Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) Rapid Initiation for HIV-1 Infection: Primary Analysis of the DIAMOND Study

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INTRODUCTION

- Rapid initiation of treatment for patients newly diagnosed with human immunodeficiency virus (HIV)–1 infection has been shown to reduce time to virologic suppression, improve patient retention in care, and decrease morbidity and mortality, and it is recommended in most cases by treatment guidelines from the World Health Organization and the International Antiviral Society (IAS)–USA; however, prospective data are lacking[1-7]
- In rapid initiation models of care, patients begin antiretroviral therapy (ART) soon after diagnosis, prior to receiving results from baseline laboratory assessments[6,7]
  - When selecting a treatment regimen with limited clinical information available, the regimen's safety profile and barrier to resistance, the patient's ability to adhere to treatment, and the potential for transmitted drug resistance should be considered
  - An ART regimen for rapid initiation is ideally a well-tolerated, abacavir-sparing, single-tablet regimen (STR) with a high barrier to resistance
- Darunavir is recommended in US Department of Health and Human Services guidelines as an initial therapy when ART needs to be started and resistance test results are pending or unavailable, in part due to its demonstrated high barrier to resistance[8,9]
- We evaluated darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg, an oral once-daily STR, in a rapid initiation model of care over 48 weeks in DIAMOND, the first phase 3 prospective study of an STR in this setting

OBJECTIVES

- To assess the efficacy and safety of D/C/F/TAF over 48 weeks in a rapid initiation model of care in newly diagnosed, HIV-1–infected, treatment-naïve patients
- To assess baseline, and development of, viral resistance in the study population
- To assess HIV Treatment Satisfaction Questionnaire status version (HIVTSQs) results at Weeks 4, 24, and 48

