Impact of Adherence on Efficacy of *Dovato*

Summary

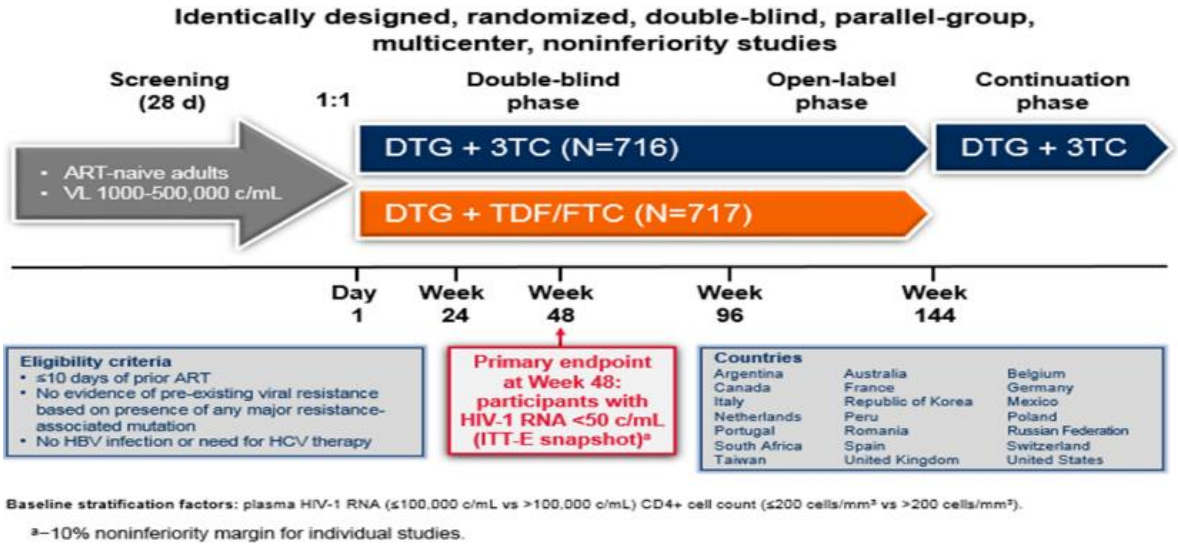
- In GEMINI-1 and GEMINI-2, the proportion of participants with HIV-1 RNA < 50 copies/mL was lower in the < 90% adherence group than the ≥ 90% group at Week 144 for both dolutegravir (DTG) + lamivudine (3TC), the components of *Dovato* (DTG/3TC) and DTG + TDF/FTC in a post-hoc analysis.[1,2]
- In a test-and-treat setting, adherence rates were greater than 95% through 48 weeks and among all participants. The proportion of participants achieving an HIV-1 RNA < 50 copies/mL was 76% (100/131) in the Snapshot analysis (missing/switch = failure) and 97% (100/103) in the Observed group (all patients on DTG + 3TC).[3,4]
- Short-cycle therapy (5 days on/2 days off) has been utilized in a small observational study utilizing DTG + 3TC.[5] After a follow-up of 8-37 months (median 14 months), 26/27 patients had an HIV-1 RNA < 20 copies/mL.
- The recommended dosage regimen of *Dovato* in adults is one table taken orally once daily with or without food.[6]
- Important safety information and boxed warning(s) can be found in the Prescribing Information link and can also be accessed at Our HIV Medicines.

To access additional scientific information related to ViiV Healthcare medicines, visit the ViiV US Medical Portal at viivhcmedinfo.com.

GEMINI-1 AND GEMINI-2

GEMINI-1 and GEMINI-2 are ongoing, randomized, double-blind (to Week 96; open label from Week 96 to Week 148), Phase III studies evaluating the efficacy and safety of DTG 50 mg once daily plus 3TC 300 mg once daily or DTG 50 mg once daily plus TDF/FTC.[7-9]

Figure 1. GEMINI Study Design[7]



Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm³ vs >200 cells/mm³).

[a]–10% noninferiority margin for individual studies.

Virologic success (snapshot HIV-1 RNA < 50 copies/mL) was achieved in 91% and 93% of participants, respectively, in the DTG + 3TC and DTG + TDF/FTC arms (ITT-E) at Week 48.[7] Through 96 weeks, 86% and 90% of participants, respectively, maintained virologic suppression.[8] Through 144 weeks, 82% and 84% of participants, respectively, maintained virologic suppression.[9] Drug-related adverse events

(AEs) were reported in 20% and 27% of participants, respectively, in the DTG + 3TC and DTG + TDF/FTC arms at Week 144. Further results on GEMINI-1 and GEMINI-2 can be found here.

