AIDS Rev. 2013;15:213-20

The Other Genome: A Systematic Review of Studies of Mitochondrial DNA Haplogroups and Outcomes of HIV Infection and Antiretroviral Therapy

Anna B. Hart[1], David C. Samuels[2] and Todd Hulgan[1]

[1]Department of Medicine, Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, TN, USA; [2]Department of Molecular Physiology and Biophysics, Center for Human Genetics Research, Vanderbilt University School of Medicine, Nashville, TN, USA

Abstract

Mitochondrial toxicity is implicated in some treatment-limiting antiretroviral therapy complications, and reports of mitochondrial dysfunction in untreated HIV infection suggest antiretroviral therapy independent effects of HIV. Several studies have explored associations between mtDNA haplogroups (patterns of mtDNA polymorphisms) and outcomes of HIV infection and/or antiretroviral therapy, but findings have been inconsistent. We systematically reviewed published studies examining mtDNA haplogroups in HIV-infected persons to summarize reported outcome associations, and to highlight potential future research directions. We identified 21 articles published from 2005-2013. Multiple different phenotypes were studied; most were antiretroviral therapy associated metabolic outcomes (e.g. lipodystrophy, insulin resistance, and dyslipidemia). Haplogroup H was associated with the most outcomes, including AIDS progression, CD4 T-cell recovery, cirrhosis (in hepatitis C coinfection), and metabolic outcomes. This review is the first to focus on the emerging area of mtDNA haplogroups in HIV, and summarizes the published literature on associations between mtDNA haplogroups and clinical outcomes in populations of European and African descent. Several reported associations require replication and ideally biological verification before definitive conclusions can be drawn, but research in this area has the potential to explain outcome disparities and impact clinical management of patients. **(AIDS Rev. 2013;15:213-20)**

Corresponding author: Todd Hulgan, todd.hulgan@vanderbilt.edu

Key words

HIV. Mitochondrial DNA. Haplogroup. Antiretroviral therapy.

Introduction

Potent antiretroviral therapy (ART) has significantly reduced the morbidity and mortality associated with HIV infection and AIDS[1]. The initial treatment for HIV-1 infection includes two nucleoside reverse-transcriptase inhibitors (NRTI) plus another agent from a second class, typically a protease inhibitor or nonnucleoside reverse-transcriptase inhibitor. Unfortunately, the use of these agents has been associated with treatment-limiting toxicities[2]. The NRTI inhibit viral replication by competing with endogenous cellular nucleotides for incorporation into proviral DNA and are relatively specific for HIV reverse transcriptase. However, NRTI also inhibit human mitochondrial DNA (mtDNA) polymerase-γ, which may lead to mtDNA depletion and mitochondrial dysfunction[3,4]. Mitochondrial dysfunction has been associated with toxicities such as peripheral neuropathy, lipodystrophy, myopathy/cardiomyopathy, pancreatitis, lactic acidosis, and hepatic steatosis[4]. Other ART classes have mitochondrial effects[5-7], and more contemporary ART-associated metabolic toxicities (e.g. dyslipidemia, insulin resistance, renal dysfunction, and bone disease) may also have a mitochondrial etiology[8-10]. Additionally, several antiretroviral drugs have been shown to induce mitochondrial toxicity through mechanisms other than the inhibition of mtDNA polymerase-γ[11-13].

Correspondence to:
Todd Hulgan
Division of Infectious Diseases
Vanderbilt University School of Medicine
A2200 MCN; 1161 21st 34 Ave South.
Nashville, TN 37232, USA
E-mail: todd.hulgan@vanderbilt.edu

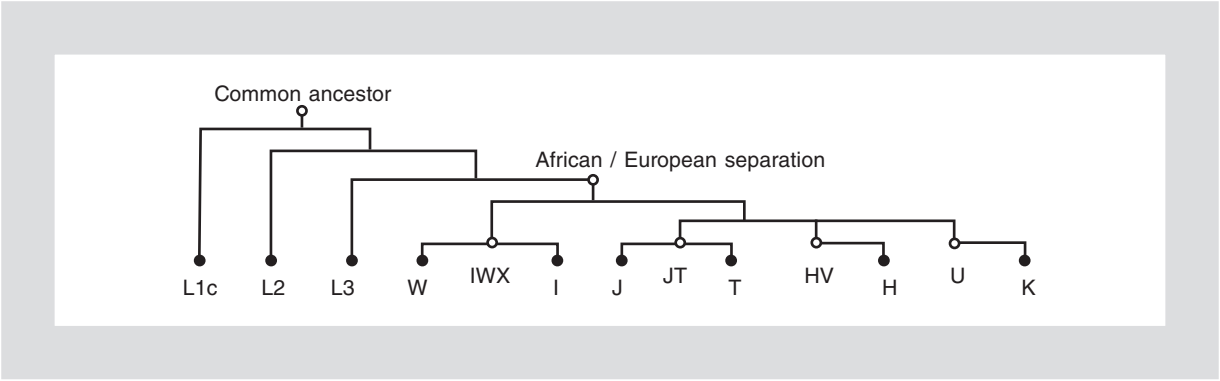

Figure 1. *Partial phylogenetic tree demonstrating approximate relationships between mtDNA haplogroups having significant associations reported in reviewed studies.*