METHODS

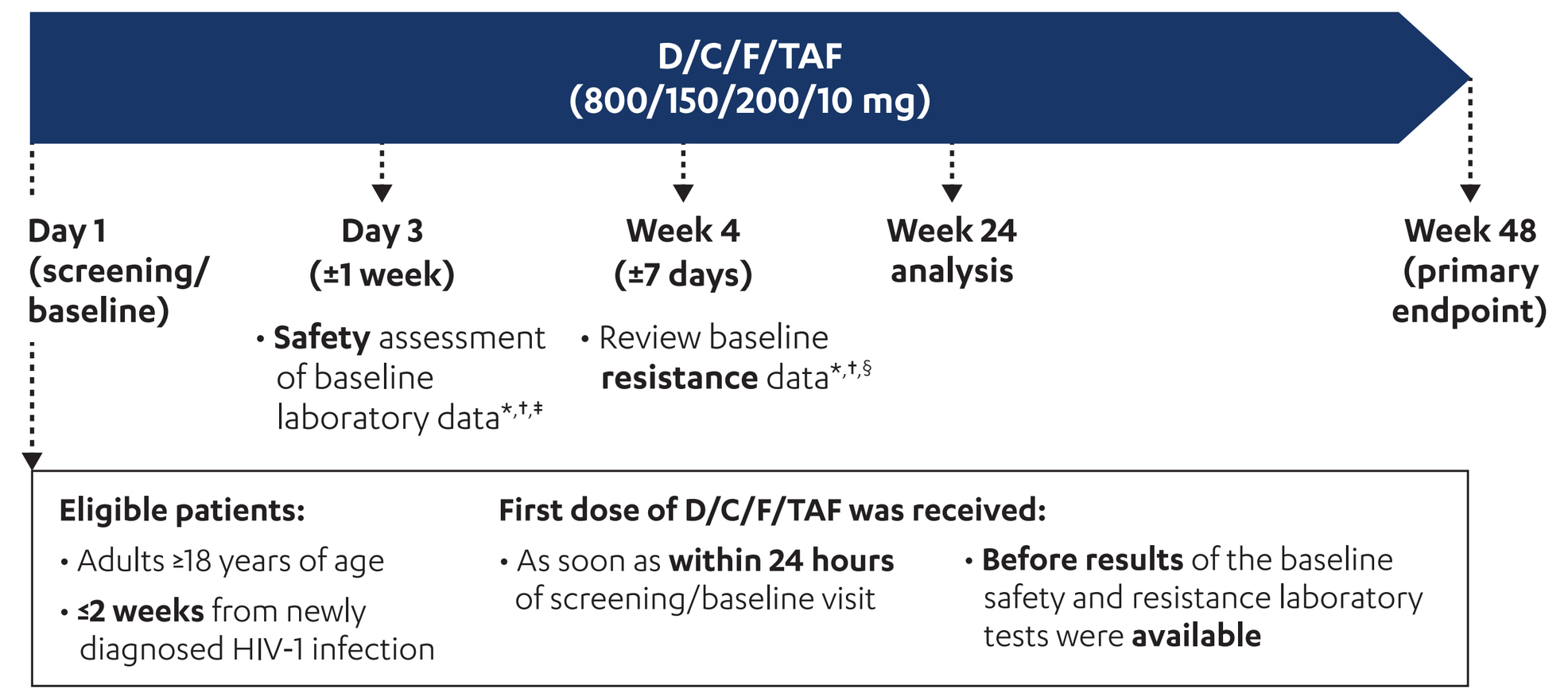
Study Design

- DIAMOND (ClinicalTrials.gov Identifier: NCT03227861) was a phase 3, open-label, single-arm, prospective, multicenter, 48-week study evaluating D/C/F/TAF rapid initiation (**Figure 1**)
- Key inclusion criteria:
  - Adults ≥18 years of age who were newly diagnosed with HIV-1 infection within 2 weeks of the screening/baseline visit
  - ART-naïve; pre-exposure prophylaxis with emtricitabine/tenofovir disoproxil fumarate was allowed
- Key exclusion criteria:
  - Certain known active infections or another acquired immunodeficiency syndrome (AIDS)–defining condition that in the investigator's judgment would increase the risk of morbidity/mortality
  - Certain clinically relevant renal and hepatic conditions
- Patients meeting eligibility requirements were enrolled and started on D/C/F/TAF within 24 hours of the screening/baseline visit, prior to the availability of laboratory information
- Investigators reviewed screening/baseline laboratory findings as results became available; patients who did not meet predefined safety or resistance stopping rules continued treatment (see **Figure 1** footnotes)

Analyses

- Primary endpoint: proportion of patients with virologic response at Week 48, defined as HIV-1 RNA <50 copies/mL (US Food and Drug Administration [FDA] snapshot)
- Efficacy was also assessed by the proportion of patients with HIV-1 RNA <50 or <200 copies/mL using the observed algorithm (excluding patients with missing values)
- Absolute CD4+ cell count at screening/baseline and Week 48 were described
- Screening/baseline resistance testing was performed using the GenoSure Prime® assay

Figure 1. DIAMOND study design.


D/C/F/TAF
(800/150/200/10 mg)
Day 1 (screening/ baseline)
Day 3 (±1 week)
Week 4 (±7 days)
Week 24 analysis
Week 48 (primary endpoint)
• Safety assessment of baseline laboratory data*,†,‡
• Review baseline resistance data*,†,§
Eligible patients:
• Adults ≥18 years of age
• ≤2 weeks from newly diagnosed HIV-1 infection
First dose of D/C/F/TAF was received:
• As soon as within 24 hours of screening/baseline visit
• Before results of the baseline safety and resistance laboratory tests were available

eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.
*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.
‡Safety stopping criteria were as follows (retesting of abnormal screening/baseline safety laboratory values allowed once): eGFR (MDRD formula) <50 mL/min; AST or ALT ≥2.5 times the ULN; serum lipase ≥1.5 times the ULN; positive pregnancy test for women of childbearing potential; laboratory results that the investigator believed should result in discontinuation of study medication; and active hepatitis C infection that in the opinion of the investigator required immediate treatment or was expected to require treatment during the study with agents not compatible with D/C/F/TAF.
§Resistance was based on predicted genotypic sensitivity (patients who did not show full sensitivity to all drugs were to be discontinued [with the exception of M184I/V]).

