



HAL
open science

Lopinavir/ritonavir Induces Mitochondrial Toxicity in HIV-exposed Uninfected Children

Audrey Monnin, Nicolas Nagot, Marianne Peries, Roselyne Vallo, Nicolas Meda, Mandisa Singata-Madliki, James K Tumwine, Chipepo Kankasa, Pascal Reynier, Thorkild Tylleskär, et al.

► **To cite this version:**

Audrey Monnin, Nicolas Nagot, Marianne Peries, Roselyne Vallo, Nicolas Meda, et al.. Lopinavir/ritonavir Induces Mitochondrial Toxicity in HIV-exposed Uninfected Children. Conference on Retroviruses and Opportunistic Infections, Mar 2018, Boston, United States. hal-03922022

HAL Id: hal-03922022

<https://hal.science/hal-03922022v1>

Submitted on 4 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Lopinavir/ritonavir Induces Mitochondrial Toxicity in HIV-exposed Uninfected Children

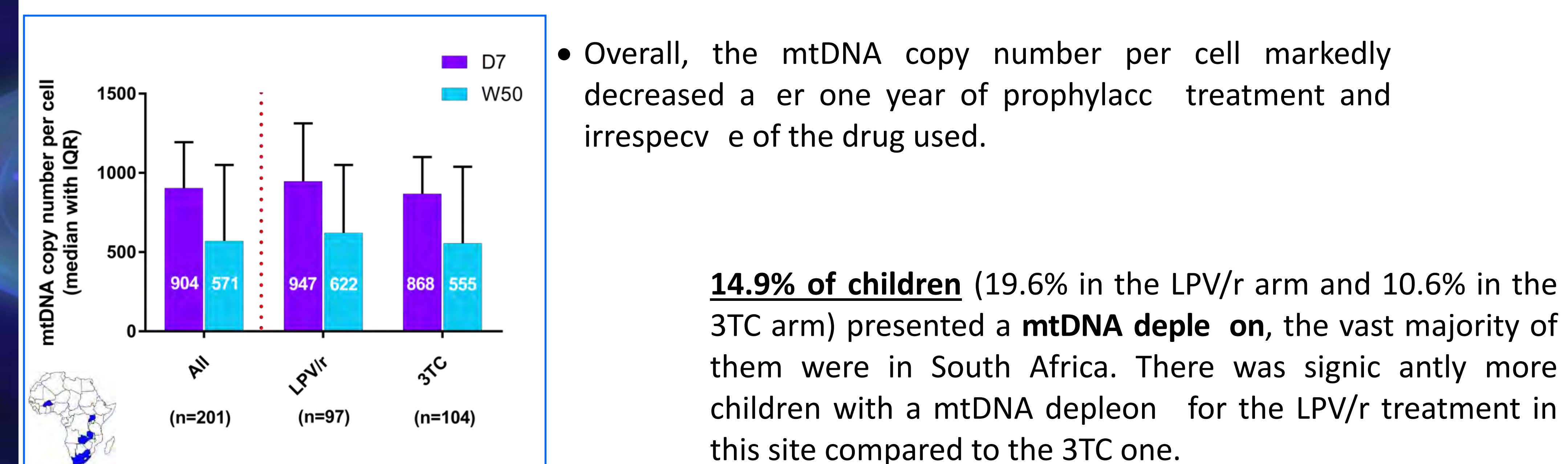
Audrey Monnin¹, Nicolas Nagot^{1,2}, Marianne Peries¹, Roselyne Vallo¹, Nicolas Meda³, Mandisa Singata-Madliki⁴, James K. Tumwine⁵, Chipepo Kankasa⁶, Pascal Reynier⁷, Thorkild Tylleskär⁸, Philippe Van de Perre^{1,2}, Jean-Pierre Molès¹, for the PROMISE PEP consortium ANRS 12174

