Effect of dolutegravir on folate and vitamin B12 status among HIV-infected children and adolescents in the ODYSSEY trial

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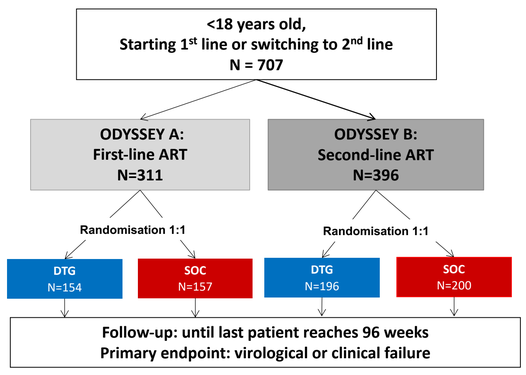
Background

- Neural tube defects are known to be associated with maternal folate and vitamin B12 deficiency
- Plasma folate reflects short-term folate dietary intake and drug effects (over the last 4 weeks), whereas red cell folate – long-term dietary intake and drug effects
- A recent study suggested an increased risk of NTDs among infants conceived by women taking dolutegravir (DTG). (Zash, NEJM 2018)
- **Aim:** We compared folate and vitamin B12 levels among HIV-infected children on DTG-based antiretroviral treatment (ART) versus Standard of Care (SOC) in the ODYSSEY trial.

Methods

- Trial design and eligible patients
  - ODYSSEY is a randomised multi-country trial evaluating dolutegravir + 2NRTIs (DTG) versus standard-of-care (SOC) in children starting first-line or second-line ART



  - All children aged ≥6 years at enrolment in the 3 Uganda sites (JCRC, Baylor, MUJHU) were eligible for this sub-study

- Sample collection and analysis:
  - Plasma folate measured on stored samples at enrolment and week 4
  - Red blood cell folate and vitamin B12 levels were measured using sample collected prospectively at ≥96 weeks
  - All samples were analysed in one laboratory using Elecys assays

- Statistical analysis:
  - Laboratory measures were truncated at 1st and 99th percentiles
  - Normal regression was used to compare change in plasma folate from enrolment to week 4 (adjusted for baseline) and cross-sectional red blood cell folate and vitamin B12 at ≥96 weeks between randomised arms, adjusting for site, sample date and randomisation stratification factors (first-/second-line ART, availability of routine resistance testing and intended NRTI backbone)
  - Compared proportion with low levels of red blood cell folate and B12, based on lower end of reference range (<523 ng/ml and <179 pg/ml respectively)

- Sensitivity analyses:
  - Treatment changes: Exclude those with treatment change defined as: (i) any time off third agent in 3 months prior to sample; or (ii) any time on non-DTG regimen if in DTG arm or on DTG if in SOC arm, at any point in trial prior to sample

Results

Population

- 229 eligible children in ODYSSEY in the recruiting sites
- At baseline, median age (IQR; range) was 12.3 (9.0, 14.7) years
- 51% were female

		JCRC (N=72)	Baylor (N=110)	MUJHU (N=47)	Total (N=229)
		n (%) or median [IQR]			
Arm	DTG	36 (50%)	52 (47%)	26 (55%)	114 (50%)
	SOC	36 (50%)	58 (53%)	21 (45%)	115 (50%)
Treatment line	First-line	12 (17%)	62 (56%)	1 (2%)	75 (33%)
	Second-line	60 (83%)	48 (44%)	46 (98%)	154 (67%)
Age at enrolment, years		13.3 (10.8, 15.9)	11.7 (7.9, 14.4)	11.8 (9.1, 14.0)	12.3 (9.0, 14.7)
CD4 count at enrolment, cells/mm^3		442 (170, 682)	561 (335, 813)	492 (144, 893)	501 (228, 795)

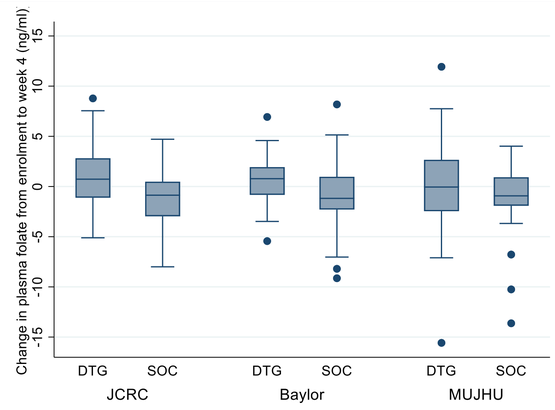
- 75 (33%) started first-line (100% efavirenz-based in SOC); 154 second-line (99% protease inhibitor-based in SOC)

- Availability of samples
  - 225 (98%) had a plasma folate result at enrolment
  - 226 in follow-up at week 4, of whom 218 (96%) had available plasma folate result
  - 215 in follow-up at week 96, of whom 214 (>99%) had an available RBC folate /vitamin B12 result

