Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) in a Test-and-Treat Model of Care for HIV-1 Infection: Interim Analysis of the DIAMOND Study

Gregory D. Huhn,[1,*] Gordon Crofoot,[2] Moti Ramgopal,[3] Joseph Gathe Jr,[4] Robert Bolan,[5] Ceyhun Bicer,[6] Richard Bruce Simonson,[7] Richard E. Nettles,[7] Keith Dunn[7]

*Presenting author.

[1]The Ruth M. Rothstein CORE Center, Chicago, IL, USA; [2]Crofoot Research Center, Houston, TX, USA; [3]Midway Immunology and Research Center, Fort Pierce, FL, USA; [4]Therapeutic Concepts, Houston, TX, USA; [5]Los Angeles LGBT Center, Los Angeles, CA, USA; [6]BICER Consulting & Research, Antwerp, Belgium; [7]Janssen Scientific Affairs, LLC, Titusville, NJ, USA.

INTRODUCTION

- Since 2012, the US Department of Health and Human Services (DHHS) guidelines have recommended initiation of antiretroviral therapy (ART) in newly diagnosed patients with human immunodeficiency virus (HIV)–1 infection regardless of CD4+ cell count to reduce the risk of acquired immunodeficiency syndrome (AIDS)–related and non–AIDS-related events and transmission to uninfected individuals[1]
  - Yet, in 2015, only 63% of patients with HIV-1 in the US were on treatment and 51% of patients were virologically suppressed[2]
- US DHHS guidelines recommend that certain laboratory testing be performed prior to starting ART to help guide initial treatment selection; however, certain tests (eg, genotypic resistance testing, testing for HLA-B*5701) may require several days or weeks for results, contributing to poor retention rates and delayed initiation of ART[1]
- In rapid initiation models of care, therapy is started (sometimes on the same day as diagnosis) prior to the availability of baseline laboratory assessments; recently, these models have shown benefits in retention in care, morbidity, mortality, and time to virologic suppression[3-5]
- The World Health Organization recommends rapid initiation of treatment for all patients newly diagnosed with HIV-1 infection[6]; although the US DHHS considers this investigational given that most supporting evidence has been generated outside the US, its guidelines recognize the importance of prompt ART initiation for some patients[1]
- Healthcare providers have less clinical information available in a rapid initiation model of care, so it is important to consider a regimen's effectiveness in the setting of possible transmitted drug resistance, its safety profile, and the patient's ability to adhere to the regimen
  - An optimal ART regimen for use in this setting should have a high barrier to resistance, be a single-tablet regimen (STR), and be abacavir-sparing
- Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg is an oral, once-daily STR approved for the treatment of naïve and experienced, suppressed patients with HIV-1 infection in Europe, Canada, and the US
  - In the phase 3 AMBER study of treatment-naïve patients, D/C/F/TAF was noninferior to control for virologic response (US Food and Drug Administration [FDA] snapshot) at Week 48 (91.4% and 88.4%, respectively)[7]
  - In the phase 3 EMERALD study of treatment-experienced, virologically suppressed patients, D/C/F/TAF was noninferior to control for cumulative virologic rebound through Week 48 (2.5% and 2.1%, respectively); by FDA snapshot, virologic response rates were 94.9% and 93.7%, and virologic failure (VF) rates were 0.8% and 0.5% with D/C/F/TAF and control, respectively[8]
  - In both studies, D/C/F/TAF was well tolerated with an improved renal/bone safety profile versus control[7,8]
- Darunavir has demonstrated a high barrier to resistance and is recommended in US DHHS guidelines as an initial ARV therapy in cases in which resistance testing records are unavailable, or when ART needs to be started prior to availability of resistance testing results[1,9]
- We evaluated the efficacy and safety of D/C/F/TAF in a rapid initiation model of care for HIV-1 infection in the DIAMOND study; interim results through Week 24 are reported here

