

Muscle and Liver Lactate Metabolism in HAART-Treated and Naive HIV-Infected Patients.

Jade Ghosn¹, Marguerite Guiguet¹, Claude Jardel¹, Rabah Benyaou¹, Valérie Zeller¹, Anne Simon¹, Marc-Antoine Valantin¹, Guillaume Boulanger¹, Bahia Amellal¹, Lambert Assoumo¹, Jean-Yves Hogrel¹, Daniel Vittecoq², Dominique Costagliola¹, Anne Lombès¹ and Christine Katlama¹.

1/ CHU Pitié-Salpêtrière AP-HP, INSERM Université Pierre et Marie Curie Paris VI ; 2/ CHU Paul Brousse, Paris, France

jade.ghosn@psl.ap-hop-paris.fr
christine.katlama@psl.ap-hop-paris.fr

Objectives

- Mitochondrial toxicity is a well recognized adverse event related to nucleoside analogue reverse transcriptase inhibitors (NRTI), which are alternative substrates of the viral reverse transcriptase but also of the DNA polymerase γ
- The ability of NRTI to inhibit polymerase γ *in vitro* is diverse, higher for D-drugs (ddC, D4T, ddI, ZDV), and lower for 3TC, abacavir and tenofovir.
- Although most treated patients receive a backbone of NRTI for lengthy periods of time, only a very small number of them will present with severe symptoms of mitochondrial toxicity.
- Hyperlactatemia in normoxic conditions is a correlate of mitochondrial dysfunction.
- Muscle and liver are the two most pertinent tissues with respect to lactate/pyruvate homeostasis.
- In the present study, we aimed to address the *in vivo* mitochondrial impact of several NRTI-combinations on production and clearance of lactate, selectively in muscle and in liver. We studied antiretroviral-naïve HIV-infected patients and patients treated with NRTI classified according to their differential ability to inhibit the polymerase γ *in vitro*.

Methods

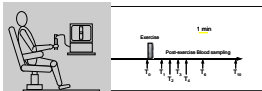
- Cross-sectional, multicenter study
- Inclusion criteria:

HIV-1 infected patients aged between 18 and 60 years, were randomly selected according to their antiretroviral treatment and regardless of any clinical symptom

- Group 1: antiretroviral naïve patients
- Group 2: stable antiretroviral treatment with at least one D-drug
- Group 3: stable antiretroviral treatment with ABC + 3TC + PI/NRTI

Investigation of muscle lactate metabolism

The measurement of lactate production was performed during a non ischemic exercise test based on hand grip contraction



Investigation of liver lactate metabolism

Liver lactate metabolism was assessed by exogenous lactate infusion (2.5 mmol/kg sodium lactate was infused over a 15-minutes period).

Lactate was measured in blood immediately before lactate infusion, then 15, 20, 25, 35, 45, 60, 75, 105, and 120 minutes thereafter.

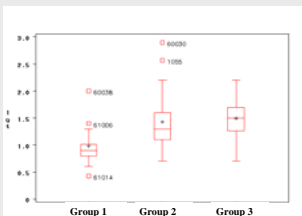
Results

Baseline characteristics (n = 65 patients)

	Naïve Patients		D-Drug	Without any D-Drug	
	Group 1	Group 2		Group 3	Group 3
Patients (n)	16	31	15	16	
Male (n)	13	28	17	11	
Age (years)	38 (33-46)	42 (38-47)	41 (39-46)		
Time on ART (months)		84 (39-144)	114 (69-156)		
Time on D-Drug (months)		54 (30-94)	93 (59-138)		
Time since D-Drug interruption			19 (14-25)		
Any exposure to NRTI					
Zidovudine (n)	25	15			
Stavudine (n)	22	18			
Didanosine (n)	22	12			
Zalcitabine (n)	4	5			
Current NRTI					
Zidovudine (n)	13	9			
Stavudine (n)	9	9			
Didanosine (n)	16	16			
Abacavir (n)	4	18			
Lamivudine (n)	24	18			
Current protease inhibitor (n)	15	14			
Current NNRTI (n)	9	2			
Viral load (log copies/mL)	4.4 (3.8-4.8)	<2.5	<2.5		
CD4 cell count (cells/mm ³)	497 (362-454)	601 (593-582)	584 (583-449)		
BMD (kg/m ²)	23.2 (20.8-26.8)	22.8 (21.8-24.3)	21.6 (21.8-24.1)		

All 65 patients were asymptomatic

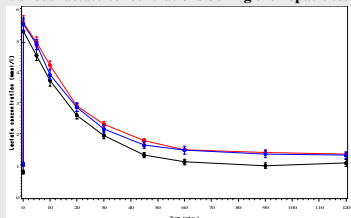
Baseline Lactatemia at rest



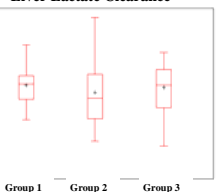
Though ranging within normal values, median baseline lactatemia in both treated groups was significantly higher than in naïve patients (G2: 1.4, G3: 1.5, and G1: 1.0 mmol/L, $P=0.005$).

Investigation of liver lactate metabolism

Venous lactate concentrations during the hepatic test



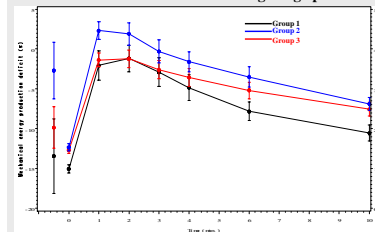
Liver Lactate Clearance



Both hepatic clearance of lactate and lactate half-life were similar in the three groups. Lactatemia returned to its basal level in less than 120 minutes in 72% of patients.

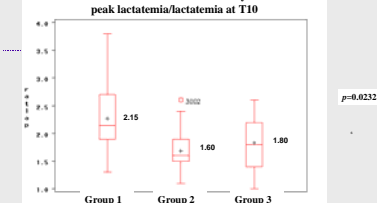
Investigation of muscle lactate metabolism

Venous lactate concentration during the grip test



Lactate production normalized to the mechanical energy produced did not differ between the three groups of patients.

Muscle Lactate clearance evaluated by the ratio peak lactatemia/lactatemia at T10



Muscle lactate clearance was significantly decreased in both treated groups in comparison to antiretroviral-naïve patients

Summary

This study evaluated lactate metabolism in muscle and in liver in 65 asymptomatic patients:

- 16 were antiretroviral-naïve (G1)
- 31 were on stable HAART including a D-drug (G2)
- 18 were on stable HAART with ABC + 3TC (G3). Of note, Group 3 patients had been pre-treated with D-drugs for a median of 7 years, and were switched for ABC and 3TC for a median of 1.5 years

- ➔ Lactatemia at rest was significantly higher in both treated groups
- ➔ In muscle, lactate clearance was significantly decreased in both treated groups
- ➔ In liver, lactate metabolism was similar in the three groups
- ➔ No difference was evidenced between patients on D-drugs and patients receiving a backbone of Abacavir and 3TC

Conclusions

- These results suggest that, in patients without symptomatic hyperlactatemia, mitochondrial damage in muscle is associated with all NRTI-containing regimens.
- In contrast, liver appears spared.
- The absence of difference between Group 2 and Group 3 raises questions about the potential reversibility of muscle mitochondrial dysfunction, and/or the ability of abacavir and lamivudine to induce such mitochondrial damage.

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