Neuropsychiatric manifestations and sleep disturbances in children and adolescents randomised to dolutegravir-based ART vs standard-of-care in the ODYSSEY trial

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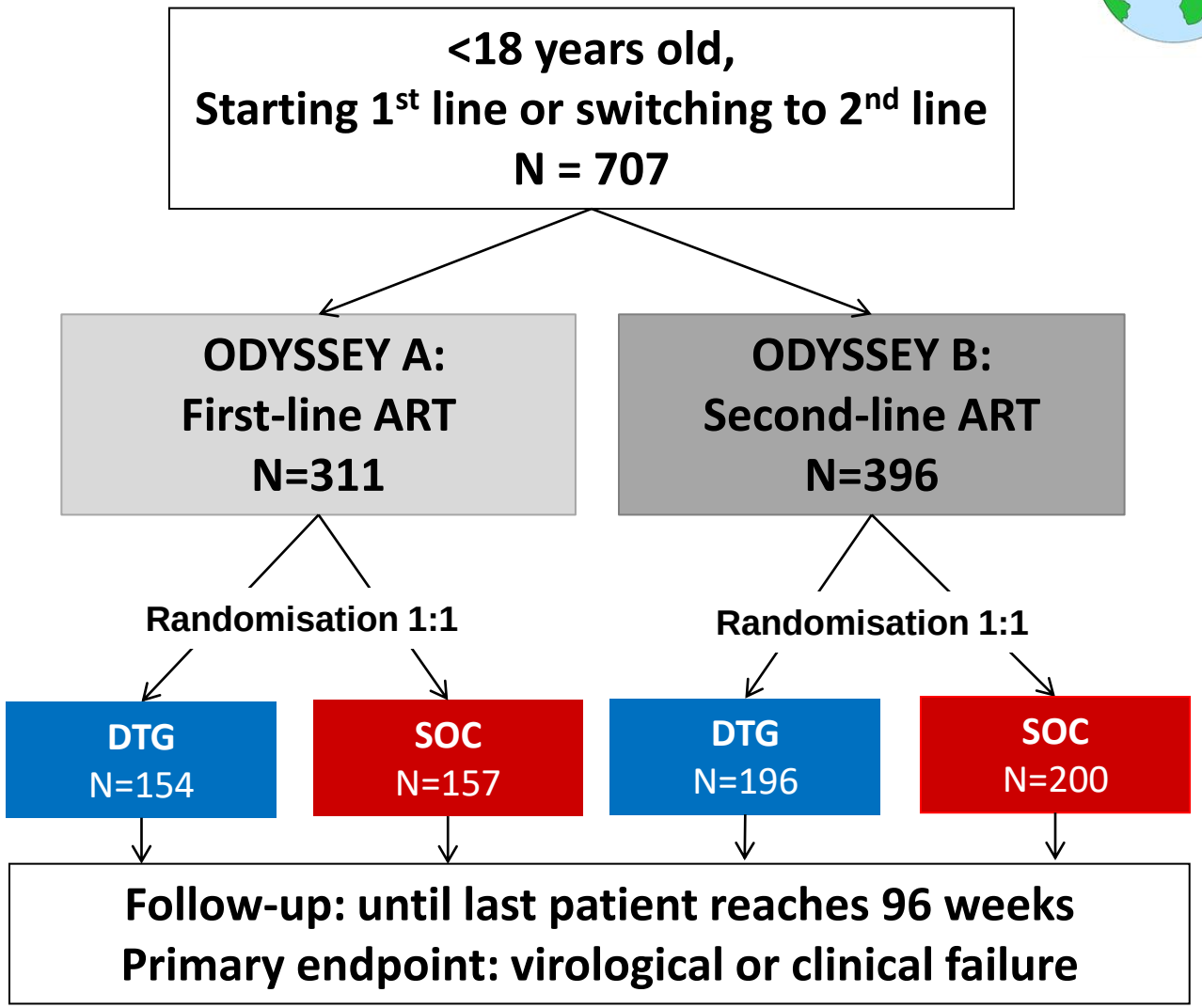
Background