OBJECTIVES

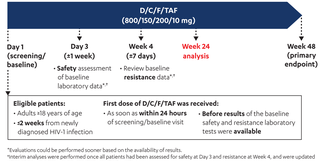
- To assess the efficacy and safety of D/C/F/TAF in a rapid initiation model of care in newly diagnosed, HIV-1–infected, treatment-naïve patients
- To assess baseline viral resistance in the study population
- To assess HIV Treatment Satisfaction Questionnaire status version (HIVTSQs) results at Weeks 4 and 24

METHODS

Study Design

- DIAMOND (ClinicalTrials.gov: NCT03227861) is an ongoing, phase 3, single-arm, open-label, prospective, multicenter study evaluating D/C/F/TAF in a rapid initiation model of care over 48 weeks (**Figure 1**)
- Key inclusion criteria
  - Adults ≥18 years of age, newly diagnosed with HIV-1 within 2 weeks of the screening/baseline visit
  - ART-naïve, except for use of emtricitabine/tenofovir disoproxil fumarate for pre-exposure prophylaxis
- Key exclusion criteria
  - Known active cryptococcal infection, active toxoplasmic encephalitis, *Mycobacterium tuberculosis* infection, or another AIDS-defining condition that in the investigator's judgement would increase morbidity/mortality risk
  - Known history of clinically relevant hepatic disease or hepatitis that in the investigator's judgement is not compatible with D/C/F/TAF; cirrhosis; or chronic (≥3 months) renal insufficiency, defined as estimated glomerular filtration rate (eGFR; according to the *Modification of Diet in Renal Disease* [MDRD] formula) <50 mL/min
- Eligible patients were immediately enrolled and started on D/C/F/TAF without screening/baseline laboratory information
- Investigators reviewed screening/baseline laboratory findings as results became available; patients not meeting pre-defined safety or resistance stopping rules continued treatment
  - Screening/baseline safety laboratory findings were evaluated on Day 3 (±1 week), with the following stopping criteria (retesting of abnormal screening/baseline safety laboratory values was allowed once):
    - eGFR (MDRD formula) <50 mL/min
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 times the upper limit of normal (ULN)
    - Serum lipase ≥1.5 times the ULN
    - Positive pregnancy test for women of childbearing potential
    - Laboratory results that the investigator believes should result in discontinuation of study medication
    - Active hepatitis C infection that, in the opinion of the investigator, requires immediate treatment or is expected to require treatment during the study with agents not compatible with D/C/F/TAF
  - Resistance was evaluated at Week 4 (±7 days) based on predicted genotypic sensitivity (assessed using GenoSure Prime®; there was no exclusion based on the presence of specific resistance-associated mutations [RAMs]). Patients who did not show full genotypic sensitivity to all D/C/F/TAF components were required to stop; an exception was resistance to lamivudine/emtricitabine associated with the M184I or M184V mutation alone

Figure 1. DIAMOND study design.



*Evaluations could be performed sooner based on the availability of results.
†Interim analyses were performed once all patients had been assessed for safety at Day 3 and resistance at Week 4, and were updated when all patients continuing treatment reached Week 24.

Analyses

- The primary endpoint in DIAMOND is the proportion of patients with virologic response at Week 48, defined as HIV-1 RNA <50 copies/mL (FDA snapshot); in this interim analysis, virologic response (same definition) at Week 24 was evaluated
- Efficacy was also assessed by the proportion of patients with HIV-1 RNA <200 copies/mL (FDA snapshot) and virologic response (HIV-1 RNA <50 or <200 copies/mL) using the observed algorithm at Week 24
- Change in $\log_{10}$ HIV-1 RNA levels from screening/baseline and absolute CD4+ cell count at screening/baseline and Week 24 were also described
- Resistance testing at screening/baseline was performed using the GenoSure Prime® assay
- Post-baseline samples were eligible for resistance testing using the Phenosense® GT assay in patients with protocol-defined VF (PDVF), defined as one of the following:
  - Virologic nonresponse: HIV-1 RNA <1 $\log_{10}$ reduction from baseline and ≥400 copies/mL at the Week 12 visit (confirmed within 2–4 weeks)
  - Virologic rebound: at any visit, after achieving confirmed suppressive HIV-1 RNA <50 copies/mL, a rebound to ≥50 copies/mL (confirmed within 2–4 weeks) or, at any visit, a >1 $\log_{10}$ increase in HIV-1 RNA from nadir (confirmed within 2–4 weeks)
- Patients who discontinued study treatment after Week 12 for any reason and had HIV-1 RNA ≥400 copies/mL at the last viral load (VL) measurement also underwent genotypic and phenotypic resistance testing
- Safety was assessed by discontinuations due to protocol-defined safety stopping rules, adverse events (AEs), adverse drug reactions (ADRs; defined as AEs at least possibly related to study drug), and laboratory abnormalities
- Patient-reported outcomes (PROs) for treatment satisfaction were evaluated using the HIVTSQs at Weeks 4 and 24

