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REVIEW

Long-term persistence of mitochondrial dysfunctions after viral infections and antiviral therapies: A review of mechanisms involved

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Abstract

Mitochondria are vital for most cells' functions. Viruses hijack mitochondria machinery for misappropriation of energy supply or to bypass defense mechanisms. Many of these mitochondrial dysfunctions persist after recovery from treated or untreated viral infections, particularly when mitochondrial DNA is permanently damaged. Quantitative defects and structural rearrangements of mitochondrial DNA accumulate in post-mitotic tissues as recently reported long after SARS-CoV-2 or HIV infection, or following antiviral therapy. These observations are consistent with the "hit-and-run" concept proposed decades ago to explain viro-induced cell transformation and it could apply to delayed post-viral onsets of symptoms and advocate for complementary supportive care. Thus, according to this concept, following exposure to viruses or antiviral agents, mitochondrial damage could evolve into an autonomous clinical condition. It also establishes a pathogenic link between communicable and non-communicable chronic diseases.

KEYWORDS

antiviral treatment, delayed disease onset, genetic alterations, hit-and-run concept, mitochondria, virus

1 | INTRODUCTION

Mitochondria are cytoplasmic organelles playing a major role in cellular energy production as well as in many metabolic and signaling pathways. This energy production is enabled by a cascade of oxidations along the mitochondrial respiratory chain (MRC).¹ Mitochondrial activities and mass are tightly regulated through a cross-talk with the nucleus, which encodes most of mitochondrial proteins, through coordinated regulatory networks.² Because of their endosymbiotic prokaryote origin, mitochondria possess their own DNA

(mtDNA), exclusively maternally transmitted with a semi-autonomous replication and maintenance (including DNA repair).³ The human mtDNA is a double-stranded circular molecule of 16.6-kp carrying 37 genes, 13 of which are coding for components of the respiratory chain, 22 for tRNA and two for rRNA.⁴ The mutation rate of mtDNA is 10-fold higher than that of nuclear DNA (nDNA), due to the limited capacity of mitochondrial DNA repair system, the lack of histone scaffold protecting DNA and the subcellular proximity of mtDNA to reactive oxygen species (ROS) that are byproducts of the respiratory chain.^{5,6} Somatic mutations and damages to mtDNA can lead to

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impairment of the oxydation system and further enhanced ROS generation, creating a deleterious vicious circle.

Mitochondrial cytopathies are a heterogeneous group of genetic disorders that are characterized by defects of the MRC caused by mutations either in the nDNA and mtDNA.⁷ Classically, mitochondrial impairments affect the tissues with high-energy demand (e.g., muscles, brain) and are mostly manifested as encephalopathies, myopathies, peripheral neuropathies, hepatopathies, neurosensorial defects, hyperlactatemia and lactic acidosis. But many other clinical presentations have been reported in most organs.

The current gold standard to analyze mitochondrial functions includes measurement of ROS generation, mitochondrial respiration, mitochondrial membrane potential, ATP production, apoptosis susceptibility and biomarkers of mitochondrial dysfunctions such as mitokines, lactate and organic acids. In addition, a good proxy for estimating mitochondrial function is the study mtDNA molecules.⁸ Possible alterations can include: (i) a variation in the number of mtDNA copies per cell, on which mitochondrial activity is directly dependent; (ii) the presence of point mutations, which can impair one or more subunits of the respiratory chain and; (iii) the presence of mtDNA molecules with deletions or duplications, also impairing the respiratory chain. Given the low efficiency of mtDNA repair, all these alterations accumulate as part of the normal ageing, but with different rates according to the cycling capacity of the cells, low rates in high-cycling cells and high rates in slow-cycling or post-mitotic cells. These outcomes may be used to determine a mitochondrial age, an additional biological ageing marker to the well-known telomeric age.⁹

In this review, we will first document the close relationship between mitochondrial toxicity of viral infection and antiviral treatments. Indeed, to increase their chances of survival, some viruses appear to have adopted a strategy to alter mitochondrial activities and mtDNA of host cells. This review will next provide new insights on the long term persistence of mitochondrial alterations and their relations with poorer health outcomes. Such a concept of deleterious effects long after viral infection was first proposed nearly 50 years ago as the "hit-and-run" theory to explain cell transformation by Herpes simplex virus (HSV)-2.¹⁰ It was further deciphered as an accumulation of genetic alteration while the virus is present followed by the loss of the said virus when the oncogenic transformation process is sufficiently advanced to be self-sustained.¹¹ This concept was more recently applied to autoimmune diseases such as in type 1 diabetes mellitus with enteroviruses or to some extent in multiple sclerosis with Epstein-Barr virus (EBV).^{12,13} This establishes a link between a previous infection and the triggering of autoimmunity or, more generally, a link between communicable and non-communicable diseases. We believe that this concept can be applied to certain classes of viruses but also to antiviral drugs, for persistent mitochondrial dysfunctions as a legacy of these exposures. Identification of this relationship and their potential mechanisms could be beneficial for diagnosis, surveillance and the improvement of supportive care, currently tested in several clinical trials.^{14,15}

2 | VIRUSES HIJACK AND MANIPULATE MITOCHONDRIAL FUNCTION

Part of the antiviral cellular defense is host by the mitochondria through several mechanisms including cellular apoptosis, autophagy, ROS signaling, mitochondrial antiviral signaling protein (MAVS) and mitochondrial DNA-dependent immune activation, mechanisms shared by immunosenescence processes. These events are regulated by mitochondrial processes in response to stress or other aggressions. It is therefore not surprising that viruses that hijack these processes have a selective advantage for persistence (Figure 1).

2.1 | Disruption of mitochondrial dynamics

Mitochondrial homeostasis is mainly maintained by two concerted and crucial processes, that is, mitochondrial dynamics (fission and fusion) and mitophagy. Fission causes mitochondrial fragmentation and facilitates the removal of damaged mitochondria by the lysosomes through mitophagy. Fusion serves to protect against autophagy and to preserve cellular integrity and involves a quick exchange of matrix metabolites, membrane components, and mtDNA copies in mitochondria. By this latter, healthy mitochondrion fuses to an impaired one and thus serves to alleviate the damage.¹⁶

Certain viral proteins modify the expression levels and function of specific proteins involved in these processes, and consequently affect the morphology and number of mitochondria. For example, HIV gp120 and Tat in human primary neurons, HCV and protein X of HBV in human hepatoma Huh7 cells, and EBV latent membrane protein 2A in gastric and breast cancer cells cause enhanced mitochondrial fission, which is manifested by elevated fission protein dynamin related protein-1 (DRP-1).^{17,18} In contrast to this, SARS coronavirus ORF-9B protein induces mitochondrial fusion and degrades fission molecules.¹⁹ Influenza A virus (IVA) M2 protein also facilitates mitochondrial fusion by enhancing the fusion machinery through the expression of optic atrophy 1 (OPA1) and mitofusins (MFN1-2), and increases mitochondrial number by increasing the mitochondrial biogenesis.²⁰ The final objective of these hijacking is to provide more energy for the viral replication.