- Dolutegravir is associated with neuropsychiatric adverse events (NPAEs) in adults
- The most prevalent symptoms are insomnia and sleep disturbance. Other associated manifestations include depression, anxiety, suicidal ideation/behaviour, headache and dizziness [1]
- A meta-analysis of RCTs in adults showed higher risk of insomnia associated with DTG (DTG 6.1% vs other non-DTG 4.5%, p=0.02), but no significant effect of DTG on the risk of suicide-related serious adverse events [2]
- There are limited data on DTG-associated neuropsychiatric manifestations in children and adolescents
- We present the data on NPAEs and patient/carer mood-and-sleep questionnaire responses for children and adolescents enrolled in the ODYSSEY trial

1. ViiV Healthcare. Dolutegravir SmPC. 2021 2. Hill A et al. Curr Opin HIV AIDS 2018

ODYSSEY

- A randomised 96-week non-inferiority trial comparing **DTG-based ART with standard-of-care** in children **starting first-line ART (ODYSSEY A) or second-line ART (ODYSSEY B)**
- Main trial enrolled children ≥14 kg between September 2016 and June 2018
- **Median follow-up (IQR) 142 weeks (124, 159)**



SOC= standard of care

Population at baseline (n=707)

Age, sex, ethnicity

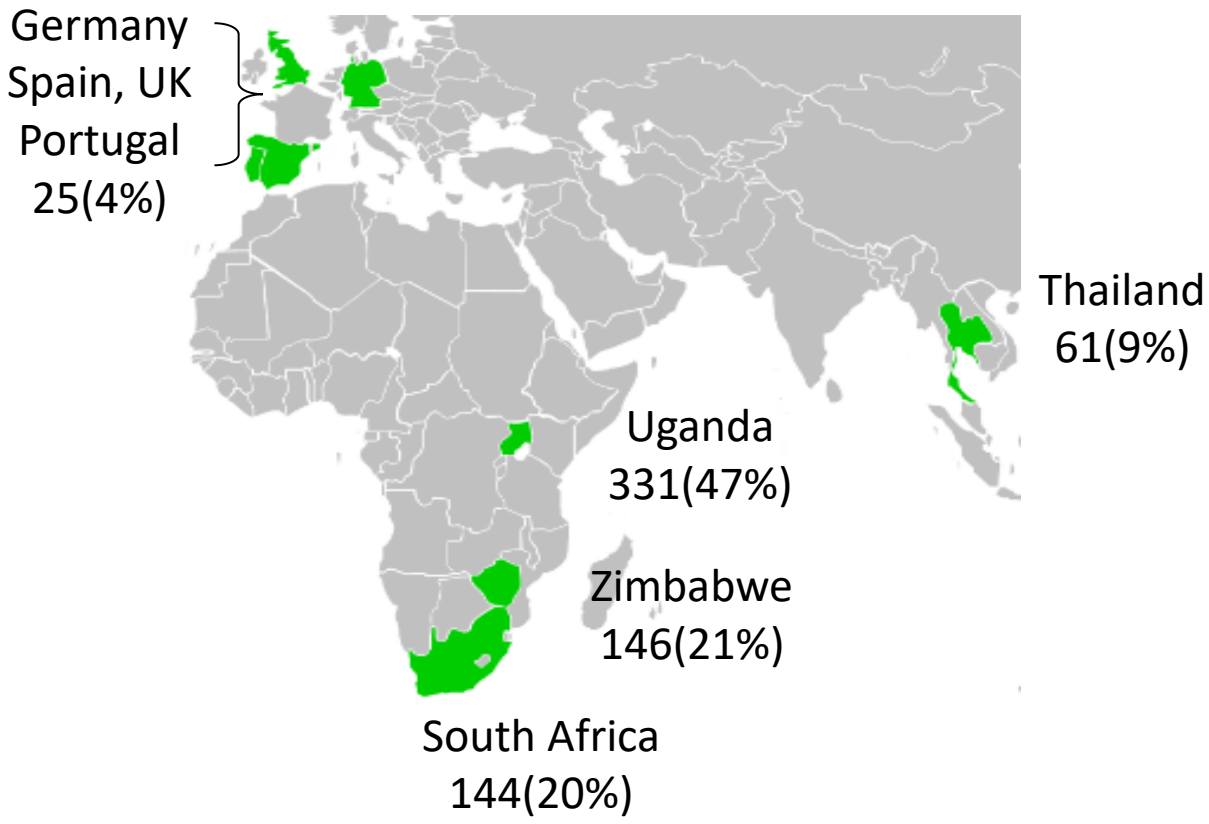
- Age, median [range]: 12.2 years [2.9-18]
- 49% female
- 88% African

