The Missing Link between HAART, Mitochondrial Damage and Insulin Resistance

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In this review how the highly active antiretroviral therapy (HAART) damage the mitochondria, followed by immune activation and insulin resistance. The introduction and evolution of HAART over the past 25 years have brought an amazing decrease in AIDS-and immunodeficiency-related reasons for death. However, deaths of these people are now related to metabolic disorder diseases, including atherosclerotic cardiovascular diseases, before from the viral infection itself. Insulin resistance is at the root causes of maladies of metabolic related disorder diseases. While it is notable that HAART metabolism and immune activation cross taking contribute advancement of insulin resistance and co-morbid illnesses. The molecular mechanisms of HAART metabolism and insulin resist is not completely understand. Emerging evidence that HAART how induced mitochondrial damage? and exacerbates the inflammatory response which leads to the development of insulin resistance are remain largely unresolved. The clarification and comprehension of these mechanisms will offer ascent to new classes of medications for the management of insulin resistance that will additionally improve the quality of life of HIV-infected patients..

Keywords: Antiretroviral Therapy (HAART).

There were roughly 36.9 million individuals living with HIV towards the end of 2017 with 1.8 million individuals recently infected in 2017 internationally. Among them 21.7 million individuals were under antiretroviral treatment, 59% of adults and 52% of children. There is no remedy for HIV disease. Notwithstanding, viable antiretroviral (ARV) medications can control the infection and help counteract transmission. New HIV positive fell by 36%, and HIV-related deaths fell by 38% with 11.4 million lives spared because of ART in a similar period[1]. Thus, HIV infection is these days considered "only" a chronic disease. There are in 20 affirmed antiretroviral drugs characterized into five groups as per the mechanisms by which they interfere with the HIV life cycle[2]. Longtime utilization of HAART has been identified with drug toxic effect that can bargain non-AIDS illnesses. A portion of these aggravations is insulin resistance followed by metabolic syndrome. This brings hypertriglyceridemia, hypercholesterolemia, hypertension, endocrine disorders, osteopenia , neurocognitive disorders, diabetes, cardiovascular disease, non-AIDS-defining cancers and lipodystrophy have been observed during therapy[3, 4, 5, 6]. Ongoing examinations likewise propose that utilization of HAART, liver disease speaks to a critical reason for morbidity and mortality in HIV-infected patients. These all complication is related to mitochondria damage induced by HAART. The following table listed FAD-approved HIV medication latest update (January 2020)

HAART

Mitochondrial Dysfunction

Every mammalian cell contains hundred to thousand mitochondria. The size, shape, and number of mitochondria change significantly in various cell types and more may change under various energy requests and distinctive physiological or natural conditions. The principle capacity of mitochondria is to incorporate ATP through electron transport and oxidative phosphorylation in combination with the oxidation of metabolites by a tricarboxylic acid cycle and catabolism of fatty acids by beta-oxidation. In this sense, the mitochondrion viewed as basically the fuel supplier for the most fundamental energy requests of the cells. On the other hand, mitochondria are presently perceived as being basic segments in the control of numerous key cellular processes, being the primary mediator in the inception and execution of apoptosis and important functions in the assurance of life and deaths of the mammalian cells.

Also, mitochondria are the principal intracellular source of reactive oxygen species (ROS)[7]. During the electron transport chain in the mitochondria, few electrons "spill" to cytosolic oxygen, forming the superoxide radical[8]. The electron transport complex I of the mitochondria leaks the electron and formation of superoxide. Mitochondria are not only important sources of ROS production, but also the major targets of ROS attack[9]. Many things influence the function of mitochondria for example, ageing, infection, and drugs, etc. These factors can injure the mitochondria, affecting the normal functions of the cell. Mitochondrial injury can change the normal functions of heart, nerves, muscles, pancreas, kidneys, and liver, causing many chronic diseases. Mitochondrial damage emerges from a deficient number of mitochondria, a failure to give essential substrates to mitochondria, or an impaired electron transport and ATP-synthesis components. The number and practical status of mitochondria in a cell can be changed by: fusion of partially damaged mitochondria to healthy mitochondria, which renews and improves its functional capacity the formation of new mitochondria by fission and completely damage mitochondria are degraded by mitophagy[10]. These occasions are controlled by complex cell processes that sense the damage of mitochondria[11].

