Analysis of HIV Patients Switching to D/C/F/TAF by Prior ARV Treatment Experience

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INTRODUCTION

- Oral, once-daily (QD) darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg is a single-tablet regimen approved for the treatment of human immunodeficiency virus (HIV)–1 infection in Europe and under regulatory review in the United States (US)[1,2]
  - Darunavir (DRV) has demonstrated a high barrier to the development of resistance (reconfirmed most recently in an analysis of 7 clinical trials of DRV 800 mg QD with study durations of up to 192 weeks[3])
- In the phase 3, 48-week EMERALD trial, treatment-experienced, virologically suppressed patients who switched to D/C/F/TAF had noninferior cumulative virologic rebound compared with patients who continued use of a boosted protease inhibitor (bPI) + emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF; primary endpoint)[2]
- Due to treatment-emergent drug resistance, switching stably suppressed, HIV-1–infected individuals with a history of prior virologic failure (VF) and prior experience with multiple antiretrovirals (ARVs) should be done with caution[4]
  - Inclusion/exclusion criteria are typically strict for patients enrolled in randomized, controlled switch studies, resulting in study populations that may not be representative of switch patients in clinical practice
- Compared with other recent switch studies,[3,7] EMERALD had relatively less strict enrollment criteria for treatment experience[2]

OBJECTIVE

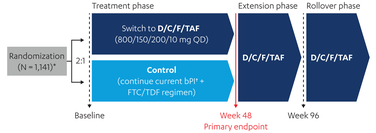
- To evaluate the efficacy, resistance, and safety of D/C/F/TAF in the EMERALD trial of treatment-experienced, virologically suppressed patients across subgroups based on prior VF and number of prior ARVs used

METHODS

Study Design

- The phase 3, randomized, noninferiority EMERALD trial enrolled treatment-experienced, virologically suppressed adults with HIV-1 infection (**Figure 1**)[2]

Figure 1. EMERALD study design.



Key inclusion criteria
- HIV-1 RNA <50 copies/mL or undetectable HIV-1 RNA 12 to 2 months prior to screening (one blip 50< VL <200 copies/mL within 12 months prior to screening was allowed)
- **Prior experience with multiple ARVs was allowed** and ≥6 months of a stable ARV regimen consisting of a bPI† + FTC/TDF prior to screening was required
- **A history of prior VF on non-DRV ARV regimens was allowed (no restriction on the number of prior VFs)**
- If historical genotype was available, an absence of DRV RAMs‡ was required (importantly, there was no restriction on FTC or TFV RAMs). If no historical genotype was available, the patient could be included (provided no documented prior VF on DRV treatment)
- eGFR ≤50 mL/min

VL, viral load; RAM, resistance-associated mutation; TFV, tenofovir; eGFR, estimated glomerular filtration rate; rtv, ritonavir; COBI, cobicistat; ATV, atazanavir; LPV, lopinavir; IAS-USA, International Antiviral Society–USA.
*Stratified by bPI (PI boosted with low-dose rtv or COBI) at screening.
†SPI was ATV with rtv or COBI, DRV with rtv or COBI, or LPV with rtv.
‡IAS-USA DRV RAMs.

Analyses

- EMERALD primary endpoint: proportion of patients with cumulative virologic rebound through Week 48
  - Virologic rebound was defined as confirmed VL ≥50 copies/mL (including premature discontinuation with last single VL ≥50 copies/mL or single VL ≥50 copies/mL at Week 48)
- Efficacy was assessed by virologic response, defined as VL <50 copies/mL (US Food and Drug Administration [FDA] snapshot)
- The difference (95% confidence interval [CI]) between the D/C/F/TAF and control groups for virologic rebound and virologic response was calculated as follows:
  - Overall population: Mantel-Haenszel test adjusted for bPI at screening (ATV with rtv or COBI, DRV with rtv or COBI, LPV with rtv)
  - Subgroups: exact CIs
- Post-baseline genotyping was performed in rebounders (VL ≥50 copies/mL) who also had a VL measurement ≥400 copies/mL at the time of VF, at later time points, or at discontinuation
- Safety was assessed by adverse events (AEs) from baseline through Week 48
- Subgroup analyses were performed in the intention-to-treat population (all randomized patients who received ≥1 dose of study drug)
- Results were evaluated in subgroups by prior VF (0 vs ≥1) and number of prior ARVs used (including ARVs used at screening [ie, PI + booster + FTC/TDF]; 4 vs 5 vs 6 vs 7 vs >7)

