Efficacy and Safety of Doravirine in Treatment-Naïve Adults ≥50 Years Old With HIV-1

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Background

- Nearly 50% of people living with HIV in the US are ≥50 years old; however, this age group is often under-represented in clinical trials
  - More likely to have late-stage HIV infection at diagnosis
  - Greater risk for cardiovascular disease and certain cancers
  - Concurrent medications for common age-related conditions
- Doravirine (DOR)[1] is a next-generation NNRTI approved for the treatment of HIV-1
  - Potent in vitro activity against wild-type HIV-1 and the most common NNRTI-resistant variants (K103N, Y181C, K103N/Y181C, G190A, and E138K)
  - Taken once daily without regard to food
  - Low potential for drug-drug interactions, including with acid-reducing agents
  - Available as a single-entity tablet (DOR 100 mg) and a fixed-dose combination tablet with lamivudine (3TC) 300 mg and tenofovir disoproxil fumarate (TDF) 300 mg (DOR/3TC/TDF)
- DOR has demonstrated efficacy and safety in adults with HIV-1
  - Treatment-naïve studies: Noninferior efficacy and superior lipid profile vs ritonavir-boosted darunavir (DRV/r)[2]; noninferior efficacy, superior CNS safety, and favorable lipid profile vs EFV/FTC/TDF[3]
  - Switch study: DOR/3TC/TDF maintained virologic suppression for up to 48 weeks after switch from a boosted PI, boosted elvitegravir, or another NNRTI[4]

Objective

- To compare the Week 96 efficacy and safety results in treatment-naïve adults who were ≥50 years old with those who were <50 years old using data from the DOR Phase 2 and Phase 3 clinical trials

Methods

Study Design

- Post-hoc analysis of 3 multicenter, double-blind, randomized, active-controlled trials
  - MK-1439A Protocol 007 (Phase 2b): DOR (25-100 mg) vs EFV (600 mg), each given with FTC/TDF
  - DRIVE-FORWARD (Phase 3): DOR (100 mg) vs DRV/r (800/100 mg), each given with FTC/TDF or ABC/3TC
  - DRIVE-AHEAD (Phase 3): Fixed-combination DOR/3TC/TDF vs EFV/FTC/TDF
- Study population: Antiretroviral-naïve adults with HIV-1 RNA ≥1000 copies/mL and no genotypic resistance to any study drugs

Statistical Methods

- Double-blind data through study Week 96 were combined by treatment group
  - DOR group: Participants who received DOR 100 mg with 2 NRTIs (in P007 or DRIVE-FORWARD) or DOR/3TC/TDF (in DRIVE-AHEAD)
  - DRV/r group: Participants who received DRV/r with 2 NRTIs (in DRIVE-FORWARD)
  - EFV group: Participants who received EFV 600 mg with FTC/TDF (in P007) or EFV/FTC/TDF (in DRIVE-AHEAD)
- Efficacy analyses were based on the full analysis sets from DRIVE-FORWARD and DRIVE-AHEAD, consisting of all participants who received at least 1 dose of study drug and had baseline data available
  - Efficacy data from P007 were excluded due to differences in entry criteria (CD4+ T-cell count ≥100 cells/mm^3 was required) and study design (virologic failure did not require treatment discontinuation)
- Missing efficacy data were handled with the observed failure (OF) approach
  - Baseline values were carried forward for participants who discontinued therapy due to lack of efficacy
  - Participants with other reasons for missing data were excluded from the analyses
- Safety analyses were based on the all-subjects-as-treated population from P007, DRIVE-FORWARD, and DRIVE-AHEAD, consisting of all randomized participants who received at least 1 dose of study drug
- Summary statistics with 95% confidence interval (CI) were calculated

Results

Study Participants

- Of 1,710 participants, 187 (11%) were 50 to 70 years of age (median 54) at study entry
- Baseline characteristics for participants <50 years of age and those ≥50 years of age are shown in **Table 1**
- The older cohort included more women, more participants with AIDS, and fewer Hispanic or Latino participants
- Baseline CD4+ T-cell counts were lower in the older participants, and baseline HIV-1 RNA was similar between the age cohorts
- Other medical conditions were more prevalent in older participants (**Table 2**)
- Use of analgesics and acid-modifying agents was higher in older participants (**Table 2**)

Reasons for Discontinuation

- The overall discontinuation rate was lower in older vs younger participants in the DOR group (14.7% vs 21.7%) and the EFV group (15.0% vs 24.4%)
- Discontinuation due to any adverse event was slightly higher in older participants in all treatment groups (DOR 3.9% vs 2.4%, DRV/r 6.5% vs 3.3%, EFV 10.0% vs 7.6%)
- Discontinuation due to lack of efficacy was lower in older participants in all treatment groups (DOR 1.0% vs 6.7%, DRV/r 4.3% vs 8.9%, EFV 0.0% vs 5.5%)