HAART and Mitochondria Damage

It is conceivable that chronic infection and inflammation and/ or adverse effect of the impacts of the drug on mitochondrial capacity would add to long-term complications in HIV-infected people. A substantial list of clinical appearances of mitochondrial toxicity has been portrayed within HAART-related adverse events, which is a noteworthy worry for the determination and long-term adherence to a specific treatment. Amid the period of monotherapy with zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor (NRTI), a few patients created skeletal muscle myopathies[12]. Histological examination of their muscle, adipose tissue, heart and liver, biopsies discovered mitochondrial damage[13, 14, 15, 16]. With the broad utilization of NRTIs, other clinical indications, for example, lactic acidosis, lipodystrophy, peripheral neuropathies, cardiomyopathies, and pancytopenia were found[17]. Inhibition of polymerase gamma (Pol- ??), the enzyme involved in the replication of mtDNA, reduces the amount of mitochondrial DNA (mtDNA) content ensuing mitochondrial damage, was embroiled as the hidden system for these toxicities[18]. Reduction of mtDNA has been widely studied in various tissues of human and animal models such as placenta, fetal cord blood, heart, adipose tissue, skeletal muscle, brain and kidney[19,20,21,22,23]. Yet, amassing proof beyond the "Pol-?? speculation" have been brought up in the most recent years proposing that there are different types of mitochondrial damage both related and unrelated to mtDNA[24]. Accordingly, inhibition of mitochondrial RNA expression by NRTI has been seen in numerous cell lines[25] which may happen through mtRNA polymerase inhibition or by the confinement of the essential cofactors for mtRNA transcription. A few NRTIs likewise have a direct inhibitory effect on the function of mitochondria. In this manner, AZT inhibits the mitochondrial adenylate kinase and adenine nucleotide translocator in mitochondria[26]. AZT additionally increases oxidative stress (OS) and applies a direct inhibitory impact on the electron transport chain, resulting in reduction of OXPHOS[27]. NRTIs also initiate a noteworthy decrease in complex IV action through a specific inhibition of complex I[28]. In vivo evaluation with AZT showed a disturbed cardiac mitochondrial ultra structure, decreased expression of cytochrome b mRNA, and increased levels of oxidative stress in mitochondria. Prolonged mitochondrial ROS production has additionally been implicated to go with or even establish a different system of NRTI-initiated mitochondrial harmfulness. Additionally, protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) don't inhibit Pol- gamma, but the cause mitochondrial damage[29,30]. Hemandez et al reported that pregnant women under HAART medication showed subclinical mitochondrial damage of themselves and their newborn by reduction of mtDNA, mitochondrial protein synthesis and mitochondrial function[31].Various studies reported that mitochondrial dysfunction in peripheral organs results in insulin insensitivity[32, 33, 34, 35] Hence healthy mitochondria and its proper functions are very important for insulin sensitivity.

HAART and Insulin Resistance

Mitochondrial irregularities related with ART have been previously reported. Literature survey shows that HIV itself and ART influence mitochondrial work through a variety of components, incorporating direct increments in ROS, diminished ATP production, and reduced mitochondrial oxygen utilization[36, 37, 38, 39]. Lower mitochondrial respiration is the potential mechanism for IR in people living with HIV[40]. A longitudinal investigation of insulin resistance (IR) in individuals living with HIV on recent ART regimens showed IR in 21%, which indicates a huge decline from 35– 63% in IR compared to older ART regimens[41]. PIs of the HAART regimens potential components cause IR[42, 43, 44, 45] even without the changes in body composition[46, 47]. PIs strongly inhibits the insulin-depended glucose transporter Glut 4, prompting to peripheral IR and impaired glucose tolerance[48].

Molecular Mechanism of Mitochondrial Damage and Insulin Resistance

Pattern recognition receptors (PPRs) are parts of the innate immune framework, whose primary job is detecting the tissue damage, cell stress and infection. The inflammatory reactions get started by NOD- linked receptor (NLR) family of cytoplasmic PRPs. There are 22 known human NLR family members, including NLRP3-inflammasome[49]. Inflammasomes are activated by a variety of physiological and pathogenic signals. Inflammasome activation is a basic segment of the innate immune reaction and is related to the basic clearance of pathogens or damaged cells. The,overall inflammasome activation is likewise a noteworthy driver of autoimmune and metabolic disorders which is fundamental for the understanding of this process in physiological and