HIV disease

- 27% WHO stage 3/4
- 22% CD4 <200 cells/mm^3

Baseline ART

- **NRTI backbone** 65% ABC+3TC
  23% TDF+XTC
  11% ZDV+3TC
- **Third agents in the SOC arm**
  ODYSSEY A 92% EFV-based
  ODYSSEY B 72% LPVr & 25% ATVr



Neuropsychiatric manifestations

- Neuropsychiatric adverse events (NPAEs)
  - System organ class
    - Nervous system (excluding infectious causes)
    - Psychiatric disorders
  - Adverse events reported
    - Grade ≥3 adverse events (AEs)
    - SAEs of any grade
    - AEs leading to treatment modification of any grade
    - Suicidality events of any grade

- Mood and sleep questionnaires
  - Carer/participant questionnaires completed for participants aged ≥6 years
  - At weeks 0, 4, 12, 24, and 24-weekly thereafter

Neuropsychiatric adverse events (NPAEs)

	DTG		SOC		Total		P-value
	N=350		N=357		N=707		
All neuropsychiatric adverse events, N [N participants]	**18**	**[15]**	**13**	**[8]**	**31**	**[23]**	**0.125***
Serious Adverse Events	7	[5]	6	[5]	13	[10	
ART-modifying AEs$^{\Psi}$	2	[2]	2	[2]	4	[4]	
Hazard Ratio for time to first NPAE§ (95% CI)	1.87 (0.79, 4.41)		1 (ref)				**0.154**

*Comparing number of participants with at least 1 event; $^{\Psi}$ One additional participant in the DTG arm changed ART due to an ongoing NPAE post trial censoring date; §Adjusted for ODYSSEY A and B

- Median (IQR) age at first event was 15.9 (10.4, 17.5) years
- Median time (IQR) from enrolment at first event was 72 (47,124) weeks
- 23/707 (3%) children had NPAEs:
  - 16/362 (4%) in males vs 7/345 (2%) in females
  - 16/311 (5%) on first-line vs 7/396 (2%) on second-line

Neurological adverse events (NAEs)

	DTG		SOC		Total		P-value
	N=350		N=357		N=707		
Neurological AEs, N [N participants]	**6**	**[6]**	**6**	**[5]**	**12**	**[11]**	**0.736***
Epilepsy, convulsions	4	[4]	4	[4]			
Dizziness	0	[0]	2	[1]			
Headache, hypertension	1	[1]	0	[0]			
Dystonia	1	[1]	0	[0]			
Serious Adverse Events	**4**	**[3]**	**4**	**[3]**			
ART-modifying AEs$^{\Psi}$	**0**	**[0]**	**1**	**[1]**			
Hazard Ratio for time to first NPAE§ (95% CI)	1.18 (0.36, 3.87)		1 (ref)				**0.784**

*Comparing number of participants with at least 1 event; §Adjusted for ODYSSEY A and B

Psychiatric adverse events (PAEs)

	DTG		SOC		Total		P-value
	N=350		N=357		N=707		
Psychiatric AEs, N [N participants]	**12**	**[10]**	**7**	**[4]**	**19**	**[14]**	**0.097***
Suicidal ideation/behaviour	8	[8¥]	7	[4]			
Depression	2	[2¥]	0	0			
Insomnia	1	[1¤]	0	0			
Psychosis	1	[1¤]	0	0			
Serious Adverse Events	**3**	**[2]**	**2**	**[1]**			
ART-modifying AEs$^{\Psi}$	**2**	**[2]**	**1**	**[1]**			
Hazard Ratio for time to first PAE§ (95% CI)	**2.48 (0.78, 7.90)**		**1(ref)**				**0.125**

*Comparing number of participants with at least 1 event; ¥ Two events: parasuicide and depression occurred in the same patient; ¤ Events occurred in the same patient; $^{\Psi}$ One additional participant in the DTG arm changed ART due to an ongoing NPAE post trial censoring date; §Adjusted for ODYSSEY A and B

NPAEs: ART and dolutegravir dosing

	Neurological AEs	Psychiatric AEs	NPAEs
DTG arm	6	12	18
On initial 'lower' doses	**3**	**9**	**11**
14-<30kg: 25mg FCT	2	1	3
≥40 kg: 50mg FCT	1	8	9
On increased doses*	**2**	**1**	**3**
14-<20kg: 25mg DT¤	1	0	1
30-<40kg: 50mg FCT	1	1	2
Not on DTG	**1 (NVP)**	**2 (EFV, NVP)**	**3**
SOC arm	6	7	**13**
EFV+2NRTI	**4**	**3**	**7**
PI/r+2NRTI	**2 (ATVr, LPVr)**	**4 (2ATVr, 2LPVr)**	**6**