Table 1. Demographic and Other Baseline Characteristics

	Age <50 Years			Age ≥50 Years		
	DOR	DRV/r	EFV	DOR	DRV/r	EFV
	N=754	N=337	N=432	N=101	N=46	N=40
Age (years)						
Median (range)	31.0 (18, 49)	32.0 (18, 49)	30.0 (18, 49)	54.0 (50, 70)	55.0 (50, 69)	52.5 (50, 69)
Sex (%)						
Male	85.1	86.6	88.7	80.2	73.9	72.5
Female	14.9	13.4	11.3	19.8	26.1	27.5
Race (%)						
White	62.7	72.4	55.3	68.3	78.3	45.0
Black	19.5	23.7	16.2	22.8	17.4	37.5
Asian	9.2	1.8	15.0	2.0	2.2	5.0
Other	8.6	1.8	13.5	6.0	2.2	12.5
Ethnicity (%)						
Hispanic or Latino	28.5	24.0	29.9	18.8	10.9	17.5
Baseline weight (kg)						
Median (range)	72.1 (37, 227)	72.0 (43, 144)	74.3 (44, 136)	76.8 (48, 123)	79.2 (48, 116)	77.1 (37, 121)
Baseline CD4 cell count (cells/mm^3)						
Median (range)	415.5 (19, 1822)	400.0 (19, 1303)	394.5 (19, 1452)	354.0 (20, 1399)	363.5 (28, 1195)	379.0 (44, 906)
Baseline CD4 cell count (%)						
≤50 cells/mm^3	1.6	4.7	1.6	3.0	6.5	7.5
>50 and ≤200 cells/mm^3	8.6	11.9	10.2	12.9	17.4	5.0
>200 cells/mm^3	89.8	83.4	88.2	84.2	76.1	87.5
Baseline plasma HIV-1 RNA (log_{10} copies/mL)						
Median (range)	4.4 (2.0, 6.5)	4.4 (2.4, 6.5)	4.5 (2.7, 6.4)	4.4 (2.8, 5.8)	4.3 (3.0, 5.6)	4.5 (2.6, 6.7)
Baseline plasma HIV-1 RNA (%)						
>100,000 c/mL	22.5	19.0	24.1	20.8	19.6	25.0
>500,000 c/mL	4.4	3.6	5.6	5.0	0.0	5.0
History of AIDS (%)						
Yes	9.3	8.6	12.0	15.8	17.4	20.0
Viral subtype (%)						
Clade B	66.2	70.6	72.2	73.3	73.9	67.5

Very few participants were 65 years or older (5 in the DOR group, 4 in the DRV/r group, and 2 in the EFV group).

Table 2. Other Medical Conditions and Concurrent Medications (incidence >30%)

	Age <50 Years			Age ≥50 Years		
	DOR	DRV/r	EFV	DOR	DRV/r	EFV
% of participants with:	N=754	N=337	N=432	N=101	N=46	N=40
Gastrointestinal disorders	23.9	27.6	24.8	30.7	41.3	45.0
Metabolism/nutrition disorders	13.9	16.0	14.6	29.7	17.4	35.0
Musculoskeletal disorders	11.8	12.5	11.8	35.6	32.6	17.5
Vascular disorders	8.0	7.4	6.5	37.6	23.9	32.5
Hypertension	6.8	5.6	4.6	33.7	23.9	32.5
Antibacterial agents	48.8	50.4	52.8	51.5	37.0	37.5
Analgesics	39.8	34.7	36.3	46.5	41.3	62.5
Anti-inflammatory agents	28.9	27.6	27.3	26.7	26.1	35.0
Antihistamines	18.8	20.5	26.2	22.8	6.5	32.5
Acid-modifying agents	11.8	11.9	11.8	19.8	21.7	35.0

References

1. Pham HT, et al. *Drugs Context.* 2020;9:2019-11-4.
2. Molina JM, et al. *Lancet HIV.* 2018;5(5):e211-e220.
3. Orkin C, et al. *Clin Infect Dis.* 2019;68(4):535-544.
4. Johnson M, et al. *J Acquir Immune Defic Syndr.* 2019;81(4):463-472.

