

Impact of hepatitis C virus (HCV) infection on mitochondrial DNA depletion in HIV-coinfected patients

C. de Mendoza, N. Zahonero, P. Barreiro, M.P. de Baar*,
L. Capa, J.M. Benito and V. Soriano

*Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain. *Primagen, Amsterdam, The Netherlands.*

Background

- ✓ The metabolic stress derived from high levels of virus replication in both HIV and HCV infections seems to result in mitochondrial damage and mtDNA depletion, which is enhanced in HCV/HIV-coinfected patients.
- ✓ Following introduction of HAART there is improvement in the mtDNA amount accompanying HIV-RNA suppression, although the use of some nucleoside analogs (d4T, ddI, ddC) subsequently reverses this benefit due to its inhibition of DNA polymerase gamma.
- ✓ Information on the impact of treatment of HCV infection on mtDNA is scarce and conflictive results have been reported.

Patients and Methods

- ✓ 59 HCV/HIV-coinfected patients (43 on HAART and 16 without antiretrovirals) who initiated treatment with pegylated interferon plus ribavirin were analyzed.
- ✓ The amount of mtDNA was measured in PBMC using Retina Mitox (Primagen) at baseline, at the end of therapy and 6 months upon treatment discontinuation.
- ✓ Ribavirin plasma levels were assessed using HPLC.

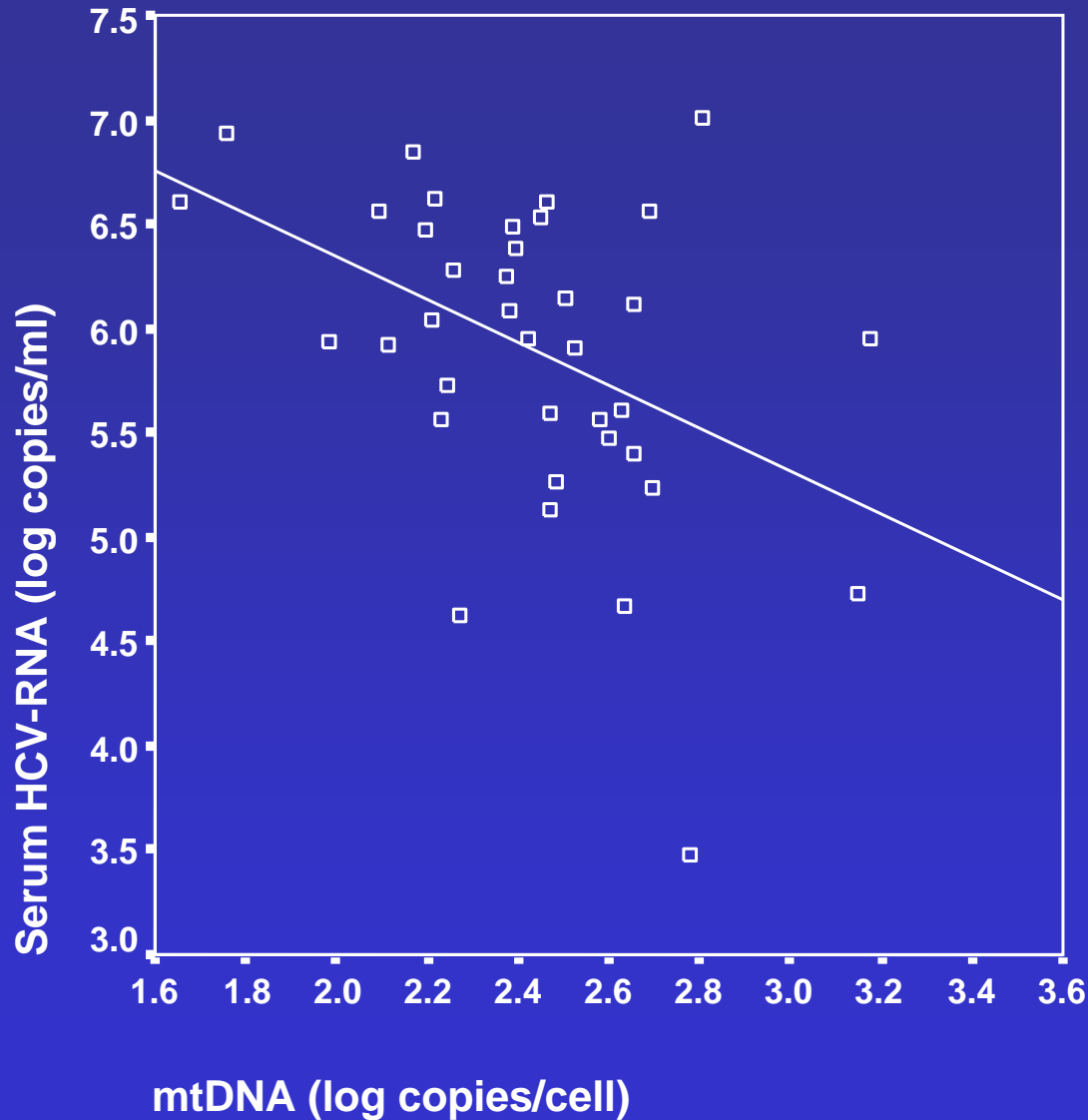
Results (I)