Statistical Analyses

- Analyses were performed on all patients who received ≥1 dose of study drug (intent-to-treat population)
- Observed values were used in descriptive statistics; missing values were not imputed

RESULTS

Patient Population and Disposition

- Overall, 109 patients were enrolled in the study; 13% were women, 32% were black/African American, 23% had HIV-1 RNA >100,000 copies/mL, and 21% had CD4+ cell count <200 cells/mm³ (**Table 1**)
- Notably, the median (range) time from HIV-1 diagnosis to screening/baseline was 5 (0-14) days and 29% of patients were enrolled within 48 hours of diagnosis
- Screening/baseline resistance patterns are summarized in **Table 2**
- As of the Week 24 interim analysis, 99 (91%) patients continued on D/C/F/TAF and only 10 (9%) patients had discontinued (3 due to protocol-defined safety stopping rules, 3 lost to follow-up, 2 withdrawal of consent, 1 protocol violation, 1 AE; **Figure 2**)

Table 1. Baseline Demographic and Clinical Characteristics

	D/C/F/TAF N = 109
Demographic characteristics	
Age, median (range), years	28 (19-66)
Women, n (%)	14 (13)
Race, n (%)	
White	64 (59)
Black/African American	35 (32)
Other	10 (9)
Clinical characteristics	
HIV-1 RNA, *n*	108*
Median (range), $\log_{10}$ copies/mL	4.6 (1.3-8.2)
>100,000 copies/mL, n (%)	25 (23)
CD4+ cell count, n	108*
Median (range), cells/mm³	369 (7-1,082)
<200 cells/mm³, n (%)	23 (21)
Time from diagnosis to screening/baseline, median (range), days	5 (0-14)
Enrolled within 48 hours of diagnosis, n (%)	32 (29)

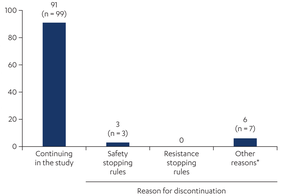
*One patient had missing values due to a shipping error of the screening/baseline samples.

Table 2. Genotype at Screening/Baseline

	D/C/F/TAF n = 102*
Genotypic susceptibility, n (%)	
Darunavir	102 (100)
Emtricitabine	100 (98)
Tenofovir	102 (100)
All PIs	97 (95)
All NRTIs	98 (96)
All NNRTIs	80 (78)
All INIs	97 (95)
≥1 RAM, n (%)	
Primary PI†	5 (5)
Secondary PI	100 (98)
Darunavir	0
Emtricitabine	2 (2)
M184V/I	1 (1)
M184M/V	1 (1)
NNRTI†	28 (28)
K103N	11 (11)
Primary INI	0
Secondary INI	5 (5)
T97T/A	3 (3)
T97A	2 (2)

PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; INI, integrase inhibitor.
*Genotypes were not available for 7 patients due to being unable to amplify (ie, low VL, reduced viral fitness, compromised sample collection/handling, primer incompatibility).
†Three patients had L90M, 1 patient had M46L, and 1 patient had Q58E.
‡Individual NNRTI RAMs are only shown for those occurring in ≥5% of patients.