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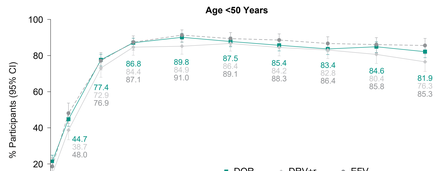
Efficacy Outcomes

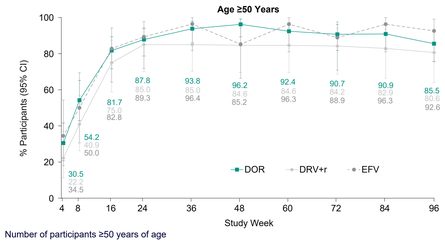
- At Week 96, the proportion of participants with HIV-1 RNA <50 copies/mL tended to be higher for older participants compared with younger participants (**Figure 1**) in all treatment groups (DOR, 85.5% vs 81.9%; DRV/r, 80.6% vs 76.3%; EFV, 92.6% vs 85.3%)
- At Week 96, the mean change in CD4+ T-cell count (**Figure 2**) was similar for older and younger participants in the DOR group (234.6 vs 230.4 cells/mm^3) and the DRV/r group (194.7 vs 208.2 cells/mm^3) but was lower for older participants in the EFV group (165.0 vs 228.5 cells/mm^3)

Figure 1. HIV-1 RNA <50 Copies/mL (Observed Failure Approach)



Number of participants <50 years of age

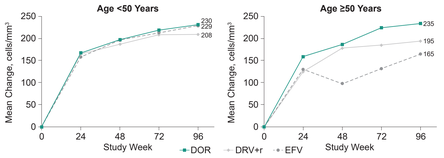
DOR	655	656	650	651	644	631	622	610	609	603
DRV/r	332	331	329	326	324	317	310	303	296	287
EFV	327	319	316	310	310	304	300	294	288	285



Number of participants ≥50 years of age

DOR	82	83	82	82	80	79	79	75	77	76
DRV/r	45	44	40	40	40	39	39	38	35	36
EFV	29	28	29	28	28	27	27	27	27	27

Figure 2. CD4+ T-cell Count, Change from Baseline (Observed Failure Approach)



Adverse Events

- The incidence of drug-related AEs was similar for older and younger participants in all treatment groups (**Table 3**)
- Serious AEs were more common in the older cohort but were classified as drug-related in only one older participant (in the EFV group)
- Discontinuations due to any AE were slightly higher in older vs younger participants in all treatment groups
- Discontinuations due to drug-related AEs were similar between age cohorts in the DOR group and were slightly higher for older participants in the DRV and EFV groups
- The most common adverse events in the DOR group were similar between older and younger participants (**Table 4**), with a slightly higher rate of diarrhea in those ≥50 years old (25.7%) vs <50 years old (13.7%)
- The most common drug-related adverse events in the DOR group were nausea (5.9%) and diarrhea (5.9%) in adults ≥50 years old and nausea (6.2%) and dizziness (5.6%) in those <50 years old (**Table 5**)

Table 3. Summary of Adverse Events (AE) Through Week 96

	Age <50 Years			Age ≥50 Years		
	DOR	DRV/r	EFV	DOR	DRV/r	EFV
% of participants with:	N=754	N=337	N=432	N=101	N=46	N=40
Any AE	86.3	84.3	94.2	90.1	71.7	90.0
Drug-related[a] AE	32.1	32.3	64.6	34.7	30.4	50.0
Serious AE	5.7	6.8	7.9	15.8	21.7	22.5
Serious drug-related AE	0.3	0.3	1.4	0.0	0.0	2.5
Discontinued[b] due to any AE	2.4	3.0	7.6	4.0	6.5	12.5
Discontinued due to drug-related AE	1.9	1.8	6.9	1.0	4.3	10.0
Discontinued due to serious AE	0.4	0.6	1.2	2.0	2.2	0.0

[a]Determined by the investigator to be related to study therapy
[b]Study medication withdrawn

Table 4. Most Common Adverse Events (>10% incidence) Through Week 96

	Age <50 Years			Age ≥50 Years		
	DOR	DRV/r	EFV	DOR	DRV/r	EFV
% of participants with:	N=754	N=337	N=432	N=101	N=46	N=40
Abnormal dreams	3.4	0.6	13.7	4.0	2.2	10.0
Arthralgia	3.4	3.0	2.1	7.9	4.3	12.5
Diarrhea	**13.7**	24.9	15.5	**25.7**	15.2	22.5
Dizziness	9.0	5.0	37.0	5.0	4.3	27.5
Headache	15.3	13.1	14.6	12.9	4.3	20.0
Nasopharyngitis	12.7	13.9	12.0	18.8	10.9	10.0
Nausea	10.2	13.9	10.9	11.9	10.9	15.0
Pharyngitis	5.7	3.9	4.2	4.0	2.2	12.5
Rash	3.6	1.2	12.5	3.0	2.2	0.0
Upper respiratory infection	11.8	8.6	8.3	12.9	2.2	15.0

Table 5. Most Common Drug-Related[a] Adverse Events (>5% incidence) Through Week 96