Poster #878

¹University of Montpellier, INSERM, EFS, Montpellier, France, ²CHU Montpellier, Montpellier, France, ³University of Ouagadougou, Ouagadougou, Burkina Faso, ⁴University of Fort Hare, East London, South Africa, ⁵University of Makerere, Kampala, Uganda, ⁶University Teaching Hospital, Lusaka, Zambia, ⁷CHU Angers, Angers, France, ⁸University of Bergen, Bergen, Norway

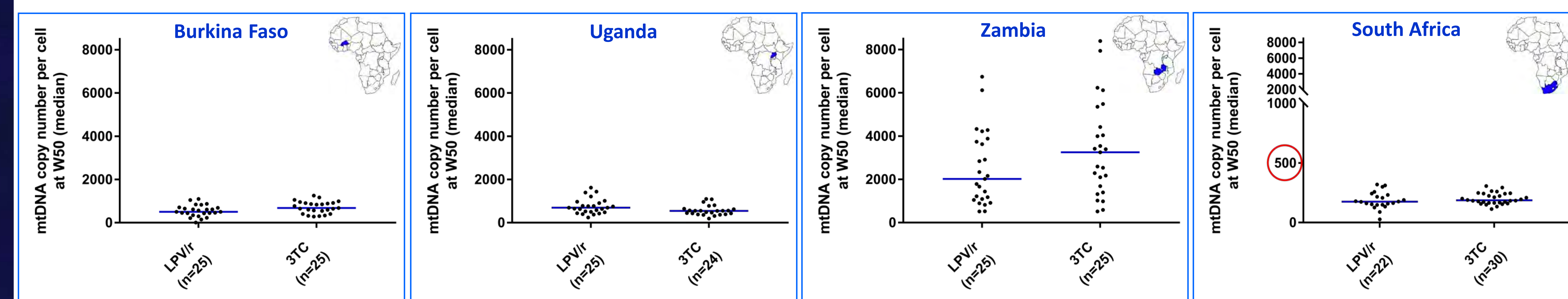
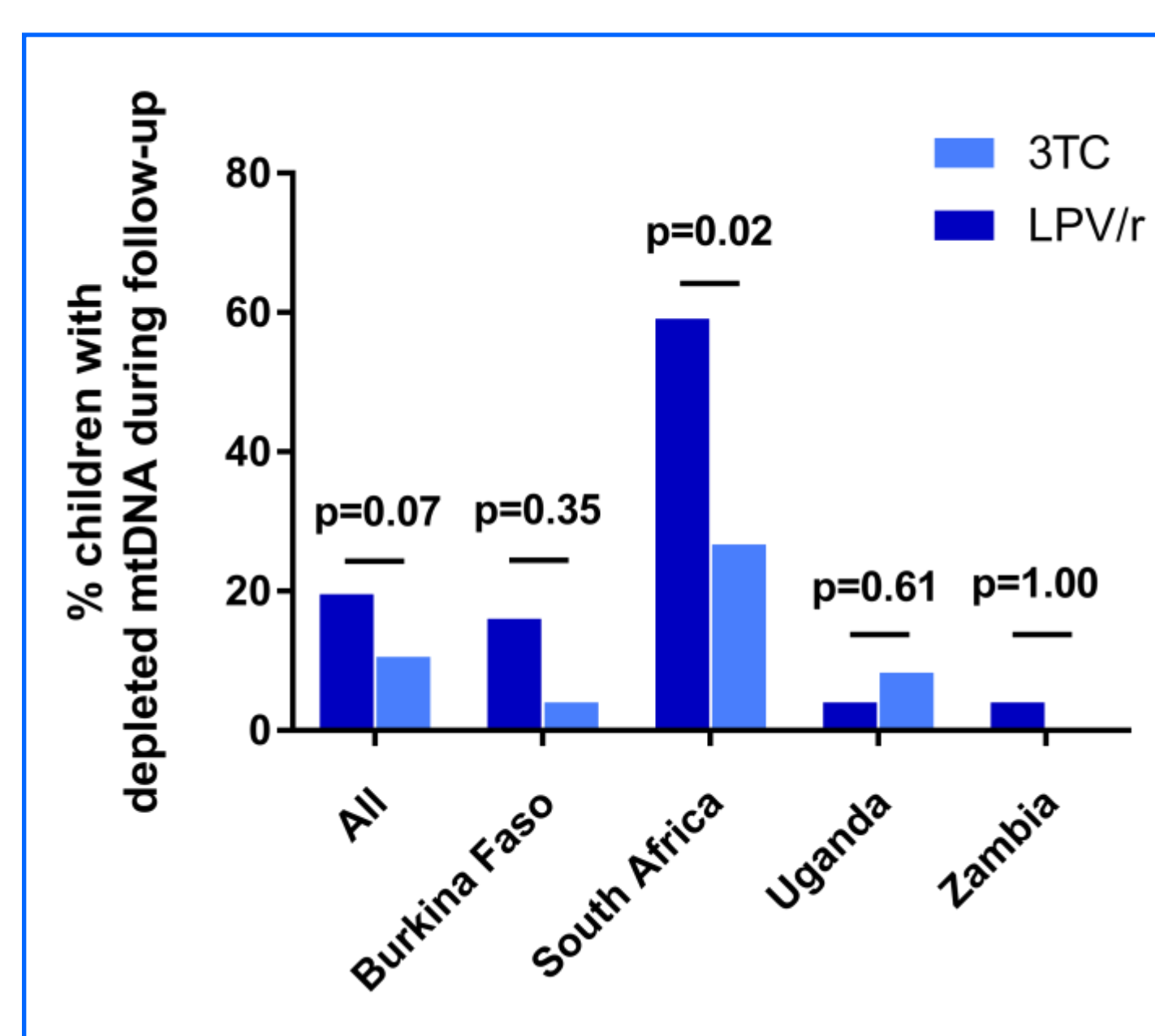
mtDNA depletion