2.2 | Alteration of mitochondrial functions

A large number of viral products localize in the mitochondria. Viral protein translocations from the cytosol to mitochondria, through pathways similar to the physiological mitochondrial proteins import system, affect mitochondrial functions such as oxidative balance, mitochondrial permeability transition pore (mPTP), mitochondrial membrane potential ($\Delta\Psi_m$), electron transport and finally energy production.²¹⁻²³

Many viral proteins affect the membrane potential through interactions with mPTP complex including the outer mitochondrial membrane voltage dependent anionic channel (VDAC), also known as mitochondrial porins form channels, and with inner membrane adenine

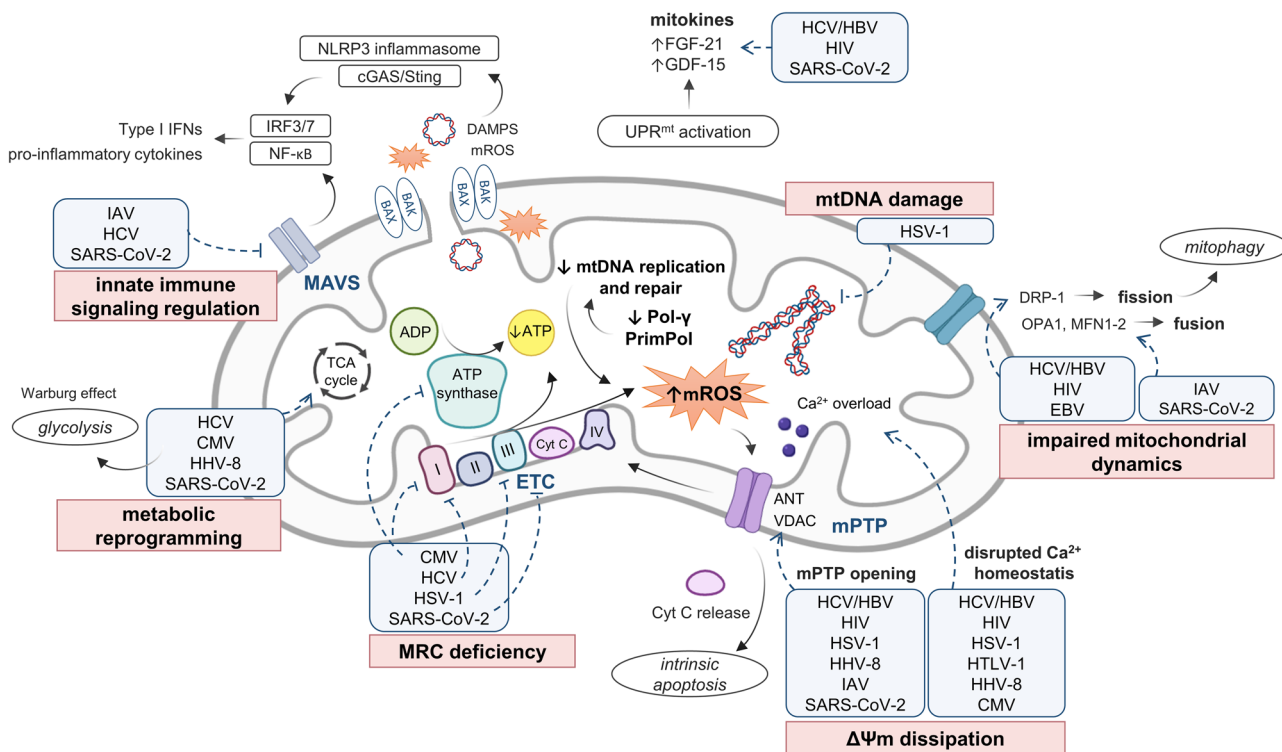


FIGURE 1 Mitochondrial changes associated to viral agents. Viruses employ their proteins to alter mitochondrial dynamics and their specific functions by a modulation of membrane potential, apoptosis, calcium homeostasis, ROS generation, and mitochondrial bioenergetics to help them achieve a state of persistent infection. Viruses may alter the tricarboxylic acid (TCA) cycle and induce the Warburg Effect, in which metabolism is reprogrammed to aerobic glycolysis as the main source of energy. ADP, adenosine diphosphate; ANT, adenine nucleotide translocase; ATP, adenosine triphosphate; Cyt C, cytochrome C; DAMP, damage-associated molecular patterns; ETC, electron transport chain; FGF, fibroblast growth factor; GDF, growth differentiation factor; MRC, mitochondrial respiratory chain; ROS, reactive oxygen species; TLR, toll-like receptor; UPR, unfolded protein response; VDAC, voltage-dependent anion channel.

nucleotide translocase (ANT). A dissipation in $\Delta\Psi_m$ led to mitochondrial fragmentation and to the cytoplasmic release of proapoptotic signals, such as cytochrome C (Cyt C), activating apoptotic caspases leading to the cell death and dissemination of viruses to neighboring cells for further infection.²¹ The PB1-F2 protein of Influenza virus, the p13 of HTLV-1, and Vpr protein of HIV induce loss of $\Delta\Psi_m$ promoting mitochondrial-induced apoptosis.²² In addition, a number of factors including calcium overload induce the formation of nonspecific mPTP in the inner mitochondrial membrane. Several viral proteins, such as NS5A, p7 and core proteins of HCV and protein X of HBV, are associated with disruption of Ca^{2+} homeostasis.^{21–23}

Changes in mitochondrial bioenergetics by viral proteins are crucial for virus replication and multiplication. HSV-1 leads to a decline in ATP caused by depletion of mtDNA mediated by UL12.5 viral protein.²³ HIV affects mitochondrial bioenergetics activity by causing a reduction in ATP-linked respiration and HCV impairs electron transport chain (ETC) by an inhibition of complex I activity and ROS generation.²² Similarly, HBV and HSV-1 are also associated with ROS generation. Recently, it was reported that SARS-CoV-2 also inhibits mitochondrial oxidative phosphorylation (OXPHOS) resulting in increased mitochondrial ROS (mROS) production.^{24,25} The elevated mROS stabilizes hypoxia-inducible factor-1 α (HIF-1 α) and consequently promotes glycolysis which facilitates SARS-CoV-2 replication.^{24,25} This phenomenon may be responsible for

persistence of SARS-CoV-2 in subjects with or without immune deficiency and for the establishment of long-term SARS-CoV-2 reservoirs.²⁶ Other viruses, such as HCV, CMV and HHV-8, may cause the Warburg effect, in which metabolism is reprogrammed to aerobic glycolysis as the main source of energy.²⁷ HCV-induced loss of mitochondrial function also results in HIF-1 α stabilization and a shift to glycolysis.