	Age <50 Years			Age ≥50 Years		
	DOR	DRV/r	EFV	DOR	DRV/r	EFV
% of participants with:	N=754	N=337	N=432	N=101	N=46	N=40
Abnormal dreams	3.2	0.3	11.3	4.0	0.0	10.0
Diarrhea	4.0	13.1	6.3	**5.9**	13.0	2.5
Dizziness	**5.6**	1.8	31.9	2.0	2.2	20.0
Headache	4.9	3.0	4.6	3.0	0.0	7.5
Nausea	**6.2**	8.3	6.7	**5.9**	6.5	7.5
Nightmare	1.9	0.6	5.3	2.0	2.2	2.5
Rash	1.1	0.3	7.9	0.0	2.2	0.0
Somnolence	1.6	0.0	5.3	0.0	2.2	7.5

[a]Determined by the investigator to be related to study therapy

Other Safety Outcomes

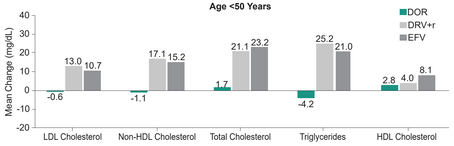
- Grade 3 increase in serum creatinine was more common in older adults receiving DOR or EFV-based regimens (**Table 7**). Grade 4 increase in lipase was more common in older adults receiving a DOR regimen. Other laboratory abnormalities were infrequent among older adults receiving a DOR regimen
- Mean changes in fasting lipid values from baseline to Week 96 were minimal in older and younger adults who received a DOR regimen (**Figure 3**)
- Mean weight gain at Week 48 and Week 96 was similar for older and younger adults in the DOR treatment group (**Figure 4**)

Table 6. Grade 3 or 4 Laboratory Values Through Week 96 (incidence ≥3%)

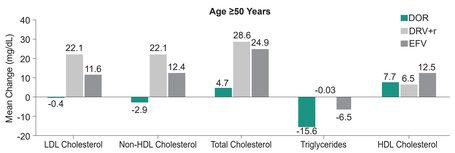
	Age <50 Years			Age ≥50 Years		
	DOR	DRV/r	EFV	DOR	DRV/r	EFV
% of participants	N=754	N=337	N=432	N=101	N=46	N=40
LDL cholesterol, grade 3	0.3	3.9	1.6	0.0	2.9	3.1
Triglycerides, grade 3	0.6	1.0	2.6	1.1	0.0	5.7
Creatinine, grade 3	2.3	3.9	0.7	**5.9**	4.3	**5.1**
Lipase, grade 3	1.9	2.4	3.0	2.0	4.3	0.0
Lipase, grade 4	0.7	1.2	1.2	**4.0**	0.0	0.0
Creatine kinase, grade 3	3.2	4.5	3.6	1.0	0.0	0.0
Creatine kinase, grade 4	2.0	2.1	3.0	0.0	2.2	0.0

Only subjects with a worsened grade from baseline were included; events with highest grade were counted.

Figure 3. Fasting Lipids, Change from Baseline at Week 96

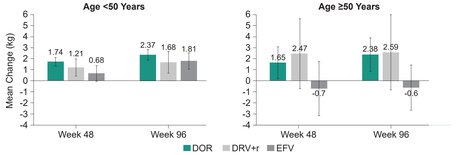


- Mean change in total cholesterol/HDL ratio: -0.13 for DOR, +0.11 for DRV/r, -0.07 for EFV



- Mean change in total cholesterol/HDL ratio: -0.35 for DOR, +0.03 for DRV/r, -0.52 for EFV

Figure 4. Weight Change From Baseline at Weeks 48 and 96, Mean (95% CI)



- Median values for weight gain also were similar for older and younger adults receiving DOR: 1.0 kg (IQR, -1.3 to 3.8) vs 1.0 kg (IQR, -1.2 to 4.0) at Week 48 and 1.5 kg (-1.6 to 4.0) vs 1.5 kg (-1.0 to 5.0) at Week 96

Conclusions

- Virologic response rates in adults ≥50 years of age were comparable across regimens and similar to response rates in adults <50 years of age
- Mean increase in CD4 T-cell count in older adults receiving DOR was similar to younger adults and higher than in the comparator groups
- Incidence of drug-related AEs and discontinuations due to drug-related AEs in older adults in the DOR group were similar to those in younger adults and lower than those in the EFV group
- Changes in fasting lipids and changes in weight through 96 weeks of treatment were similar for older and younger adults receiving DOR-based regimens
- DOR appears to be a useful treatment option for adults ≥50 years old, demonstrating a similar efficacy and safety profile compared with younger adults, a neutral lipid profile, and minimal effect on weight

https://bit.ly/315fBoB

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