*Studied in the PK substudies in ODYSSEY and subsequently approved by FDA, EMA;

¤ Dispersible tablets (DT) have 1.6-1.8 times higher bioavailability than film-coated tablets (FCTs)

Mood & sleep questionnaires

MOOD AND SLEEP WITHIN THE LAST MONTH

For Week 0
Complete Sleep and Mood section (Q7-15) only

7. In the last month has your child experienced any of the following? *Tick all that apply*

Dizziness or room spinning ☐	Low mood or feeling sad often ☐	Other 1: ☐ (Give details).....
Problems concentrating ☐	Hurting or harming him/herself *(e.g. taking an overdose, cutting)* ☐	Other 2: ☐ (Give details).....
Feeling worried often ☐	Thinking life is not worth living ☐	Other 3: ☐ (Give details).....
Feeling angry or aggressive often ☐	Expressing thoughts about ending life (suicidal thoughts) ☐	None of the above ☐
		Not applicable as child is less than 6 years of age ☐

8. In the last month, what time did your child usually go to bed at night? *(24h)* h h m m

9. In the last month, how long did your child usually take to fall asleep each night? *Tick one answer only*

Less than 15 minutes ☐ 15 minutes to half an hour ☐ Half an hour to an hour ☐ More than an hour ☐ I don't know ☐

10. In the last month, approximately how many hours of sleep did your child get each night? *(Write the number of hours)* ☐

		Never	Infrequently *(e.g. once or twice a month)*	Occasionally *(e.g. once or twice a week)*	Frequently *(e.g. 3 or more times a week)*	Don't know
11.	**In the last month, how often did your child wake during the night?** *Tick one only*	☐	☐	☐	☐	☐
12.	**In the last month, how often did your child experience nightmares?** *Tick one only*	☐	☐	☐	☐	☐
13.	**In the last month, how often did your child experience vivid dreams? (not nightmares)** *Tick one only*	☐	☐	☐	☐	☐
14.	**In the last month, how often has your child had trouble staying awake at school or during everyday activities?** *Tick one only*	☐	☐	☐	☐	☐

15. In the last month how would you rate your child's sleep quality overall? *Tick one answer only*

 Very Good ☐

 Good ☐

 Fair ☐

 Not that good ☐

 Very bad ☐

- Questionnaires completed for participants ≥6 years old
- At weeks 0, 4, 12, 24, and 24-weekly thereafter

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Mood questions: reports across follow-up

- No difference between treatment arms in “low mood or feeling sad often”, “feeling worried often” and “feeling angry or aggressive often”
- More participants/carers reported symptoms of self-harm, “life was not worth living” or suicidal thoughts in DTG vs SOC:

N Reports, N [N participants]	TOTAL						
	DTG		SOC		Total		P-value*
Self-harm	8	[8]	1	[1]	9	[9]	0.038
Life not worth living	20	[17]	5	[5]	25	[22]	0.009
Suicidal thoughts	13	[13]	0	[0]	13	[13]	<0.001
Life not worth living or suicidal thoughts combined	27	[23]	5	[5]	32	[28]	0.001

* Comparison between participants ever reporting (carer or participant or both)

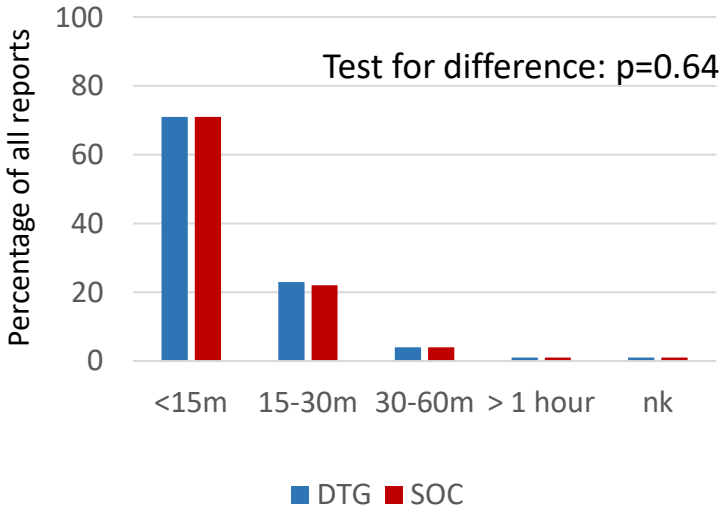
- Most reported symptoms were transient and did not lead to treatment change
- Only 4/23 patients in DTG arm and none in SOC reported “life was not worth living” or suicidal thoughts more than once; the reports did not lead to treatment change