Mitochondrial DNA copy number at day 7 and a year one year of PrEP



Overall, the mtDNA copy number per cell markedly decreased a year one year of prophylactic treatment and irrespectively of the drug used.

14.9% of children (19.6% in the LPV/r arm and 10.6% in the 3TC arm) presented a **mtDNA depletion**, the vast majority of them were in South Africa. There was significantly more children with a mtDNA depletion for the LPV/r treatment in this site compared to the 3TC one.



Children from Burkina Faso and Uganda presented similar levels of mtDNA copy number per cell at W50. Children from Zambia showed the highest whereas those from South Africa showed the lowest.

Introduction

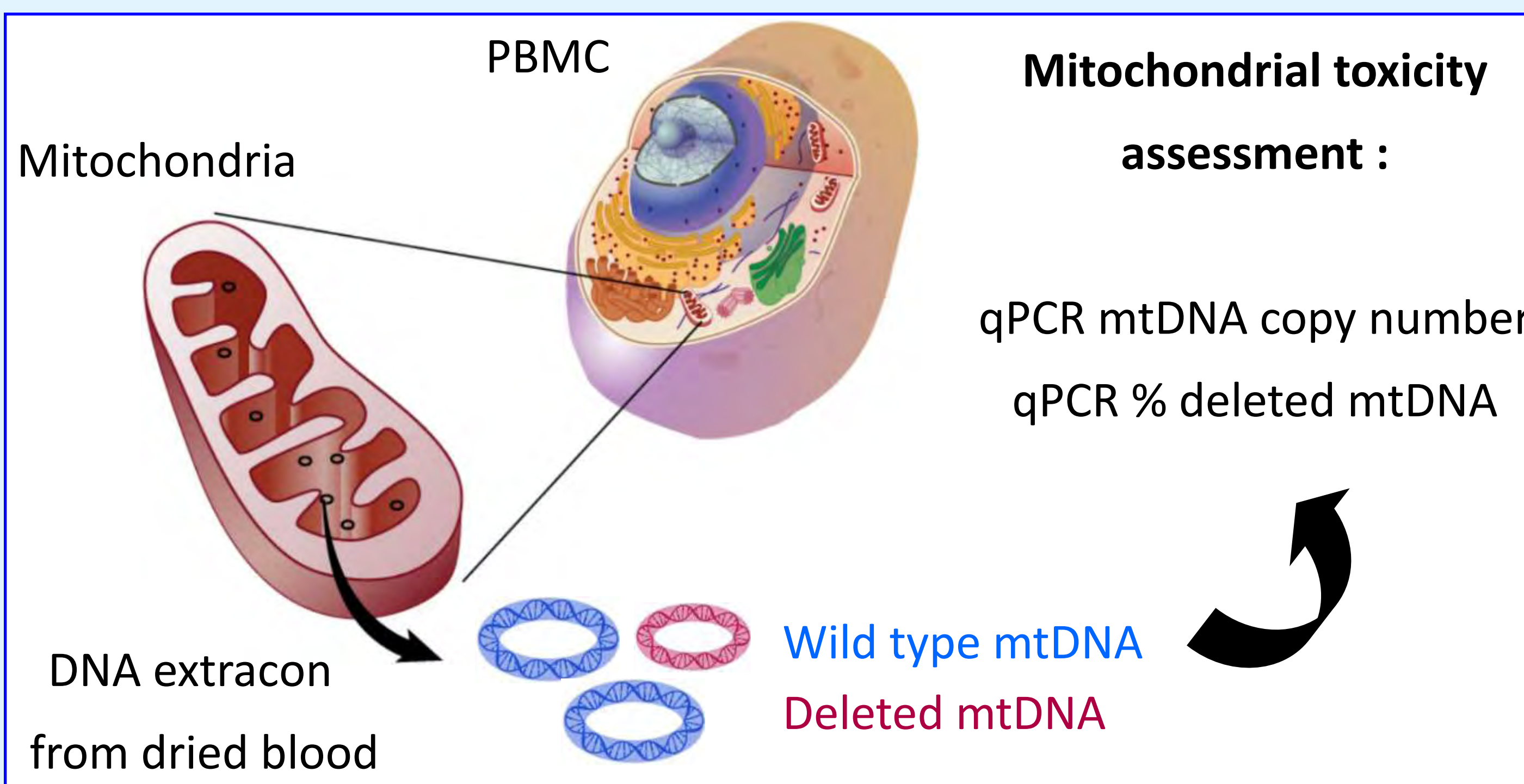
