Virological outcomes and genotypic resistance on dolutegravir-based antiretroviral therapy versus standard of care in children and adolescents: a secondary analysis of the ODYSSEY trial

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Summary

Background ODYSSEY showed superior efficacy for dolutegravir-based antiretroviral therapy (ART) versus standard of care (SOC) in children living with HIV starting first-line or second-line ART aged 4 weeks or older. Here, we aim to compare virological outcomes and resistance in the dolutegravir group versus SOC for first-line and second-line ART up to 96 weeks.

Methods ODYSSEY was an open-label, multicentre, randomised, non-inferiority trial done in 29 centres in seven countries (Germany, Spain, South Africa, Thailand, the UK, Uganda, and Zimbabwe). ODYSSEY recruited children living with HIV aged at least 28 days and younger than 18 years, weighing at least 3 kg, starting first-line ART (ODYSSEY A), or switching to second-line therapy after treatment failure (ODYSSEY B). Children were randomly assigned (1:1) to dolutegravir plus two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs; dolutegravir group) versus the SOC group (non-nucleoside reverse transcriptase inhibitor [NNRTI], boosted protease inhibitor, or non-dolutegravir integrase strand-transfer inhibitor, plus two NRTIs). Two randomised cohorts were combined in this exploratory analysis: children weighing at least 14 kg were enrolled between Sept 20, 2016, and June 22, 2018, and children weighing less than 14 kg were enrolled between July 5, 2018, and Aug 26, 2019. Virological failure was defined as an inadequate virological response at week 24 with an ART switch or confirmed HIV-1 RNA viral load of at least 400 copies per mL after week 36. Virological suppression was defined as two consecutive viral loads of less than 400 copies per mL and was compared between groups, including an ART switch and death as competing risks. Children with virological failure were tested for post-failure genotypic resistance, with baseline results used to identify emergent resistance. Development of emergent resistance was a secondary trial outcome and all other outcomes are exploratory. ODYSSEY was registered with ClinicalTrials.gov (NCT02259127), EUDRACT (2014–002632–14), and ISRCTN (ISRCTN91737921).

Findings In ODYSSEY at enrolment, 381 participants started first-line ART (ODYSSEY A: 189 in the dolutegravir group and 192 in the SOC group) and 407 participants started second-line ART (ODYSSEY B: 202 in the dolutegravir group and 205 in the SOC group). 72 participants in ODYSSEY A and 13 participants in ODYSSEY B weighed less than 14 kg. 401 (51%) of 788 participants were female and 387 (49%) were male. Virological suppression occurred significantly earlier in the dolutegravir group (adjusted [cause-specific] hazard ratio [HR] 1·57 [95% CI 1·35 to 1·83]; p<0·0001). Overall, 51 (13%) participants had virological failure by 96 weeks in the dolutegravir group versus 86 (22%) in the SOC group (including 18 [10%] *vs* 43 [22%] in ODYSSEY A and in 33 [16%] *vs* 43 [21%] in ODYSSEY B; adjusted HR 0·56 [0·40 to 0·79]; p=0·0011). Among ODYSSEY B participants starting dolutegravir, virological failure was higher in children starting zidovudine (HR 2·22 [1·01 to 4·88]; p=0·048) and similar in those starting tenofovir disoproxil fumarate (1·19 [0·50 to 2·83]; p=0·70) compared with abacavir. Time to virological suppression was marginally faster in participants receiving second-line dolutegravir and abacavir with high-level abacavir resistance at baseline compared with those with no, low-level, intermediate-level resistance (cause-specific HR 1·70 [1·01 to 2·85]; p=0·046); and failure rates by week 96 were similar (HR 0·90 [0·23 to 3·61]; p=0·88). An estimated 1% (95% CI 0 to 2) of participants in the dolutegravir group versus 20% (14 to 26) in the SOC group in ODYSSEY A had emergent resistance to at least one drug-class within their first-line regimen (risk difference –20% [–25 to –14]; p<0·0001); 4% (1 to 6) versus 5% (2 to 8) had resistance to drug within their initial second-line regimen (risk difference –1% [–5 to 3]; p=0·60). 3% (0 to 5) of participants in the dolutegravir group had emergent integrase strand-transfer inhibitors resistance compared with 3% (1 to 6) of participants in the SOC group who had emergent resistance to the anchor drug (risk difference 0% [–4 to 3]; p=0·78).

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Interpretation Dolutegravir led to faster virological suppression and lower risk of virological failure than NNRTIs and boosted protease inhibitor-based SOC. Participants starting second-line dolutegravir-based ART with an abacavir or tenofovir backbone were at lower risk of virological failure than those starting zidovudine. During first-line therapy, dolutegravir protected against emergent resistance; starting second-line therapy, the risk of emergent resistance to nucleoside reverse transcriptase inhibitor backbone, and anchor drugs, was similar among participants starting dolutegravir within their second-line regimen and those starting mainly boosted protease inhibitor-based SOC.

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Research in context

Evidence before this study

A network meta-analysis showed superior virological efficacy until 144 weeks of dolutegravir-based first-line antiretroviral therapy (ART) compared with efavirenz in adult trials. The estimated risks of emergent resistance to the anchor drug or nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) were lower with dolutegravir than with efavirenz and no dolutegravir resistance was observed. Infrequent cases of dolutegravir resistance have been reported during first-line therapy outside randomised trials. Two randomised controlled trials in adults have evaluated dolutegravir-based second-line ART, with DAWNING showing superior virological efficacy with dolutegravir at 48 weeks compared with ritonavir-boosted lopinavir and NADIA showing non-inferior efficacy at 96 weeks compared with ritonavir-boosted darunavir. In both trials, few participants developed dolutegravir resistance (two [1%] in DAWNING *vs* nine [4%] in NADIA), whereas none developed lopinavir or darunavir resistance. The ODYSSEY trial has previously reported superior efficacy and lower resistance rates after treatment failure by 96 weeks with dolutegravir-based ART than seen with other standard of care (SOC) drugs for first-line and second-line treatment in two cohorts (children weighing ≥14 kg and <14 kg). We searched PubMed for studies evaluating dolutegravir in children between database inception and Oct 24, 2023, using the search terms: (dolutegravir [Title/Abstract]) AND (children [Title/Abstract] OR pediatric [Title/Abstract] OR paediatric [Title/Abstract]). The search yielded 119 publications, including three reporting virological or resistance outcomes in paediatric dolutegravir trials. Two publications were from the ODYSSEY trial team. The third publication was from the IMPAACT P1093 trial in a highly treatment-experienced population, which reported that eight (6%) participants had resistance to integrase strand transfer inhibitors (INSTIs) with dolutegravir-based ART. African cohorts and programmes have reported high levels of virological suppression (<1000 copies per mL) in children and adolescents after switching to dolutegravir-based regimens, even when patients did not have suppression before treatment change and their NRTI backbone after a treatment switch was compromised or not changed.

Added value of this study

This study combines the ODYSSEY randomised trial cohorts (children weighing ≥14 kg and <14 kg) to describe virological outcomes and resistance, comparing dolutegravir to SOC during first-line and second-line ART. Children starting dolutegravir reached virological suppression more quickly and were less likely to have virological failure over 96 weeks than children starting SOC. New exploratory analyses presented here show that 30 (59%) of 51 children in the dolutegravir group reached resuppression after virological failure without switching ART, suggesting that most children who do not have virological suppression when receiving dolutegravir should receive adherence support, before a treatment switch is considered. Notably, the rate of virological failure on second-line dolutegravir-based treatment was lower in children starting abacavir or tenofovir disoproxil fumarate than in those switching to zidovudine. Building on previous work, we provide estimates of treatment emergent resistance in the total ODYSSEY population; among participants starting first-line ART, an estimated 1% (95% CI 0–2) receiving dolutegravir versus 20% (14–26) receiving SOC had emergent resistance to at least one drug-class in their regimen. On second-line, emergent NRTI resistance was infrequent and similar in both groups (estimated 2% [0–4] in the dolutegravir group and 2% [0–5] in the SOC group). Five participants (estimated 3% [0–5]) receiving second-line dolutegravir developed INSTI resistance. Emergent protease inhibitor resistance in the SOC group was low (1% [0–2]).