2.3 | Host mtDNA damages

Several studies have reported mtDNA depletion during infections with HIV and HCV. Mitochondrial impairment was first associated with HIV in the 1990s. It was observed that muscle and nerve biopsies from untreated individuals with HIV-associated myopathy or neuropathy may have low mtDNA levels.²⁸ Subsequently, mtDNA depletion was described in PBMCs of HIV-infected patients who had never received anti-retroviral (ARV) drugs compared with healthy people.^{29,30}

Similar to HIV infection, HCV infection results in mitochondrial damage and mtDNA depletion in PBMCs, which seems to be further enhanced in coinfecting patients.³¹ This may explain the higher incidence of mitochondrial-related toxicities seen in this population compared with either HIV or HCV-monoinfected individuals. In addition, hepatic mtDNA levels were also decreased by 19% in the HCV-monoinfected group and

by 27% in the HIV/HCV-coinfected subjects compared to controls.³² More recently, mtDNA damage, including mtDNA depletion and multiple mtDNA deletions, were identified in treatment-naïve chronic hepatitis B (CHB) mono-infected patients.³³ The mtDNA levels significantly declined in patients with CHB to 43% of control values. Patients with CHB and advanced fibrosis or cirrhosis had higher mtDNA depletion and deletions when compared to patients with no/mild-moderate fibrosis.

In vitro, SARS-CoV-2 triggers a dramatic reduction in mtDNA content in microglial cells.³⁴ It has been hypothesized that alterations are caused by increased synthesis of ROS in these organelles. In circulating blood cells, a decrease in mtDNA copy number was also observed in severe COVID-19 patients and associated with mortality.^{35,36} Such alterations may result in adverse clinical events with impact on the quality of life of the infected people.

2.4 | Regulation of apoptotic and mitochondrial innate immune signaling

Viruses can furthermore directly target components of apoptotic pathway and mitochondrial innate immune system to enhance their own replication.

Mitochondria-induced apoptosis is mediated by BAK and BAX, two proteins that induce mitochondrial outer membrane permeabilization, leading to Cyt C release and activation of apoptotic caspases. Apoptosis pathway is governed by the interplay among members of the B cell lymphoma- (BCL-2) family of proteins, which mediate mitochondrial integrity. Many viruses encode homologs of BCL-2 proteins to regulate apoptosis. HBV protein X is a homolog of proapoptotic BCL-2 proteins which localizes to the mitochondria and interacts with the VDAC, inducing the loss of $\Delta\Psi_m$ leading to apoptosis.²¹ Some pro/anti-apoptotic viral proteins show no homology with BCL-2 proteins, such as the human papilloma virus (HPV) E6 protein, which prevents apoptosis by downregulating upstream the BAX signal.²¹ Finally, viruses also encode proteins which act as viral mitochondrial inhibitors of apoptosis (vMIA), such as a splice variant of UL37 of HCMV. It localizes to mitochondria via its N-terminal mitochondrial targeting domain while the C-terminal acts as the antiapoptotic domain which prevents $\Delta\Psi_m$ loss and cell death by recruiting BAX to mitochondria.^{21,22}

Mitochondrial activities can induce nuclear gene expression programs important for antiviral defense. Specifically, signaling can be triggered by interactions occurring on the mitochondrial surface and the release of mtDNA due to alterations of mitochondrial morphology. Mitochondrial antiviral signaling (MAVS) is the prototype for antiviral signaling at the mitochondrial surface and functions as a key adapter molecule to transduce signals from upstream pattern-recognition receptors (PRRs), like retinoic acid-inducible gene I (RIG-I) to trigger type I interferon (IFN) response. However, viral-encoded proteins antagonize MAVS function. For example, the Influenza virus PB1-F2, HCV NS3/4A and SARS-CoV-2 ORF10 suppress IFN responses by degrading MAVS.^{37,38}

Along with signal transduction on the surface, release of molecules into the cytosol, such as mtDNA, results in gene expression changes.

When mtDNA are leaked from mitochondria, they act as damage-associated molecular pattern (DAMPs) which then initiates an immune response and inflammation by activating the NLRP3 inflammasome and by activating DNA-sensing pathways, such as Toll-like receptor 9 (TLR9) or cGAS/STING.^{39,40} Recent studies have demonstrated that mtDNA is released through the BAK/BAX macropore during viral infections such as Influenza virus, SARS-CoV-2 and severe fever with thrombocytopenia syndrome virus.^{41,42} Interestingly, viral factors have been shown to drive mtDNA release. Specifically, viroporin activity of Influenza virus M2 or encephalomyocarditis virus 2B protein triggers translocation of mtDNA into the cytosol in a MAVS-dependent manner.⁴¹ Finally, mtDNA may end into the blood circulation and contribute to the exacerbation of inflammatory processes, that is, the “cytokine storm”, which can result in severe immune response and fatal infection outcome.^{43,44} The value of circulating mtDNA has been demonstrated as a potential biomarker to predict COVID-19 severity and the pro-inflammatory response in patients.^{45,46}

The regulation of mtDNA release upon mitochondrial stress remains uncharacterized, but recently mitochondria-associated vacinia virus-related kinase 2 (VRK2) has been identified as an essential regulator of mtDNA release and play a crucial role in the mtDNA-triggered innate immune response.⁴⁷ VRK2 deficiency inhibited the induction of antiviral genes and caused earlier and higher mortality in mice after viral infection. Thus, VRK2 may be a potential therapeutic target for infections associated with mtDNA release.

2.5 | Alterations of mitokines level

Mitochondrial stress stimulates the mitochondrial unfolded protein response (UPR_{mt}) and induces the production of stress response molecules known as mitokines.^{48,49} Alterations of mitokine-levels are associated with general aging processes and could influence the development of age-related chronic metabolic, cardiovascular and neurological diseases.^{48,49} The best established mitokines, fibroblast growth factor 21 (FGF-21) and growth differentiation factor 15 (GDF-15), are emerging biomarkers of mitochondrial dysfunctions and diseases.