Figure 2. Patient disposition through Week 24.



*Other reasons were: lost to follow-up (n = 3), withdrawal of consent (n = 2), protocol violation (n = 1), and AE (n = 1).

Safety Stopping Rules

- Five patients met the safety stopping rules criteria; all had confirmed evidence of AST or ALT elevations ≥2.5 times the ULN at the screening/baseline visit (see patient details in **Table 3**)
  - Three of these patients discontinued according to the protocol and the other 2 patients remained in the study based on clinical assessment by the investigator and agreement of the sponsor
  - Transaminases appeared to normalize after screening/baseline in all 5 patients, indicating that treatment may have been beneficial for these patients

Resistance Stopping Rules

- No patients met the resistance stopping rules criteria (**Figure 2**)

Table 3. Clinical Summary of Patients Who Met Safety Stopping Rules Criteria

Patient	Hepatitis serology, –/+				Relevant medical history	Screening/baseline			Post-baseline transaminase laboratory values, U/L
	HCV Ab	HBs Ab	HBc Ab	HBs Ag		Transaminase laboratory values, U/L	CD4+ cell count, cells/mm³	HIV-1 RNA, copies/mL	
1*	–	–	–	–	Alcoholic hepatitis without ascites	Baseline: AST, 114 Day 10 retest: AST, 103	150	34,200	Day 15 ESTD: AST, 69
2*	–	–	–	–	Gastritis, oral thrush	Baseline: AST, 299; ALT, 188 Day 10 retest: AST, 140; ALT, 128	17	445,000	Day 16 ESTD: AST, 112; ALT, 116
3	+	+	+	–	None	Baseline: AST, 171 Retest: AST, 183	151	17,000	Week 4: AST, 69 Week 12: AST, 93 Week 24: AST, 59
4†	–	+	+	–	None	Baseline: AST, 113; ALT, 183 Day 3 retest: AST, 84; ALT, 151	226	311,000	Day 14 ESTD: AST, 53 ALT, 71
5	–	+	+	–	Recent secondary syphilis infection	Baseline: AST, 118; ALT, 146 Retest: AST, 70; ALT, 123	242	144,000,000	Week 2: AST, 15; ALT, 28 Week 4: AST, 14; ALT, 15 Week 8: AST, 17; ALT, 23 Week 12: AST, 18; ALT, 24 Week 24: AST, 14; ALT, 16

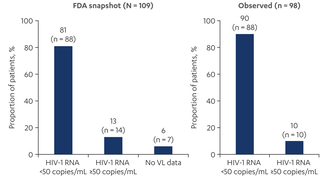
HCV, hepatitis C virus; Ab, antibody; HBs, hepatitis B surface; HBc, hepatitis B core; Ag, antigen; ESTD, early study treatment discontinuation.
*Patient discontinued treatment on Day 15.
†Patient discontinued treatment on Day 15.
‡HCV RNA tested negative.
§Patient discontinued treatment on Day 13.

Efficacy

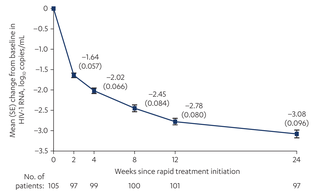
- At Week 24, 88 of 109 (81%) patients had achieved HIV-1 RNA <50 copies/mL (**Figure 3A**) and 95 of 109 (87%) patients had achieved HIV-1 RNA <200 copies/mL (FDA snapshot)
  - Using the observed algorithm, 86 of 98 (90%) patients had achieved HIV-1 RNA <50 copies/mL (**Figure 3A**) and 95 of 98 (97%) patients had achieved HIV-1 RNA <200 copies/mL at Week 24
  - Mean HIV-1 RNA decreased from baseline to Week 24 by 3.08 $\log_{10}$ copies/mL (**Figure 3B**)
- No patients discontinued the study due to lack of efficacy and no patients had PDVF
  - For the 10 patients with HIV-1 RNA >50 copies/mL at Week 24, VLs over time are plotted in **Figure 4**
  - No patients met the criteria for post-baseline resistance testing
- The mean (standard error [SE]) CD4+ cell count was 413 (24) cells/mm³ at screening/baseline and 589 (30) cells/mm³ at Week 24

Figure 3. Virologic efficacy of D/C/F/TAF in a rapid initiation model of care through Week 24.