- Post-baseline samples were eligible for resistance testing using the PhenoSense® GT assay in patients with HIV-1 RNA values ≥400 copies/mL and protocol-defined virologic failure (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 consecutive 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)
  - Viremic at final time point: on-treatment HIV-1 RNA ≥400 copies/mL at the study endpoint or study discontinuation after Week 12
- 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 the study drug), and laboratory abnormalities
- Patient-reported outcomes for treatment satisfaction were evaluated using the HIVTSQs (Weeks 4, 24, and 48)[10]

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, and missing values were not imputed

RESULTS

Patient Population and Disposition

- Overall, 109 patients were enrolled in the study; 87% were men, 32% were black/African American, 25% had HIV-1 RNA ≥100,000 copies/mL, and 21% had CD4+ cell count <200 cells/μL (**Table 1**)
- Median (range) time between HIV-1 diagnosis and screening/baseline was 5 (0-14) days; 31% of patients were enrolled within 48 hours of diagnosis (**Table 1**)
  - Overall, 52% of patients were believed to have been infected within 6 months of diagnosis at study entry, with 12% being acutely infected; 32% of patients were believed to be chronically infected
- No darunavir resistance-associated mutations (RAMs) were observed among patients with available genotype data at screening/baseline (**Table 2**)
  - At screening/baseline, all patients had full genotypic susceptibility to darunavir and tenofovir; 2 patients had emtricitabine RAMs (M184M/I and M184M/V)
  - Among patients with a primary protease inhibitor (PI) RAM, 3 had L90M, 1 had M46L, and 1 had Q58E
  - Five patients were found to have a transmitted secondary integrase inhibitor (INI) mutation at position T97 (T97A may be considered a primary INI RAM[11,12])

Table 1. Baseline Demographic and Clinical Characteristics

	D/C/F/TAF N = 109
Demographic characteristics	
Age, median (range), years	28 (19-66)
Men, n (%)	95 (87)
Race, n (%)	
White	65 (60)
Black/African American	35 (32)
Other	9 (8)
Clinical characteristics	
HIV-1 RNA, n	108*
Median (range), copies/mL	38,700 (19†-144,000,000)
≥100,000 copies/mL, n (%)	27 (25)
CD4+ cell count, n	108*
Median (range), cells/μL	369 (7-1,082)
<200 cells/μL, n (%)	23 (21)
<50 cells/μL, n (%)	7 (7)
Time from diagnosis to screening/baseline, median (range), days	5 (0-14)
Enrolled within 48 hours of diagnosis, n (%)	34 (31)
Duration of infection, n	108†
Acute infection, n (%)‡	13 (12)
Early infection, n (%)§	43 (40)
Chronic infection, n (%)‖	34 (32)
Unknown, n (%)	18 (17)

*One patient had missing values due to a shipping error of the screening/baseline samples.
†One patient was HIV-1 negative (false positive fourth generation test).
‡Acute infection was defined as HIV-1 antibody negative and HIV-1 RNA positive/p24 positive.
§Early infection was defined as HIV-1 antibody positive and suspected infection ≤6 months prior to screening/baseline.
‖Chronic infection was defined as HIV-1 antibody positive and suspected infection >6 months prior to screening/baseline.

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)
M184M/I	1 (<1)
M184M/V	1 (<1)
Tenofovir	0
NNRTI†	28 (28)
K103N	11 (11)
Primary INI	0
Secondary INI	5 (5)
T97T/A	3 (3)
T97A	2 (2)

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; VL, viral load.
*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).
†Individual NNRTI RAMs are only shown for those occurring in ≥10% of patients.