- ✓ Baseline characteristics of the study population are recorded in table 1. Overall, there were no statistical differences between patients on HAART and those without HAART except for age, and HIV viral load
- ✓ An inverse correlation between serum HCV-RNA titers and mtDNA content in PBMC was recognized at baseline in all patients ($r = -0.370$; $p = 0.006$) (Figure 1) (Table 2).
- ✓ Genotype 3 seems to present lower levels of mtDNA at baseline than non-3 genotypes (Table 2).

Table 1. Baseline characteristics of the study population

	Total (n = 59)	On HAART (n 43)	No HAART (n = 16)	p
Male (%)	77	79.1	70	0.495
Median age (years)	43	44	41	0.007
Mean baseline CD4 count (cells/ μ L)	569	576	546	0.625
Mean baseline plasma HIV-RNA (log)	2.2	1.9	3.2	< 0.001
Mean baseline serum HCV-RNA (log)	5.8	5.7	6.1	0.107
HCV genotypes (1 / 2 / 3 / 4)	33 / 2 / 20 / 4	24 / 2 / 14 / 3	9 / 0 / 6 / 1	ns

Figure 1. Correlation between baseline HCV replication and baseline mtDNA



Spearman's rho: - 0.370
p = 0.006

Table 2. Baseline effect on mtDNA (univariate analyses)

	Median (IQR)	p
HCV-RNA (log IU/mL) > 6 vs < 6	247 vs 414 (161 - 342) (295 - 511)	0.008
Genotype 3 vs non-3	254 vs 340 (172 - 401) (245 - 462)	0.065
HAART no vs yes	273 vs 334 (150 - 430) (234 - 462)	0.137

Results (II)

✓ However at the multivariate analyses only baseline HCV viremia was significantly associated with lower baseline mtDNA values (Table 3).

**Table 3. Baseline effect on mtDNA
(multivariate analyses)**

	B- coefficient	95% CI	p
HCV-RNA > 6 log IU/mL	- 162	- 307 to - 18	0.028
Genotype 3	- 124	- 277 to + 28	0.109
HAART	95	- 62 to + 253	0.229

Results (III)

- ✓ Treatment with peg-IFN + ribavirin lead to an overall increase on mitochondrial DNA in those individuals with high levels of viremia, genotype 3 and without HAART therapy.
- ✓ By contrast, those individuals taking HAART showed a significant depletion on mtDNA (Table 4 and Figure 2).
- ✓ Moreover, ribavirin levels were inversely associated with Δ mtDNA (Figure 3).
- ✓ In a multivariate analyses, only the concomitant use of HAART along HCV therapy was related with significant depletion on mtDNA (Table 5).

Table 4. Effect of HCV therapy on mtDNA variation

	mtDNA (Baseline)	Δ mtDNA 1 (end of tx – baseline)	Δ mtDNA 2 (6 mo after tx – end of tx)
HCV-RNA > 6 log vs < 6 log	247 vs 414 $p = 0.008$	+ 61 vs – 30 $p = 0.033$	+ 0 vs + 10 $p = 0.113$
Genotype 3 vs non-3	254 vs 340 $p = 0.065$	+ 64 vs + 10 $p = 0.197$	- 17 vs – 2.5 $p = 0.396$
HAART no vs yes	273 vs 334 $p = 0.137$	+ 133 vs – 13 $p = 0.021$	+ 52 vs – 33 $p = 0.101$