FGF-21 and GDF-15 are indicators of cardio-metabolic complications in adults living with HIV.^{50,51} Increased GDF-15 was also associated with cardiac abnormalities in children with perinatally-acquired HIV (PHIV).⁵² In addition, circulating levels of FGF-21 and GDF-15 were higher in children with PHIV displaying “possible” mitochondrial disease than in those presenting no detectable mitochondrial disease criteria.⁵³ FGF-21 appear to be related to muscular system presentation,^{54,55} while GDF-15 may be linked to more generalized mitochondrial disease and indicative of disease severity and/or progression.⁵³ This is the case in hepatic viral infections where increased GDF-15 levels are associated with disease progression, and in patients with septic shock where they are associated with increased mortality.⁵⁶ Interestingly, GDF-15 and also FGF-21 emerged as a significant predictors of disease severity and mortality in patients with COVID-19.^{56–60} Thus, in the context of infection, these two mitokines might have a potential role in the assessment of

prognosis in patients, who are at higher risk of developing mitochondrial dysfunction such as cardio-metabolic complications.

3 | VIRAL TREATMENTS INDUCE MITOCHONDRIAL TOXICITY

Given the endosymbiogenesis of mitochondria, their prokaryotic origin should be kept in mind. Indeed, numerous antibacterial treatments are known for long time to have mitochondrial side effects. One best example is the ethambutol, one of the backbone drug of tuberculosis treatment that shows mitochondria toxicity through copper chelation and clinical outcomes such as optic neuropathies.⁶¹

The mitochondria are also considered to be the main target of certain anthracyclines, which are effective chemotherapeutic agents for the treatment of cancer, such as doxorubicin. Mitochondrial dysfunction is the hallmark of doxorubicin-induced cardiotoxicity.⁶² Many antiviral drugs also interfere with the mitochondrial machinery, via mechanisms not all well elucidated.

3.1 | Mitochondrial dysfunction upon antiviral treatments

The first generation of approved ARV drugs was nucleoside-analog reverse transcriptase inhibitors (NRTIs). NRTIs prevent viral replication by inhibiting HIV reverse transcriptase (RT) but can act as chain terminators by incorporation into any DNA including the mtDNA which leads to an aborted replication, and/or by directly inhibiting DNA polymerase gamma (Pol- γ), the main enzyme responsible for mtDNA replication.^{63,64} Reduction of the number of mtDNA copies is a well-known side effect of NRTIs, supported by both clinical and experimental observations.^{64,65} Depending on the nature of the different NRTI drugs, different degrees of inhibition have been estimated with the following decreasing drug toxicity scheme: zalcitabine (ddC) \geq didanosine (ddI) \geq stavudine (d4T) \gg lamivudine (3TC) $>$ tenofovir (TDF) $>$ emtricitabine (FTC) \geq zidovudine (AZT) $>$ abacavir (ABC).⁶⁶ As a consequence of the decrease of mtDNA copy number, the cellular oxidative phosphorylation is disturbed, which leads to an increased production of ROS that in turn may generate mtDNA point mutations and/or deleted mtDNA.^{65,66} For example, a recent study reported altered mitochondrial ETC proteins and mtDNA quantity and relative abundance of the "common deletion" in peripheral nerve tissues from donors with HIV sensory neuropathy.⁶⁷ On the other hand, PrimPol, was discovered more recently, as a primase polymerase localized to the mitochondria with repriming and translesion synthesis capabilities. Similar to Pol- γ , PrimPol incorporate NRTIs into nascent DNA with effective incorporation of ABC, ddC $>$ ddI $>$ AZT, but not of d4T, 3TC, and TDV.⁶⁴ Of note, it should be stressed that these *in vitro* results can only partially reflect *in vivo* situation as these drugs are administered in combination to a minimum of two others, and that such combination have never been tested *in vitro*.

Accumulating evidence points to a complex relationship between mitochondria and NRTI toxicity that goes beyond the "mitochondrial

dysfunction hypothesis" based on DNA polymerase inhibition, mitochondrial oxidative stress and mtDNA mutations.⁶⁸ Indeed, NRTIs can interact with other essential proteins and interfere with mitochondrial function, notably mitochondrial respiration capabilities.^{68,69} AZT has been shown to inhibit ETC complexes and ANT-mediated ADP/ATP exchange, which inhibits ATP synthesis.⁷⁰ These alternative pathways have also been involved in mitochondrial dysfunction induced by other groups of ARVs including non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs), drug classes not disrupting Pol- γ activity (Figure 2).⁶⁹

NRTIs including AZT and d4T, has the ability to inhibit autophagic flux in hepatocytes, adipocytes and myocytes, which in turn leads to the accumulation of dysfunctional mitochondria with increased ROS generation and compromised cell viability.⁷¹ In mice, AZT treatment induces mitochondrial derived oxidative stress in the heart that hinders cardiac DNA methylation, alters cardiac gene expression, and promotes characteristic pathophysiological changes of cardiomyopathy.⁷² The induction of mROS production upon AZT exposure was also associated with increased spontaneous apoptosis *in vitro* and *in vivo* T cells, and may help to explain the inferior immunological recovery in patients treated with AZT-containing regimens.⁷³ In the absence of HIV infection, short-term prophylactic antiretroviral treatment can cause subclinical mitochondrial damage.^{74,75} 4-week postexposure prophylaxis (PEP) regimen containing AZT + 3TC led to higher mitochondrial toxicity than regimen containing TDF + FTC.⁷⁵ On the other hand, TDF and adefovir (ADV), weak inhibitors of Pol- γ , can cause mitochondrial dysfunction in renal tubular cells by reprogramming glucose metabolism.⁷⁶ The resulting accumulation of glycogen may contribute in part to TDV- and ADV-induced nephropathy. In addition, TDV and ADV accumulate in the renal cortex via a kidney-specific transporter (human organic anion transporter-1) suggesting that the adverse effects of TDV or ADV-containing NRTI regimen on mitochondrial functions are primarily restricted to renal proximal tubule cells.⁷⁷