- Overall, 97 (89%) patients completed the study (**Table 3**)
  - By Week 48, 12 (11%) patients had discontinued (3 due to protocol-defined safety stopping rules, 1 withdrawal due to AEs, 4 lost to follow-up, 1 protocol violation, 1 withdrawal of consent, and 2 for other reasons)
  - No patients discontinued due to resistance stopping rules

Table 3. Patient Disposition Through Week 48

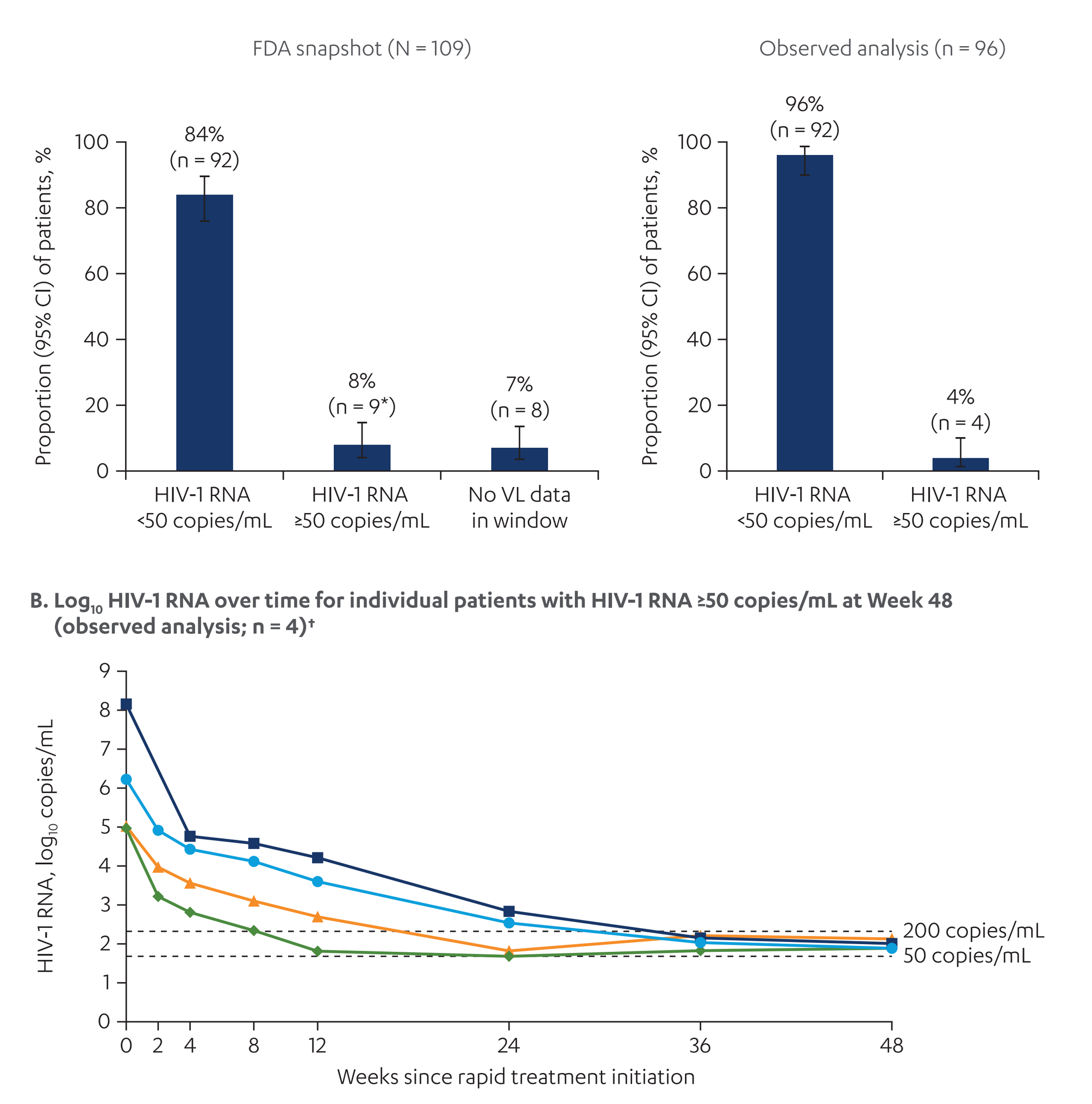
Disposition	D/C/F/TAF N = 109
Completed, n (%)	97 (89)
Discontinued, n (%)	12 (11)
Baseline resistance	0
Safety stopping rules*	3 (3)
AEs	1 (<1)
Lost to follow-up	4 (4)
Protocol violation	1 (<1)
Withdrawal of consent	1 (<1)
Other†	2 (2)