Table 1. FDA-Approved HIV Medicines

Drug	Generic Name (other Names and Acronyms	Brand name	FAD Approval date
1.Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
NRTIs block reverse transcriptase, an enzyme HIV needs to make copies of itself.	abacavir (abacavir sulfate, ABC)	Ziagen	December 17, 1998
	emtricitabine (FTC)	Emtriva	July 2, 2003
	lamivudine (3TC)	Epivir	November 17, 1995
	tenofovir disoproxil fumarate (tenofovir DF, TDF)	Viread	October 26, 2001
	zidovudine (azidothymidine, AZT, ZDV)	Retrovir	March 19, 1987
2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
NNRTIs bind to and later alter reverse transcriptase, an enzyme HIV needs to make copies of itself.	doravirine (DOR)	Pifeltro	August 30, 2018
	efavirenz (EFV)	Sustiva	September 17, 1998
	etravirine (ETR)	Intelence	January 18, 2008
	nevirapine (extended-release nevirapine, NVP)	Viramune Viramune XR (extended release)	June 21, 1996 March 25, 2011
	rilpivirine (rilpivirine hydrochloride, RPV)	Edurant	May 20, 2011
3. Protease Inhibitors (PIs)			
PIs block HIV protease, an enzyme HIV needs to make copies of itself.	atazanavir (atazanavir sulfate, ATV)	Reyataz	June 20, 2003
	darunavir (darunavir ethanolate, DRV)	Prezista	June 23, 2006
	fosamprenavir (fosamprenavir calcium, FOS-APV, FPV)	Lexiva	October 20, 2003
	ritonavir (RTV) Although ritonavir is a PI, it is generally used as a pharmacokinetic enhancer as recommended in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV and the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.	Norvir	March 1, 1996
	saquinavir (saquinavir mesylate, SQV)	Invirase	December 6, 1995
	tipranavir (TPV)	Aptivus	June 22, 2005
4. Fusion Inhibitors			
Fusion inhibitors block HIV from entering the CD4 cells of the immune system.	enfuvirtide (T-20)	Fuzeon	March 13, 2003
5. CCR5 Antagonists			
CCR5 antagonists block CCR5 coreceptors on the surface of certain immune cells that HIV needs to enter the cells.	maraviroc (MVC)	Selzentry	August 6, 2007
6.Integrase Inhibitors			
Integrase inhibitors block HIV integrase, an enzyme HIV	dolutegravir (DTG, dolutegravir sodium) raltegravir	Tivicay	August 13, 2013

needs to make copies of itself.	(raltegravir potassium, RAL)	Isentress	October 12, 2007
		Isentress HD	May 26, 2017

7.Post-Attachment Inhibitors

Post-attachment inhibitors block CD4 receptors on the surface of certain immune cells that HIV needs to enter the cells.	ibalizumab-uiyk (Hu5A8, IBA, Ibalizumab, TMB-355, TNX-355)	Trogarzo	March 6, 2018

8. Pharmacokinetic Enhancers

Pharmacokinetic enhancers are used in HIV treatment to increase the effectiveness of an HIV medicine included in an HIV regimen.	cobicistat (COBI, c)	Tybost	September 24, 2014

9. Combination HIV Medicines

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Combination HIV medicines contain two or more HIV medicines from one or more drug classes.	abacavir and lamivudine (abacavir sulfate / lamivudine, ABC / 3TC)	Epzicom	August 2, 2004
	abacavir, dolutegravir, and lamivudine (abacavir sulfate / dolutegravir sodium / lamivudine, ABC / DTG / 3TC)	Triumeq	August 22, 2014
	abacavir, lamivudine, and zidovudine (abacavir sulfate / lamivudine / zidovudine, ABC / 3TC / ZDV) atazanavir and cobicistat	Trizivir	November 14, 2000
	(atazanavir sulfate / cobicistat, ATV / COBI) bictegravir, emtricitabine, and tenofovir alafenamide	Evotaz	January 29, 2015
	(bictegravir sodium / emtricitabine / tenofovir alafenamide fumarate, BIC / FTC / TAF) darunavir and cobicistat	Biktarvy	February 7, 2018
	(darunavir ethanolate / cobicistat, DRV / COBI) darunavir, cobicistat, emtricitabine, and tenofovir alafenamide	Prezcobix	January 29, 2015
	(darunavir ethanolate / cobicistat / emtricitabine / tenofovir AF, darunavir ethanolate / cobicistat / emtricitabine / tenofovir alafenamide, darunavir / cobicistat / emtricitabine / tenofovir AF, darunavir / cobicistat / emtricitabine / tenofovir alafenamide fumarate, DRV / COBI / FTC / TAF) dolutegravir and lamivudine	Symtuza	July 17, 2018
	(dolutegravir sodium / lamivudine, DTG / 3TC) dolutegravir and rilpivirine	Dovato	April 8, 2019
	(dolutegravir sodium / rilpivirine hydrochloride, DTG / RPV) doravirine, lamivudine, and tenofovir disoproxil fumarate	Juluca	November 21, 2017
	(doravirine / lamivudine / TDF, doravirine / lamivudine / tenofovir DF, DOR / 3TC / TDF) efavirenz, emtricitabine, and tenofovir disoproxil fumarate	Delstrigo	August 30, 2018
	(efavirenz / emtricitabine / tenofovir DF, EFV / FTC / TDF) efavirenz, lamivudine, and tenofovir disoproxil fumarate	Atripla	July 12, 2006
	(EFV / 3TC / TDF) efavirenz, lamivudine, and tenofovir disoproxil fumarate (EFV / 3TC / TDF)	Symfi	March 22, 2018
	elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	Symfi Lo	February 5, 2018
	(elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide fumarate, EVG / COBI / FTC / TAF) elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil	Genvoya	November 5, 2015

