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Title: Virological failures and genotypic resistance in children and adolescents randomised to dolutegravir-based ART vs. standard-of-care in the ODYSSEY trial

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Background: ODYSSEY demonstrated superiority of dolutegravir (DTG) based ART versus standard-of-care (SOC) in children ≥14kg starting first- or second-line. We evaluate drug resistance by 96 weeks.

Methods: Virological failure (VF) was defined as confirmed viral load (VL)≥400c/mL after week 36 or lack of virological response at week 24 with ART switch. Children with VF were tested for post-failure resistance (major IAS mutation); if resistance was identified, a baseline sample was sequenced. The proportion with emergent resistance post-failure was estimated in those exposed to each drug class in ODYSSEY.

Results: 311 children started first-line ART (154 DTG,157 SOC[92% efavirenz]) and 396 second-line (196 DTG,200 SOC[72% lopinavir/r,25% atazanavir/r]). On first-line, 11(7%) DTG vs 30(19%) SOC experienced VF by 96 weeks, and on second-line, 31(16%) DTG vs 40(20%) SOC. First-line: no new DTG or NRTI resistance on first-line DTG versus estimated 62% and 88% children with new NRTI and NNRTI resistance respectively among failures in SOC (Table). Second-line: no new resistance to NRTIs on DTG vs estimated 9% among failures in SOC. One child (estimated 3%) with VF on PIs had new PI resistance and two children (100%) on NNRTIs had new NNRTI resistance. 4(18%) with VF on DTG had INSTI mutations.

Conclusion: ODYSSEY demonstrated that DTG has a high genetic resistance barrier and prevents emergent resistance to NRTIs in children. We identified no post-failure resistance on first-line DTG, significantly less than first-line SOC. On second-line DTG, there was no new NRTI resistance, however 4 children developed new INSTI resistance, highlighting the need for ongoing adherence support among children.

Table: Genotypic resistance in the ODYSSEY trial

	First-line					Second-line				
	DTG		SOC		DTG vs. SOC	DTG		SOC		DTG vs. SOC
Children with resistance post-failure⁀										
NRTI	0/11	0%	18/29	62%	p<0.001	20/28	71%	28/39	72%	P=0.97
NNRTI	0/11	0%	27/29	93%	p<0.001	21/28	75%	35/39	90%	p=0.18
PI	0/11	0%	0/29	0%		2/28	7%	2/39	5%	p=1.00
INSTI	0/10	0%	-	-		4/22	18%	-	-	
Children and estimated proportion with emergent resistance post-failure~										
NRTI	0	0%	13	62%		0	0%	3	9%	
NNRTI	-	-	18	88%		-	-	2	100%	
PI	-	-	-	-		-	-	1	3%	
INSTI	0	0%	-	-		4	18%	-	-	

⁀Post-failure resistance up to week 96, using the latest sample with VL≥1000c/mL after VF and prior to ART switch. % with resistance post-failure, of those with post-failure resistance test available
~Among those with VF and exposed to drug-class, estimated assuming same proportion of new resistance in those with and without available baseline test