*Five patients met safety stopping rules criteria, all with confirmed elevations in AST or ALT ≥2.5 times the ULN identified at the screening/baseline visit (ie, prior to D/C/F/TAF administration). Three of these patients discontinued according to the protocol and 2 remained in the study based on clinical assessment by the investigator and agreement of the sponsor. Transaminases normalized after screening/baseline in all 5 patients, suggesting that treatment may have been beneficial for these patients and that safety stopping rules may have been overly stringent.
†Other reasons were patient incarceration and switch to another antiretroviral due to D/C/F/TAF food requirements.

Efficacy

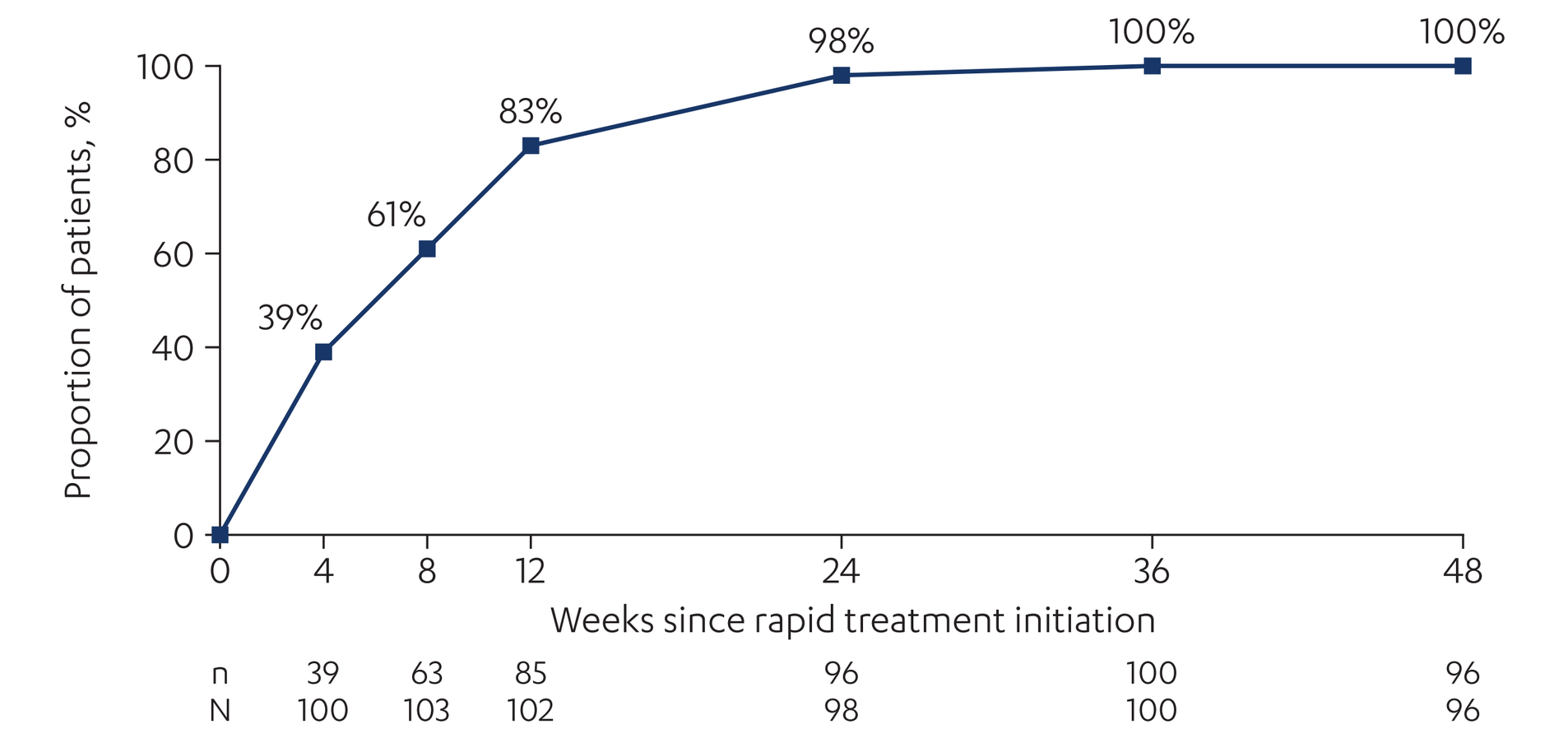
- At Week 48, 92 of 109 (84%; 95% confidence interval [CI]: 76-90) patients had achieved HIV-1 RNA <50 copies/mL (FDA snapshot; **Figure 2A**)
  - According to the observed algorithm, at Week 48, 92 of 96 (96%; 95% CI: 90-98) patients had achieved HIV-1 RNA <50 copies/mL; the remaining 4 patients all had HIV-1 RNA <200 copies/mL (**Figure 2B**)
  - No patients had PDVF, and there were no study discontinuations due to lack of efficacy
  - No patients were eligible for post-baseline resistance testing
- At Week 12, 85 of 102 (83%) patients had achieved HIV-1 RNA <200 copies/mL and, by Week 24, 96 of 98 (98%) had achieved this threshold (observed analysis; **Figure 3**)
- The mean (standard error [SE]) CD4+ cell count was 413 (24) cells/μL at screening/baseline and 628 (30) cells/μL at Week 48