A. Virologic response at Week 24



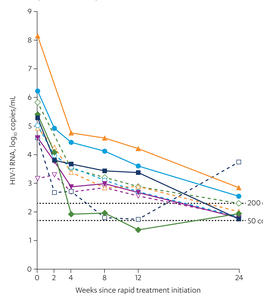
B. Change from baseline in $\log_{10}$ HIV-1 RNA over time (observed)



Safety

- Most AEs were grade 1 or 2; incidences of grade 3 AEs and serious AEs were low, and there were no grade 4 AEs or deaths (**Table 4**)
  - No serious AEs were related to study drug
  - The most common AEs and ADRs are summarized in **Tables 5** and **6**, respectively
  - There were no cases of immune reconstitution inflammatory events
- There were no discontinuations due to central nervous system, gastrointestinal, renal, or bone AEs
  - One patient discontinued due to AEs; this patient had allergic dermatitis (grade 3), pyrexia (grade 2), and lip swelling (grade 2), and all AEs resolved after discontinuation of study treatment
- One grade 3-4 laboratory abnormality occurred in ≤2% of patients (increased AST in 4 [4%] patients)

Figure 4. $\log_{10}$ HIV-1 RNA over time for individual patients with HIV-1 RNA ≤50 copies/mL at Week 24 (observed; n = 10).*



*HIV-1 RNA levels were not available for 2 patients at the Week 2 visit.

7 of 10 patients demonstrated HIV-1 RNA <200 copies/mL at the Week 24 timepoint

Table 4. Summary of AEs

Parameter, n (%)	D/C/F/TAF N = 109	
	Overall	Related
≥1 AE	80 (73)	33 (30)
≥1 serious AE	7 (6)	0
≥1 grade 1 AE	40 (37)	25 (23)
≥1 grade 2 AE	31 (28)	6 (6)
≥1 grade 3 AE*	9 (8)	2 (2)
≥1 grade 4 AE	0	0

*Two grade 3 AEs were considered related to study drug: allergic dermatitis (resolved after discontinuation of study treatment) and nausea (resolved with no changes to study drug dosing).

Table 5. Most Common AEs (≥5% of Patients; All Grades)

Parameter, n (%)	D/C/F/TAF N = 109	
	Overall	Related
Diarrhea	23 (21)	10 (9)
Nausea	17 (16)	13 (12)
Rash*,†	15 (14)	5 (5)
Vomiting	9 (8)	4 (4)
Headache	9 (8)	2 (2)
Pyrexia	8 (7)	1 (1)
Fatigue	6 (6)	3 (3)

*Pooled preferred terms of dermatitis, allergic dermatitis, rash, macular rash, maculo-papular rash, papular rash, and pruritic rash.
†All rash AEs were grade 1 or 2, except for one that was grade 3.

Table 6. Most Common ADRs (≥2% of Patients)

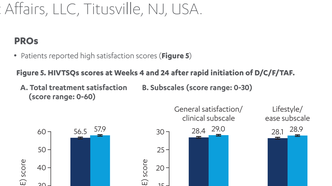
Parameter, n (%)	D/C/F/TAF N = 109	
	Any grade	≥Grade 2
Nausea	13 (12)	2 (2)
Diarrhea	10 (9)	1 (1)
Rash*	5 (5)	4 (4)
Vomiting	4 (4)	0
Fatigue	3 (3)	0

*Pooled preferred terms of dermatitis, allergic dermatitis, rash, macular rash, maculo-papular rash, papular rash, and pruritic rash.

PROs

- Patients reported high satisfaction scores (**Figure 5**)

Figure 5. HIVTSQs scores at Weeks 4 and 24 after rapid initiation of D/C/F/TAF.