Implications of all the available evidence

In line with adult trials and observational data in children, this study shows sustained virological outcomes for children starting first-line and second-line dolutegravir-based treatment. Dolutegravir is protective against emergent resistance to the anchor drug and NRTI backbone for children starting first-line therapy. Our findings provide reassurance that the rate of virological suppression in children switching to second-line dolutegravir following WHO guidelines is high and contribute to the growing evidence that a change to zidovudine is more likely to lead to virological failure than continuing or switching to abacavir or tenofovir disoproxil fumarate, even in the presence of resistance. A small number of children developing INSTI resistance with dolutegravir-based second-line ART highlights the need for ongoing adherence support for children starting second-line ART.

Introduction

Globally, 2·7 million children and adolescents are living with HIV.[1] Transition to dolutegravir-based antiretroviral therapy (ART) is occurring rapidly,[2] which underlies the importance of understanding virological outcomes and resistance profiles in children starting dolutegravir compared with those starting other anchor drugs.

Several adult trials have shown that dolutegravir has a non-inferior or superior virological efficacy as first-line and second-line combination ART.[3–6] Dolutegravir has a high barrier to resistance, but the selection of resistance to integrase strand-transfer inhibitors (INSTIs) has not been reported in phase 3/4 trials of first-line dolutegravir in adults[3] and a few cases have been observed in second-line trials.[5,6] Unlike adults, many children have been exposed to antiretrovirals for the prevention of vertical transmission; infants also have higher viral loads at ART initiation and take longer to reach virological suppression.[7,8] Adults predominantly receive tenofovir disoproxil fumarate as one of the nucleoside or nucleotide reverse transcriptase inhibitor (NRTI) backbone drugs due to data suggesting higher efficacy of this drug than seen with abacavir[9] or zidovudine.[10] Children should not receive tenofovir disoproxil fumarate until they reach 30 kg due to concerns of renal and bone toxic effects and an absence of paediatric-friendly formulations.[11] Most paediatric non-comparative dolutegravir studies report virological suppression in more than 70% of children and adolescents 12 months after dolutegravir initiation.[12] Reported rates of INSTI resistance in children given dolutegravir-based ART range from 0% to 6%.[13,14]

ODYSSEY was a randomised controlled trial (RCT) evaluating dolutegravir-based ART versus standard of care (SOC) in infants, children, and adolescents with HIV starting first-line or second-line treatment.[15] Dolutegravir-based ART was superior to SOC based on treatment failure up to 96 weeks in children weighing at least 14 kg[16] and less than 14 kg at enrolment.[17] We have previously described, by enrolment cohort, the proportion of participants who had virological failure by 96 weeks with any resistance and with treatment-emergent resistance.[16,17] Here, we combine the two weight cohorts in exploratory analyses of virological and resistance outcomes, including emergent resistance in the full ODYSSEY trial population, and time to virological failure by NRTI backbone and resistance at treatment switch among children starting second-line ART.

Methods

Study design and participants

ODYSSEY was an open-label, multicentre, randomised, non-inferiority trial done in 29 centres in seven countries (Germany, Spain, South Africa, Thailand, the UK, Uganda, and Zimbabwe). ODYSSEY recruited children living with HIV aged at least 28 days and younger than 18 years, weighing at least 3 kg. ODYSSEY A enrolled children starting first-line ART and ODYSSEY B enrolled children switching to second-line therapy after treatment failure. Two randomised cohorts were enrolled; children recruited weighing at least 14 kg were enrolled between Sept 20, 2016, and June 22, 2018, and children weighing less than 14 kg were enrolled between July 5, 2018, and Aug 26, 2019.

Children or their carers (or both) gave written informed consent and assent as appropriate. The trial was approved by national or local ethics committees and is registered with ClinicalTrials.gov, NCT02259127.

Randomisation and masking

Children were randomly assigned (1:1) to dolutegravir plus two NRTIs (dolutegravir group) versus the SOC group (non-nucleoside reverse transcriptase inhibitor [NNRTI], boosted protease inhibitor, or non-dolutegravir INSTI, plus two NRTIs). Randomisation was stratified by ODYSSEY A and B, with additional stratification factors depending on the enrolment cohort.[16,17]

Procedures

At enrolment, the choice of first-line NRTIs was made according to WHO or national guidelines used in participating countries. Resistance testing was not performed as per local SOC for most participants switching to second-line therapy at enrolment (ODYSSEY B); second-line regimens included a new anchor drug and at least one NRTI with preserved activity assumed from treatment history or based on resistance tests, if available.

Participants were seen at screening; enrolment; and weeks 4, 12, and every 12 weeks, until the last participant reached 96 weeks of follow-up (April 24, 2020, in the ≥14 kg cohort and June 28, 2021, in the <14 kg cohort). Real-time HIV-1 RNA viral loads were done according to local practice (usually every 12 weeks in Europe and Thailand, every 24 weeks in Uganda, every 48 weeks in Zimbabwe, and at week 24 and then every 48 weeks in South Africa). Plasma samples stored at baseline, weeks 4 and 12, and then every 12 weeks were used for retrospective viral load testing at timepoints where real-time viral loads were not performed.

Stored samples from participants meeting a virological component of the trial's primary endpoint by 96 weeks (including a small number in whom virological failure was documented after clinical failure) were retrospectively tested for HIV-1 drug resistance mutations using Sanger sequencing. Resistance testing was performed using the latest sample after virological failure (up to week 96) with a viral load of at least 1000 copies per mL and before any change in ART. If a major mutation was identified after failure according to the International Antiviral Society–USA (IAS-USA),[18] earlier samples, including baseline, were sequenced to establish whether resistance had emerged during trial follow-up. This approach assumes that later samples in participants who had ongoing viraemia when receiving the same ART could accumulate