Non-nucleoside analog reverse transcriptase inhibitors (NNRTI), such efavirenz (EFV) and nevirapine (NVP), also induce mitochondrial dysfunction through bioenergetics stress manifesting by a reduction of $\Delta\Psi_m$, release of proapoptotic signals and cell death.^{68,69} In contrast to the NNRTI rilpivirine, the integrase strand transfer inhibitor (INSTI) raltegravir (RAL) and the protease inhibitor (PI) darunavir (DRV), EFV affect mitochondrial function in hepatocytes and neurons *in vitro*.⁷⁸ This supports existing clinical evidence in which EFV induce more liver toxicity than other ARVs, up to 10% of HIV patients treated with EFV exhibit increases in liver enzymes that sometimes require discontinuation of therapy.⁷⁹ The relationship between plasma concentration and the adverse effects of EFV, in particular those related to the liver and central nervous system is well established.⁷⁹

There is a significant amount of data supporting the role of PIs in inducing oxidative stress among a large number of cell types and model systems, ultimately leading to the main side effects associated with PIs, including cardiovascular disease and lipodystrophy. Indeed, PIs are tightly correlated with metabolic disruption of lipid metabolism and glucose transport.⁶⁸ PI-induced mitochondrial effects are principally related to ROS generation, reduced $\Delta\Psi_m$, impaired respiration

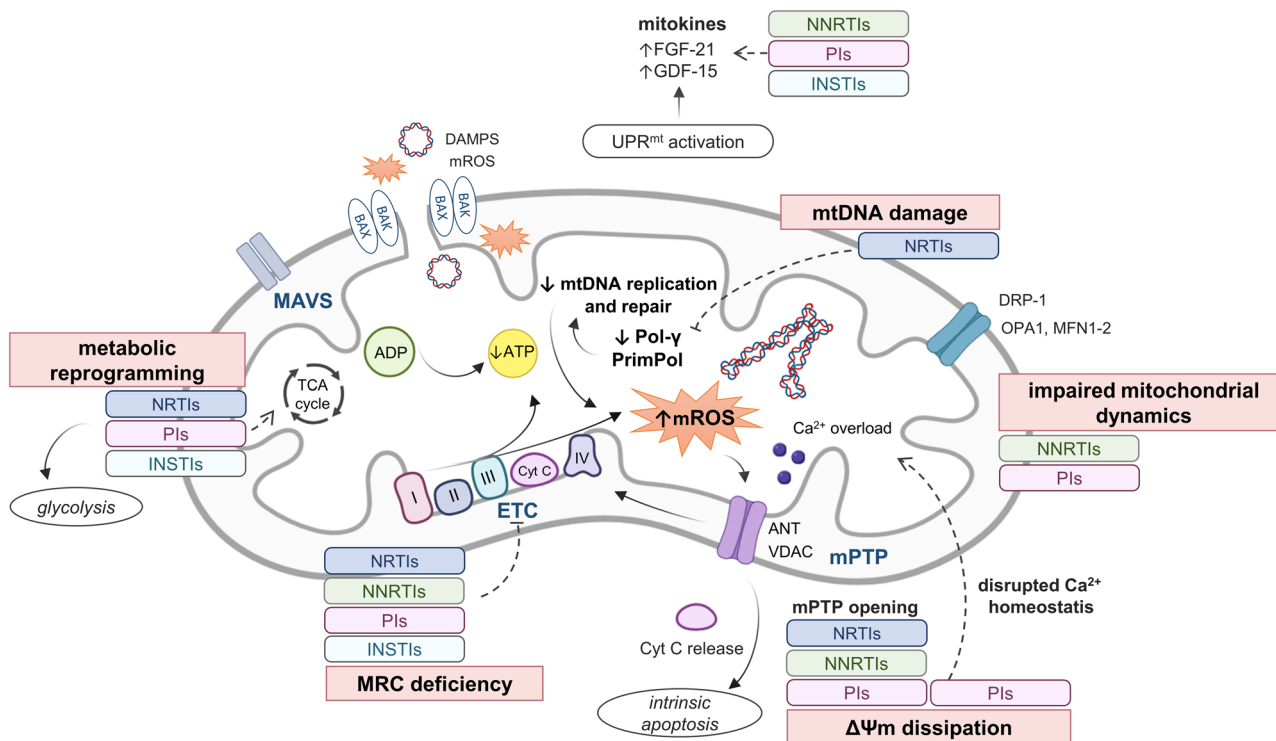


FIGURE 2 Antiviral drugs and reported effect on mitochondria. NRTIs classically associated to mtDNA depletion, due to off-target inhibition of endogenous polymerases, can also interfere with mitochondrial function. These alternative pathways have also been involved in mitochondrial dysfunction induced by other groups of anti-retroviral drug classes. ADP, adenosine diphosphate; ANT, adenine nucleotide translocase; ATP, adenosine triphosphate; Cyt C, cytochrome C; DAMP, damage-associated molecular patterns; ETC, electron transport chain; FGF, fibroblast growth factor; GDF, growth differentiation factor; INSTI, integrase strand transfer inhibitor; MRC, mitochondrial respiratory chain; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ROS, reactive oxygen species; TLR, toll-like receptor; UPR, unfolded protein response; VDAC, voltage-dependent anion channel.

and apoptosis which have been reported in several cellular models.⁶⁸ For example, lopinavir (LPV) and ritonavir (RTV) raise ROS production and diminish $\Delta\Psi_m$ in cardiomyocytes. Atazanavir (ATV) also disrupts $\Delta\Psi_m$ and induces apoptosis and autophagy in pre-adipocytes.⁶⁹

Regarding INSTIs, their effect on mitochondrial function has not been systematically assessed, but there are limited data suggesting that this may be a concern. INSTI dolutegravir (DTG) and elvitegravir (EVG) impaired CD4 T cell mitochondrial respiration, then leading to a skewing of CD4 T cell immune responses toward a reduced and monofunctional CD4 response, increased ROS production, and increased cytoplasmic mtDNA release, indicative of a leaky mitochondrial membrane.⁸⁰ Generation of ROS and damaged mitochondria suggest that the mechanism of mitochondrial toxicity observed in INSTIs might share the same or similar pathways observed in NRTI-related mitochondrial toxicity.

Finally, the drug treatments that induced ER stress/oxidative stress also elicited FGF-21 induction in human hepatic, adipose, and skeletal muscle cells.⁸¹ In vitro PIs, the NNRTI EFV, and the INSTI EVG were the drugs most capable of inducing FGF-21 gene expression. Therefore, attention should be paid to the potential of particular drugs in the ART cocktails to disturb the FGF21 system.

Overall, although the administration of combined ART creates an increasingly difficult landscape, there remains a need to assess the

disruption of mitochondrial function by ART regimens individually. All these mechanisms reflect the possibility that each agent may act on specific target tissues and contribute to the understanding of the long-term side effects of ARV agents.