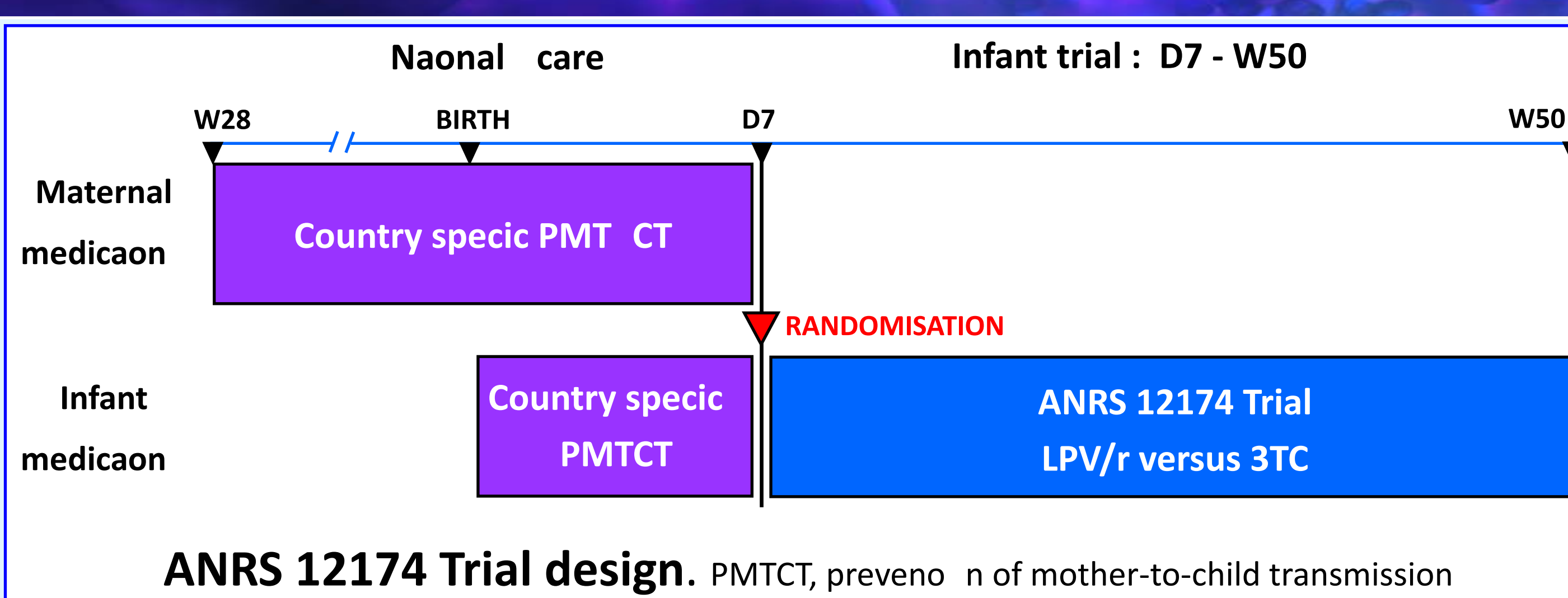
- Adverse outcomes in HIV-exposed uninfected (HEU) children have been reported, including **mitochondrial toxicity** (1).
- HEU children are exposed to HIV and ARV during the pregnancy and breastfeeding periods.
- Pre-exposure prophylaxis (PrEP) is widely deployed in populations at risk of acquiring HIV but still not widely promoted among HEU children.
- Beside the well-known side effect of NRTI on mitochondria (2), protease inhibitors such as LPV/r were not reported to be mitotoxic.
- The aim of this study was to quantify the mitochondrial toxicity of lopinavir/ritonavir (LPV/r) and lamivudine (3TC) used as PrEP among breastfed HEU children.