	Total population			ODYSSEY A (first-line therapy)			ODYSSEY B (second-line therapy)		
	Dolutegravir (n=391)	SOC (n=397)	Total (n=788)	Dolutegravir (n=189)	SOC (n=192)	Total (n=381)	Dolutegravir (n=202)	SOC (n=205)	Total n=407)
Randomisation cohort*									
≥14 kg	349 (89%)	354 (89%)	703 (89%)	154 (81%)	155 (81%)	309 (81%)	195 (97%)	199 (97%)	394 (97%)
<14 kg	42 (11%)	43 (11%)	85 (11%)	35 (19%)	37 (19%)	72 (19%)	7 (3%)	6 (3%)	13 (3%)
Sex									
Female	192 (49%)	209 (53%)	401 (51%)	81 (43%)	100 (52%)	181 (48%)	111 (55%)	109 (53%)	220 (54%)
Male	199 (51%)	188 (47%)	387 (49%)	108 (57%)	92 (48%)	200 (52%)	91 (45%)	96 (47%)	187 (46%)
Age, years									
Median	11·1 (8·4 to 14·7)	11·6 (7·6 to 14·3)	11·4 (8·0 to 14·6)	10·5 (6·9 to 13·6)	10·5 (6·4 to 14·1)	10·5 (6·5 to 14·0)	12·3 (9·0 to 15·2)	12·3 (8·8 to 14·6)	12·3 (9·0 to 14·8)
Weight, kg									
Median	28·2 (21·1 to 41·8)	29·2 (20·6 to 41·0)	28·7 (20·9 to 41·5)	26·3 (18·4 to 41·0)	26·4 (18·1 to 40·8)	26·4 (18·4 to 41·0)	30·3 (22·9 to 42·3)	31·5 (23·1 to 41·0)	30·5 (23·0 to 41·6)
3 to <6 kg	11 (3%)	12 (3%)	23 (3%)	11 (6%)	12 (6%)	23 (6%)	0	0	0
6 to <10 kg	20 (5%)	20 (5%)	40 (5%)	17 (9%)	18 (9%)	35 (9%)	3 (1%)	2 (1%)	5 (1%)
10 to <14 kg	11 (3%)	11 (3%)	22 (3%)	7 (4%)	7 (4%)	14 (4%)	4 (2%)	4 (2%)	8 (2%)
14 to <20 kg	39 (10%)	43 (11%)	82 (10%)	18 (10%)	20 (10%)	38 (10%)	21 (10%)	23 (11%)	44 (11%)
≥20 kg	310 (79%)	311 (78%)	621 (79%)	136 (72%)	135 (70%)	271 (71%)	174 (86%)	176 (86%)	350 (86%)
Country or region									
Uganda	191 (49%)	180 (45%)	371 (47%)	63 (33%)	68 (35%)	131 (34%)	128 (63%)	112 (55%)	240 (59%)
Zimbabwe	91 (23%)	77 (19%)	168 (21%)	49 (26%)	37 (19%)	86 (23%)	42 (21%)	40 (20%)	82 (20%)
South Africa	69 (18%)	94 (24%)	163 (21%)	44 (23%)	52 (27%)	96 (25%)	25 (12%)	42 (20%)	67 (16%)
Thailand	28 (7%)	33 (8%)	61 (8%)	24 (13%)	26 (14%)	50 (13%)	4 (2%)	7 (3%)	11 (3%)
Europe	12 (3%)	13 (3%)	25 (3%)	9 (5%)	9 (5%)	18 (5%)	3 (1%)	4 (2%)	7 (2%)
Resistance test at second-line ART initiation†									
Not available	..	..	..	..	..	..	195 (97%)	194 (95%)	389 (96%)
Available	..	..	..	..	..	..	7 (3%)	11 (5%)	18 (4%)
Viral load, copies per mL‡									
<10 000	97 (25%)	129 (33%)	226 (29%)	44 (23%)	51 (27%)	95 (25%)	53 (26%)	78 (38%)	131 (32%)
10 000 to <100 000	171 (44%)	162 (41%)	333 (43%)	72 (38%)	60 (32%)	132 (35%)	99 (49%)	102 (50%)	201 (49%)
100 000 to <500 000	94 (24%)	75 (19%)	169 (22%)	51 (27%)	55 (30%)	106 (28%)	43 (21%)	20 (10%)	63 (15%)
≥500 000	29 (7%)	25 (6%)	54 (7%)	22 (12%)	20 (11%)	42 (11%)	7 (3%)	5 (2%)	12 (3%)
Missing	0	6	6	0	6	6	0	0	0
Log_{10} viral load, copies per mL‡									
Median	4·6 (4·0 to 5·2)	4·5 (3·8 to 5·0)	4·5 (3·9 to 5·1)	4·7 (4·1 to 5·3)	4·8 (3·9 to 5·3)	4·7 (4·0 to 5·3)	4·4 (3·9 to 5·0)	4·2 (3·7 to 4·7)	4·3 (3·8 to 4·8)
Prevention of vertical transmission ART exposure									
No	271 (83%)	271 (86%)	542 (84%)	144 (84%)	143 (87%)	287 (85%)	127 (82%)	128 (84%)	255 (83%)
Yes§	55 (17%)	45 (14%)	100 (16%)	28 (16%)	21 (13%)	49 (15%)	27 (18%)	24 (16%)	51 (17%)
Unknown	65	81	146	17	28	45	48	53	101
Drug class exposure as first-line therapy (before enrolment)									
NRTI, NNRTI, and protease inhibitor	..	..	..	..	..	..	1 (<1%)	3 (1%)	4 (1%)
NRTI and NNRTI	..	..	..	..	..	..	194 (96%)	193 (94%)	387 (95%)
NRTI and protease inhibitor	..	..	..	..	..	..	7 (3%)	8 (4%)	15 (4%)
Monotherapy	..	..	..	..	..	..	0	1 (<1%)	1 (<1%)
NRTI backbone at randomisation									
Abacavir plus lamivudine	269 (69%)	265 (67%)	534 (68%)	161 (85%)	156 (81%)	317 (83%)	108 (53%)	109 (53%)	217 (53%)
Tenofovir disoproxil fumarate or tenofovir alafenamide¶ plus lamivudine or emtricitabine	80 (20%)	84 (21%)	164 (21%)	28 (15%)	32 (17%)	60 (16%)	52 (26%)	52 (25%)	104 (26%)
Zidovudine plus lamivudine	41 (10%)	46 (12%)	87 (11%)	0	4 (2%)	4 (1%)	41 (20%)	42 (20%)	83 (20%)
Abacavir plus tenofovir disoproxil fumarate	1 (<1%)	2 (1%)	3 (<1%)	0	0	0	1 (<1%)	2 (1%)	3 (1%)

(Table 1 continues on next page)

	Total population			ODYSSEY A (first-line therapy)			ODYSSEY B (second-line therapy)		
	Dolutegravir (n=391)	SOC (n=397)	Total (n=788)	Dolutegravir (n=189)	SOC (n=192)	Total (n=381)	Dolutegravir (n=202)	SOC (n=205)	Total n=407)
(Continued from previous page)									
Anchor drug at randomisation									
NNRTI	..	161 (41%)	161 (20%)	..	155 (81%)	155 (41%)	..	6 (3%)	6 (1%)
Efavirenz	..	152 (38%)	152 (19%)	..	147 (77%)	147 (39%)	..	5 (2%)	5 (1%)
Nevirapine	..	7 (2%)	7 (1%)	..	6 (3%)	6 (2%)	..	1 (<1%)	1 (<1%)
Rilpivirine	..	2 (1%)	2 (<1%)	..	2 (1%)	2 (1%)	..	0	0
Protease inhibitor	..	233 (59%)	233 (30%)	..	36 (19%)	36 (9%)	..	197 (96%)	197 (48%)
Atazanavir	..	49 (12%)	49 (6%)	..	0	0	..	49 (24%)	49 (12%)
Darunavir	..	6 (2%)	6 (1%)	..	4 (2%)	4 (1%)	..	2 (1%)	2 (<1%)
Lopinavir	..	178 (45%)	178 (23%)	..	32 (17%)	32 (8%)	..	146 (71%)	146 (36%)
INSTI	391 (100%)	3 (1%)	394 (50%)	189 (100%)	1 (1%)	190 (50%)	202 (100%)	2 (1%)	204 (50%)
Dolutegravir	391 (100%)	..	391 (50%)	189 (100%)	..	189 (50%)	202 (100%)	..	202 (50%)
Elvitegravir	..	1 (<1%)	1 (<1%)	..	1 (1%)	1 (<1%)	..	0	0
Raltegravir	..	2 (1%)	2 (<1%)	..	0	0	..	2 (1%)	2 (<1%)

Data are n (%) or median (IQR). ART=antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor. INSTI=integrase strand-transfer inhibitor. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor. SOC=standard of care. *Numbers recruited into ODYSSEY A or B and ≥14 kg or <14 kg cohorts, as per the study design. †Nine of 20 sites did not have resistance testing routinely available for patients starting second-line therapy (specifically, all African sites did not have availability, and all Thai and European sites had availability). ‡Mean of viral load and $\log_{10}$ viral load at screening and randomisation (if available). §Exposure to ART to prevent vertical transmission was reported in 100 (16%) of 642 children, and, when known, was predominantly nevirapine (43 [77%] of 56). ¶Two participants in the SOC group initiated tenofovir alafenamide and emtricitabine (one in ODYSSEY A and one in ODYSSEY B).

Table 1: **Baseline characteristics in the ODYSSEY virology and resistance population**

more resistance and therefore provides maximum information on resistance mutations. Resistance testing was also performed on baseline samples for all ODYSSEY B participants to assess associations between resistance present at switch to second-line ART (trial enrolment) and treatment outcomes. The reverse transcriptase and protease genes were sequenced at all timepoints requested by the trial statistician; the integrase gene was sequenced after baseline for those with virological failure in the dolutegravir group (not requested at baseline or in the SOC group due to absence of INSTI exposure). Retrospective viral loads and resistance tests were returned to the treating site after trial results had been reported.