RESULTS

Patient Population

- Overall, baseline demographic characteristics were generally similar in the D/C/F/TAF and control groups (**Table 1**)
- Including their ARV regimen at screening, 476 (42%) patients had used 4 ARVs, 154 (13%) had used 5 ARVs, 99 (9%) had used 6 ARVs, 99 (9%) had used 7 ARVs, and 312 (27%) had used >7 ARVs (**Table 1**)
  - Overall, prior to their ARV regimen at screening, 477 (42%) patients had never taken an ARV and 664 (58%) had prior exposure to ARVs
  - 472 (41%) patients had used ≥1 PI prior to their screening ARV regimen, 474 (42%) had used ≥1 nucleos(t)ide reverse transcriptase inhibitor, and 340 (30%) had used ≥1 nonnucleoside reverse transcriptase inhibitor
    - There were no relevant differences in prior ARV use between treatment arms
    - The most common reasons for discontinuation of prior ARVs were convenience (n = 377 [33%]) and AEs (n = 335 [29%])
      - 169 (15%) patients discontinued prior ARVs due to VF
      - 80 (7%) patients discontinued a PI due to VF
- Relative to patients in other subgroups, patients with ≥1 prior VF or a higher number of prior ARVs used tended to have a longer median time since diagnosis and median time since first ARV therapy (**Table 1**)

Efficacy

- Overall, cumulative virologic rebound rates were similar in the D/C/F/TAF (19/763 patients [2.5%]) and control (8/378 [2.1%]) arms, and results were consistent across subgroups based on prior VF and number of prior ARVs used (**Figure 2**)
  - Rebound rates were lower using a VL cutoff of ≥200 copies/mL in both the D/C/F/TAF (3/763 [0.4%]) and control (0/378 [0.0%]) arms
- Prior VF or number of prior ARVs used did not impact the efficacy of D/C/F/TAF (**Figure 3**)

Table 1. Baseline Demographic and Clinical Characteristics (Overall Population)

Parameter	D/C/F/TAF (N = 763)	Control (N = 378)
Demographic characteristics		
Age, median (range), y	46 (19-75)	45 (20-78)
Female, n (%)	140 (18)	65 (17)
Race, n (%)*		
White	573 (75)	282 (75)
Black or African American	155 (20)	82 (22)
Other	35 (5)	14 (4)
Clinical characteristics		
CD4+ cell count, median (range), cells/µL	630 (111-1,921)	624 (131-1,764)
Prior VF, n (%)		
0	647 (85)	325 (86)
≥1	116 (15)	53 (14)
Number of prior ARVs used, n (%)†		
4‡	316 (41)	160 (42)
5	98 (13)	56 (15)
6	69 (9)	30 (8)
7	69 (9)	30 (8)
>7	211 (28)	101 (27)
Time since diagnosis, median (range), y	9.34 (0.6-35.0)	8.94 (0.6-32.6)
Patients with 0 prior VFs	7.78 (0.6-33.9)	7.48 (0.6-32.6)
Patients with ≥1 prior VF	17.96 (3.6-35.0)	18.12 (1.8-31.0)
Patients with 4 prior ARVs used‡	4.46 (0.6-29.8)	4.35 (0.6-27.7)
Patients with >7 prior ARVs used	19.75 (3.9-33.9)	18.96 (3.7-31.6)
Time since first ARV therapy, median (range), y	6.23 (0.6-32.9)	5.75 (0.6-27.5)§
Patients with 0 prior VFs	5.20 (0.6-32.9)	4.66 (0.6-26.7)
Patients with ≥1 prior VF	16.00 (3.3-24.4)	14.78 (1.7-27.5)
Patients with 4 prior ARVs used‡	3.51 (0.6-24.6)	3.49 (0.6-15.9)
Patients with >7 prior ARVs used	17.28 (3.2-32.9)	16.51 (2.9-27.5)

*Percentages may not total 100% due to rounding.
†Includes ARVs used at screening and boosting agents. One (<1%) patient was included in the study, despite having only 3 prior ARVs used, due to a data recording error; this patient was in the control arm and was excluded from the subgroup analyses.
‡ARV regimen used at screening (bPI + FTC/TDF).
§n = 377.

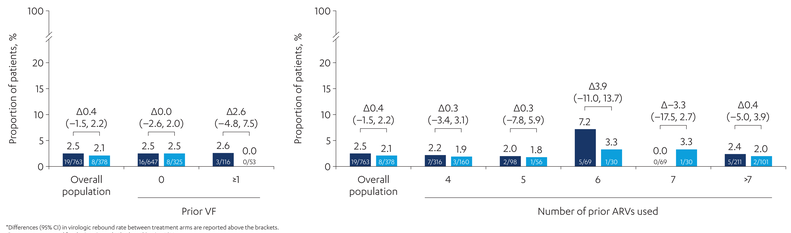
Resistance

- Post-baseline genotypes were available for 4 rebounders (1 in the D/C/F/TAF arm and 3 in the control arm)
  - The D/C/F/TAF patient had used 8 prior ARVs (no prior VF)
  - Two control patients had used 4 prior ARVs, and 1 control patient had used 6 prior ARVs (none of the 3 patients had prior VF)
- No DRV, primary PI, FTC, or TFV RAMs were observed in any arm across subgroups[2]