Figure 2. Effect of HCV therapy on Δ mtDNA

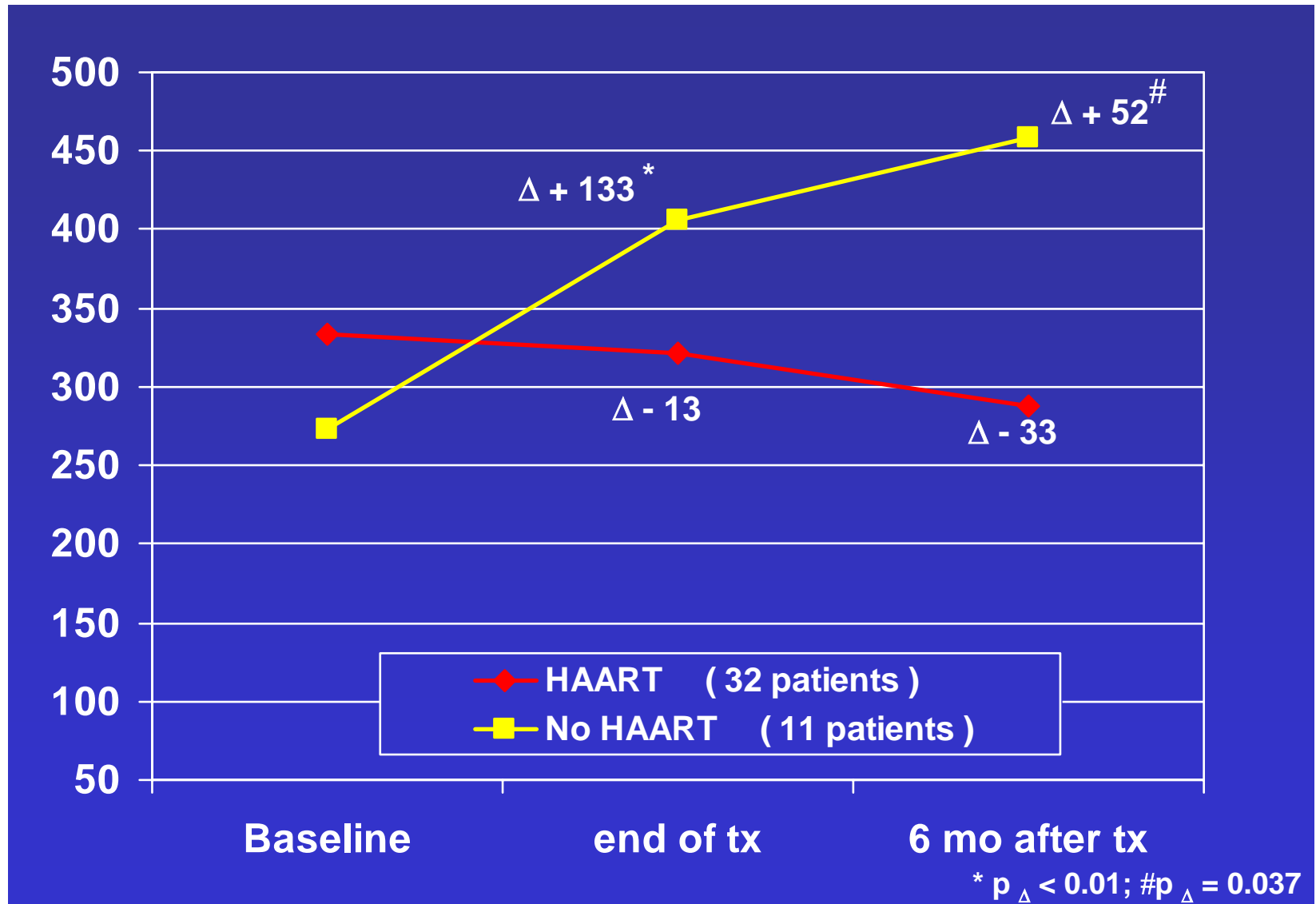


Figure 3. Ribavirin levels at the end of HCV therapy and Δ mtDNA in patients on HAART (43)