Figure 2. D/C/F/TAF virologic efficacy in a rapid initiation model of care.


A. Virologic response at Week 48
FDA snapshot (N = 109)
Observed analysis (n = 96)
Proportion (95% CI) of patients, %
84% (n = 92)
8% (n = 9*)
7% (n = 8)
96% (n = 92)
4% (n = 4)
HIV-1 RNA <50 copies/mL
HIV-1 RNA ≥50 copies/mL
No VL data in window
B. Log10 HIV-1 RNA over time for individual patients with HIV-1 RNA ≥50 copies/mL at Week 48 (observed analysis; n = 4)†
HIV-1 RNA, log10 copies/mL
200 copies/mL
50 copies/mL
Weeks since rapid treatment initiation

*Three patients discontinued early due to protocol-defined safety stopping rules.
†HIV-1 RNA level was not available for 1 patient at the Week 2 visit.

Figure 3. Virologic response over time (HIV-1 RNA <200 copies/mL; observed analysis).



Safety

- Most AEs were grade 1 or 2; incidences of grade 3 or 4 and serious AEs were low (**Table 4**)
  - No serious AEs or grade 4 AEs were related to D/C/F/TAF, and there were no deaths
- One patient discontinued due to AEs, with allergic dermatitis (grade 3), pyrexia (grade 2), and lip swelling (grade 2); the AEs were considered study drug–related and all resolved after discontinuation of study treatment
- There were no cases of immune reconstitution inflammatory events and no discontinuations due to central nervous system, gastrointestinal, renal, or bone AEs
- Among the most common ADRs, most were grade 1 (**Table 5**)
- Few grade 3 and 4 laboratory abnormalities occurred in ≥2% of patients (increased bilirubin in 3 [3%] patients, increased ALT in 3 [3%] patients, and increased AST in 5 [5%] patients)

Table 4. Summary of AEs

	D/C/F/TAF N = 109	
AE, n (%)	Overall	Related
≥1	92 (84)	36 (33)
≥1 serious	10 (9)	0
≥1 grade 1	30 (28)	27 (25)
≥1 grade 2	48 (44)	7 (6)
≥1 grade 3*	13 (12)	2 (2)
≥1 grade 4†	1 (<1)	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).
†Abdominal injury (grade 4, not related) secondary to motor vehicle accident (grade 3, not related).