CONCLUSIONS

- **In the first known phase 3 trial of an STR in a rapid initiation model of care, high proportions of patients using D/C/F/TAF achieved HIV-1 RNA <50 copies/mL and 91% (99/109) of patients continued treatment through the interim analysis at Week 24**
- **No patients discontinued treatment due to receipt of baseline resistance reports and only 3 discontinued due to safety stopping rules**
  - **Some newly diagnosed patients may present with elevations in transaminases, which in this study appeared to normalize with initiation of ART; based on these early findings, such patients should be considered for inclusion in future rapid initiation studies**
- **No patients had PDVF or discontinued due to lack of efficacy, and there was only 1 discontinuation due to AEs**
- **At Weeks 4 and 24, the mean total HIVTSQs score approached the maximum score of 60, indicating high levels of patient satisfaction**
- **These findings, together with the demonstrated efficacy, high barrier to resistance, safety profile, and convenience of the D/C/F/TAF STR, suggest that D/C/F/TAF should be considered a recommended treatment option in a rapid initiation model of care**

REFERENCES

1. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. http://aidsinfo.nih.gov/contentfiles/lyguidelines/adultandadolescentgl.pdf. Accessed October 17, 2017.
2. Centers for Disease Control and Prevention. Understanding the HIV care continuum. https://www.cdc.gov/hiv/pdf/library/factsheets/cdc-hiv-care-continuum.pdf. Accessed July 5, 2018.
3. Bacon O, et al. Poster presented at: Conference on Retroviruses and Opportunistic Infections; March 4-7, 2018; Boston, MA.
4. Koenig SP, et al. *PLoS Med.* 2017;14(7):e1002357.
5. Rosen S, et al. *PLoS Med.* 2016;13(3):e1002015.
6. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. July 2017.
7. Eron JJ, et al. *AIDS.* 2018;32(11):1459-1469.
8. Orkin C, et al. *Lancet HIV.* 2018;5(1):e23-e34.
9. Lathouwers E, et al. *HIV Clin Trials.* 2017;18(5):e1-196-204.

ACKNOWLEDGEMENTS

This study was funded by Janssen Scientific Affairs, LLC. Medical writing support was provided by Courtney St. Amour, PhD, of MedErgy, and was funded by Janssen Scientific Affairs, LLC.

If you have any additional questions or would like to request a copy of this poster, call +1-800-JANSSEN (+1-800-526-7736) or go to www.janssenMD.com.

DISCLOSURES

G.D. Huhn, G. Crofoot, M. Ramgopal, J. Gathe Jr, and R. Bolan contributed to the conduct of the study as investigators and to the interpretation of the data. C. Bicer contributed to the conduct of the study as investigator, to the interpretation of the data, R.B. Simonson, R.E. Nettles, and K. Dunn contributed to the design of the study and interpretation of the data. All authors contributed to drafting the poster and approved the final version.

G.D. Huhn has received research or grant support from Gilead, ViiV, Janssen, Proteus, and the US National Institutes of Health. G. Crofoot has received grants and speaker fees from Gilead, Janssen, ViiV, and Merck. M. Ramgopal has served as a speaker for Gilead, AbbVie, Bristol-Myers Squibb, ViiV, and Cubist and has served on advisory boards for Bristol-Myers Squibb, Merck, and Gilead. J. Gathe Jr has been a consultant or speaker in conferences supported by AbbVie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, ViiV, Boehringer Ingelheim, Pfizer, Janssen, Merck, and Gilead and has served as an investigator for Abbott, Avexa, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Merck, Pfizer, Roche, Partext, Hiesped, and Janssen. R. Bolan has no disclosures to report. C. Bicer is a consultant for Janssen. R.B. Simonson, R.E. Nettles, and K. Dunn are full-time employees of Janssen.

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

An electronic version of the poster can be viewed by scanning the QR code. The QR code is intended to provide scientific information for individual reference. The PDF should not be altered or reproduced in any way.