Outcomes

The primary outcome of ODYSSEY was virological failure (<1 $\log_{10}$ drop in viral load at week 24 [or viral load ≥50 copies per mL at week 24 when viral load was <500 copies per mL at baseline] and switch to second or third-line ART for treatment failure; or two consecutive viral load results of ≥400 copies per mL with the first at or after week 36) or clinical failure (WHO stage 4 or severe stage 3, or death due to any cause) by 96 weeks assessed in the intention-to-treat population (defined as all randomly assigned participants with available follow-up, except those randomly assigned in error). Development of emergent resistance was a secondary outcome; these outcomes have been previously published for both trial cohorts (≥14 kg and <14 kg).[16,17] Here, we report additional exploratory analyses focusing on virological and resistance outcomes in the total ODYSSEY population.

Virological failure was defined as meeting the virological component of the primary outcome. Virological suppression was defined as two consecutive viral loads of less than 400 copies per mL. Drug resistance mutations were defined according to the 2019 IAS-USA major mutations update.[18] Predicted drug resistance levels to antiretroviral drugs were estimated using the Stanford HIV Drug Resistance Database algorithm (version 9.0)[19] as none or susceptible, potential low-level, low-level, intermediate-level, or high-level resistance. When participants had more than one resistance result available, mutations identified in earlier samples (not present in later samples) were assumed to remain—as they were likely archived in the viral reservoir—and the highest level of Stanford predicted resistance (as per the individual study drug) was taken. Emergent resistance was defined as the presence of a major IAS-USA mutation observed after virological failure, which was not present at baseline (NRTI, NNRTI, or protease inhibitor), or any major INSTI mutation.

Statistical analysis

Participants were included if a viral load was available after baseline, or the participant died during follow-up. Follow-up was censored when the last participant reached 96 weeks (censoring date on April 24, 2020, for the ≥14 kg cohort and on June 28, 2021, for the <14 kg cohort), or at the latest viral load for participants who were lost to follow-up, or at the date of death for participants who died before a viral load during follow-up. All comparisons by treatment group were in the intention-to-treat population. Treatment effects were estimated using SOC

as the reference group; adjusted analyses included randomisation stratification factors (n=8 for the ≥14 kg stratification factors: ODYSSEY A or B, routine availability of resistance tests, and intended NRTI backbone [abacavir and lamivudine or other]; n=2 for the <14 kg stratification factor: ODYSSEY A or B). Comparisons made within treatment groups (eg, by NRTI backbone) were observational.

Time to virological suppression from baseline to week 96 was estimated from cause-specific hazards and the overall survival curve, in which competing risks were defined as a switch in the anchor drug due to treatment failure, toxicity, pregnancy, or a major protocol deviation, or a switch in NRTI backbone for treatment failure, and death.[20] Hazard ratios (HRs) based on cumulative incidence were numerically similar to cause-specific HRs. Participants with baseline viral load of less than 400 copies per mL were excluded from time-to-suppression analyses. Time to virological failure up to week 96 was compared between groups using Cox regression. Time to subsequent suppression after virological failure and until the trial censoring date was estimated using the same approach as time-to-suppression from baseline. We assessed Kaplan–Meier plots visually to ensure that there were no obvious deviations from the proportional hazards assumption of the Cox models. Sensitivity analyses used at least 1000 copies per mL and at least 50 copies per mL cutoffs for confirmed failure after week 36 instead of at least 400 copies per mL. Virological outcomes were explored in ODYSSEY B participants by use of abacavir, tenofovir disoproxil fumarate, or zidovudine in the NRTI backbone as a second-line regimen from enrolment.

Associations between baseline resistance to the initial trial regimen (according to the Stanford algorithm) and virological outcomes were explored in those with a baseline resistance test available. Prevalence of resistance after failure was tabulated in participants with at least one resistance test available at or after the date of the first viral load defining virological failure.

To estimate proportions of participants with emergent resistance among all participants exposed to a drug-class between enrolment and resistance testing, and in those with virological failure, multiple imputation by chain equations (ten imputations) was performed to account for missing resistance tests at baseline or after virological failure (or both). Participants not meeting the virological failure endpoint were assumed to have no emergent resistance. Emergent resistance to each drug-class was assumed independent; four imputation models were run (one for each drug class). Imputation models included trial group, first-line or second-line ART, an interaction between trial group and first-line or second-line ART, and resistance after virological failure (only NRTI and NNRTI) as predictors of emergent resistance. All p values presented are two-sided. Analyses were performed using STATA software (version 16.1).

Role of the funding source

ViiV Healthcare reviewed and commented on the initial manuscript. Employees of the Medical Research Council Clinical Trials Unit (University College London, London, UK) and the Penta Foundation had a role in the study design, data collection, data analysis, data interpretation, and writing of the manuscript.

Results

Of the 792 children and adolescents in ODYSSEY, 788 were included in the virology and resistance analysis population (four were excluded due to loss to follow-up at random assignment); 391 were randomly assigned to the dolutegravir-based ART group and 397 to the SOC group. At enrolment, 381 participants started first-line ART (ODYSSEY A: 189 in the dolutegravir group and 192 in the SOC group) and 407 participants started second-line ART (ODYSSEY B: 202 in the dolutegravir group and 205 in the SOC group). 72 participants in ODYSSEY A and 13 participants in ODYSSEY B weighed less than 14 kg. 401 (51%) of 788 participants were female and 387 (49%) were male. At baseline, median age was 11·4 years (IQR 8·0–14·6) and viral load (log_{10}) was 4·5 copies per mL (3·9–5·1). All nine African sites did not have resistance testing routinely available for patients starting second-line ART (389 [96%] ODYSSEY B participants). Median previous exposure to ART in ODYSSEY B was 5·3 years (3·3–8·1); 391 (96%) participants were receiving an NNRTI-based first-line regimen before joining the trial.

ODYSSEY A participants in the SOC group mostly initiated NNRTI-based ART (155 [81%]; 147 [77%] initiated efavirenz and six [3%] initiated nevirapine) and 36 (19%) initiated a boosted protease inhibitor-based regimen (32 [17%] initiated ritonavir-boosted lopinavir; table 1), with most in the less than 14 kg cohort (29 [81%] of 36). ODYSSEY B participants in the SOC group primarily started boosted protease inhibitor-based ART (197 [96%], with 146 [71%] starting ritonavir-boosted lopinavir and 49 [24%] starting ritonavir-boosted atazanavir). NRTI backbones were balanced across trial groups: in ODYSSEY A, 317 (83%) received abacavir plus lamivudine, 59 (15%) received tenofovir disoproxil fumarate plus lamivudine or emtricitabine, and four (1%) received zidovudine plus lamivudine; whereas in ODYSSEY B, 217 (53%) received abacavir plus lamivudine, 103 (25%) received tenofovir disoproxil fumarate plus lamivudine or emtricitabine, 83 (20%) received zidovudine plus lamivudine, and three (1%) received abacavir plus tenofovir disoproxil fumarate. At enrolment, nearly all participants in ODYSSEY B changed the NRTI backbone (376 [92%] switched one drug in their NRTI backbone, 26 [6%] switched both drugs, and five [1%] switched neither), but most (380 [95%]) retained lamivudine in their NRTI backbone. Two (<1%) participants in the SOC group initiated tenofovir alafenamide plus emtricitabine (one in ODYSSEY A and one in ODYSSEY B).