Table 5. Most Common ADRs (≥2% of Patients)

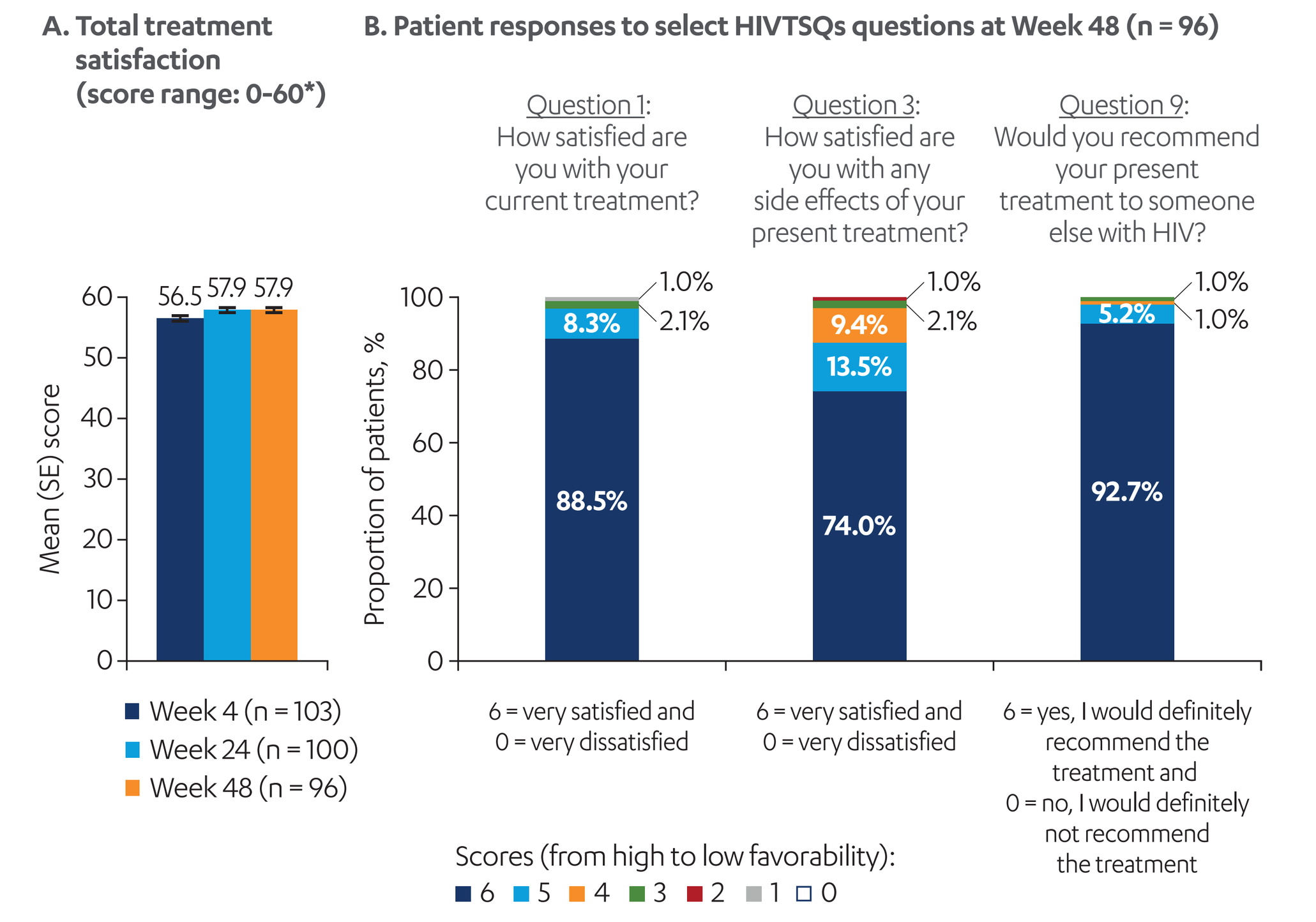
	D/C/F/TAF N = 109	
ADR, n (%)	Any grade	≥Grade 2
Diarrhea	13 (12)	2 (2)
Nausea	13 (12)	2 (2)
Rash*,†	5 (5)	4 (4)
Vomiting	4 (4)	0
Fatigue	3 (3)	0