3.2 | Other antiviral drugs and mitochondrial toxicity

Receiving direct-acting antivirals (DAA) drugs against HCV, a combination of sofosbuvir, daclatasvir and ribavirin drugs, are associated with mitochondrial genotoxicity among a population of drug users. After 12 weeks of treatment, although the mtDNA copy number per cell remained unchanged, the proportion of deleted mtDNA increased. After a 9-month follow-up, the mtDNA copy number per cell dropped drastically and the percentage of the deleted mtDNA genome increased over time.⁸²

More recently, nucleoside and nucleotide analogs have been proposed for treatment options for COVID-19. The key enzyme involved in the replication of SARS-CoV-2 is RdRp and therefore, the drugs that can target RdRp-like structures can be effectively repurposed against coronaviruses. For example, sofosbuvir/daclatasvir is currently evaluated for the safety and efficacy in participants with

moderate to severe COVID-19. Other drugs such as remdesivir (RDV), originally developed as a treatment for Ebola virus, and molnupiravir (MOV) have shown potent inhibition of SARS-CoV-2 and were approved in 2020 as effective antiviral agents for treating hospitalized patients with moderate to severe COVID-19.⁸³ There is no evidence of deleterious effects of RDV treatment on mitochondrial genome integrity in human cells in culture.⁸³ Bjork and Wallace have also shown that neither RDV nor MOV altered mtDNA copy number or gene expression, nor did it inhibit mitochondrial respiration in the HepG2 cell line.⁸⁴ In addition, a 3-month treatment with RDV does not affect mtDNA copy number or deletion frequency in heart, kidney and skeletal muscle in aged male rats.⁸⁵ These data support the idea that these nucleoside analogs do not compromise mtDNA quality or quantity in animal models, however, their impacts have not been evaluated either in other relevant tissues such as the liver and brain, nor in humans.

Nucleoside analogs, such as acyclovir (ACV) and ganciclovir (GCV), are used to target herpes viruses and cytomegaloviruses. A reduction of mitochondrial membrane potential, altered mitochondrial size and shape, and mtDNA damage were found after ACV administration in human lung cancer cell line. Furthermore, an increment of intracellular ROS levels as well as the upregulation of NudT3 involved in DNA repair mechanisms were observed.⁸⁶ Some studies have also shown that GCV produces alterations in the mtDNA of senescent cells.²³ Indeed, GCV incorporates into the mtDNA and causes mtDNA damage. Altogether, these findings suggest that mitochondria may be possible initial targets and/or sites of cytotoxicity for these drugs.

4 | LONG-TERM PERSISTENCE OF MITOCHONDRIAL TOXICITY AFTER VIRUSES/ANTIVIRAL DRUGS EXPOSURE

Damaged mitochondria are physiologically eliminated through a mitophagy process. Several mechanisms have been proposed for the accumulation and/or maintenance of mtDNA deletions, duplications or point mutations,⁸⁷ but the main driver remains the replication capacity of the cell that hosts them. Even when the virus has been cleared or antiviral treatment has been discontinued, mitochondrial dysfunction may persist in certain tissues with a low cellular renewal rate and could contribute to poorer health outcomes or long-lasting symptoms, such as in COVID (Figure 3) (Table 1).

4.1 | Long-lasting mitochondrial toxicity in HIV- and ARV-exposed population

The long-term consequences of antiviral exposure were well-illustrated in NRTI-exposed newborn *patas* monkeys, mitochondrial morphological damage and mtDNA loss persist in heart and brain up to 3 years of age (human equivalent of 15 years).⁸⁸ Similar observations were reported among HIV-exposed but uninfected (HEU)

children who are exposed to ARV and HIV *in utero* and postpartum during breastfeeding, or through infant prophylaxis.^{89,90} These children are at increased risks for immune system, cardiac abnormalities, metabolic complications, growth impairments and neurodevelopment delays compared to HIV-unexposed uninfected (HUU) children.^{91,92} In HEU newborns, aberrant mtDNA levels are frequently observed.^{93–95} In HEU children who had mtDNA copy number decreased after 1 year of postnatal prophylaxis and, at 5–7 years of age, their mtDNA copy number had returned to baseline.⁹⁶ In HIV-infected adults, mtDNA levels rebound has also been observed upon drug discontinuation.^{97,98} However, these alterations could persist longer in certain tissues where cells, such as muscle, heart or nerve cells, have a low renewal rate.^{99,100}

The integrity of the mtDNA molecules is of greater concern as they may persist for several years after virus/treatment exposures. A recent study found that mtDNA point mutations remained prevalent in HEU children a few years after the cessation of triple antiretroviral drugs.¹⁰¹ Among them, D-loop, ND1 and CYTB were the main three mutated regions. This pattern of mutations is similar to, but not exactly consistent with, HIV-infected children receiving standard ART. Other mtDNA instabilities persist over time. In HEU newborns, these instabilities appear common with 75% of them harboring significant amounts mtDNA deletions when none were observed in healthy controls.¹⁰² These mtDNA deletions and duplications observed at birth persisted for many years in children after HIV and ARV drug exposure.⁹⁹ The consequences of these genetic alterations may or may not have clinical consequences. They are compensated by the wild type molecule as the two types of molecules coexist in a single mitochondria (also named heteroplasmy). Median heteroplasmy rate of these rearranged mtDNA increased at 1 year of life and then returned to baseline by 6 years of age. Translated into mitochondrial age, these 6-years old children have a blood mtDNA genetic material that can be found in tissues with low renewal of aged people.¹⁰⁰

The clinical signs can be very subtle and their visible onset is usually delayed for several years, if not decades. For example, HEU children who were exposed to ART and HIV *in utero* have subclinical yet significant differences in specific left ventricular (LV) diastolic indices. These children have reduced LV muscle mass and impaired LV compliance and relaxation during the first years of life.¹⁰³ But the long-term consequence of such impairment in LV diastolic function early in life is yet to be determined. Mitochondrial dysfunction linked to ART therapy is a plausible mechanism of cardiovascular dysfunction, given the high-energy requirements of the heart contraction. In children living with HIV, increased mitokine GDF-15 levels was associated with cardiac abnormalities, notably LV diastolic dysfunction and LV hypertrophy.⁵² The results of this study suggest that biomarkers such as GDF-15 may be used to monitoring HEU children at increased risk of mitochondrial dysfunction such as deleterious cardiac effects. In a small case series, any association was reported between health outcomes at 6 years and mtDNA instability,⁹⁹ but cardiac function was not explored and longer follow-up is needed.