Mitochondria play an important role in energy production and in other metabolic pathways such as biosynthesis of heme, cholesterol, and phospholipids, and are also major regulators of apoptosis[14,15]. Through oxidative phosphorylation, mitochondria convert calories to adenosine triphosphate (ATP) and generate reactive oxygen species (ROS). Each human cell contains hundreds of mitochondria and thousands of mtDNA. The human mitochondrial genome is inherited maternally and is made up of a circular double-stranded mtDNA molecule that encodes ribosomal RNA, transfer RNA, and 13 polypeptides that are essential for oxidative phosphorylation. Over millennia, single nucleotide polymorphisms in the mitochondrial genome have emerged. The combinations of these polymorphisms define mitochondrial haplotypes (generally referred to as "haplogroups")[16]. Mitochondrial haplogroups have a well defined phylogeny that has been used to map and understand prehistoric human migrations and genetic differences among populations[14]. Nine major haplogroups (H, T, U, V, W, X, J, I, and K) have been identified in persons of European descent (Fig. 1)[17]. Typically, a large proportion (approximately 40%) of any population of European descent is haplogroup H. Haplogroup structures are more complex in populations of African and Asian descent[16]. For a full description of the human mitochondrial phylogenetic tree we recommend the Phylotree resource (www.phylotree.org)[18].

Numerous studies have shown possible associations between haplogroups and aging and various diseases. For example, haplogroup J has been associated with longevity in northern Italians[19] and Finns[20]. It has also been shown to be protective against Parkinson's disease[21] and to increase the phenotypic expression of certain mutations associated with Leber hereditary optic neuropathy (LHON), a rare cause of adult-onset blindness[22]. Molecular mechanisms underlying functional differences between haplogroups are unknown, but may reflect impaired energy production. One possibility is that subtle functional effects of mtDNA variation represented by different haplogroups influence ATP production, ROS, heat generation, and apoptosis[23]. It is plausible that exposure to certain drugs, especially NRTI, may precipitate clinical mitochondrial dysfunction in genetically predisposed individuals. Case reports of late-onset LHON occurring in HIV-infected persons only after NRTI exposure lend support to this hypothesis[24].

In the last decade, several studies have explored associations between mtDNA haplogroups and outcomes of HIV infection and ART. Our objective was to systematically review published studies of mtDNA haplogroups in HIV-infected persons. We wanted to focus on this emerging and potentially important area, summarizing reported associations between mtDNA haplogroups and clinical outcomes that have been studied to date, assessing strengths and limitations of these data, and highlighting potential future research directions. The clinical implications of this area of research are not yet known, but could include: better genomic predictors of HIV disease and/or treatment outcomes; an improved understanding of host factors underlying outcome disparities; and informing the application of existing (and development of new) mitochondria-targeted interventions.

Search strategy and article selection

A systematic review was performed using PubMed and the search terms: Mitochondrial haplogroups OR mitochondrial genomics OR mitochondrial haplotypes AND HIV, without publication year restriction. Bibliographies

Table 1. Significant associations between outcomes and haplogroups by $p \leq 0.05$, and directions of association

Phenotypes	References	Haplogroups											
		L1c	L2	L3	W	IWX	I	J	JT	T	HV	H	U	K
Lipoatrophy	[35-37]				↓		↑			↓		↑		↑
Insulin resistance	[50, 51]										↓	↓	↑	
Dyslipidemia	[36, 41]			↑ (L3e1)*			↑†↓‡							
Atherogenic risk	[50]								↑	↑	↓	↓		
Peripheral neuropathy	[31-33]	↑↓								↑				
Hepatic fibrosis/ cirrhosis	[63]										↓	↓	↑§	
Neuroretinal disorders	[66]							↓				↓ (H3)	↓ (U5a)	
CD4 cell recovery	[73, 76]		↓¶					↓	↓			↑		
AIDS progression	[72, 75]					↓		↑			↓	↓ (H3)	↓ (Uk) ↑ (U5a)	

*Median fasting triglyceride and likelihood of hypertriglyceridemia; †Median total cholesterol, non-HDL, and LDL at baseline; ‡Median change in total cholesterol, non-HDL, LDL, and triglycerides at 96 weeks; §Association only seen with cirrhosis; ¶Same population and haplogroup had association with lower baseline and lower relative decrease in CD4 T-cell activation (% $CD38+/HLA^{-}DR^{+}$) at 48 weeks of ART[74].

were reviewed for additional publications. We included peer-reviewed studies that reported associations between mtDNA haplogroups and any phenotype in HIV-infected adults or HIV/ART-exposed children; non-English language publications were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[25] checklist and flow diagram were used (Supplementary data) to guide this review. After the initial PubMed search, article abstracts were reviewed to determine if inclusion criteria were met. All authors were required to agree that an article reported mtDNA haplogroups in an HIV-infected or exposed population, and that an association with an HIV-related phenotype was assessed. A single author (Hart) reviewed included articles and collected specific study information using a data abstraction table (Supplementary table). Uncertainties regarding specific study information were resolved by consensus decision of the authors.