fumarate (QUAD, EVG / COBI / FTC / TDF)	Stribild	August 27, 2012
emtricitabine, rilpivirine, and tenofovir alafenamide (emtricitabine / rilpivirine / tenofovir AF, emtricitabine / rilpivirine / tenofovir alafenamide fumarate, emtricitabine / rilpivirine hydrochloride / tenofovir AF, emtricitabine / rilpivirine hydrochloride / tenofovir alafenamide, emtricitabine / rilpivirine hydrochloride / tenofovir alafenamide fumarate, FTC / RPV / TAF)	Odefsey	March 1, 2016
emtricitabine, rilpivirine, and tenofovir disoproxil fumarate (emtricitabine / rilpivirine hydrochloride / tenofovir disoproxil fumarate, emtricitabine / rilpivirine / tenofovir, FTC / RPV / TDF)	Complera	August 10, 2011
emtricitabine and tenofovir alafenamide (emtricitabine / tenofovir AF, emtricitabine / tenofovir alafenamide fumarate, FTC / TAF)	Descovy	April 4, 2016
emtricitabine and tenofovir disoproxil fumarate (emtricitabine / tenofovir DF, FTC / TDF)	Truvada	August 2, 2004
lamivudine and tenofovir disoproxil fumarate (Temixys, 3TC / TDF)	Cimduo	February 28, 2018
lamivudine and zidovudine (3TC / ZDV)	Combivir	September 27, 1997
lopinavir and ritonavir (ritonavir-boosted lopinavir, LPV/r, LPV / RTV)	Kaletra	September 15, 2000

pathological settings[50].Latest investigations reported that mitochondria are connected with immune responses[51] and non communicable diseases[52, 53, 54]. At the point when mitochondria are injured, the dysfunctional mitochondria raise the level of reactive oxygen species (ROS) in cells and enhance immune response by activating NALP3 inflammasome[55, 56, 57]. Also, current reports suggested that different mitochondrial particles known as damage-associated molecular patterns (DAMPs) for example, mtDNA, cardiolipin, or dynamin-related protein 1 etc. can be dislocated to the exterior of mitochondria (e.g., cytosol, cell surface, or extracellular spaces) and activates the immune response. Different DAMPs can be discharged into cytosol by stressing cells undergoing autophagy or damage without obvious cell deaths. Proof has been brought forth regarding the autophagy-mediated release of high-mobility group protein B1 (HMGB1), ATP, and mtDNA etc[58]. DAMPs directly activate the inflammasome (Figure 1) , however, ROS initiation of NLRP3 can be done through thioredoxin (TRX). At the point when the cytoplasmic ROS are increased, the reduced TRX gets oxidized and detached from thioredoxin restricting protein (TXNIP) which binds to NLRP3 for activation[59]. NLRP3 inflammasome activation prompts the activation of caspase-1[60]. The activated caspase 1 is converting pronflammatory inactive form of cytokines interleukin-1β (IL-1β) and IL-18 to their active form[61](Figure 1).Recently, the role of the IL-1β pathway in insulin resistance was well described[62, 63, 64]. With regards to the exact fundamental mechanism, an amazing number of genetic animal models presently showed the function of the inflammasome in interceding IL-1β-initiated insulin resistance[64]. IL-1β signaling pathway works not only for

insulin resistance but also for defective insulin secretion. It has been accounted for the beta cell failure[65, 66, 67, 68] since the cell itself produces IL-1β upon overload of glucose[65]. This is further supported by an earlier study showing that antagonist IL-1Ra treatment and defect in NALP3, caspase 1 or IL-1β in animal model recovered from hyperglycemia by improving both β cell insulin production and insulin sensitivity in peripheral organs[63, 69].