	Total population				$p_{interaction}$ (treatment group *vs* first-line or second-line therapy)	ODYSSEY A (first-line therapy)				ODYSSEY B (second-line therapy)			
	Dolutegravir (n=391)	SOC (n=397)	Adjusted HR (95% CI)	p value		Dolutegravir (n=189)	SOC (n=192)	Adjusted HR (95% CI)	p value	Dolutegravir (n=202)	SOC (n=205)	Adjusted HR (95% CI)	p value
Virological suppression on initial regimen during 96 weeks follow-up*													
Suppression without ART switch†‡	373 (96%)	343 (88%)	1·57§ (1·35–1·83)	<0·0001	0·88	178 (95%)	159 (85%)	1·63§ (1·30–2·04)	<0·0001	195 (97%)	184 (90%)	1·53§ (1·25–1·88)	<0·0001
No suppression	10 (3%)	28 (7%)	..	..	..	6 (3%)	1 (6%)	..	..	4 (2%)	16 (8%)	..	..
Switched ART¶	4 (1%)	16 (4%)	..	..	..	1 (1%)	12 (6%)	..	..	3 (1%)	4 (2%)	..	..
Died‖	3 (1%)	5 (1%)	..	..	..	3 (2%)	4 (2%)	..	..	0	1 (<1%)	..	..
Virological failure by 96 weeks**													
Participants with virological failure‡	51/391 (13%)	86/397 (22%)	0·56 (0·40–0·79)	0·0011	0·086	18/189 (10%)	43/192 (22%)	0·39 (0·23–0·68)	0·0009	33/202 (16%)	43/205 (21%)	0·73 (0·46–1·15)††	0·17
Insufficient virological response at 24 weeks	0	4 (1%)	..	..	..	0	3 (2%)	..	..	0	1 (<1%)	..	..
Confirmed viral load ≥400 copies per mL after 36 weeks	51 (13%)	82 (21%)	..	..	..	18 (10%)	40 (21%)	..	..	33 (16%)	42 (20%)	..	..
Virological suppression without ART switch after virological failure*‡‡													
Suppression without ART switch‡	30 (59%)	31 (39%)	1·71§ (1·01–2·88)	0·045	0·57	11 (61%)	10 (26%)	2·04§ (0·83–5·02)	0·12	19 (58%)	21 (51%)	1·52§ (0·80–2·87)	0·20
Did not suppress	19 (37%)	27 (34%)	..	..	..	7 (39%)	13 (34%)	..	..	12 (36%)	14 (34%)	..	..
Switched ART¶	2 (4%)	21 (27%)	..	..	..	0	15 (39%)	..	..	2 (6%)	6 (15%)	..	..
Sensitivity analyses for virological failure by 96 weeks (viral load ≥50 copies per mL at or after week 36)**													
Participants with virological failure by 96 weeks‡	112/391 (29%)	145/397 (37%)	0·74 (0·58–0·94)	0·015	0·39	47/189 (25%)	68/192 (35%)	0·65 (0·45–0·95)	0·024	65/202 (32%)	77/205 (38%)	0·81 (0·58–1·13)	0·22
Sensitivity analyses for virological failure by 96 weeks (viral load ≥1000 copies per mL at or after week 36)**													
Participants with virological failure by 96 weeks‡	41/391 (10%)	72/397 (18%)	0·54 (0·37–0·79)	0·0015	0·12	15/189 (8%)	37/192 (19%)	0·38 (0·21–0·70)	0·0017	26/202 (13%)	35/205 (17%)	0·70 (0·42–1·16)	0·17

Data are n (%) or n/N, unless stated otherwise. For the sensitivity analyses, viral load of at least 50 copies per mL or at least 1000 copies per mL was used to define virological failure at or after week 36 instead of 400 copies per mL (lack of virological response defined as per main analysis). ART=antiretroviral therapy. HR=hazard ratio. SOC=standard of care. *Associations between trial arm and time to suppression were estimated using cause-specific HRs (competing risks: switch from initial trial regimen or switch in backbone for failure and death). †Six ODYSSEY A participants (one dolutegravir and five SOC) with baseline viral load (<400 copies per mL) were excluded from time to virological suppression analysis. ‡Models were adjusted for randomisation stratification factors (n=8 for the ≥14 kg stratification factors: ODYSSEY A or B, routine availability of resistance tests, and intended NRTI backbone [abacavir and lamivudine or other]; n=2 for the <14 kg stratification factor: ODYSSEY A or B). §Cause-specific HR. ¶Switch in ART was defined as a switch in the third agent due to treatment failure, toxicity, pregnancy, or a major protocol deviation, or a switch in NRTI backbone for treatment failure. ‖Causes of death included: disseminated tuberculosis, cause unknown, pneumonia and presumed septicaemia, pneumonia, kwashiorkor, severe malnutrition, pulmonary tuberculosis and severe malnutrition, and traumatic event. **Associations between trial arm and time to failure were estimated using HRs from Cox regression. ††Eight ODYSSEY B participants in the SOC group initiated a non-protease inhibitor-based ART regimen (six initiated NNRTI and two initiated INSTI). A sensitivity analysis, excluding these eight participants from the time to virological failure at 96 weeks, showed an adjusted HR of 0·76 (95% CI 0·45–1·28; p=0·30). ‡‡Seven participants in the SOC group switched ART (until the trial censoring date on April 24, 2020, for the ≥14 kg cohort and June 28, 2021, for the <14 kg cohort) before or at the time of virological failure and were excluded from time to virological suppression after failure analysis.

Table 2: **Virological outcomes comparing dolutegravir-based ART with standard of care**

Median follow-up was 140 weeks (IQR 122–156). Virological status was available for 760 (96%) of 788 children at 96 weeks. Virological suppression occurred significantly earlier in the dolutegravir group (adjusted [cause-specific] HR 1·57 [1·35–1·83]; p<0·0001; table 2; appendix p 5). 51 (13%) participants had virological failure by 96 weeks in the dolutegravir group versus 86 (22%) in the SOC group (including 18 *vs* 43 in ODYSSEY A and 33 *vs* 43 in ODYSSEY B; adjusted HR 0·56 [0·40–0·79]; p=0·0011). Most participants (133 [97%] of 137) with virological failure met the endpoint due to confirmed viral load of at least 400 copies per mL after week 36; of these, 39 (76%) of 51 in the dolutegravir group had virological suppression before virological failure (*vs* 43 [52%] of 82 in the SOC group). Close to half of those who had virological failure subsequently reached suppression without switching ART, with a higher proportion in the dolutegravir group (30 [59%] *vs* 31 [39%] in the SOC group; p=0·045). There was no statistically significant difference between treatment effects on first-line (ODYSSEY A) versus second-line (ODYSSEY B) therapy for any virological outcome. In the SOC group participants with a viral load less than 5000 copies per mL at failure were more likely to have virological suppression after failure than those with viral load of at least 5000 copies per mL (adjusted [cause-specific] HR 2·87 [1·34–6·12]; p=0·0065), but this was not seen in the dolutegravir group (HR 0·31 [0·10–0·92]; p=0·035; appendix p 8).

In sensitivity analyses using confirmed viral load of at least 1000 copies per mL or at least 50 copies per mL for virological failure after 36 weeks, the benefit of dolutegravir over SOC was similar than that seen in the primary analysis using confirmed viral load of at least 400 copies per mL (table 2).

Baseline resistance tests were available in 287 (71%) of 403 ODYSSEY B participants starting second-line on an abacavir-based, tenofovir disoproxil fumarate-based, or zidovudine-based NRTI backbone with lamivudine or emtricitabine (table 3). In the SOC group, no participants had baseline high-level resistance (according to the Stanford HIV Drug Resistance Database algorithm) to the anchor drug of their study regimen. In the dolutegravir group, no integrase sequencing was performed at baseline. Across both study groups, 265 (92%) of 287 participants had high-level baseline resistance to lamivudine or emtricitabine (all had Met184Val/Ile), 40 (29%) to abacavir, three (4%) to tenofovir disoproxil fumarate, and one (2%) to zidovudine, where these drugs were included in their backbone.