Forty-four non-duplicate reports were identified through the initial search strategies (Flow diagram; Supplemental figure). After review, 21 of these met criteria for inclusion and qualitative review (Supplementary table). Of these, 11 were cohorts and 10 were cross-sectional analyses from cohort studies. Studies primarily included persons of either European or African descent, and sample sizes ranged from 29 to 1,833. The populations studied are difficult to define as multiple publications used study participants from the same cohorts. For example, five out of the 21 studies included participants from the AIDS clinical trials group (ACTG) study 384, two included subjects from the Multicenter AIDS Cohort Study (MACS), and two studies included subjects from a Spanish hepatitis C virus (HCV)/HIV-coinfection cohort. Therefore, 13 distinct populations and multiple phenotypes were evaluated in the reviewed articles. Genetic material for most reviewed studies was from peripheral blood or buccal smears; two studies used lymphoblastoid B-cell lines and one study used frozen leukocyte pellets. Various genotyping platforms were used (predominantly TaqMan and Affymetrix), and haplogroups were determined using multiple methods. In the sections that follow, we highlight relevant data from HIV-uninfected populations, then summarize findings from studies of related phenotypes in HIV-infected populations. Significant associations ($p \leq 0.05$) from these studies are summarized in table 1.

Associations with classic nucleoside reverse transcriptase inhibitor mitochondrial toxicities

Inherited mtDNA diseases commonly include neurodegenerative and/or neuropathy phenotypes. Familial amyloidotic polyneuropathy (FAP) is an autosomal, dominant-inherited systemic amyloidosis presenting clinically as a progressive sensory-motor peripheral neuropathy. Oxidative damage, caused by free radical injury and protein misfolding are thought to play a role in the pathogenesis of this disease. Since both of these processes involve mitochondria, a possible association has been investigated and haplogroup K was found to be associated with early-onset FAP in Swedish and French patients[26]. Peripheral neuropathy is common in HIV-infected persons, and is characterized by distal, symmetric anesthesia, and/or painful dysesthesia[27]. Peripheral neuropathy can develop in untreated HIV infection, but most cases have been seen in ART-treated individuals, particularly those treated with a NRTI[28]. Mitochondrial injury is thought to play a role in NRTI-associated peripheral neuropathy. Studies have shown depletion of mtDNA content in the neurons exposed to certain NRTI[29] and selective inhibition of the mtDNA polymerase-γ in neuronal cell lines[30]. In the reviewed studies, individuals with European haplogroup T and African haplogroup L1c had an increased risk of developing peripheral neuropathy (Table 1) in the ACTG study 384[31,32], but L1c was associated with a lower likelihood of HIV-associated sensory neuropathy in the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study[33]. These contrasting results highlight the need for careful selection of population and study design, and phenotype ascertainment.

Lipoatrophy is another consequence of NRTI exposure[34]. Mitochondrial toxicity is thought to play a primary role in the pathogenesis of this syndrome[34]. Associations between mtDNA haplogroups and lipoatrophy have been reported in US populations of non-Hispanic white race, and in an Italian population. Haplogroups H, I, and K were associated with increased lipoatrophy in HIV treated individuals, while haplogroups T and W were protective[35-37]. One of these studies[35] defined lipoatrophy clinically and used a cross-sectional analytic approach; the other[36] defined lipoatrophy as change in limb fat from baseline during ART using dual-energy X-ray absorptiometry (DEXA). The third study used both clinical criteria and anthropometric measurements[37]. Four other studies did not find statistically significant associations between haplogroups and lipoatrophy or lipodystrophy (a syndrome of mixed lipoatrophy and visceral lipohypertrophy, usually including dyslipidemia and insulin resistance), although two of these reported trends[38-41].

One study examined HIV-uninfected children that were exposed to antiretrovirals *in utero* and evaluated possible mtDNA haplogroup associations with diseases linked with mitochondrial dysfunction. Although haplogroup H tended to be less frequent in children with mitochondrial dysfunction, these results lacked statistical significance[42]. Finally, Arenas-Pinto, et al.[43] examined relationships between mtDNA polymorphisms and severe hyperlactatemia in small South African and European populations, and did not find statistically significant associations in either.

Associations with HIV-related and/or antiretroviral therapy related complications potentially having mitochondrial mechanisms

Mitochondria are known to play a key role in glucose metabolism, cellular energy balance, and ATP production, which has been linked to insulin secretion in pancreatic beta cells[44], and insulin resistance[45]. Therefore, it is thought that mtDNA alterations are involved in type 2 diabetes mellitus (T2DM). Associations between mtDNA haplogroups and T2DM have been observed in a Jewish population[46], persons from southern Brazil[47], and Asians[48]. Mechanisms by which mtDNA haplogroups modulate susceptibility to T2DM still remain elusive. Of note, a population-based study of Europeans did not find significant associations between common mtDNA variants and T2DM[49].

Insulin resistance is also part of the lipodystrophy syndrome, and its association with mtDNA haplogroups has been recently evaluated. Micheloud, et al. found that individuals with insulin resistance, defined by the homeostatic model assessment (HOMA), were more likely to belong to haplogroup U and less likely to belong to haplogroup H or the combined haplogroup HV[50]. Although not a primary outcome, we also recently reported an association between haplogroup U and increased HOMA after 24 weeks of ART in a small ACTG cardiovascular substudy (A5152s) population[51].

Mitochondria are also thought to play a role in cardiovascular diseases. One study proposed that failure in DNA repair and mitochondrial dysfunction contributes to hyperlipidemia and increased fat storage, promoting atherosclerosis and the metabolic syndrome[52]. Various mtDNA haplogroups have been associated

with hypertrophic cardiomyopathy in a cohort of HIV-uninfected Spanish patients[53], increased risk for coronary atherosclerosis in elderly Japanese[54], and protection against the development of metabolic syndrome in Japanese women[55]. However, a study conducted by Benn, et al.[56] did not find associations between mitochondrial haplogroups and risk of ischemic cardiovascular disease in a large population of European descent. Mitochondria play a major role in energy metabolism; thus, mitochondrial dysfunction is thought to play a role in cardiovascular risk factors like metabolic disorders and obesity. Haplogroup X was found to be strongly associated with both body mass index and body fat mass in Caucasian subjects[57]. In another study, no associations between body mass index and common mtDNA variants were seen[49].

