Safety and efficacy of darunavir/ritonavir in treatment-experienced pediatric patients aged 3 to <6 years: Week 48 analysis of the ARIEL trial

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Background

- DRV/r is approved for HIV-1-infected children and adolescents aged 3 to <18 years
- The primary 24 week analysis of ARIEL[1,*] led to the approval of DRV/r for treatment-experienced children aged 3 to <6 years weighing at least 10kg
- 48-week safety and efficacy outcomes from ARIEL are reported

DRV/r = darunavir/ritonavir
*TMC114-TiDP29-C228; NCT00919854
ARIEL=d**A**runavir in t**R**eatment exper**I**enced p**E**diatric popu**L**ation

1. Violari A, et al. 18th CROI 2011. Abstract 713

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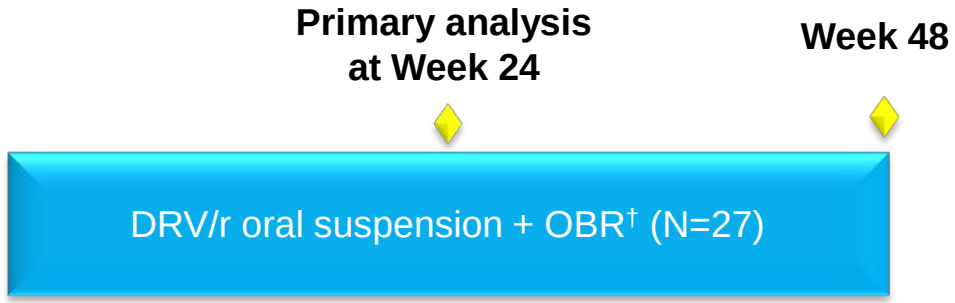
ARIEL: Phase II open-label trial

- Treatment-experienced children aged 3 to <6 years
- Bodyweight 10 to <20kg
- HIV-1 RNA >1,000 copies/mL
- <3 DRV RAMs[1] at screening
- On HAART for ≥12 weeks



†Investigator-selected OBR of ≥2 allowed antiretrovirals

- Primary objective
  - Assess pharmacokinetics, short-term safety and efficacy to support dose recommendations of DRV/r by bodyweight in children
- Dosing
  - Initial dose of DRV/r 20/3mg/kg bid
  - DRV 100mg/mL oral suspension and ritonavir 80mg/mL solution
- After Week 2 analysis and Data Safety Monitoring Board recommendations
  - 25/3mg/kg bid for patients weighing 10 to <15kg
  - 375/50mg bid fixed for patients weighing 15 to <20kg

*Argentina, Brazil, India, Kenya, and South Africa

1. Johnson VA, et al. Top HIV Med 2009;17:138–45

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ARIEL: baseline demographics and disease characteristics

	N=21*
Demographics	
Male, n (%)	10 (47.6)
Median (range) age, years	4.4 (3–6)
Race, n (%)	
White	6 (29)
Black or African-American	12 (57)
Asian	1 (5)
Multiple‡	2 (10)
Baseline virologic and immunologic parameters	
Mean (SE) BL log_{10} HIV-1 RNA	4.34 (0.18)
Median (range) $CD4^+$ cell count, cells/mm^3	927 (209–2,429)
Median (range) $CD4^+$ cell, percentage	27.7 (15.6–51.1)
Median (range) number of baseline IAS-USA[1] RAMs	
Primary PI mutations	0 (0–3)
Secondary PI RAMs	4 (1–14)
DRV RAMs	0 (0–2)
NRTI RAMs§	1 (0–5)
NNRTI RAMs	1 (0–4)
Median (range) fold change in EC_{50} for DRV	0.55 (0.2–2.3)

1. Johnson VA, et al. Top HIV Med 2010;18:156–63

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ARIEL Week 48 analysis: previously used antiretrovirals

	N=21
Number of previously used antiretrovirals	**n (%)**
PIs	
0	5 (24)
1	12 (57)
≥2	4 (19)
NRTIs	
2	17 (81)
≥3	4 (19)
NNRTIs	
≥ 1	13 (62)
Type of antiretrovirals	**n (%)**
Lopinavir/ritonavir	16 (76)
Lamivudine	21 (100)
Stavudine	12 (57)
Nevirapine	10 (48)

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ARIEL Week 48 overall safety analysis

	N=21
Mean exposure, weeks	47.9
AE incidence	**n (%)**
≥1 AE (regardless of cause or severity)	20 (95)
≥1 AE* at least possibly related to DRV	1 (5)
Total discontinuations‡	1 (5)
≥1 AE leading to permanent discontinuation	1 (5)
≥1 grade 3 or 4 AE §	2 (10)
≥1 AE ≥ grade 2 at least possibly related to treatment	0
Deaths	0