Sleep questions: reports across follow-up

- No difference in time to sleep, sleep quality or reported nightmares/vivid dreams by trial arm
- Similar results in children on first- and second-lines

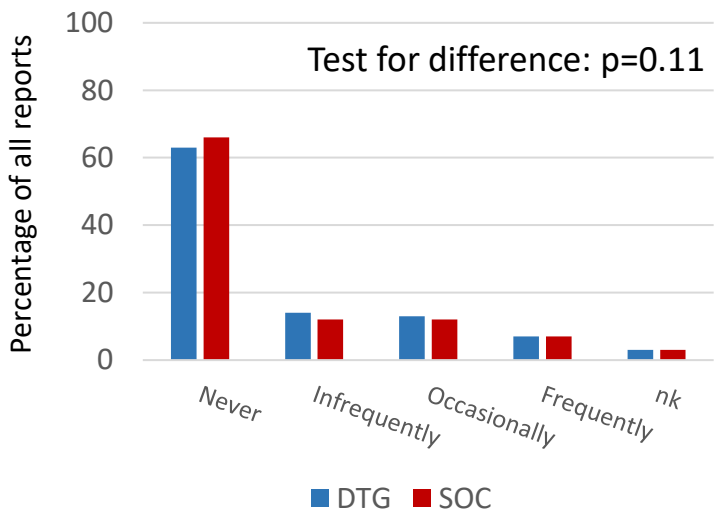
Time to fall asleep

Total population



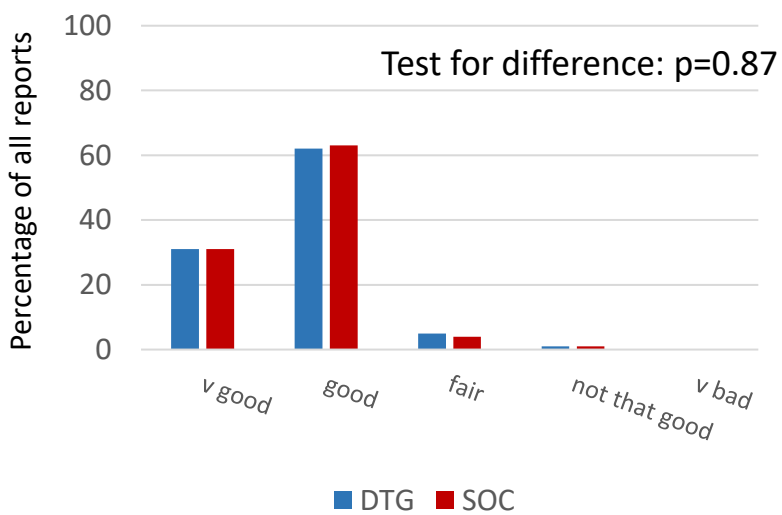
Nightmares and/or vivid dreams

Total population



Sleep quality

Total population



*ordered logistic mixed models adjusted for repeated measures in same participants

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Summary

- Neuropsychiatric adverse events and patient-reported neuropsychiatric symptoms were infrequent
- Numerically there were more psychiatric events in the DTG arm, but numbers were low and the difference between trial arms was not significant
- More participants reported self-harm or suicidality ideation on mood questionnaires in the DTG arm vs SOC
  - This difference should be interpreted with caution in an open-label trial
- No difference in the reported low mood or anxiety symptoms
- No difference in sleep problems by trial arm

- **Overall, the results on NP manifestations from the ODYSSEY trial are reassuring**
- **However, clinicians should be aware of suicidality ideation among adolescents and screen appropriately**

Thank you

- ODYSSEY participants
- ODYSSEY investigators
- Trial Management Team
- Trial Steering Committee
- Data Monitoring Committee
- Endpoint Review Committee
- Penta (sponsor)
- ViiV Healthcare (funder)
- Mylan

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Penta