Metabolic syndrome and increased cardiovascular risk have been seen in HIV-infected patients treated with ART including protease inhibitors[8]. Mechanisms by which mtDNA variation may influence ART-associated dyslipidemia are not known, but mitochondrial function is thought to play a role in lipid metabolism[58] and cardiovascular disease[59]. Two studies reported significant associations between haplogroups and lipid parameters[36,50]. Non-Hispanic white individuals in the ACTG study A5142 belonging to haplogroup I had higher lipids at baseline (pre-ART), and also had significantly greater percentage decreases in non-HDL cholesterol at week 96 of ART[36]. Micheloud, et al. further investigated cardiovascular risk using the atherogenic index (total cholesterol/HDL) and observed that haplogroups T and JT were associated with a high atherogenic index, while haplogroups H and HV were protective[50]. In a cross-sectional analysis of an Italian metabolic clinic cohort, no statistically significant associations between European mtDNA haplogroups and metabolic abnormalities (glucose and lipids), viro-immunological features (HIV viral load, CD4 cell count, and nadir CD4 cell count), or acid-base parameters (lactate level and anion gap) were observed[39]. A recent study of black South Africans in Cape Town identified an association between a L3 sub-haplogroup (L3e1) and hypertriglyceridemia in predominantly protease-inhibitor-treated subjects[41].

Persons coinfected with HIV and HCV exhibit a higher rate of liver fibrosis and cirrhosis as compared to HCV mono-infected patients[60]. Hepatitis C is thought to lead to liver damage in part by increasing lipoperoxidation, which may lead to the depletion of mtDNA and eventually increased ROS production[61]. Recent data also demonstrated adverse effects of HCV infection on hepatic mitochondrial function, particularly in complex IV[62]. Three European haplogroups were found to be associated with fibrosis and cirrhosis in a Spanish cohort: haplogroups H and HV were less likely to have advanced fibrosis and cirrhosis, while haplogroup U was associated with greater likelihood of cirrhosis[63].

As mentioned above, background mitochondrial haplogroup variations have been found in various genetic and acquired neuro-ophthalmic diseases such as LHON, and haplogroup J has been associated with the expression of certain LHON mutations[24,64]. Neuroretinal disorder (NRD) is a cause of visual dysfunction that results in abnormal contrast sensitivity, color vision, and visual fields[65]. The pathogenesis of HIV-associated NRD is unknown, but mitochondria and mtDNA variation likely play a role in this disease, based on studies of LHON[24]. Hendrickson, et al. examined associations between NRD and haplogroups in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) cohort. They observed that haplogroups J, U5a, and H3 were associated with delayed progression to NRD in HIV-infected individuals of European descent[66].

Associations with HIV disease progression and CD4 T-cell recovery

Apart from the potential relationships between mtDNA and ART toxicity, mitochondrial function plays a critical role in T-cell function and turnover[6,67-71]. Progression of AIDS and CD4 cell recovery after ART initiation have not been confirmed to be linked to mitochondrial function, but investigations by several groups suggest there might be a relationship between these outcomes and mtDNA variation. Haplogroups J and U5a were associated with accelerated progression to AIDS and death, while haplogroups Uk, H3, and IWX appeared to be protective against AIDS progression[72]. In another study, African haplogroup L2 was associated with poorer CD4 cell recovery 48 weeks after ART initiation among non-Hispanic blacks in the ACTG Study 384[73], and the same haplogroup was associated with lower CD4 T-cell activation (measured by CD38/HLA-DR expression) at baseline, and less decrease in activation after 48 weeks of ART in this population[74]. No European haplogroups were statistically associated with CD4 cell recovery in that analysis. Two recent studies from Spain have also reported associations between European haplogroup H (and clade HV) and lower likelihood of AIDS progression[75] and improved CD4 count recovery during at least 24 months of follow-up after initiating ART[76].

Summary and limitations of reviewed studies

The field of mitochondrial medicine has exhibited a major expansion in the last two decades[14,77]. The fundamental question of why human mtDNA haplogroups could have functional differences remains controversial[23,78-81]. This review focused on the emerging area of mtDNA haplogroups in HIV infection, and we have summarized associations between mtDNA haplogroups and clinical outcomes to date. Similar to HIV-uninfected populations, mitochondrial haplogroups have been found to be associated with insulin resistance, cardiovascular disease, lipids, neuroretinal disorders, and abnormal fat metabolism and/or distribution (lipodystrophy) in HIV-infected individuals. Additionally, associations between mitochondrial haplogroups and HIV-specific phenotypes such as AIDS progression and CD4 recovery have also been reported. Though the effects of some ART on mitochondrial function and their associated clinical toxicities are well recognized, it is also important to note that there are direct effects of HIV on mitochondrial function and mtDNA that may be influenced by mtDNA variation and/or affected by subsequent ART. Several studies in recent years have observed abnormal mitochondrial phenotypes (including decreased mtDNA quantity) in peripheral blood mononuclear cells from ART-naive HIV-infected compared with HIV-negative individuals[68,70,82,83].