*ECG QT prolonged (QTcF was normal); ‡Occurred ≤Week 24 and was due to grade 2 vomiting, considered very likely related to ritonavir; § Two patients had grade 4 AEs (stenosing tenosynovitis and asthmatic crisis), both considered serious but not treatment related

AE = adverse event; ECG = electrocardiogram

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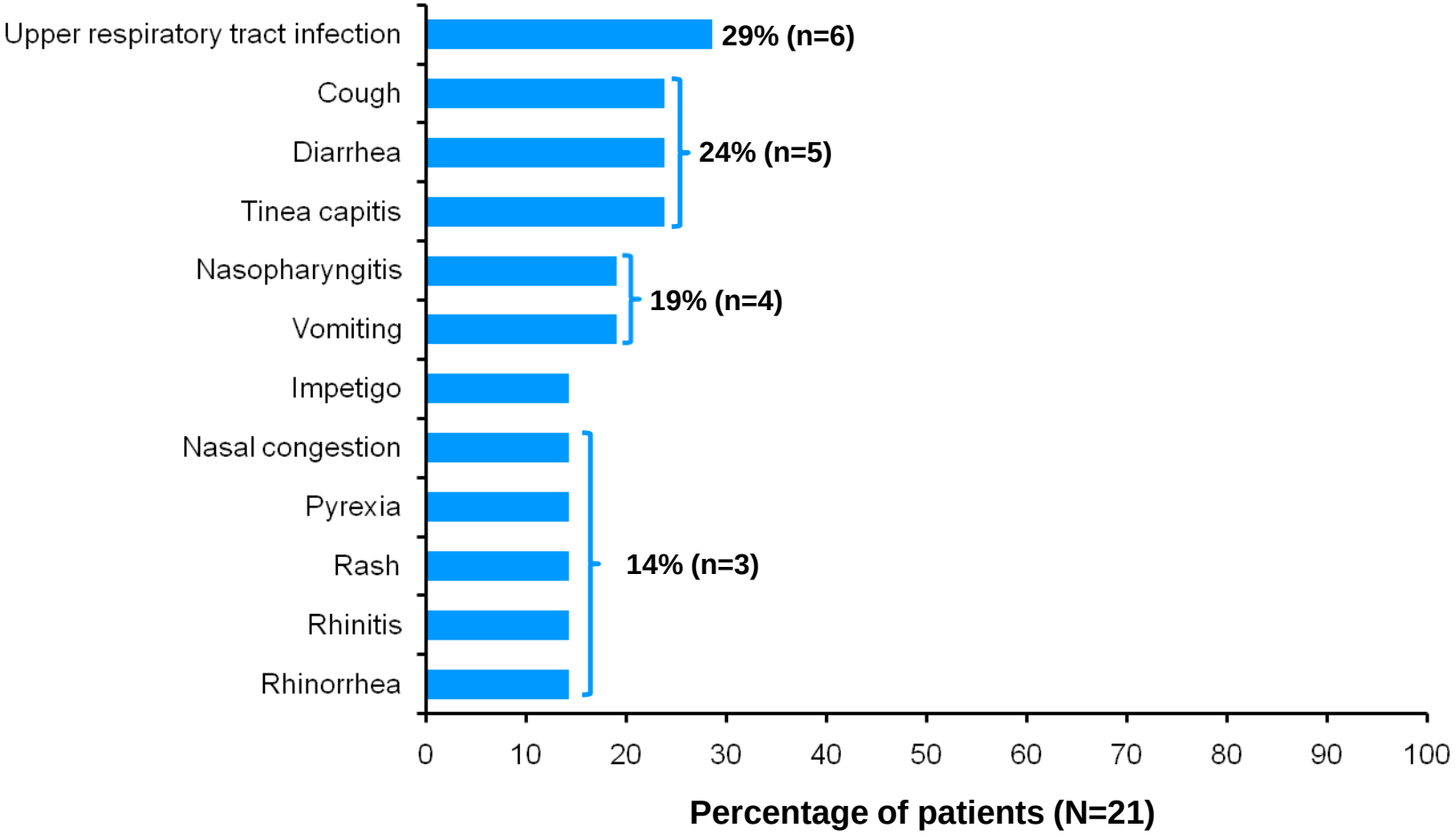
ARIEL Week 48 analysis: most commonly reported AEs*



*Occurring in ≥3 patients, regardless of causality or severity and excluding laboratory abnormalities reported as AEs

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ARIEL Week 48 laboratory safety analysis

- There were no clinically relevant changes from BL for any laboratory parameter
- All laboratory abnormalities were grade 1 or 2 in severity, with the exception of grade 3 neutropenia reported in one patient, which was present since BL and not considered treatment related