Among ODYSSEY B participants in the dolutegravir group, virological failure was higher in children starting zidovudine (HR 2·22 [1·01–4·88]; p=0·048; table 3; appendix p 7) and similar in those starting tenofovir disoproxil fumarate (1·19 [0·50–2·83]; p=0·70) compared with abacavir; virological failure was also numerically higher in children starting zidovudine with no, low-level, or intermediate-level zidovudine resistance at baseline than in children starting abacavir with high-level abacavir resistance, although the difference was not statistically significant (2·56 [0·70–9·31]; p=0·15; appendix p 9). Among those starting abacavir with dolutegravir in

	Dolutegravir	p value	SOC	p value
Virological failure by week 96 (as per NRTI backbone at baseline)				
Abacavir	14/108 (13%)	..	22/109 (20%)	..
Tenofovir disoproxil fumarate	8/52 (15%)	..	5/51 (10%)	..
Tenofovir disoproxil fumarate versus abacavir	1·19 (0·50–2·83)	0·70	0·47 (0·18–1·23)	0·12
Zidovudine	11/41 (27%)	..	14/42 (33%)	..
Zidovudine versus abacavir	2·22 (1·01–4·88)	0·048	1·74 (0·89–3·40)	0·11
Zidovudine versus tenofovir disoproxil fumarate	1·87 (0·75–4·64)	0·18	3·73 (1·34–10·36)	0·012
Baseline resistance tests				
Test available	144/201 (72%)	..	143/202 (71%)	..
High-level resistance to third agent*†	..	..	0/142	..
Met184Val/Ile present	132/144 (92%)	..	133/143 (93%)	..
High-level resistance to NRTI backbone†	132/144 (92%)	..	133/143 (93%)	..
Participants with high-level resistance to NRTI backbone at baseline				
Drugs in NRTI backbone with high-level resistance†				
Lamivudine and emtricitabine	132/144 (92%)	..	133/143 (93%)	..
Abacavir	24/68 (35%)	..	16/70 (23%)	..
Tenofovir disoproxil fumarate	2/40 (5%)	..	1/45 (2%)	..
Zidovudine	1/36 (3%)	..	0/28	..
Number of drugs in NRTI backbone with high-level resistance†				
None	12 (8%)	..	10 (7%)	..
One	105 (73%)	..	116 (81%)	..
Two	27 (19%)	..	17 (12%)	..
Virological outcomes in participants initiating abacavir in second-line regimen				
Virological suppression on initial regimen at 96-week follow-up according to abacavir resistance (second-line regimen)†				
No, low, or intermediate-level resistance	40/44 (91%)	..	48/54 (89%)	..
High-level resistance	24/24 (100%)	..	16/16 (100%)	..
High-level versus no, low, intermediate-level resistance‡	1·70 (1·01–2·85)§	0·046	1·02 (0·58–1·81)§	0·93
Virological failure by week 96 according to abacavir resistance (second-line regimen)†				
No, low, or intermediate-level resistance	6/44 (14%)	..	16/54 (30%)	..
High-level resistance	3/24 (13%)	..	1/16 (6%)	..
High-level versus no, low, or intermediate-level resistance¶	0·90 (0·23–3·61)	0·88	0·18 (0·02–1·33)	0·093

Data are n/N (%) or adjusted HR (95% CI), unless stated otherwise. Four participants were excluded: three receiving abacavir and tenofovir disoproxil fumarate (one in the dolutegravir group and two in the SOC group) and one receiving tenofovir alafenamide and emtricitabine (in the SOC group). HR=hazard ratio. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor. SOC=standard of care. *The integrase gene was not sequenced at baseline, therefore baseline resistance to the third agent could not be determined in the dolutegravir group. One participant in the SOC group initiated elvitegravir (an integrase inhibitor); therefore, baseline resistance to the third agent could not be determined for this participant. †Predicted drug resistance concentrations to antiretroviral drugs were estimated using Stanford HIVdb algorithm (version 9.0); high-level resistance to a drug was defined as a total score of at least 60. ‡Associations between the trial group and time to suppression by baseline abacavir resistance were estimated using cause-specific HRs (competing risks: switch from the initial trial regimen or switch in the backbone for failure and death), including an interaction between the treatment group and high-level abacavir resistance (p=0·20). §Cause-specific HRs. ¶Associations between the trial group and time to failure by baseline abacavir resistance were estimated using HRs from Cox regression, including treatment group, high-level abacavir resistance, and an interaction term (p=0·19).

Table 3: **Baseline resistance and association with virological outcomes in ODYSSEY B (second-line therapy)**

ODYSSEY B, time to virological suppression was marginally faster in participants with high-level abacavir resistance at baseline compared with those with no, low-level, or intermediate-level resistance (cause-specific HR 1·70 [1·01–2·85]; p=0·046), whereas failure rates by week 96 were similar (HR 0·90 [0·23–3·61]; p=0·88; table 3).

Of the 137 participants with virological failure by week 96 (ODYSSEY A and B), resistance tests after failure were available for the reverse transcriptase and protease HIV encoding region in 133 (97%) of 137 participants across both groups, and integrase region in 42 (82%) of 51 in the dolutegravir group (table 4).

Of those receiving first-line (ODYSSEY A) with virological failure, six (35%) of 17 participants in the dolutegravir group and 40 (98%) of 41 in the SOC group had at least one major IAS-USA resistance mutation to at least one drug class after failure (NRTI, NNRTI, protease inhibitor, or INSTI [only in the dolutegravir group]; risk difference –62% [–85 to –39]; p<0·0001; table 4; appendix pp 11). One (6%) participant in the dolutegravir group versus 28 (68%) in the SOC group had resistance to NRTI, six (35%) versus 38 (93%) had resistance to NNRTI, and zero (0%) versus two (5%) had resistance to a protease inhibitor. None of the 16 participants receiving first-line dolutegravir had major INSTI resistance after failure. An estimated 1% (95% CI 0 to 2) of participants in the dolutegravir group versus 20% (14 to 26) in the SOC group in ODYSSEY A had emergent resistance to at least one drug-class within their first-line regimen (risk difference –20% [–25 to –14]; p<0·0001), including new NRTI resistance in 1% (0 to 2) of participants in the

	ODYSSEY A (first-line therapy)				ODYSSEY B (second-line therapy)			
	Dolutegravir	SOC	Risk difference (95% CI)	p value	Dolutegravir	SOC	Risk difference (95% CI)	p value
Virological failure by 96 weeks	18/189 (10%)	43/192 (22%)	..	..	33/202 (16%)	43/205 (21%)	..	..
Availability of resistance tests after virological failure*	17/18 (94%)	41/43 (95%)	..	..	32/33 (97%)	43/43 (100%)	..	..
Reverse transcriptase gene	17 (94%)	41 (95%)	..	..	32 (97%)	43 (100%)	..	..
Protease gene	17 (94%)	41 (95%)	..	..	32 (97%)	43 (100%)	..	..
Integrase gene	16 (89%)	..	..	..	26 (79%)	..	..	..
Major drug resistance after failure†‡	6/17 (35%)	40/41 (98%)	–62% (–85 to –39)	<0·0001	27/32 (84%)	40/43 (93%)	–9% (–23 to 6)	p=0·23
NRTI	1 (6%)	28 (68%)	..	..	23 (72%)	35 (81%)	..	..
NNRTI§	6 (35%)	38 (93%)	..	..	26 (81%)	40 (93%)	..	..
Protease inhibitor	0	2 (5%)	..	..	2 (6%)	3 (7%)	..	..
INSTI¶	0	..	..	..	5 (19%)	..	..	..
Participants with virological failure initiating drug-class with emergent resistance‖	6% (0 to 17)	90% (80 to 100)	–84% (–99 to –69)	<0·0001	23% (8 to 38)	23% (8 to 37)	0% (–20 to 21)	p=0·98
NRTI	6% (0 to 17)	64% (47 to 80)	..	..	13% (1 to 25)	10% (0 to 22)	..	..
Third agent	0% (0 to 19)**	66% (51 to 80)	..	..	17% (3 to 30)	15% (4 to 26)	..	..
NNRTI	..	85% (71 to 99)	..	..	..	100%	..	..
Protease inhibitor	..	9% (0 to 27)	..	..	..	5% (0 to 13)	..	..
INSTI	0% (0 to 19)**	..	..	..	17% (3 to 31)	..	..	..
All participants initiating drug-class with emergent resistance††	1% (0 to 2)	20% (14 to 26)	–20% (–25 to –14)	<0·0001	4% (1 to 6)	5% (2 to 8)	–1% (–5 to 3)	p=0·60
NRTI	1% (0 to 2)	14% (9 to 20)	–14% (–19 to –8)	<0·0001	2% (0 to 4)	2% (0 to 5)	0% (–3 to 3)	p=0·95
Third agent	0% (0 to 2)**	15% (10 to 20)	–15% (–20 to –10)	<0·0001	3% (0 to 5)	3% (1 to 6)	0% (–4 to 3)	p=0·78
NNRTI	..	17% (11 to 24)	..	..	..	67% (29 to 100)	..	..
Protease inhibitor	..	3% (0 to 7)	..	..	..	1% (0 to 2)	..	..
INSTI	0% (0 to 2)**	..	..	..	3% (0 to 5)	..	..	..