A post hoc analysis evaluated the impact of treatment adherence on efficacy after 144 weeks of DTG + 3TC vs DTG + TDF/FTC in GEMINI-1 and GEMINI-2.[1,2] Percent adherence was calculated as the number of pills taken (the difference between the number of pills available and the number of pills returned) per number of pills prescribed estimated using pill count data. Proportion with HIV-1 RNA < 50 c/mL was assessed using Snapshot (missing/switch/discontinuation = failure) and last on-treatment viral load (not accounting for discontinuations for non-virologic reasons) for which adherence could be derived.

In each treatment group, 5% of participants had < 90% adherence through Week 144.[8]

By both ITT-E Snapshot and last on-treatment viral load analysis, the proportion of participants with HIV-1 RNA <50 copies/mL was lower in the <90% adherence group than the ≥90% adherence group, but similar between the two treatment groups within the same adherence category (see Figure 2 and Table 1).[1,2] The difference in response rates observed with the Snapshot analysis was driven by non-virologic failures (see Table 1).

Figure 2. Treatment Differences Between Groups in Proportion of Participants Achieving HIV-1 RNA < 50 c/mL at Week 144

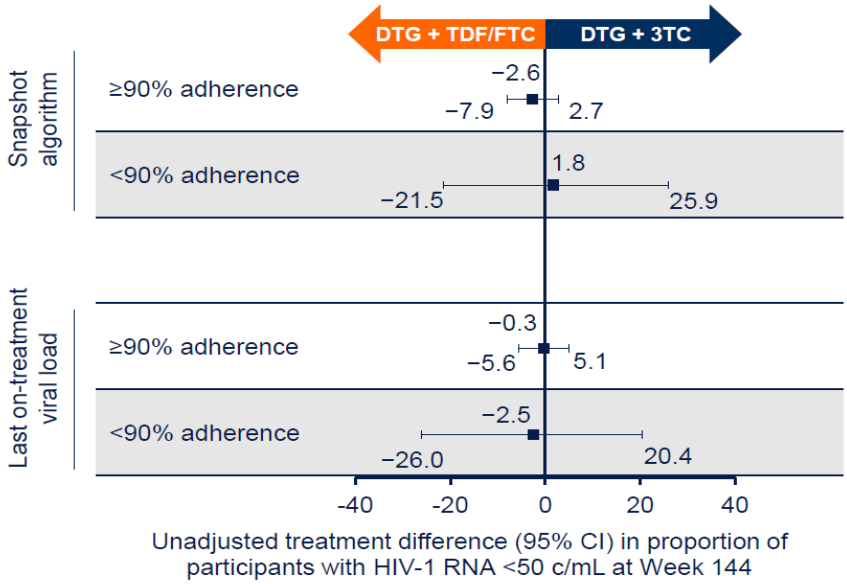


Table 1. Snapshot Outcomes by Adherence Category

	DTG + 3TC		DTG + TDF/FTC	
Outcomes, n (%)	**≥ 90% (N = 679)**	**< 90% (N=35)**	**≥ 90% (N=677)**	**< 90% (N=34)**
HIV-1 RNA < 50 c/mL	570 (84)	14 (40)	586 (87)	13 (38)
HIV-1 RNA ≥ 50 c/mL	17 (3)	6 (17)	18 (3)	3 (9)
Data in window and HIV-1 RNA ≥ 50 c/mL	3 (< 1)	1 (3)	5 (< 1)	0
Discontinued for lack of efficacy	7 (1)	3 (9)	4 (< 1)	0
Discontinued for other reason and HIV-1 RNA ≥ 50 c/mL	6 (< 1)	1 (3)	8 (1)	3 (9)
Change in ART	1 (< 1)	1 (3)	1 (< 1)	0
No virologic data at Week 144	92 (14)	15 (43)	73 (11)	18 (53)
Discontinued study for AE or death	28 (4)	1 (3)	26 (4)	5 (15)
Discontinued study for other reason[a]	63 (9)	13 (37)	47 (7)	12 (35)
On study but missing data in window	1 (< 1)	1 (3)	0	1 (3)

[a] Other reasons included lost to follow-up, investigator discretion, withdrawal of consent, and protocol deviations.