Method

- 201 children from the ANRS 12174 trial were randomly included in this study with a sex and treatment ratio around 1.
- The ANRS 12174 trial was conducted in four African countries (Burkina Faso, South Africa, Uganda and Zambia) between 2009 and 2014. 1273 breastfed HEU children born to HIV-infected mothers were recruited (3).
- At day seven (D7), children were randomized to receive either 3TC or LPV/r as PrEP until the end of breastfeeding (max 50 weeks W50).

Conclusions

- A marked decrease of mtDNA copy number per cell was observed in children under PrEP, significantly and independently more important for those taking LPV/r regimen.
- Unexpectedly, the proportion of deleted mtDNA, assessed for the first time in this population, was high at birth and remained unchanged at the end of the prophylaxis period.
- Mitochondrial toxicity of LPV/r came as a surprise since LPV/r was not reported as responsible for this adverse event in the literature.
- At an individual level, whether none of the children included in this study presented any clinical symptom of mitochondrial diseases, several of them showed level of



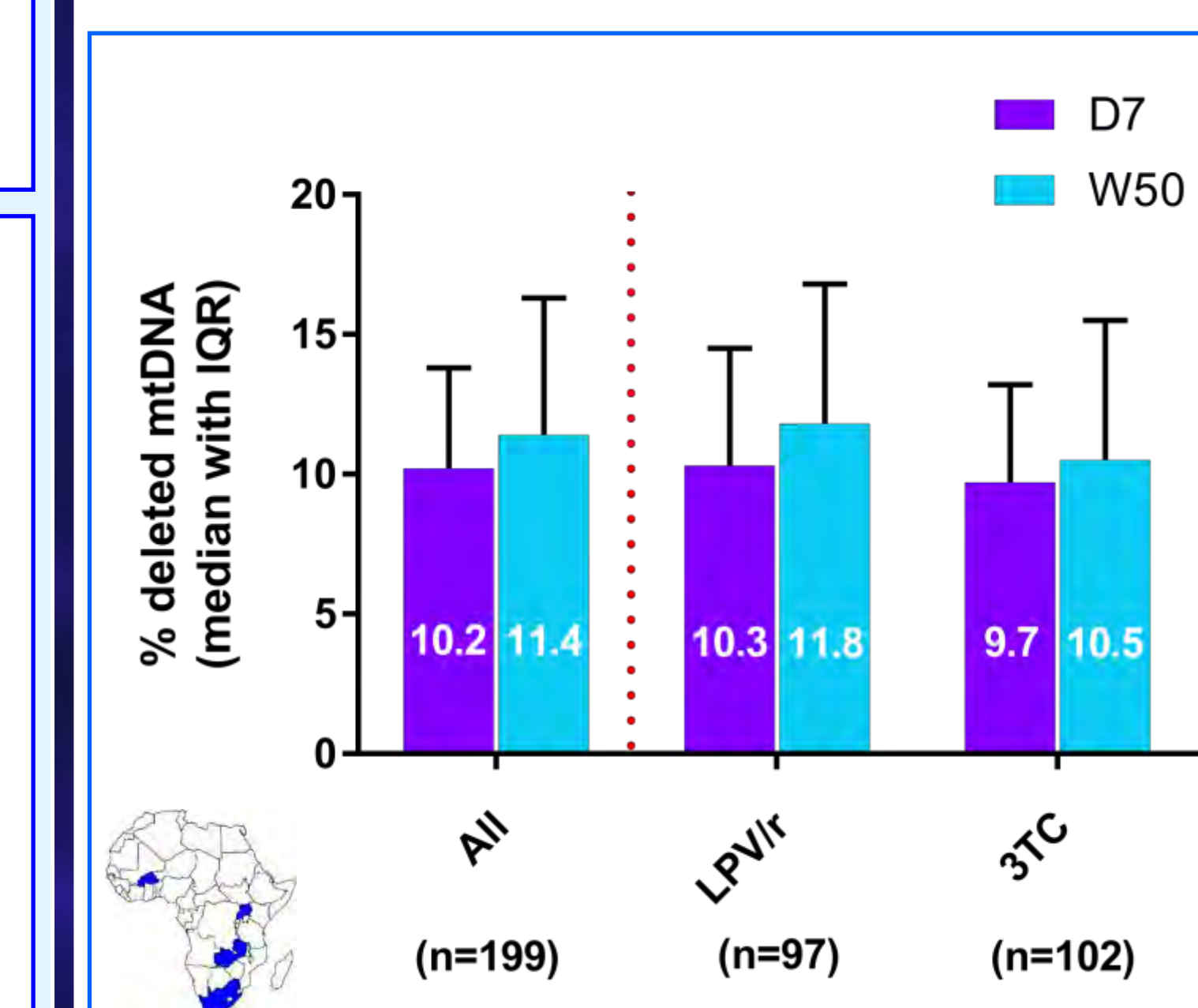
- We used definitions of mitochondrial DNA parameters according to a reference center for mitochondrial disorders:
- mtDNA depletion** at W50 was defined by a mtDNA copy number per cell (mtDNA) 30% lower than its value at D7.
- % deleted mtDNA** at W50 was considered at risk when it exceeds 40%.
- Wilcoxon rank test was used to compare continuous variables. Multivariate logistic regression were performed to identify the risk factors associated with a mtDNA depletion and an increase proportion of deleted mtDNA at W50.

References
 [1]Aldrovandi G, et al. Antiretroviral exposure and lymphocyte mtDNA content among uninfected infants of HIV-1-infected mothers. *Pediatrics*, 2009, 124(6):e1189-97.
 [2]Köhler J, et al. A Brief overview of mechanisms of mitochondrial toxicity from NRTIs. *Mitochondrial DNA A DNA Mapp Seq Anal*, 2016, 27(3):1685-7.
 [3]Nagot N, et al. Lopinavir/ritonavir versus Lamivudine peri-exposure prophylaxis to prevent HIV-1 transmission by breastfeeding: the PROMISE-PEP trial Protocol ANRS 12174. *BMC Infect Dis*, 2012, 12:246.