There are several limitations of the reviewed studies. Genetic association studies require large sample sizes in order to identify significant differences in populations. The largest study in our review had only 1,833 subjects[72], with most others having substantially fewer, limiting the capacity to identify significant associations. Many studies reported trends in their data that might (or might not) have been significant with a larger sample size. While this may have introduced type II error and false negative associations, type I error and false positive associations are also likely. Few studies explicitly addressed adjustment of p-value to correct for multiple comparisons, perhaps in part because there is no standard approach. Additionally, there is inconsistency in the reporting of combined haplogroups used in some studies. As mentioned previously, not only were the studied populations small, but many included overlapping cohort populations. Furthermore, most of the studies included HIV-infected populations of European ancestry, thus there is a notable lack of published studies in populations of African descent, and none to date in Asian populations. This is discordant with the populations most affected by the HIV pandemic. Multiple phenotypes were investigated and multiple studies examined similar phenotypes using different methods and/or definitions, therefore introducing the potential for ascertainment bias in phenotypic classification. For example, lipoatrophy/lipodystrophy was assessed in some studies using DEXA[36,38,39,41], while others used clinical assessments and physical exam[35,37,40]. Antiretroviral therapy is associated with mitochondrial injury and clinical toxicities; most of the reviewed studies either excluded ART-treated subjects or adjusted for ART use (Supplementary Table). Finally, the most glaring limitation of the studies in this area is the lack of replication to confirm preliminary associations. It is well known that initial associations tend to overestimate effect size and are rarely replicated in independent datasets[84]. Due to several of the factors discussed above (e.g. small sample sizes, inconsistent phenotype definitions), as well as limited cohorts available, replication studies in this field have lagged.

The methods of defining mitochondrial haplogroups have developed rapidly in recent years. The earliest studies relied on limited single nucleotide polymorphism lists with nucleotide calls based on TaqMan Assays. These older methods relied on haplogroup definitions[17] that were sufficient for the definition of the major European haplogroups, but that are insufficient for the full range of African or Asian haplogroups. More recent studies[32,33,73] have used chip-based sequencing methods that give more sequence information and allow for more robust haplogroup assignments, though methods based on a more limited number of target single nucleotide polymorphisms are still used due to their low cost.

Conclusions

Our paper offers the first review of the emerging area of mitochondrial haplogroups, HIV infection, and clinical outcomes. Although provocative, reported associations are inconclusive due to heterogeneous methods and outcomes, limited racial/ethnic groups, lack of replication, and inadequate statistical power. Further studies are needed to clarify the role of mitochondrial genetics in the pathogenesis of various clinical outcomes and toxicities associated with ART, and to elucidate the importance of mitochondrial function and genetic variation in HIV disease outcomes and aging, independent of drug toxicities. Future investigations could combine existing study populations using uniform phenotype definitions and a meta-analytic approach in increased

sample sizes. New studies in larger populations (either existing cohort studies with capacity for genetic analyses or inclusion of mtDNA haplogroups in prospective studies that incorporate genetic studies and DNA collection[85]) would allow for replication (or refutation) of previous associations and identification of associations previously missed due to limited sample sizes. Finally, as mentioned earlier, there is only a limited amount of information available about possible mechanisms behind the various associations, and the role of mitochondrial function in these phenotypes will require continued investigation. Definitive conclusions cannot yet be drawn, but research in this area has the potential to explain, at least in part, disparities in outcomes and impact patient management across diverse populations affected by HIV.

Conflicts of interest and source of funding

This work was supported in part by funding from the National Institutes of Health, grants DA029506 and MH095621 (to Hulgan). The funding agencies were not involved in the performance of the work, interpretation of results, or the writing of the manuscript. Hulgan has served as PI of research grants provided to his institution by Merck & Co. The other authors report no potential conflicts of interest.