The utilization of HAART in the course of the last 20 years has changed death rates among people living with HIV. As we keep on utilized these medications clinically, we shall mind their multifaceted mitochondrial toxicity. Mitochondrial toxicity could represent a tremendous risk of HIV-AIDS patients taking HAART treatments for a prolonged period of time. The discovery of mitochondrial toxicity could be utilized, for example, tests of mitochondrial work (e.g. ATP content, enzyme activity), assessment of the mitochondrial membrane potential, mitochondrial RNA levels or evaluation of mitochondrial proteins, the action of cytochrome C oxidase, estimation of mitochondrial mass and investigation of mitochondrial morphology. In any case, in the interest of a clear interpretation of HAART, mitochondrial toxicity mediated insulin resistance mechanisms need to be investigated. Studies such as these may help to obviously characterize the degree of HAART mediated mitochondrial dysfunction and development of IR, and furthermore decide how focusing on mitochondria might be beneficial for the treatment of IR in HIV patients.

Figure 1. The connection between HAART medication and Mitochondrial damage, and stimulating IL-1β and IL-18-mediated inflammatory cascade.
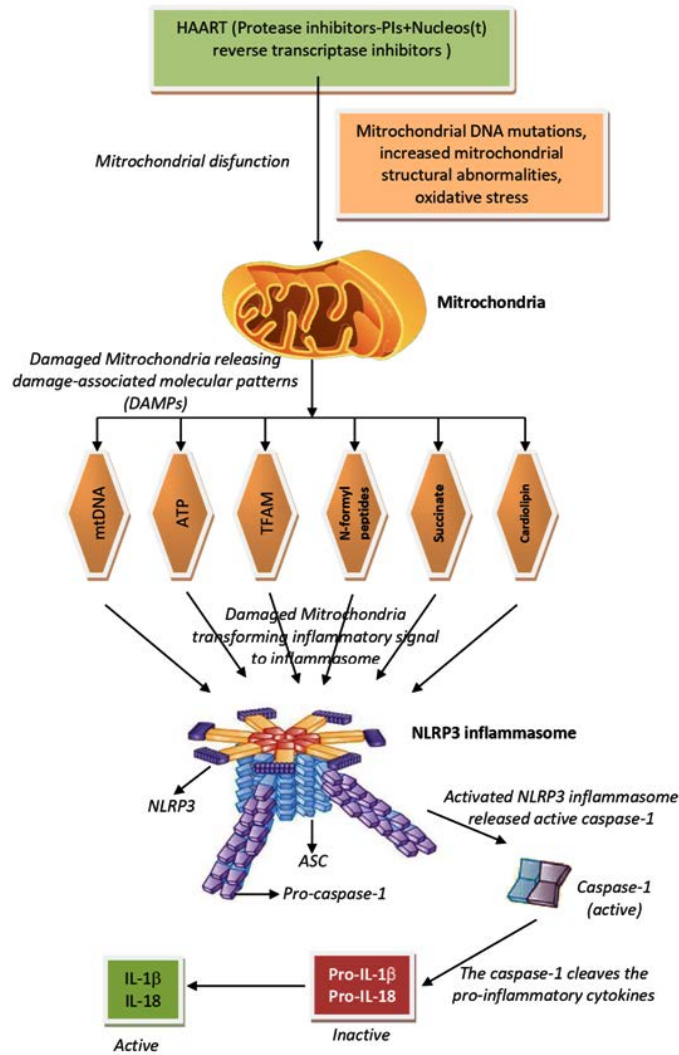
Fig. 1. The connection between HAART medication and Mitochondrial damage, and stimulating IL-1â and IL-18-mediated inflammatory cascade

NRTIs can also bind to mitochondrial DNA polymerase gamma, which is exclusively responsible for the replication of mitochondrial DNA (mtDNA). As to NNRTI (Non-Nucleoside-Transcriptase Inhibitor) or PI (Protease Inhibitors), evidence of the damage the mitochondria .Result damaged mitochondria triggers the inflammasome NLRP3, stimulating the IL-1β and IL-18-mediated inflammatory insulin resistance cascade.

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