Additional resistance tests were received for three ODYSSEY B participants (≥14 kg) after analysis of the main trial results (one previously had no test after failure and two with additional results showed resistance). INSTI=integrase strand-transfer inhibitor. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. SOC=standard of care. *54 participants had a resistance test after virological failure by week 96 and 79 were tested earlier (20 due to treatment change before week 96 and 59 had no later sample available with viral load ≥1000 copies per mL or the later sample failed to amplify); the remaining four participants had samples that could not be amplified after failure. †Major drug resistance mutations defined according to the 2019 update of the International Antiviral Society–USA drug resistance mutations. No additional dolutegravir-associated mutations were present based on the November, 2022, update of the International Antiviral Society–USA. ‡The proportion of participants with resistance after failure, of those with virological failure by week 96 and the resistance test being available after failure for drug-class (integrase gene not sequenced for the SOC group). §All six participants with NNRTI resistance after failure in the dolutegravir group had been exposed to NNRTI-based prevention of vertical transmission before trial enrolment; of the ten SOC participants receiving a non-NNRTI-based first-line regimen with NNRTI resistance after failure, three had NNRTI-based prevention of vertical transmission exposure. ¶Five participants receiving second-line dolutegravir had at least one major INSTI resistance mutation after failure (plus accessory or minor mutations): one Gln148Gln/Arg (plus Thr97Thr/Ala, Glu138Ala, and Gly140Gly/Ala), one Gln148Lys (plus Glu138Lys and Gly140Ala), one Asn155Asn/His, one Gly118Arg/Ser (plus Leu74Met and Glu138Glu/Lys), and one Gly118Gly/Arg/Ser and Arg263Arg/Lys. ‖Estimated in participants with virological failure by drug-class, using multiple imputation to account for missing resistance tests at baseline or after failure (or both). **One-sided 97·5% CI. ††Estimated in all participants exposed to drug class, using multiple imputation to account for missing resistance tests at baseline or after failure (or both).

Table 4: **Genotypic resistance comparing dolutegravir-based antiretroviral therapy versus standard of care**

dolutegravir group versus 14% (9 to 20) in the SOC group (risk difference –14% [–19 to –8]; p<0·0001). Among SOC participants, an estimated 15% (10 to 20) had emergent resistance to their anchor drug (17% [11 to 24] starting NNRTI and 3% [0 to 7] starting protease inhibitor-based ART) compared with none in the dolutegravir group (risk difference –15% [–20 to –10]; p<0·0001).

Of those with virological failure who were receiving second-line ART (ODYSSEY B), 84% (27 of 32) of participants in the dolutegravir group and 93% (40 of 43) in the SOC group had at least one major IAS-USA resistance mutation to at least one drug class after failure (risk difference –9% [–23 to 6]; p=0·23; table 4). 23 (72%) participants in the dolutegravir group versus 35 (81%) in the SOC group had resistance to NRTI, 26 (81%) versus 40 (93%) had resistance to NNRTI, and two (6%) versus three (7%) had resistance to a protease inhibitor. Five (19%) participants receiving second-line dolutegravir had at least one major INSTI resistance mutation after virological failure (one with Gln148Gln/Arg, one with Gln148Lys, one with Asn155Asn/His, one with Gly118Arg/Ser, and one with Gly118Gly/Arg/Ser plus Arg263Arg/Lys); all five had cross-resistance to cabotegravir (appendix p 12). Of the five, four received zidovudine plus lamivudine twice a day and at baseline had high-level resistance to lamivudine, and one also had high-level zidovudine resistance (of the remaining three: one had low-level resistance and two had no resistance).[19] The fifth participant started abacavir plus lamivudine with no resistance to NRTI at baseline. Four of five participants with INSTI resistance had virological suppression before virological failure (time of confirmatory viral load for virological failure: three at week 48, one at week 60, and one at week 72) and all remained on their initial therapy at the end of follow-up (range 108–156 weeks since randomisation), and one of five had virological suppression. An estimated 4% (1 to 6) of participants in the dolutegravir group versus 5% (2 to 8) in the SOC group in ODYSSEY B had emergent resistance to at least one drug class within their initial second-line regimen (risk difference –1% [–5 to 3]; p=0·60; table 4), including 2% in each group ([0 to 4] in dolutegravir; [0 to 5] in SOC) with emergent NRTI resistance (risk difference 0% [–3 to 3]; p=0·95). 3% (0 to 5) of participants in the ODYSSEY B dolutegravir group had emergent INSTI resistance compared with 3% (1 to 6) in the SOC group who had emergent resistance to their anchor drug (risk difference 0% [–4 to 3]; p=0·78; 67% [29 to 100] of those receiving NNRTI regimens and 1% [0 to 2] of those receiving protease inhibitor).

Discussion

ODYSSEY is the first study, to our knowledge, which provides randomised trial data on HIV virological and genotypic resistance outcomes comparing dolutegravir with SOC for first-line and second-line ART in children. We have previously described superior treatment outcomes with dolutegravir than with SOC, based on a combined clinical and virological outcome at 96 weeks, and reported low treatment-emergent resistance among children with virological failure.[16,17] Here, we present exploratory analyses focusing on virological and resistance outcomes in the total ODYSSEY population.

Compared with SOC, children starting dolutegravir reached virological suppression quicker, were less likely to have virological failure over 96 weeks, and were more likely to reach suppression after protocol-defined virological failure without changing the ART regimen. Advantages in virological outcomes of dolutegravir-based ART versus SOC appeared more pronounced in children initiating first-line than second-line ART. However, there was no statistical significance for heterogeneity. The paediatric CHAPAS-4 trial has provided further evidence for virological superiority for dolutegravir-based second-line therapy with significantly higher rates of virological suppression at 96 weeks in participants receiving dolutegravir than those receiving ritonavir-boosted lopinavir or atazanavir.[21]

Fewer children and adolescents initiating dolutegravir-based first-line ART developed emergent NRTI resistance over 96 weeks compared with SOC, and none developed resistance to the anchor drug compared with an estimated 17% (95% CI 11 to 24) starting NNRTI-based ART and 3% (0 to 7) starting protease inhibitor-based ART. ODYSSEY results are in line with results from the meta-analysis of RCTs in adults receiving first-line therapy showing faster viral suppression and protection against treatment-emergent NRTI and anchor drug resistance, with no patients (of 2639) in nine trials developing INSTI resistance.[3]

On second-line treatment, emergent NRTI resistance was infrequent and similar in both groups (2% [0 to 4] in the dolutegravir group *vs* 2% [0 to 5] in the SOC group). Emergent resistance to the anchor drug was also infrequent (3% [0 to 5] *vs* 3% [1 to 6]), and low in those receiving dolutegravir (3% [0 to 5]) or protease inhibitor (1% [0 to 2]). Our estimate that 3% of participants who initiated dolutegravir-based second-line therapy developed emergent dolutegravir resistance is similar to second-line trials in adults (two [1%] in DAWNING by 48 weeks and nine [4%] in NADIA by 96 weeks).[5,6] In ODYSSEY, of the five participants with dolutegravir resistance, four had dolutegravir coadministered with zidovudine. This finding is similar to those seen in second-line trials in adults, in which six of nine participants with dolutegravir resistance in NADIA and one of two in DAWNING were receiving zidovudine.[5,6] Zidovudine coformulated with lamivudine is taken twice a day, which results in increased adherence challenges; missed doses would lower the daily NRTI drug exposure, possibly increasing the risk of developing dolutegravir resistance.