Several studies have reported an impact of *in utero* exposure to ARV drugs including NRTIs, NNRTIs, PIs and INSTIs on the

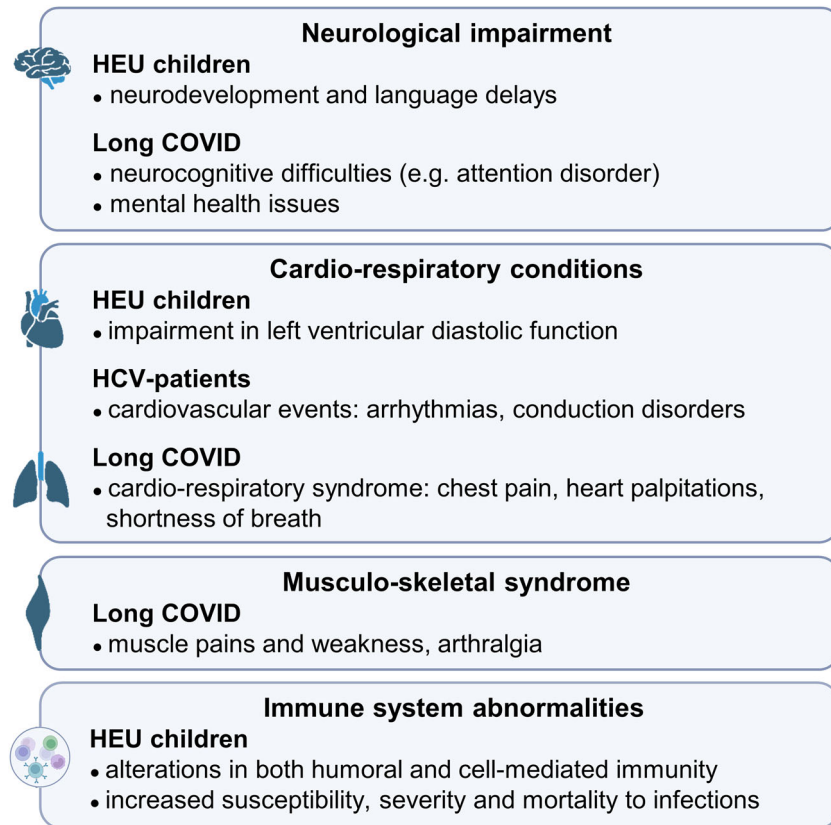


FIGURE 3 Subclinical/poorer health outcomes after viruses/antiviral drugs exposures. HEU, HIV-exposed but uninfected.

neurodevelopment and language delays of HEU children.^{91,92} Elevated blood mtDNA contents have also been described in HEU children diagnosed with autism spectrum disorder, suggesting mitochondrial dysfunction may contribute to autism spectrum disorder risk in HEU children.⁹² Although the benefits of ARV drugs during pregnancy are unquestionable, all data on potential toxicity are a matter of concern and stress the need for longer follow-up and further research on the long-term health outcomes, notably cardiac and neurodevelopmental, in the rapidly growing HEU population worldwide.¹⁰⁴ Given the increasing number of ARV drugs available, a comparative evaluation is needed to identify the therapeutic strategies that present the lowest risk of mitochondrial disorders for exposed infants.

4.2 | Mitochondrial dysfunction as cause of long COVID

About 10% of patients who recover from SARS-CoV-2 infection complain persistent symptoms of multiorgan complications lasting weeks or months such as lung injury, and other inflammatory manifestations, including neurodegenerative events, called long COVID. The underlying pathogenic mechanisms involved in the long COVID are still unclear. However, some authors have proposed that it could be attributed to mitochondrial dysfunction, given that the most common manifestations of long COVID are similar to the array of manifestations of known mitochondrial diseases and due to the

mitochondrial toxicity induced by SARS-CoV-2.^{105,106} As described above, SARS-CoV-2 cause the dissipation of $\Delta\Psi_m$ leading to apoptosis and the release of ROS from mitochondria thus causing the oxidative stress and induce mtDNA damage.

Mitochondrial dysfunction with altered $\Delta\Psi_m$ has also been reported in PBMCs from long recovered COVID subjects, indicating that these events can persist long after the acute infection has ended. For recovered subjects at 11 months post-COVID-19, data indicate that these subjects restore $\Delta\Psi_m$ as compared with subjects recently recovered from infection (at ~40 days after infection), however, with respect to controls, the $\Delta\Psi_m$ is still significantly decreased.¹⁰⁷ These results suggest that the loss of $\Delta\Psi_m$ in subjects recovered 11 months after SARS-CoV-2 infection can be associated with long COVID, since of the 18 individuals who participated, 85% reported symptoms. Previously, we have seen that a decrease in mtDNA copy number in circulating blood cells was observed in severe COVID-19 patients and associated with mortality.^{35,36} Mitokines, GDF-15 and FGF-21, have also emerged as a significant indicators of disease severity and mortality in patients with COVID-19.^{56,57} It would be interesting to assess these different mitochondrial parameters in patients recovered from COVID-19 to see whether levels return to baseline or whether abnormal levels persist and may be associated with long-lasting COVID symptoms.

Patients with COVID-19 have a compromised mitochondrial function and an energy deficit that is compensated by a metabolic switch to glycolysis.⁶⁰ Interestingly, in long COVID patients, intracellular energy production also tends to use glycolysis rather than

TABLE 1 Mitochondrial genotoxicity after viruses/antiviral drugs exposures.