ARIEL Week 48 analysis: growth parameters

- Mean age-adjusted z-scores at BL showed patients were below normal population values
  - z-scores remained stable throughout the trial
- The mean increase from BL to Week 48 for height was 5cm, weight 1.7kg and BMI 0.1kg/m^2

BMI = body mass index
*Wilcoxon's matched pairs signed ranks test

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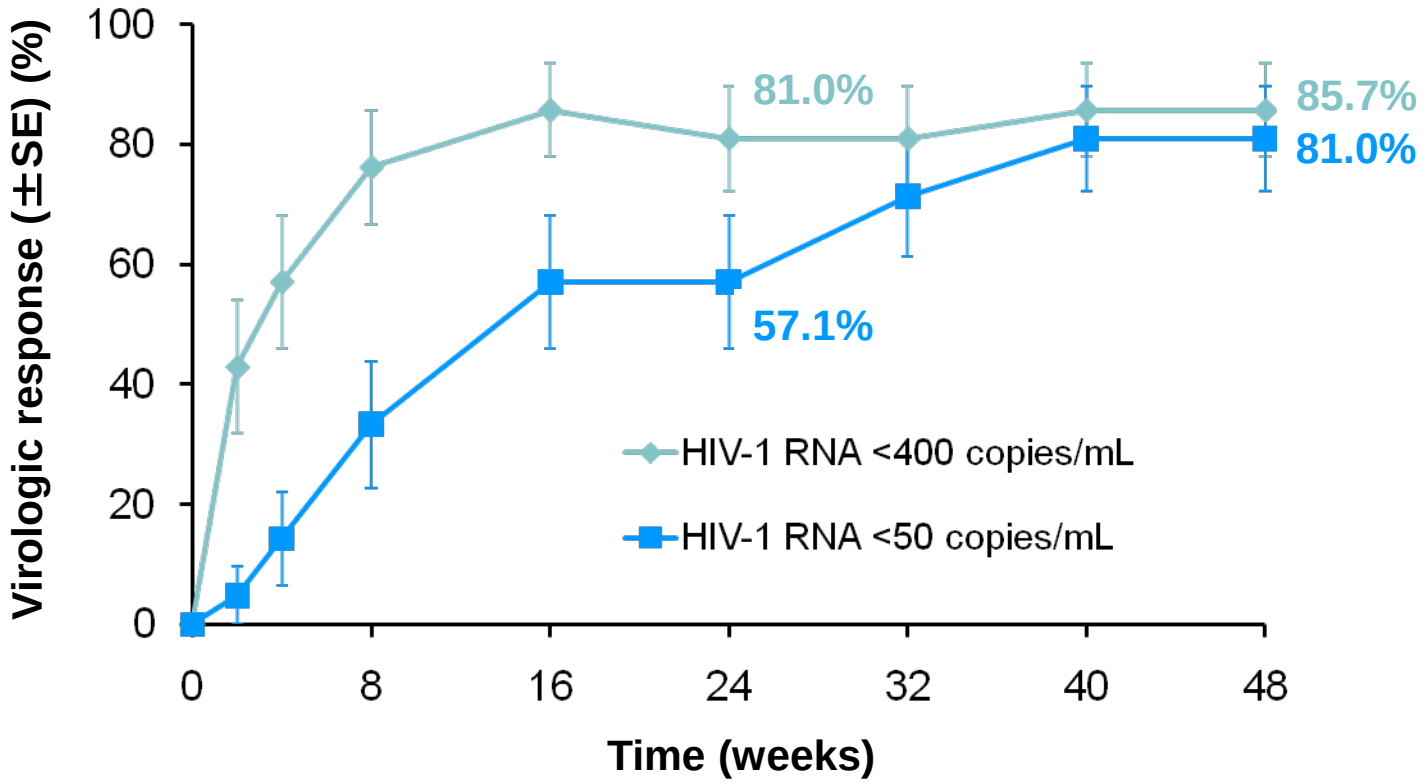
ARIEL: proportion of patients achieving virologic response over 48 weeks of treatment (ITT-TLOVR; N=21)