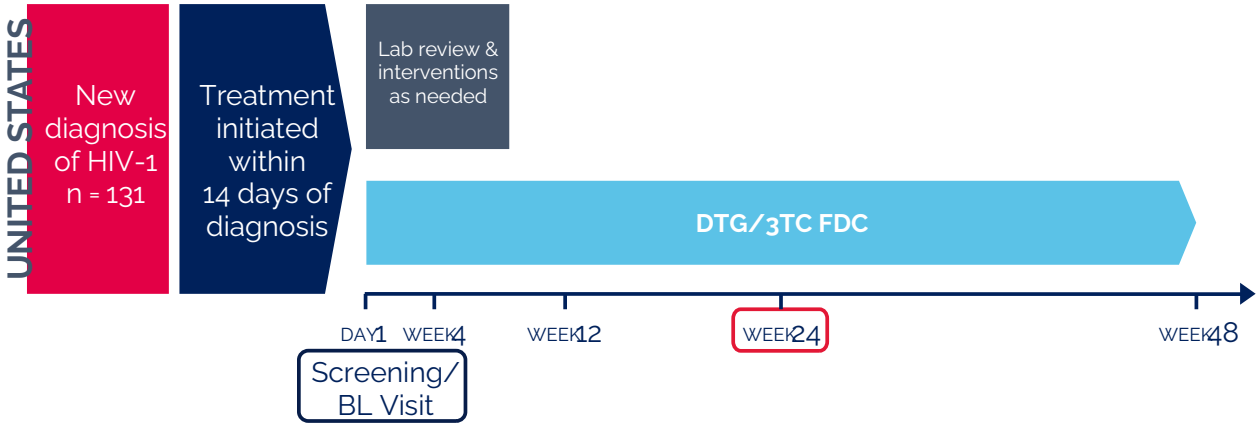
DTG = dolutegravir; 3TC = lamivudine; FTC = emtricitabine; TDF = tenofovir disoproxil fumarate.

Limitations of this analysis include the small number of participants in the < 90% adherence subgroup and difficulty in accurately measuring adherence.

TEST-AND-TREAT SETTING

The STAT study was a phase 3b, multicenter, open-label, single-arm, pilot study assessing the feasibility, efficacy, and safety of using DTG/3TC as a first-line regimen in a 'test-and-treat' model of care in the United States.[10]

Figure 3. STAT Study Design[10]



Eligible patients were ART-naive adults aged ≥18 years diagnosed with HIV within 14 days of study entry for whom laboratory results were not available at baseline. DTG/3TC treatment was adjusted if baseline testing indicated HBV co-infection, genotypic resistance to DTG or 3TC, or creatinine clearance <30 mL/min/1.73 m², or as required during the study, and all patients with treatment adjustments remained on study. The primary endpoint was the proportion of patients with HIV-RNA <50 copies/mL at week 24, regardless of ART regimen (ITT-E, missing=failure). Patients with HIV-1 RNA ≥50 copies/mL at Week 24 or with no HIV-1 RNA assessment at Week 24 due to early discontinuation or still on study but with missing data are classified as HIV-1 RNA ≥50 copies/mL.

Among all patients, 102/131 (78%) achieved HIV-1 RNA <50 copies/mL at Week 24, irrespective of ART.[10] Through 48 weeks 82% of patients maintained virologic suppression. ITT-E non-suppression rates were driven by non-virologic factors (eg missing data in window and high discontinuation rates).[3] Further results from the STAT study can be found here.

Assessment of adherence to study treatment was an exploratory endpoint and was assessed by patient recall on the number of doses missed over the 7 days prior to visit.[11] At Week 48, adherence data were available for 96/131 (73%) of patients with a mean adherence rate of 96% [SD: 13%]. While adherence was unknown for approximately 27% of patients, the proportion of patients achieving an HIV-1 RNA < 50 copies/mL was 76% (100/131) in the Snapshot analysis (missing/switch = failure) and 97% (100/103) in the Observed group (all patients on DTG/3TC).

SHORT-CYCLE THERAPY

A short-cycle ART strategy has been studied in 3-drug ART regimens.[12,13] An observational study was conducted in 27 virologically-suppressed adults receiving a combination of DTG + 3TC.[5] These patients had been on ART for > 1 year, had ≥ 12 months of virologic suppression (< 20 copies/mL), CD4 cell count > 200 cells/mm³ for > 6 months, and no evidence of drug resistance mutations or regimen failure. These patients then began to take their ART regimen 5 days on (Monday to Friday) and two days off (Saturday and Sunday).

After a mean follow-up of 10.4 months (range 8-37 months), 26/27 patients had an HIV-1 RNA < 20 c/mL.[5] One subject had 47 c/mL of HIV-RNA; 1 month later, the viral load of the same patient was undetectable (HIV RNA <20 copies/ml). Pharmacokinetic analysis showed that in 60% (49/81) of samples examined, the C_{trough} 60-72 hours after the last dose was below the *in vitro* protein-adjusted 90% inhibitory concentration (IC_{90}) of DTG for wild-type virus (64 ng/mL). Safety data was not included within this analysis. No resistance was reported.

ViiV Healthcare has not formally evaluated the efficacy and safety of DTG + 3TC utilizing a short-cycle ART strategy. The recommended dosage regimen of *Dovato* in adults is one tablet taken orally once daily with or without food.[6]

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