Results

Change in plasma folate from enrolment to week 4

	N	Mean (SE), ng/ml
DTG	110	0.4 (0.3)
SOC	107	-1.1 (0.3)

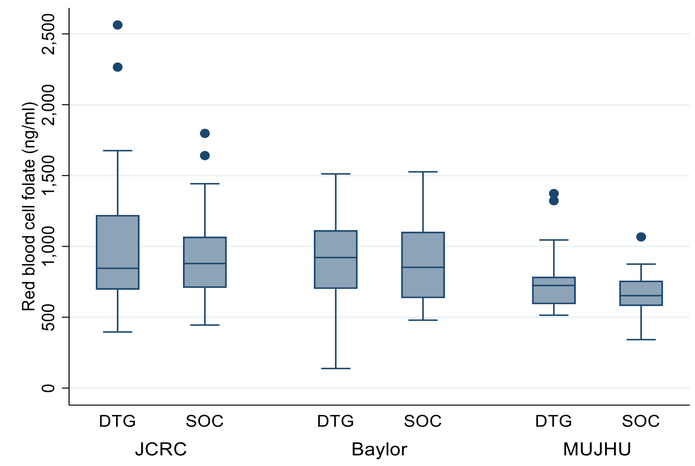


	Mean	95% CI	p-value	Arm x site interaction p-value
Unadjusted difference (DTG-SOC)	1.5	0.7, 2.3	<0.01	-
Adjusted difference (DTG-SOC)	1.6	0.8, 2.4	<0.01	0.66

- In adjusted analysis, mean plasma folate was higher in DTG arm compared to SOC by 4 weeks
- Excluding those with treatment changes prior to week 4 (n=3) did not alter results

Red blood cell folate at week ≥96

	N	Mean (SE), ng/ml
DTG	109	887 (29)
SOC	105	855 (28)

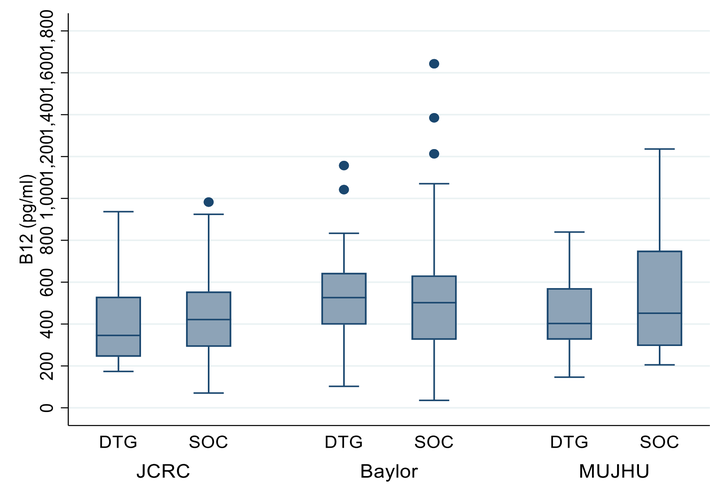


	Mean	95% CI	p	Arm x site interaction p-value
Unadjusted difference (DTG-SOC)	36	-44, 115	0.38	-
Adjusted difference (DTG-SOC)	73	3, 143	0.04	0.82

- After adjustment, mean red blood cell folate higher in DTG arm vs. SOC
- Similar results when excluding those with a treatment change (n=9)
- No difference in the proportion with insufficient level: 8/109 (7%) in DTG arm vs. 8/105 (8%) in SOC (p=0.938)

Plasma Vitamin B12 at week ≥96

	N	Mean (SE), pg/mL
DTG	109	478 (21)
SOC	105	504 (26)



	Mean	95% CI	p	Arm x site interaction p-value
Unadjusted difference (DTG-SOC)	-25	-90, 41	0.46	-
Adjusted difference (DTG-SOC)	-26	-91, 39	0.42	0.57

- No difference between treatment arms
- Similar results when excluding those with a treatment change (n=9)
- No difference in the proportion with insufficient level: 7/109 (6%) in DTG arm vs. 6/105 (8%) in SOC (p=0.828)

Conclusions

- We found no evidence that DTG-based ART was associated with decreased levels of plasma folate or RBC folate
- Plasma folate levels at 4 weeks and RBC folate levels at week ≥96 were higher in the DTG arm than on NNRTI-/PI-based ART though the mechanism is unclear.
- Vitamin B12 levels were similar in both arms.
- These results suggest any increased risk of neural tube defects in infants conceived on DTG is unlikely to be due to DTG causing decreased folate and vitamin B12 levels.

References

- Zash R, Makhema J, Shapiro RL. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med. 2018 Sep 6;379(10):979-981.