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

Patient-reported Outcomes

- Patients reported high treatment satisfaction scores at Weeks 4, 12, and 48 (**Figure 4A**)
  - At Week 48, a majority of patients reported they were satisfied (score of 5 or 6) with their treatment (97%), satisfied (score of 5 or 6) with any side effects of their present treatment (88%), and that they would recommend (score of 5 or 6) their present treatment to someone else with HIV (98%; **Figure 4B**)

Figure 4. HIVTSQs results after D/C/F/TAF rapid initiation.


A. Total treatment satisfaction (score range: 0-60*)
Mean (SE) score
56.5
57.9
57.9
Week 4 (n = 103)
Week 24 (n = 100)
Week 48 (n = 96)
B. Patient responses to select HIVTSQs questions at Week 48 (n = 96)
Question 1: How satisfied are you with your current treatment?
Question 3: How satisfied are you with any side effects of your present treatment?
Question 9: Would you recommend your present treatment to someone else with HIV?
Proportion of patients, %
88.5%
8.3%
2.1%
1.0%
74.0%
13.5%
9.4%
2.1%
1.0%
92.7%
5.2%
1.0%
1.0%
6 = very satisfied and 0 = very dissatisfied
6 = very satisfied and 0 = very dissatisfied
6 = yes, I would definitely recommend the treatment and 0 = no, I would definitely not recommend the treatment
Scores (from high to low favorability):
6 5 4 3 2 1 0

*Higher scores indicate greater treatment satisfaction.

CONCLUSIONS

- **In the first known phase 3 trial of an STR in a rapid initiation model of care, 89% of patients continued D/C/F/TAF treatment through Week 48 and rates of virologic response (HIV-1 RNA <50 copies/mL) were high, ranging from 84% to 96%**
  - **Early in the study, a high proportion of patients achieved HIV-1 RNA <200 copies/mL (>80% of patients by Week 12), which may help prevent HIV-1 transmission to uninfected individuals, according to the Prevention Access Campaign's Undetectable = Untransmittable (U = U)[13]**
  - **No patients discontinued due to lack of efficacy, and none had PDVF**
- **No patients discontinued treatment due to screening/baseline resistance results, and none were eligible for post-baseline resistance testing**
- **D/C/F/TAF was well tolerated; most ADRs were grade 1, and only 1 (<1%) patient discontinued due to study drug–related AEs**
  - **Upon receipt of baseline laboratory results, 3 patients discontinued due to safety stopping rules**
- **The mean total HIVTSQs score approached the maximum of 60 at Week 4 and remained high through Weeks 24 and 48, 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**

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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. D. Luo contributed to statistical analysis and 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, GlaxoSmithKline, ViiV, Janssen, Merck, and Gilead; is affiliated with an institution that received research grants from AbbVie, Bristol-Myers Squibb, 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, Parexel, Hiesped, and Janssen. R. Bolan has no disclosures to report. D. Luo, R.B. Simonson, R.E. Nettles, and K. Dunn are full-time employees of Janssen and may be stockholders in Johnson & Johnson.

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