| Mitochondrial genotoxicity | | | | |
|----------------------------|---|---|--|-----------------------|
| Groups | Exposure | Hit phase | Run phase | Reference |
| Virally exposed person | HEU children: HIV alone (mothers taking no ARV) | mtDNA copy number ↘ | N/A | [88, 93] |
| | HEU children: HIV and ARV prophylaxis | At birth: aberrant mtDNA levels mtDNA deletions + After one year of postnatal prophylaxis: mtDNA copy number ↘ mtDNA deletions + | 2 years old: mtDNA mutations + 6 years old: mtDNA copy number recovery mtDNA deletions/duplications + | [93–96, 99, 101, 102] |
| | Adult and ARV prophylaxis (4-week PEP) | $\Delta\Psi_m$ ↘ mtDNA copy number ↘ mtDNA mutations? | 2 months after finishing PEP: $\Delta\Psi_m$ recovery mtDNA copy number? mtDNA mutations? | [74, 75] |
| Virally infected person | HIV and naïve-treatment | mtDNA copy number ↘ mtDNA mutations? | N/A | [29, 30] |
| | Chronic HCV and naïve-treatment | mtDNA copy number ↘ mtDNA mutations? | N/A | [32] |
| | Chronic HBV and naïve-treatment | mtDNA copy number ↘ multiple mtDNA deletions + | N/A | [33] |
| | HIV and ARV and drug discontinuation | mtDNA copy number ↘ mtDNA point mutations + | one year after drug discontinuation: mtDNA copy number recovery mtDNA mutations? | [97, 98] |
| | HCV and DAA and drug discontinuation | mtDNA copy number → mtDNA deletions + | 9 months after drug discontinuation: mtDNA copy number ↘ mtDNA deletions ↗ | [82] |
| | COVID-19 | $\Delta\Psi_m$ ↘ mtDNA copy number ↘ mtDNA mutations? | 11 months postinfection: $\Delta\Psi_m$ recovery compared with subjects recently recovered from infection $\Delta\Psi_m$ still ↘ compared with controls | [35, 36, 107] |
| Patas monkey | ARV <i>in utero</i> | At birth: mitochondrial morphological damage mtDNA copy number ↘ mtDNA mutations? | 3 years old (human equivalent 15 years old): mitochondrial morphological damage mtDNA copy number ↘ mtDNA mutations? | [88] |

Abbreviations: ?, not yet described; +, described; ↗, increased; →, unchanged; ↘, decreased; ARV, anti-retroviral; DAA, direct-acting antivirals; HEU, HIV-exposed but uninfected; mtDNA, mitochondrial DNA; N/A, not applicable; PEP, postexposure prophylaxis; $\Delta\Psi_m$, mitochondrial membrane potential.

using mitochondrial oxidative phosphorylation.¹⁰⁶ The restructuring of cellular energy metabolism is mediated in part by SARS-CoV-2 ORF8 and ORF10 whose expression restructures nDNA and mtDNA OXPHOS gene expression. These viral proteins likely alter the epigenome, either by directly altering histone modifications or by modulating mitochondrial metabolites which alter histone modifications, potentially silencing OXPHOS gene expression.¹⁰⁸ It has been suggested that prolonged metabolic alterations could result in the consolidation of inhibitory histone marks resulting in irreversible OXPHOS transcriptional inhibition even after SARS-CoV-2 has been cleared.¹⁰⁸ Consequently, the postviral epigenomic suppression of OXPHOS gene expression may be an important factor in the pathophysiology of long COVID.

Another study has described the elevation of a protein called WASF3, which interferes with and reduces the bioenergetic function of mitochondria, in the muscle in patients with myalgic encephalitis (or chronic fatigue syndrome).¹⁰⁹ This could be related to the physical exhaustion with little exercise and the cerebral dullness reported by patients with chronic fatigue. Identifying WASF3 as a direct mediator of bioenergetic deficiency raises questions about its potential role in other chronic fatigue-associated conditions such as long COVID. Patients with long COVID may have limited capacity to return to normal exercise routine due to impaired oxygenation in muscle tissue and mitochondrial therapy has been suggested to help patients with long COVID symptoms for faster recovery.¹¹⁰

Altogether, both viral infections and antiviral drugs mitochondrial toxicities persist long after exposure, which is very reminiscent of the “hit-and-run” concept. This concept was first described with a deterministic aim, that is, cell immortalization. Rather all the processes after infections or treatments resemble accelerated ageing, with the production of deleterious mtDNA during the “hit phase”. Examples of HEU children is very suggestive with a “mitochondrial ageing” in blood sample resembling the condition of a “healthy” adult of more than 50 years. The same applies to antiviral drug exposure with mitochondrial genotoxicity of prophylactic ARV treatment after occupational blood exposure. During the “run phase”, these mtDNA alterations never repair or eliminate but at best maintain in a steady state and at worse accumulate. In that respect, the “hit-and-run” concept is fulfilled. Whether such a concept can be generalized to other viral infections and antiviral treatments needs to be investigated.

The identification of mitochondrial damage as causal mechanism for long term side effect of viral infections or antiviral treatments opens the consideration to possible treatments that restore mitochondrial function. Given that the severe mROS generation damages mitochondria and mtDNA, leading to reduced oxidative phosphorylation and shift to glycolysis, anti-ROS agents have been proposed as a treatment tool to mitigate acute and long COVID-19 and perhaps prevent persistent SARS-CoV-2 infection.²⁶ Treatment of SARS-CoV-2-infected monocytes with the ROS scavengers N-acetyl cysteine (NAC) and MitoQ reduced mROS production, HIF-1 α , glycolytic proteins, pro-inflammatory cytokine mRNAs, and viral loads.^{24,25} In the case of HCV and HBV, where mitochondrial function is impaired with high levels of ROS, these mitochondrial-targeted antioxidants also help to restore mitochondrial function.^{111,112} Several compounds, including antioxidants, mitochondrion-targeted peptides, and modulators of mitochondrial biogenesis, have shown promise for the treatment of mitochondrial dysfunction, in preclinical studies.^{14,15} Further studies are needed to determine the safety and efficacy of mitochondrial-targeted therapies in the context of acute viral infections and antiviral treatments.

5 | CONCLUSION

Over the course of evolution, numerous mechanisms of interaction between viruses and mitochondria have been deployed. They affect most mitochondrial functions, such as mitochondrial dynamics, energy production, maintenance of membrane potential, control of ROS production, apoptosis, and maintenance and regulation of mitochondrial genome expression. Viruses can thus hijack mitochondrial energy production and metabolic functions, while interfering with apoptosis and other mitochondria-driven host cell defense systems. In terms of antiviral therapies, mitochondria are also a prime target. Here too, mtDNA, ROS production, membrane potential and mitochondrial metabolism in general can be affected. This clearly raises the question of the long-term effects of viral infections and antiviral therapies on mitochondrial somatic functions and genetics, since

slow-cycling cells (neuron, muscle cells, etc.) could be durably affected, with a risk of secondary symptomatology.

AUTHOR CONTRIBUTIONS

Conceptualization: Pascal Reynier, Jean-Pierre Molès. *Methodology:* Not applicable. *Investigation:* Laetitia Gay, Valérie Desquirit-Dumas. *Visualization:* Not applicable. *Funding acquisition:* Pascal Reynier, Jean-Pierre Molès. *Project administration:* Not applicable. *Supervision:* Not applicable. *Writing—original draft:* Laetitia Gay, Pascal Reynier, Jean-Pierre Molès. *Writing—review and editing:* All authors

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CONFLICT OF INTEREST STATEMENT

No conflict of interest declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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