Safety and Efficacy of Dolutegravir-Based ART in TB/HIV Co-Infected Adults at Week 48

P015

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Introduction

- Characterizing efficacy, safety, and drug–drug interactions of dolutegravir (DTG) in patients with HIV/tuberculosis (TB) co-infection is a high priority
- In the interim Week 24 results of the INSPIRING study, DTG 50 mg twice daily (BID) appeared to be effective and well tolerated in participants with HIV-associated TB who were taking isoniazid, rifampicin (RIF), pyrazinamide, and ethambutol for TB treatment, with low rates of immune reconstitution inflammatory syndrome (IRIS)[1]
  - Primary Week 48 results are presented here

Methods

Study design

- INSPIRING is a phase IIIb, open-label, noncomparative, active-controlled, parallel-group study (ClinicalTrials.gov, NCT02178592)
- Antiretroviral therapy–naive individuals on RIF-based TB treatment for ≤8 weeks were randomized (3:2) to receive DTG (50 mg BID during and 2 weeks post-TB therapy, followed by 50 mg once daily [QD]) or efavirenz (EFV; 600 mg QD), with 2 nucleoside reverse transcriptase inhibitors (NRTIs) for 52 weeks
- Primary endpoint was the proportion of DTG-treated participants with plasma HIV-1 RNA <50 c/mL at Week 48 (responders) using the modified US Food and Drug Administration Snapshot algorithm (ie, NRTI switch for tolerability not counted as failure) in the intention-to-treat–exposed (ITT-E) population
- Secondary endpoints included the proportion of EFV-treated participants who were responders, incidence and severity of safety events, and proportion of participants with TB- and non–TB-associated IRIS (assessed by independent committee)
- The study was not powered to show a difference between arms; no formal statistical hypothesis was tested

Results

- 113 participants were enrolled from South Africa (n=65), Brazil (n=15), Peru (n=14), Russia (n=7), Mexico (n=6), Argentina (n=4), and Thailand (n=2; Table 1)

Table 1. Demographics and Baseline Characteristics

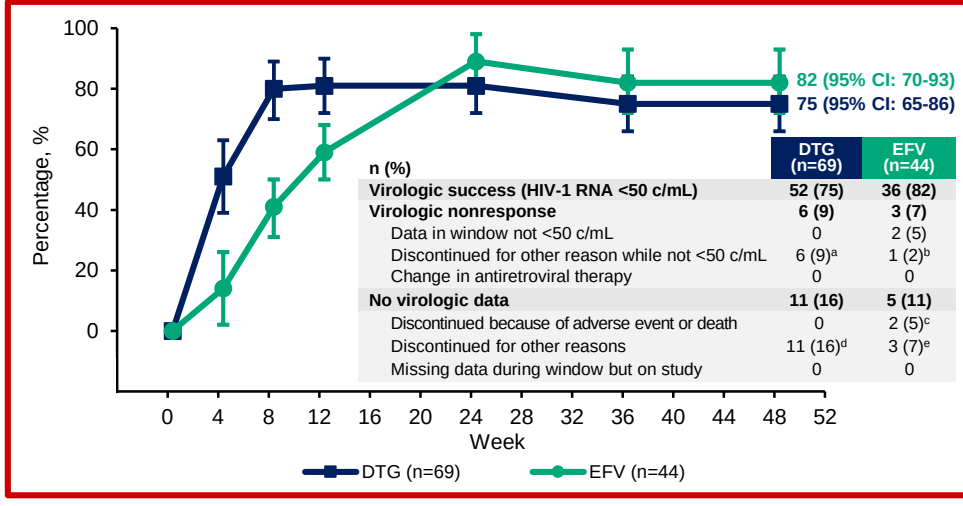
	DTG (n=69)	EFV (n=44)
Age, median (range), y	33 (18-62)	32 (20-50)
≥50 y, n (%)	9 (13)	2 (5)
Female, n (%)	30 (43)	16 (36)
African heritage/African, n (%)	47 (68)	29 (66)
HIV-1 RNA, median (Q1, Q3), log_{10} c/mL	5.10 (4.74, 5.47)	5.24 (4.50, 5.67)
>100,000 c/mL, n (%)	44 (64)	24 (55)
CD4+ cell count, median (Q1, Q3), cells/mm^3	208 (128, 410)	202 (92, 354)
≤100 cells/mm^3, n (%)	13 (19)	12 (27)
Current TB conditions, n (%)[a]		
Pulmonary TB	65 (94)	44 (100)
Lymph node TB	5 (7)	2 (5)
Pleural TB	5 (7)	0

[a]Participants could have had pulmonary TB with pleural or lymph node TB.

