND

- People with HIV (PWH) have a higher prevalence of left ventricular diastolic dysfunction (LVDD) compared to people without HIV (PWoH).
- Mitochondrial DNA (mtDNA) haplogroups are derived from a phylogenetic tree of global human mtDNA variation and can trace ancestral lineages and geographic origins. Variations have been associated with complex metabolic diseases.
- The mechanism for the relationship between cardiac dysfunction and HIV serostatus remains unclear, but may be related to mitochondrial dysfunction as metabolic changes occur in both.
- Exposure to mitochondrially toxic antiretroviral therapy, specifically D-drugs, are known to induce long-term mitochondrial dysfunction.
- Our objective was to evaluate the association between mtDNA haplogroups and LVDD in men and women with European and/or African ancestry. We further evaluated effects of D-drugs on LVDD.

METHODS

- We included men from the Multicenter AIDS Cohort Study (MACS) and women from the Women's Interagency HIV Study (WIHS) from previous echocardiographic studies.
- LVDD was defined using the Characterizing Heart Function on Antiretroviral Therapy (CHART) study criteria.
- mtDNA haplogroups were inferred from genotyping data with HaploGrep.
- Multivariable logistic regression models were used to examine the sex- and race-stratified association between LVDD and common African-ancestry haplogroups (L0L1, L2, L3, or "other") for males and females or European-ancestry haplogroups (H, UK, JT, or "other") for males. In PWH, we examined the association with and without D-drug exposure (previous use of stavudine, zalcitabine, and didanosine), as well as with a statistical interaction term between D-drug exposure and mitochondrial haplogroups.
- Models were controlled for principal components of nuclear genetic ancestry, age, enrollment site, BMI, educational level, alcohol intake, HCV status, smoking, non-injection + injection drug use, and clinical variables relevant for LVDD (HTN, DM, dyslipidemia, and eGFR). D-drug analysis controlled for CD4/CD8 ratio, history of clinical AIDS, 3-yr average HIV viremia, and nadir CD4.

Mitochondrial haplogroup **H** may *protect* against cardiac diastolic dysfunction, while **JT** may put people *at risk* in people living with HIV

Table 1. Characteristics of males and females by HIV status

	Overall		HIV-		HIV+	
	Female (n=898)	Male (n=842)	Female (n=278)	Male (n=387)	Female (n=620)	Male (n=455)
Age at visit (median, IQR)	52 (45, 57)	59 (53, 66)	51 (43, 58)	63 (56, 69)	52 (46, 57)	57 (50, 63)
BMI, kg/m² (median, IQR)	32 (27, 39)	27 (24, 30)	32 (26, 38)	27 (24, 30)	32 (26, 38)	27 (24, 30)
LVDD CHART (n, %)	264 (29%)	204 (24%)	89 (32%)	94 (24%)	175 (28%)	110 (24%)
Undetectable (n, %)	-	-	-	-	453 (73%)	355 (78%)
Previous D-drug use (n, %)					171 (28%)	206 (45%)

RESULTS

- Among men with HIV of European ancestry, odds of LVDD were 50% lower in haplogroup H than for men in non-H haplogroups (OR: 0.50, 95% CI: 0.26-0.93; **Figure 1**) and 109% higher in haplogroup JT than for men in non-JT haplogroups (OR: 2.09, 95% CI: 1.00, 4.36; **Figure 1**).
- Among women with haplogroups L2 and L3, HIV status modified the association (P_{int_L2}=0.036; **Figure 1**) (P_{int_L3}=0.045; **Figure 1**) .
- No significant associations between mtDNA haplogroups of African ancestry and LVDD among men or women living with HIV.
- Among PWoH, there were no significant associations between mtDNA haplogroups and LVDD.
- Previous D-drug exposure significantly increased the odds of LVDD among males, but had no significant effect on females (**Table 2**).
- No significant difference of LVDD with previous D-drug exposure by haplogroups, and no significant interaction between previous D-drug exposure and haplogroup on LVDD.

Figure 1. Adjusted odds ratio of LVDD for select haplogroups in males and females by HIV status

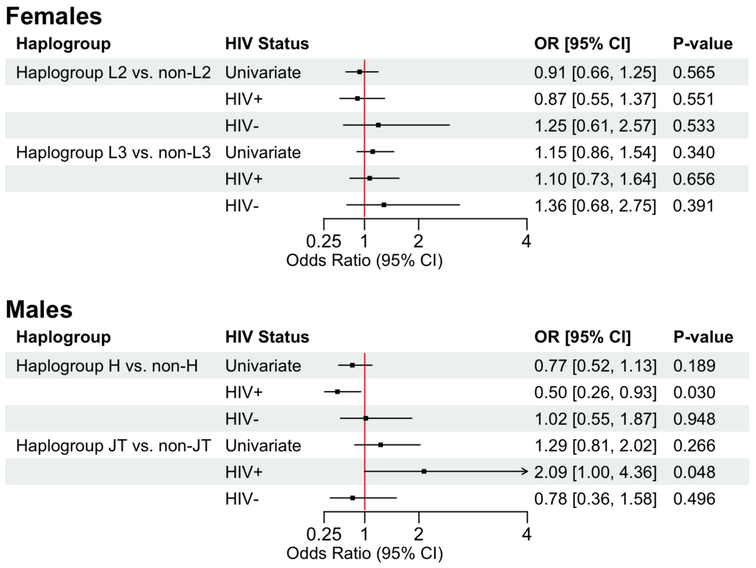


Table 2. Unadjusted and adjusted odds ratio of LVDD for PWH and previous D-drug exposure

	Univariate OR (95% CI)	Controlled for HIV disease severity OR (95% CI)
Overall	1.37 (1.04, 1.79)	1.31 (0.99, 1.74)
Female	1.11 (0.77, 1.58)	1.09 (0.74, 1.58)
Male	2.09 (1.35, 3.25)	1.94 (1.21, 3.13)

CONCLUSIONS

- Mitochondrial genetic variation may affect susceptibility to LVDD in men with HIV of European ancestry.
- Previous D-drug exposure increased the odds of LVDD among men with HIV.

MWCCS MACS/WIHS COMBINED COHORT STUDY

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