This work was funded by the Pierre Bergé endowment fund in collaboration with Sidaction and sponsored by the French National Agency for Research on AIDS and Viral Hepatitis [ANRS12174].

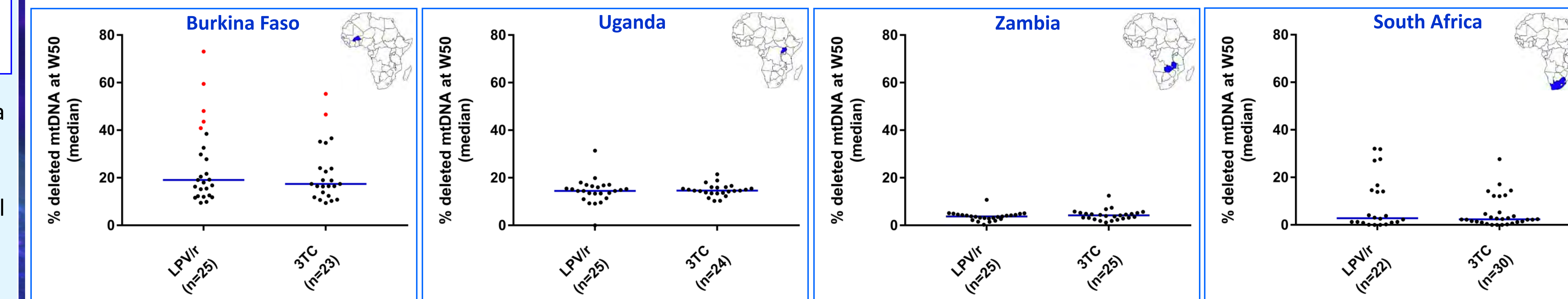
Proportion of deleted mtDNA

Proportion of deleted mtDNA at day 7 and a year one year of PrEP



Overall, the proportion of deleted mtDNA remained unchanged a year one year of prophylactic treatment, despite being high at day 7.

During the follow-up, 51.8% of children presented an increase in the proportion of deleted mtDNA (55.3% in the LPV/r arm and 44.7% in the 3TC arm).



Children from Burkina Faso and Uganda presented the highest rates of deleted mtDNA, children from Zambia and South Africa the lowest. Seven children (5 in the LPV/r arm and 2 in the 3TC arm), all in Burkina Faso, presented a depletion rate over 40% (red dots).

Risk factors associated with an increase deleted mtDNA rate a year one year of PrEP

Independent variable	OR	95% CI	p value	AOR	95% CI	p value
Gender						
Boy versus Girl	0.98	0.56-1.70	0.93			
Site						
Burkina Faso versus South Africa	3.75	1.64-8.59	0.002	2.99	1.27-7.04	0.01
Uganda versus South Africa	3.88	1.70-8.85	<0.01	4.04	1.73-9.45	<0.01
Zambia versus South Africa	1.75	0.79-3.92	0.19	1.69	0.74-3.85	0.19
PrEP						
LPV/r versus 3TC	1.60	0.91-2.80	0.10	1.42	0.79-2.57	0.25
Duration of pre-partum maternal ARV treatment (weeks)	0.99	0.93-1.04	0.61			
Duration of breastfeeding (weeks)	1.00	0.98-1.03	0.89			
Mother plasma HIV RNA (copies/mL)						
Uncontrolled (≥1000) versus Controlled (<1000) at D7	0.91	0.52-1.59	0.76			
Uncontrolled (≥1000) versus Controlled (<1000) at W38	0.64	0.35-1.16	0.14	0.42	0.20-0.88	0.02
Gestational age (weeks)	1.05	0.89-1.24	0.58			
Weight of the baby at D7 (kg)	0.39	0.20-0.78	0.01	0.37	0.18-0.75	0.01
Haemoglobin concentration at D7 (g/dL)	0.99	0.95-1.04	0.70			

OR, odd ratio; A OR, adjusted odd ratio; CI, confidence interval

After adjustment, LPV/r treatment was not associated with an increase proportion of deleted mtDNA a year one year of PrEP.