Efficacy

- At Week 48, 75% of participants in the ITT-E population treated with DTG 50 mg BID and concomitant RIF-based TB therapy were virologically suppressed (Figure 1)

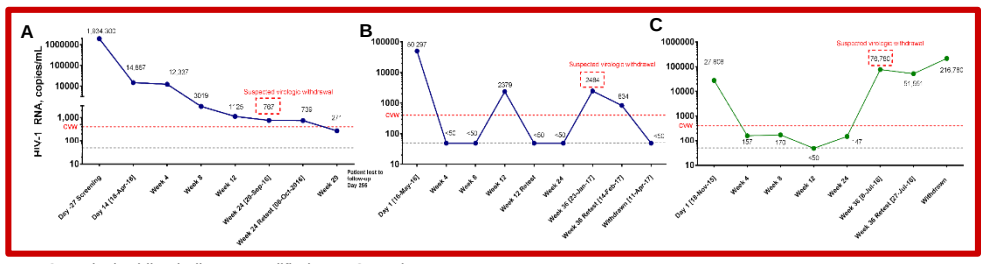
Figure 1. Virologic Results in the ITT-E Population at Week 48



Proportion of participants with HIV-1 RNA <50 c/mL (95% CI) in the modified FDA Snapshot analysis. [a]Discontinued for other reasons while not <50 c/mL: 3 lost to follow-up; 2 withdrew consent; 1 pregnancy. [b]Discontinued for other reasons while not <50 c/mL: 1 lost to follow-up. [c]Discontinued due to adverse event: 1 hypersensitivity to EFV; 1 increased GGT. [d]No virologic data/Discontinued for other reasons: 7 lost to follow-up; 2 pregnancies; 1 physician decision; 1 withdrew consent. [e]No virologic data/Discontinued for other reasons: 2 lost to follow-up; 1 withdrew consent (participant relocated).

- Median changes from baseline in CD4+ cell count (Q1, Q3) at Week 48 were 220 cells/mm^3 (111, 271) in the DTG group and 190 cells/mm^3 (104, 252) in the EFV group
- 3 participants had virologic withdrawal (2 consecutive values of confirmed plasma HIV-1 RNA ≥400 c/mL at or after Week 24; Figure 2)
  - Man aged 50 years in the DTG group with a NRTI background regimen of didanosine/lamivudine
    - No treatment-emergent resistance mutations were detected
  - Man aged 36 years in the DTG group with a NRTI background regimen of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)
    - No treatment-emergent resistance mutations were detected
    - Study drug nonadherence reported Weeks 11 to 12 and Weeks 18 to 20
  - Man aged 26 years in the EFV group with a NRTI background regimen of TDF/FTC
    - Treatment-emergent NRTI and non-NRTI resistance was observed; no treatment-emergent integrase strand transfer inhibitor resistance was observed

Figure 2. Participants With Confirmed Virologic Withdrawal: (A) Man Aged 50 y Randomized to DTG; (B) Man Aged 36 y Randomized to DTG; and (C) Man Aged 26 y Randomized to EFV.



Gray dashed line indicates modified FDA Snapshot.

- TB treatment success was high in both groups
  - In the DTG group, 28 participants were cured (all with pulmonary TB) and 33 completed treatment (31 with pulmonary TB and 2 with pleural or lymph node TB)
  - In the EFV group, 18 were cured and 22 completed treatment (all with pulmonary TB)

Pharmacokinetics

- DTG concentration at steady state when administered BID with RIF was similar to DTG 50 mg QD without RIF and to prior phase II/III data for DTG 50 mg QD (Table 2)[2,3]

Table 2. Pre-Dose Dolutegravir Concentrations During and After RIF Treatment

Week	n	DTG concentration, geometric mean (90% CI) [%CV], ng/mL
		Pre-dose concentration: DTG 50 mg BID with RIF
8	42	870 (208-2340) [118]
24	23	964 (BLQ-3380) [263]
		Pre-dose concentration: DTG 50 mg QD without RIF (post-TB treatment phase)
36	27	854 (65-3310) [208]
48	26	881 (47-3310) [281]

%CV, coefficient of variation.

Safety

- Adverse events (AEs) reported at the Week 48 data cutoff are shown in Table 3

Table 3. Adverse Events at the Week 48 Data Cutoff

n (%)	DTG (n=69)	EFV (n=44)
Any AE	52 (75)	40 (91)
AE occurring in ≥10% of participants in either group		
Headache	9 (13)	6 (14)
Upper respiratory tract infection	5 (7)	8 (18)
Lower respiratory tract infection	9 (13)	3 (7)
Diarrhea	3 (4)	10 (23)
Dizziness	3 (4)	6 (14)
Arthralgia	7 (10)	0
Gastroenteritis	1 (1)	5 (11)
Any serious AE[a]	5 (7)	5 (11)
Drug-related serious AE	1 (1)	1 (2)
Any drug-related AE	19 (28)	14 (32)
AEs leading to withdrawal	0	2 (5)[b]
Any psychiatric AE	5 (7)	6 (14)[c]

[a]No fatal serious AEs in either group. [b]1 participant with EFV drug hypersensitivity and 1 with GGT elevation. [c]Included 1 serious AE of grade 2 suicidal ideation considered unrelated to study drug and resolved the same day.

- Criteria for TB-associated IRIS were met in 6% (n=4) of participants in the DTG group and 9% (n=4) in the EFV group; 1 participant (DTG group) met the criteria for non–TB-associated IRIS
- 1 (1%) participant in the DTG group and 1 (2%) in the EFV group experienced maximum post-baseline alanine aminotransferase levels ≥5 to <10 × upper limit of normal

Conclusions

- DTG 50 mg BID during concomitant RIF-based TB therapy demonstrated high efficacy and a good immunologic response through Week 48
- DTG was well tolerated; the majority of AEs were grade 1/2, with low rates of drug-related AEs and serious AEs as well as no AEs leading to withdrawal
- This study provides evidence that DTG is effective and well tolerated in adults with HIV/TB co-infection who are receiving RIF-based TB treatment

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