References

1. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet. 2003;362:22-9.
2. Lewis W, Dalakas M. Mitochondrial toxicity of antiviral drugs. Nat Med. 1995;1:417-22.
3. Mallon P, Unemori P, Sedwell R, et al.; SAMA Investigators. In vivo, nucleoside reverse-transcriptase inhibitors alter expression of both mitochondrial and lipid metabolism genes in the absence of depletion of mitochondrial DNA. J Infect Dis. 2005;191:1686-96.
4. Brinkman K, ter Hofstede H, Burger D, Smeitink J, Koopmans P. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS. 1998;12:1735-44.
5. Matarrese P, Tinari A, Gambardella L, et al. HIV protease inhibitors prevent mitochondrial hyperpolarization and redox imbalance and decrease endogenous uncoupler protein-2 expression in gp 120-activated human T lymphocytes. Antivir Ther. 2005;10(Suppl 2):M29-45.
6. Karamchand L, Dawood H, Chuturgoon A. Lymphocyte mitochondrial depolarization and apoptosis in HIV-1-infected HAART patients. J Acquir Immune Defic Syndr. 2008;48:381-8.
7. Viengchareun S, Caron M, Auclair M, et al. Mitochondrial toxicity of indinavir, stavudine and zidovudine involves multiple cellular targets in white and brown adipocytes. Antivir Ther. 2007;12:919-29.
8. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med. 2005;352:48-62.
9. McComsey G, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010;51:937-46.
10. Rodriguez-Novoa S, Alvarez E, Labarga P, Soriano V. Renal toxicity associated with tenofovir use. Expert Opin Drug Saf. 2010;9:545-59.
11. Apostolova N, Blas-Garcia A, Esplugues J. Mitochondrial interference by anti-HIV drugs: mechanisms beyond Pol-gamma inhibition. Trends Pharmacol Sci. 2011;32:715-25.
12. Lewis W, Copeland W, Day B. Mitochondrial DNA depletion, oxidative stress, and mutation: mechanisms of dysfunction from nucleoside reverse transcriptase inhibitors. Lab Invest. 2001;81:777-90.
13. Olivero O. Mechanisms of genotoxicity of nucleoside reverse transcriptase inhibitors. Environ Mol Mutagen. 2007;48:215-23.
14. Wallace D. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. Annu Rev Genet. 2005;39:359-407.
15. Dzikaite V, Kanopka A, Brock J, Kazlauskas A, Melefors O. A novel endoproteolytic processing activity in mitochondria of erythroid cells and the role in heme synthesis. Blood. 2000;96:740-6.
16. Wallace D. Mitochondrial DNA sequence variation in human evolution and disease. Proc Natl Acad Sci USA. 1994;91:8739-46.
17. Torroni A, Huoponen K, Francalacci P, et al. Classification of European mtDNAs from an analysis of three European populations. Genetics. 1996;144:1835-50.
18. van Oven M, Kayser M. Updated comprehensive phylogenetic tree of global human mitochondrial DNA variation. Hum Mutat. 2009;30: E386-94.
19. De Benedictis G, Rose G, Carrieri G, et al. Mitochondrial DNA inherited variants are associated with successful aging and longevity in humans. Faseb J. 1999;13:1532-6.
20. Niemi A, Hervonen A, Hurme M, Karhunen P, Jylha M, Majamaa K. Mitochondrial DNA polymorphisms associated with longevity in a Finnish population. Hum Genet. 2003;112:29-33.
21. van der Walt J, Nicodemus K, Martin E, et al. Mitochondrial polymorphisms significantly reduce the risk of Parkinson disease. Am J Hum Genet. 2003;72:804-11.
22. Brown M, Starikovskaya E, Derbeneva O, et al. The role of mtDNA background in disease expression: a new primary LHON mutation associated with Western Eurasian haplogroup J. Hum Genet. 2002; 110:130-8.
23. Gomez-Duran A, Pacheu-Grau D, Lopez-Gallardo E, et al. Unmasking the causes of multifactorial disorders: OXPHOS differences between mitochondrial haplogroups. Hum Mol Genet. 2010;19:3343-53.
24. Mackey D, Fingert J, Luzhansky J, et al. Leber's hereditary optic neuropathy triggered by antiretroviral therapy for human immunodeficiency virus. Eye (Lond). 2003;17:312-17.
25. Moher D, Liberati A, Tetzlaff J, Altman D, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
26. Olsson M, Hellman U, Plante-Bordeneuve V, Jonasson J, Lang K, Suhr O. Mitochondrial haplogroup is associated with the phenotype of familial amyloidosis with polyneuropathy in Swedish and French patients. Clin Genet. 2009;75:163-8.
27. Keswani S, Pardo C, Cherry C, Hoke A, McArthur J. HIV-associated sensory neuropathies. AIDS. 2002;16:2105-17.
28. Kelleher T, Cross A, Dunkle L. Relation of peripheral neuropathy to HIV treatment in four randomized clinical trials including didanosine. Clin Ther. 1999;21:1182-92.
29. Cui L, Locatelli L, Xie M, Sommadossi J. Effect of nucleoside analogs on neurite regeneration and mitochondrial DNA synthesis in PC-12 cells. J Pharmacol Exp Ther. 1997;280:1228-34.
30. Dalakas M, Semino-Mora C, Leon-Monzon M. Mitochondrial alterations with mitochondrial DNA depletion in the nerves of AIDS patients with peripheral neuropathy induced by 2'3'-dideoxycytidine (ddC). Lab Invest. 2001;81:1537-44.
31. Hulgan T, Haas D, Haines J, et al. Mitochondrial haplogroups and peripheral neuropathy during antiretroviral therapy: an adult AIDS clinical trials group study. AIDS. 2005;19:1341-9.
32. Canter J, Robbins G, Selph D, et al. African mitochondrial DNA subhaplogroups and peripheral neuropathy during antiretroviral therapy. J Infect Dis. 2010;201:1703-7.
33. Holzinger E, Hulgan T, Ellis R, et al. Mitochondrial DNA variation and HIV-associated sensory neuropathy in CHARTER. J Neurovirol. 2012;18:511-20.
34. Feeney E, Mallon P. Impact of mitochondrial toxicity of HIV-1 antiretroviral drugs on lipodystrophy and metabolic dysregulation. Curr Pharm Des. 2010;16:3339-51.
35. Hendrickson S, Kingsley L, Ruiz-Pesini E, et al. Mitochondrial DNA haplogroups influence lipoatrophy after highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2009;51:111-16.
36. Hulgan T, Haubrich R, Riddler S, et al. European mitochondrial DNA haplogroups and metabolic changes during antiretroviral therapy in AIDS Clinical Trials Group Study A5142. AIDS. 2011;25:37-47.
37. De Luca A, Nasi M, Di Giambenedetto S, et al. Mitochondrial DNA haplogroups and incidence of lipodystrophy in HIV-infected patients on long-term antiretroviral therapy. J Acquir Immune Defic Syndr. 2012;59:113-20.
38. Hulgan T, Tebas P, Canter J, et al. Hemochromatosis gene polymorphisms, mitochondrial haplogroups, and peripheral lipoatrophy during antiretroviral therapy. J Infect Dis. 2008;197:858-66.
39. Nasi M, Guaraldi G, Orlando G, et al. Mitochondrial DNA haplogroups and highly active antiretroviral therapy-related lipodystrophy. Clin Infect Dis. 2008;47:962-8.
40. Ortiz M, Poloni E, Furrer H, et al. No longitudinal mitochondrial DNA sequence changes in HIV-infected individuals with and without lipoatrophy. J Infect Dis. 2011;203:620-4.
41. Sinxadi P, Dave J, Samuels D, et al. Mitochondrial genomics and antiretroviral therapy-associated metabolic complications in HIV-infected Black South Africans: A pilot study. AIDS Res Hum Retroviruses. 2013;29:1031-9.