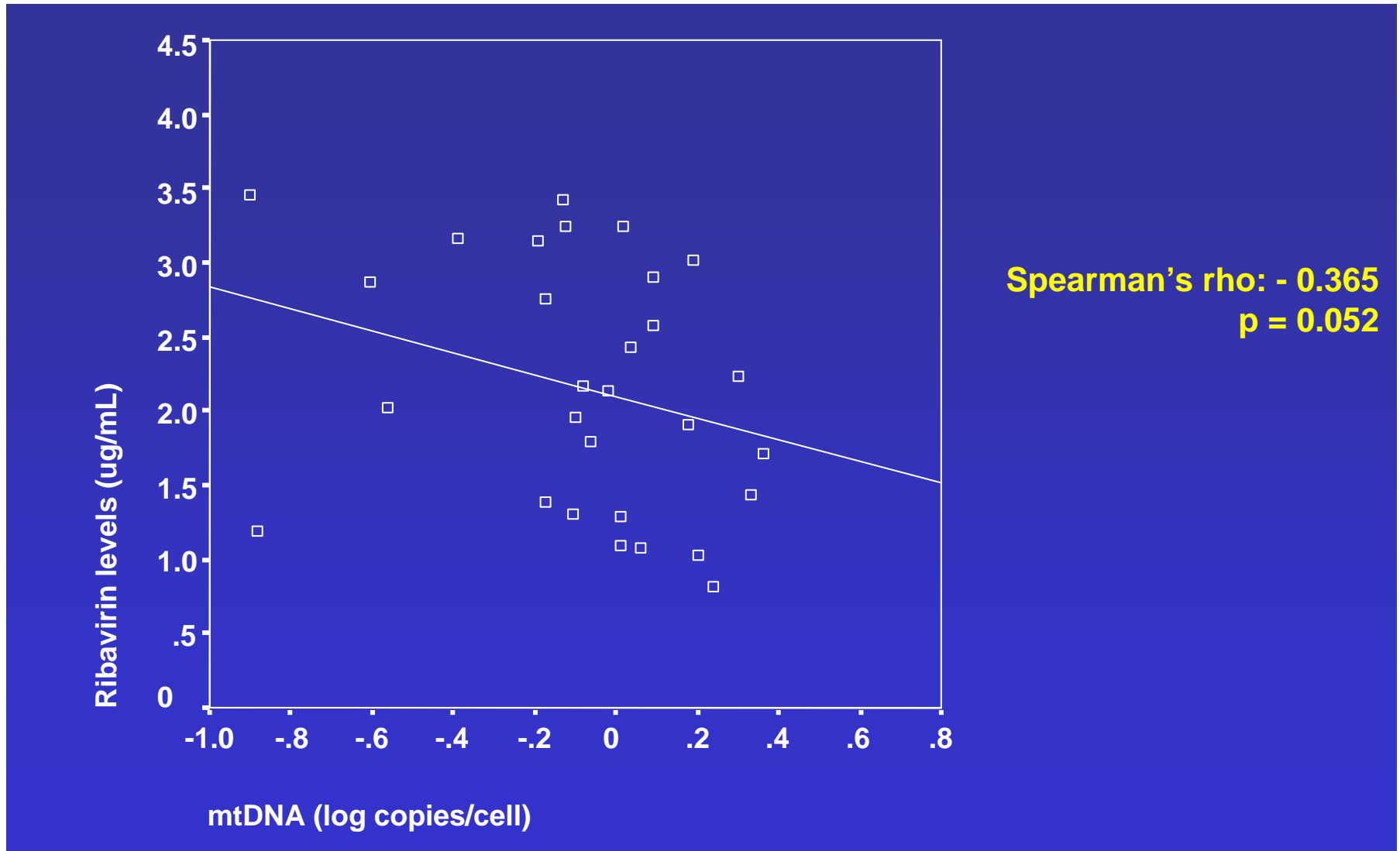


Table 5. Impact of HCV therapy in mtDNA variation (multivariate analyses)

	B- coefficient	95% CI	p
HAART	- 154	- 394 to -14	0.032
d4T	99	- 108 to + 305	0.337
Ribavirin levels	- 16	- 94 to + 61	0.668
HCV-RNA > 6 log	102	- 25 to + 201	0.113

Conclusions

- ✓ Mitochondrial toxicity is a complex phenomenon with multiple factors involved.
- ✓ Our results are consistent with the concept that HCV replication inversely correlates with the extent of mtDNA depletion in PBMC.
- ✓ Treatment of chronic hepatitis C is associated with a significant improvement in mtDNA content in individuals without concomitant antiretroviral therapy.
- ✓ Our data suggest that there is a deleterious synergistic effect on mtDNA when RBV is taken along with nucleoside analogues.