ITT-TLOVR = intent-to-treat/time-to-loss of virologic response

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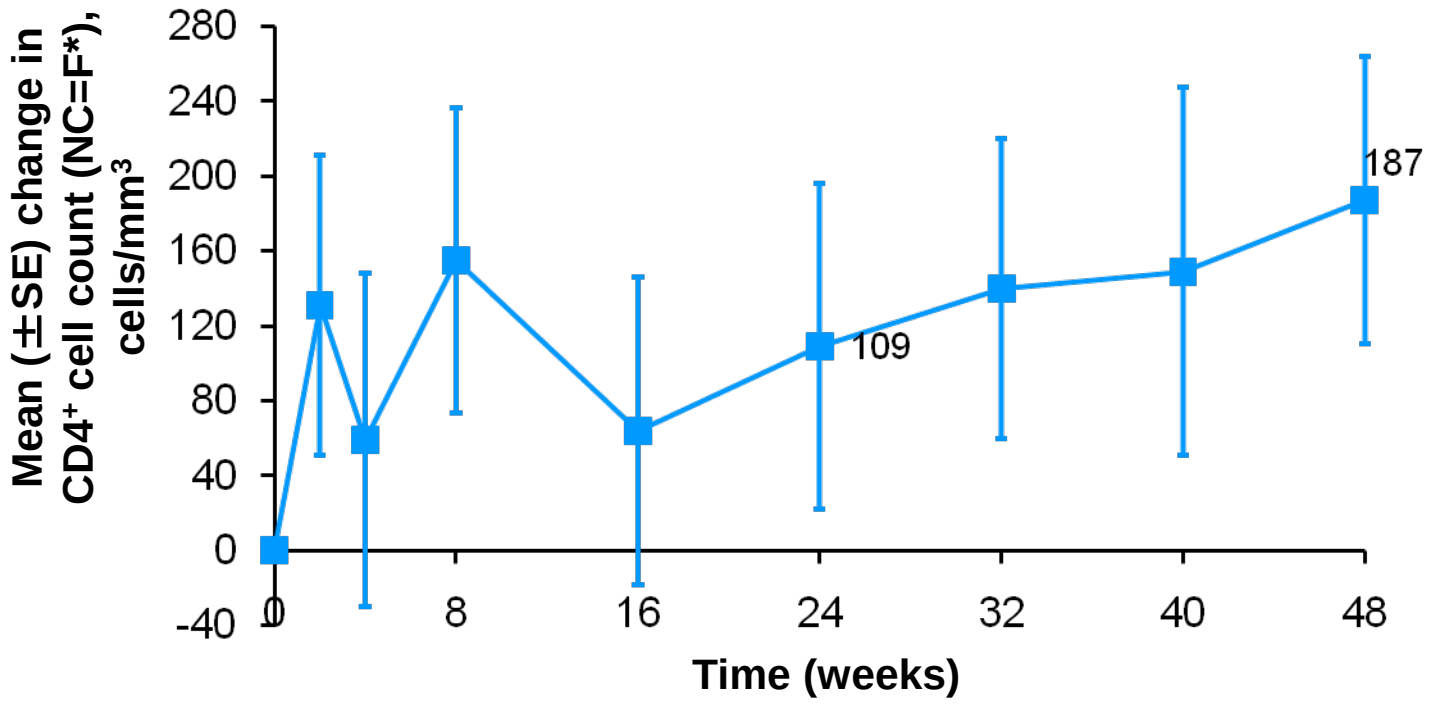
ARIEL: change in CD4$^+$ cell count (N=21)



- Mean (SE) change in CD4$^+$ % from BL to Week 48: 4.0 (1.3)%

NC=F = non-completer=failure
*Missing values were imputed as a change of 0 (using the NC=F analysis; The mean change in absolute CD4$^+$ cell count from BL (cells/mm^3) is shown at each timepoint

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ARIEL Week 48 resistance analysis

- Two patients with BL DRV RAMs (L33F/L + L76V [n=1] and L76V [n=1]) had HIV-1 RNA <50 copies/mL at Weeks 24 and 48
- There were three (14%) VFs at Week 48 (two never suppressed; one rebounder)
- Two VFs with paired BL/endpoint genotypes
  - neither developed IAS-USA[1] PI or NRTI RAMs
  - both remained susceptible to DRV and NRTIs in the OBR

VFs = virologic failures: rebounders or never achieved HIV-1 RNA <50 copies/mL using a TLOVR non-VF censored analysis
Responses after discontinuation were not imputed for patients who discontinued for reasons other than VF

1. Johnson VA, et al. Top HIV Med 2010;18:156–63

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ARIEL Week 48 safety and efficacy analysis: summary

- Over 48 weeks, treatment-experienced, HIV-1-infected children aged 3 to <6 years receiving DRV/r and an OBR showed a high virologic response and a favorable safety profile
  - 81% of patients had HIV-1 RNA <50 copies/mL (ITT-TLOVR)
  - no new safety concerns were reported compared with the known safety profile of DRV/r
- No development of resistance (development of RAMs or loss of susceptibility to DRV or NRTIs in the OBR) was observed in VFs
- Doses of DRV/r have been established and recommended in treatment-experienced, HIV-1-infected patients aged 3 to <6 years[1]

1. Kakuda TN, et al. IWCPHIV 2013; Abstract O_13

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