42. Brogly S, DiMauro S, Van Dyke R, et al. Short communication: transplacental nucleoside analogue exposure and mitochondrial parameters in HIV-uninfected children. AIDS Res Hum Retroviruses. 2011;27:777-83.
43. Arenas-Pinto A, Weller I, Ekong R, et al. Common inherited mitochondrial DNA mutations and nucleoside reverse transcriptase inhibitor-induced severe hyperlactataemia in HIV-infected adults: an exploratory study. Antivir Ther. 2012;17:275-82.
44. Maechler P, Wollheim C. Mitochondrial function in normal and diabetic beta-cells. Nature. 2001;414:807-12.
45. Szendroedi J, Phielix E, Roden M. The role of mitochondria in insulin resistance and type 2 diabetes mellitus. Nat Rev Endocrinol. 2011; 8:92-103.
46. Feder J, Ovadia O, Blech I, et al. Parental diabetes status reveals association of mitochondrial DNA haplogroup J1 with type 2 diabetes. BMC Med Genet. 2009;10:60.
47. Crispim D, Canani L, Gross J, Tschiedel B, Souto K, Roisenberg I. The European-specific mitochondrial cluster J/T could confer an increased risk of insulin-resistance and type 2 diabetes: an analysis of the m.4216T > C and m.4917A > G variants. Ann Hum Genet. 2006;70:488-95.
48. Fuku N, Park K, Yamada Y, et al. Mitochondrial haplogroup N9a confers resistance against type 2 diabetes in Asians. Am J Hum Genet. 2007;80:407-15.
49. Saxena R, de Bakker P, Singer K, et al. Comprehensive association testing of common mitochondrial DNA variation in metabolic disease. Am J Hum Genet. 2006;79:54-61.
50. Micheloud D, Berenguer J, Guzman-Fulgencio M, et al. European mitochondrial DNA haplogroups and metabolic disorders in HIV/HCV-coinfected patients on highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2011;58:371-8.
51. Hulgan T, Stein J, Cotter B, et al. Mitochondrial DNA variation and changes in adiponectin and endothelial function in HIV-infected adults after antiretroviral therapy initiation. AIDS Res Hum Retroviruses. 2013;29:1293-9.
52. Mercer J, Cheng K, Figg N, et al. DNA damage links mitochondrial dysfunction to atherosclerosis and the metabolic syndrome. Circ Res. 2010;107:1021-31.
53. Castro M, Huerta C, Reguero J, et al. Mitochondrial DNA haplogroups in Spanish patients with hypertrophic cardiomyopathy. Int J Cardiol. 2006;112:202-06.
54. Sawabe M, Tanaka M, Chida K, et al. Mitochondrial haplogroups A and M7a confer a genetic risk for coronary atherosclerosis in the Japanese elderly: an autopsy study of 1,536 patients. J Atheroscler Thromb. 2011;18:166-75.
55. Tanaka M, Fuku N, Nishigaki Y, et al. Women with mitochondrial haplogroup N9a are protected against metabolic syndrome. Diabetes. 2007;56:518-21.
56. Benn M, Schwartz M, Nordestgaard B, Tybjaerg-Hansen A. Mitochondrial haplogroups: ischemic cardiovascular disease, other diseases, mortality, and longevity in the general population. Circulation. 2008;117:2492-501.
57. Yang T, Guo Y, Shen H, et al. Genetic association study of common mitochondrial variants on body fat mass. PLoS One. 2011;6:e21595.
58. De Pauw A, Tejerina S, Raes M, Keijer J, Arnould T. Mitochondrial (dys) function in adipocyte (de)differentiation and systemic metabolic alterations. Am J Pathol. 2009;175:927-39.
59. Madamanchi N, Runge M. Mitochondrial dysfunction in atherosclerosis. Circ Res. 2007;100:460-73.
60. Graham C, Baden L, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001;33:562-9.
61. Barbaro G, Di Lorenzo G, Asti A, et al. Hepatocellular mitochondrial alterations in patients with chronic hepatitis C: ultrastructural and biochemical findings. Am J Gastroenterol. 1999;94:2198-205.
62. Chapplain J, Tattevin P, Guyader D, et al. Mitochondrial abnormalities in patients with HIV-HCV co-infection as compared to patients with HCV mono-infection. HIV Clin Trials. 2011;12:54-60.
63. Garcia-Alvarez M, Guzman-Fulgencio M, Berenguer J, et al. European mitochondrial DNA haplogroups and liver fibrosis in HIV and hepatitis C virus coinfected patients. AIDS. 2011;25:1619-926.
64. Torroni A, Petrozzi M, D'Urbano L, et al. Haplotype and phylogenetic analyses suggest that one European-specific mtDNA background plays a role in the expression of Leber hereditary optic neuropathy by increasing the penetrance of the primary mutations 11778 and 14484. Am J Hum Genet. 1997;60:1107-21.