NADIA showed that adults starting second-line therapy had higher rates of virological suppression while continuing to receive tenofovir disoproxil fumarate plus lamivudine than those who changed to a zidovudine plus lamivudine backbone.[6] In fact, the presence of baseline Lys65Arg/Asn conferring an intermediate-to-high level tenofovir resistance and Met184Val/Ile causing high-level lamivudine resistance were each independently and paradoxically associated with a higher chance of virological suppression while receiving tenofovir disoproxil fumarate plus lamivudine at week 96.[6] CHAPAS-4 also showed superior virological suppression with a tenofovir alafenamide-based NRTI backbone than with an abacavir-based or zidovudine-based NRTI backbone in children starting second-line ART.[21] Most children in low-income and middle-income countries (LMICs) currently receive abacavir as part of first-line regimen regimen.[2] WHO guidelines recommend changing the anchor drug and an NRTI (preserving lamivudine or emtricitabine) when the patient switches to a second-line regimen as done in ODYSSEY B. Given that children can only take adult tenofovir disoproxil fumarate formulations when they weigh at least 30 kg (due to concerns about renal and bone toxic effects[11]) and tenofovir alafenamide, a less toxic tenofovir formulation and a priority drug on the Paediatric Antiretroviral Drug Optimisation list, is not yet available in LMICs, the only recommended NRTI backbone for second-line ART for children weighing less than 30 kg (who have already received abacavir) is twice a day zidovudine plus lamivudine. An important question remains as to whether children receiving abacavir plus lamivudine can recycle their backbone when switching to dolutegravir-based second-line therapy. Abacavir might be less efficacious than tenofovir disoproxil fumarate,[9,22,23] and a highly prevalent Met184Val/Ile mutation in children with treatment failure reduces abacavir activity in vitro by around three-fold.[19] Conversely, there are data suggesting that multiple mutations are required before substantial phenotypic resistance to abacavir occurs.[19,24] Furthermore, abacavir plus lamivudine is taken once a day and has a better safety and tolerability profile than zidovudine,[25] providing advantages for children starting second-line therapy. In ODYSSEY, children receiving second-line were less likely to have virological failure while receiving abacavir or tenofovir disoproxil fumarate than zidovudine in the dolutegravir group. A substantial proportion (40 [29%]) of children who switched from zidovudine to abacavir had high-level abacavir resistance at baseline (identified retrospectively from stored samples). However, children in the dolutegravir group with high-level abacavir resistance had similar rates of virological failure (three [13%] of 24) to those with no, low-level, or intermediate-level abacavir resistance (six [14%] of 44) and lower rates of virological failure than those starting zidovudine plus lamivudine with no, low, or intermediate resistance to zidovudine (ten [29%] of 35). Although these numbers are small, they are similar to results from the BIPAI and IeDEA paediatric cohorts which showed that children who had a single anchor drug substitution (with no change in the backbone therapy) while transitioning to dolutegravir had high rates of virological suppression.[26,27] Considering these findings alongside the resistance data, ODYSSEY adds to the evidence suggesting that zidovudine is a suboptimal NRTI option for dolutegravir-based second-line therapy.

We could not assess the effect of baseline tenofovir disoproxil fumarate, zidovudine, or lamivudine resistance on virological outcomes in second-line therapy, as too few children had high-level baseline resistance to tenofovir disoproxil fumarate (n=3) or zidovudine (n=1), and nearly all children (265 [92%] of 287) had the Met184Val/Ile mutation at baseline conferring high-level resistance to lamivudine (table 3).

In line with second-line studies in adults,[5,6,28,29] ODYSSEY showed excellent virological suppression in children receiving second-line ART with high-level baseline NRTI resistance (mainly to abacavir and lamivudine). In children starting second-line ART, the presence of baseline resistance might indicate better adherence to first-line ART than seen in children with no baseline resistance, and this adherence pattern possibly continues during second-line therapy. Another explanation is that genotypic resistance tests might not predict clinical NRTI activity well.[28,29] In line with EARNEST and NADIA,[6,29] ODYSSEY results imply that resistance testing in LMICs might not be helpful for selecting the NRTI backbone when switching children to second-line therapy.

Participants in the dolutegravir group were more likely to suppress without ART switch after virological failure than in the SOC group. In this open-label study in children, clinicians might have been less likely to switch dolutegravir than to switch SOC anchor drugs for virological failure; however, the competing risk analysis confirmed a higher likelihood of suppression in the dolutegravir group after virological failure. ARROW showed lower resuppression rates when children receiving NNRTI-based ART had viral rebound higher than 5000 copies per mL,[30] whereas in ODYSSEY we showed no such difference in the dolutegravir group (comparing those with a viral load of <5000 copies per mL at failure with those who had a viral load of at least 5000 copies per mL). Our study findings suggest that dolutegravir shows a high barrier to resistance, even in cases of high viral rebound, particularly in children and adolescents receiving first-line therapy where infrequent emergent NRTI resistance and no emergent dolutegravir resistance were observed.

As dolutegravir rolls out globally, there will be less distinction between treatment lines. ODYSSEY results show that most children will reach suppression while

receiving dolutegravir-based regimens, and those with viraemia are mostly non-adherent and are susceptible to the INSTI class, so could continue dolutegravir provided that adherence is supported, or use another second-generation INSTI-based ART, such as injectable cabotegravir plus rilpivirine. Injectable cabotegravir plus rilpivirine has shown excellent efficacy and safety and strong patient preference in adult trials[31] and might be most beneficial to patients struggling with daily oral treatment,[32] although data in children are still awaited. Targeted resistance tests—where available—might inform regimen choice for those consistently unsuppressed while receiving INSTI-based ART.

The main strength of ODYSSEY is the pragmatic global design, including children mostly from LMICs. Real-time viral load monitoring was performed as per country guidelines (every 6–12 months in sub-Saharan African countries and Thailand, and every 3 months in European countries). Additional viral loads measured in stored samples to allow viral load analyses at 3-month intervals until end of randomised follow-up did not influence patient management. We had excellent retention in the trial with virological status available for 760 (96%) of 788 children at 96 weeks and 133 (97%) of 137 resistance tests after failure. Thus, our results on virological outcomes and after failure resistance are reliable and generalisable to children and adolescents starting first-line and second-line ART.

The main limitation of our study is that baseline resistance tests were available for only 287 (71%) participants receiving second-line therapy. We addressed the issue of missing baseline resistance tests using multiple imputation, assuming missing at random, which seems likely since all baseline resistance tests were conducted retrospectively. Nearly all children (402 [99%]) starting second-line switched the NRTI backbone when joining the trial, thus we have no direct evidence on the effects of recycling NRTI backbone drugs versus switching the NRTI backbone and have made inferences based on baseline resistance tests. Our analyses are exploratory, and the trial was not powered to address the outcomes presented; in particular we had low statistical power to detect differences in virological outcomes when making subgroup comparisons based on NRTI backbones and presence or absence of baseline resistance.

In summary, dolutegravir showed excellent virological outcomes for children starting first-line and second-line therapy. Dolutegravir-based first-line ART is protective against emergent resistance. Our results provide reassurance that in the absence of resistance testing, the rate of virological suppression for children switching to second-line dolutegravir using the WHO-recommended algorithm is high, even in the presence of baseline NRTI resistance. However, combining dolutegravir with abacavir or tenofovir as opposed to zidovudine is likely to lead to better treatment outcomes. A small proportion of children developing INSTI resistance while receiving dolutegravir-based second-line ART highlights the need for ongoing adherence support for children starting second-line ART.

Contributors

EW, AT, DF, and DMG designed the resistance and virology substudy. EW and DF had full access to all the data in the study, EW performed the statistical analysis, and EW and DF verified the data reported. EW, DF, and AT drafted the manuscript. All authors reviewed, made updates to, and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AT is co-chair of the WHO-led Paediatric Antiretroviral Working Group and chief investigator for the D3/Penta 21 trial (ISRCTN17157458) funded by Penta Foundation, ViiV Healthcare, and the UK Medical Research Council. AB is chair of the Penta–European AIDS Clinical Society paediatric HIV treatment guidelines working group and has received fixed-term consultancy fees from the WHO-hosted Global Accelerator for Paediatric Formulations. AT and AB are members of the Penta ID scientific steering committee. RK is a board member of the German Society of Pediatric Infectious Diseases and Society of Tropical Pediatrics and International Child Health, and a coauthor of Pediatric Infectious Diseases guidelines. All other authors declare no competing interests.

Data sharing

The ODYSSEY data are held at the Medical Research Council Clinical Trials Unit at University College London (London, UK), which encourages optimal use of data by using a controlled access approach to data sharing, incorporating a transparent and robust system to review requests, and provide secure data access consistent with the relevant ethics committee approvals. We will consider all requests for data sharing, which can be initiated by contacting mrcctu.ctuenquiries@ucl.ac.uk.

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