Safety

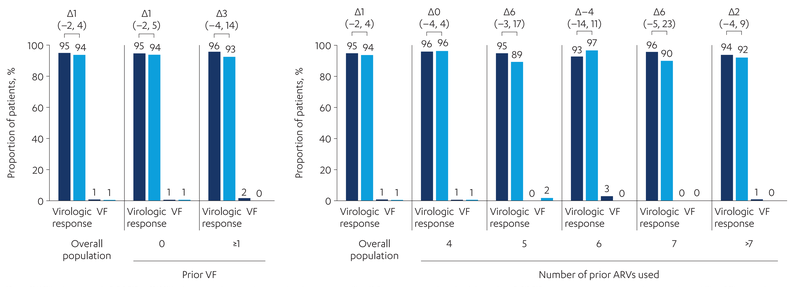
- The overall incidence of AEs was generally similar for the D/C/F/TAF and control arms in the overall population and across subgroups (**Tables 2** and **3**)
- Rates of discontinuation due to AEs and serious AEs were low in the D/C/F/TAF and control arms, overall and across subgroups

Figure 2. Cumulative virologic rebound through Week 48.*



*Differences (95% CI) in virologic rebound rate between treatment arms are reported above the brackets.
†Data are not reported for the 1 patient who had used 3 prior ARVs.

Figure 3. Virologic response and VF at Week 48 (FDA snapshot).*,†



*Overall, 33 (4.3%) patients treated with D/C/F/TAF and 22 (5.8%) patients treated with control did not have virologic response data at Week 48. For each subgroup, patients with missing data in the D/C/F/TAF and control treatment groups, respectively, were as follows: 4.6% and 5.5% of those with 0 prior VFs, 2.6% and 7.5% of those with ≥1 prior VF, 3.5% and 3.3% of those who used 4 prior ARVs, 5.1% and 8.9% of those who used 5 prior ARVs, 4.3% and 13.3% of those who used 6 prior ARVs, 4.3% and 10.0% of those who used 7 prior ARVs, and 5.2% and 7.9% of those who used >7 prior ARVs.
†Differences (95% CI) in virologic response rate between treatment arms are reported above the brackets.
‡Data are not reported for the 1 patient who had used 3 prior ARVs.

Table 2. Incidence (%) of AEs Through Week 48 by Prior VF

	Overall population		Prior VF: 0		Prior VF: ≥1	
Parameter, %	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control
n	763	378	647	325	116	53
≥1 AE	82	82	82	82	82	83
Discontinued due to an AE	1	1	1	1	2	4
≥1 grade 3-4 AE	7	8	7	7	6	13
≥1 serious AE	5	5	4	4	6	8

Table 3. Incidence (%) of AEs Through Week 48 by Number of Prior ARVs Used

	Overall population		Number of prior ARVs used: 4		5		6		7		>7	
Parameter, %	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control	D/C/F/TAF	Control
n	763	378	316	160	98	56	69	30	69	30	211	101
≥1 AE	82	82	85	84	82	71	73	93	74	80	83	83
Discontinued due to an AE	1	1	1	1	1	2	1	0	0	3	2	2
≥1 grade 3-4 AE	7	8	8	9	2	7	4	10	6	10	9	7
≥1 serious AE	5	5	5	4	2	7	0	7	4	7	7	4

CONCLUSIONS

- **In EMERALD, virologically suppressed adults with HIV-1 infection who switched to D/C/F/TAF had low cumulative virologic rebound and high virologic response rates over 48 weeks; results were consistent regardless of prior VF and prior experience with multiple ARVs**
- **No resistance to any study drug was observed, consistent with the high barrier to resistance of DRV**
- **D/C/F/TAF was associated with a favorable safety profile similar to that of the control arm in the overall population and across subgroups**
- **Switching to D/C/F/TAF may be an effective strategy for stably suppressed individuals who would like to simplify therapy, including patients with a history of prior VF or prior experience with multiple ARVs (without history of DRV RAMs or VF on a DRV-based regimen)**

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DISCLOSURES

J.J. Eron, C. Orkin, and J.-M. Molina contributed to the conduct of the study as investigators and interpretation of the data. E. Van Landuyt, E. Lathouwers, R.E. Nettles, and K. Brown contributed to the design of the study and interpretation of the data. R. Petrovic contributed to statistical analysis and interpretation of the data. All authors contributed to drafting the poster and approved the final version.

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