65. Shah K, Holland G, Yu F, Van Natta M, Nusinowitz S. Contrast sensitivity and color vision in HIV-infected individuals without infectious retinopathy. Am J Ophthamol. 2006;142:284-92.
66. Hendrickson S, Jabs D, Van Natta M, Lewis R, Wallace D, O'Brien S. Mitochondrial haplogroups are associated with risk of neuroretinal disorder in HIV-positive patients. J Acquir Immune Defic Syndr. 2010;53:451-5.
67. Petrovas C, Mueller Y, Dimitriou I, et al. Increased mitochondrial mass characterizes the survival defect of HIV-specific CD8(+) T cells. Blood. 2007;109:2505-13.
68. Casula M, Vrisekoop N, Wit F, et al. Mitochondrial DNA decline in T cells of HIV-1 seroconverters may be dependent on immune activation. J Infect Dis. 2007;196:371-6.
69. Grimaldi M, Denizot M, Espert L, Robert-Hebmann V, Biard-Piechaczyk M. Mitochondria-dependent apoptosis in T-cell homeostasis. Curr Opin Investig Drugs. 2005;6:1095-102.
70. Maagaard A, Holberg-Petersen M, Kvittingen E, Sandvik L, Bruun J. Depletion of mitochondrial DNA copies/cell in peripheral blood mononuclear cells in HIV-1-infected treatment-naive patients. HIV Med. 2006;7:53-8.
71. Mussini C, Pinti M, Bugarini R, et al. Effect of treatment interruption monitored by CD4 cell count on mitochondrial DNA content in HIV-infected patients: a prospective study. AIDS. 2005;19:1627-33.
72. Hendrickson S, Hutcheson H, Ruiz-Pesini E, et al. Mitochondrial DNA haplogroups influence AIDS progression. AIDS. 2008;22:2429-39.
73. Grady B, Samuels D, Robbins G, et al. Mitochondrial genomics and CD4 T-cell count recovery after antiretroviral therapy initiation in AIDS clinical trials group study 384. J Acquir Immune Defic Syndr. 2011;58:363-70.
74. Hulgan T, Robbins G, Kalams S, et al. T cell activation markers and African mitochondrial DNA haplogroups among non-Hispanic black participants in AIDS clinical trials group study 384. PLoS One. 2012;7:e43803.
75. Guzman-Fulgencio M, Jimenez J, Garcia-Alvarez M, et al. Mitochondrial haplogroups are associated with clinical pattern of AIDS progression in HIV-infected patients. J Acquir Immune Defic Syndr. 2013;63:178-83.
76. Guzman-Fulgencio M, Berenguer J, Micheloud D, et al. European mitochondrial haplogroups are associated with CD4+ T cell recovery in HIV-infected patients on combination antiretroviral therapy. J Antimicrob Chemother. 2013;68:2349-57.
77. Dimauro S, Davidzon G. Mitochondrial DNA and disease. Ann Med. 2005;37:222-32.
78. Pereira L, Soares P, Radivojac P, Li B, Samuels D. Comparing phylogeny and the predicted pathogenicity of protein variations reveals equal purifying selection across the global human mtDNA diversity. Am J Hum Genet. 2011;88:433-9.
79. Kivisild T, Shen P, Wall D, et al. The role of selection in the evolution of human mitochondrial genomes. Genetics. 2006;172:373-87.
80. Ruiz-Pesini E, Mishmar D, Brandon M, Procaccio V, Wallace D. Effects of purifying and adaptive selection on regional variation in human mtDNA. Science. 2004;303:223-6.
81. Mishmar D, Ruiz-Pesini E, Golik P, et al. Natural selection shaped regional mtDNA variation in humans. Proc Natl Acad Sci USA. 2003;100:171-6.
82. Miura T, Goto M, Hosoya N, et al. Depletion of mitochondrial DNA in HIV-1-infected patients and its amelioration by antiretroviral therapy. J Med Virol. 2003;70:497-505.
83. Sternfeld T, Tischleder A, Schuster M, Bogner J. Mitochondrial membrane potential and apoptosis of blood mononuclear cells in untreated HIV-1 infected patients. HIV Med. 2009;10:512-19.
84. Zollner S, Pritchard J. Overcoming the winner's curse: estimating penetrance parameters from case-control data. Am J Hum Genet. 2007;80:605-15.
85. Haas D, Kuritzkes D, Ritchie M, et al. Pharmacogenomics of HIV therapy: summary of a workshop sponsored by the National Institute of Allergy and Infectious Diseases. HIV Clin Trials. 2011;12:277-85.
86. Herrnstadt C, Elson J, Fahy E, et al. Reduced-median-network analysis of complete mitochondrial DNA coding-region sequences for the major African, Asian, and European haplogroups. Am J Hum Genet. 2002;70:1152-71.
87. Behar D, Rosset S, Blue-Smith J, et al. The Genographic Project public participation mitochondrial DNA database. PLoS Genet. 2007;3:e104.