FEASIBILITY, EFFICACY, AND SAFETY OF DOLUTEGRAVIR/LAMIVUDINE (DTG/3TC) AS A FIRST-LINE REGIMEN IN A TEST-AND-TREAT SETTING FOR NEWLY DIAGNOSED PEOPLE LIVING WITH HIV (PLWH): 48-WEEK RESULTS OF THE STAT STUDY

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Introduction

- Rapid treatment of HIV-1 infection has been associated with improved linkage to and retention in care and reduced time to virologic suppression in people living with HIV (PLWH)[1]
- Dolutegravir (DTG)/Lamivudine (3TC) is indicated for treatment-naive and treatment-experienced PLWH
- The STAT study (ClinicalTrials.gov, NCT03945981) is a phase IIIb, 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 newly diagnosed patients where potential transmitted resistance and baseline (BL) hepatitis B virus (HBV) co-infection are unknown[2]
  - In the primary analysis at Week 24, 78% (102/131) of all participants and 92% (102/111) of those with data available irrespective of treatment achieved HIV-1 RNA <50 c/mL[2]

Methods

- Eligible participants were ART-naive adults in the United States aged ≥18 years diagnosed with HIV-1 within 14 days of study entry for whom BL laboratory results were not available
- DTG/3TC treatment was adjusted if BL testing indicated HBV co-infection, genotypic resistance to DTG or 3TC, or creatinine clearance <30 mL/min/1.73 m^2, or as required during the study, and all participants who modified treatment remained on study
- Key secondary efficacy analyses at Week 48
  - **Observed:** Proportion of participants with plasma HIV-1 RNA <50 c/mL, **regardless of ART regimen**, **among those with available** HIV-1 RNA
  - **Intention-to-treat–exposed (ITT-E) missing = failure:** Proportion of **all** participants with plasma HIV-1 RNA <50 c/mL, **regardless of ART regimen**
    - Participants with HIV-1 RNA ≥50 c/mL or with no HIV-1 RNA assessment at Week 48 due to early discontinuation or still on study but with missing data are classified as HIV-1 RNA ≥50 c/mL
  - **FDA Snapshot:** Proportion of **all** participants with plasma HIV-1 RNA <50 c/mL **still taking DTG/3TC**
- Safety of DTG/3TC was assessed as incidence and severity of adverse events (AEs), drug-related AEs, discontinuation of DTG/3TC due to AEs, and laboratory abnormalities

Results

Participant Characteristics

- Overall, 131 participants were enrolled in the study across 16 sites (Table 1)
  - 2 participants had false-positive HIV tests at diagnosis and were enrolled, but subsequent HIV-1 RNA testing failed to reveal viral replication and they were withdrawn

Table 1. Selected Baseline Demographics and Participant Characteristics (ITT-E Population)

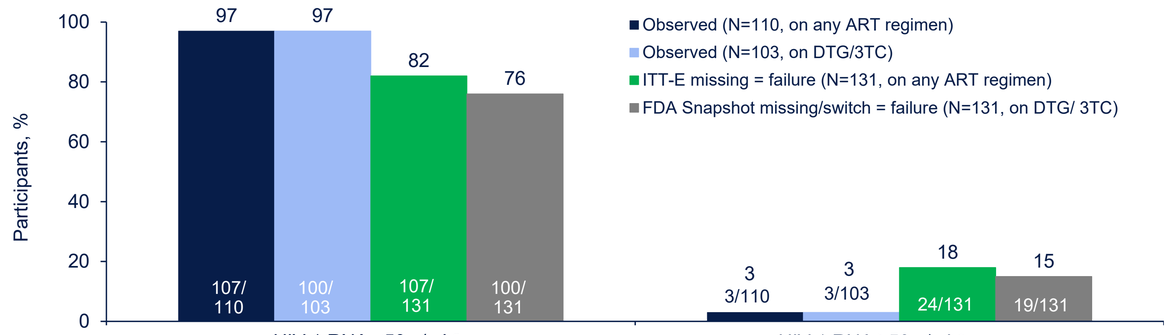
Characteristic	DTG/3TC (N=131)
Age, median (range), years	31 (18-63)
≥50 years, n (%)	20 (15)
Cisgender female, n (%)	10 (8)
Transgender female, n (%)	1 (<1)
Ethnicity, n (%)	
Hispanic/Latino	38 (29)
Not Hispanic/Latino	93 (71)
Race, n (%)	
Black/African American	61 (47)
White	65 (50)
Other	5 (4)
Weight, median (IQR), kg	74.2 (66.0-86.7)
BMI, median (IQR), kg/m^2	24.3 (21.1-27.2)
Time to enrollment since diagnosis, median (range), days	5 (0-15)[a]
HIV-1 RNA, median (range), c/mL, n (%)[b]	63,056 (<40 to 68,706,840)[c]
<100,000	79 (60)
100,000 to <500,000	32 (24)
500,000 to <1,000,000	9 (7)
≥1,000,000	10 (8)
CD4+ cell count, median (range), cells/mm^3	389 (<20 to 1466)[d]
<200, n (%)	37 (28)
HBV co-infection, n (%)[e,f]	7 (5)
M184V resistance mutation, n (%)[e]	1 (<1)
Enrolled on day of diagnosis, n (%)	34 (26)

[a]1 participant joined the study past the 14-day window after diagnosis (15 days) due to error in entry of diagnosis date; participant remained on study. [b]1 (<1%) participant had missing plasma HIV-1 RNA results at BL. [c]Lower limit of quantification is 40 c/mL. [d]Lower limit of quantification is 20 cells/mm^3. [e]Baseline HIV-1 resistance was identified at Week 4 and HBV co-infection was identified at Week 1 from samples taken at baseline. [f]2 participants with HBV co-infection but no evidence of ongoing HBV viral replication remained on DTG/3TC.

Virologic Outcomes at Week 48

- Most participants in the observed, ITT-E, and Snapshot analyses achieved HIV-1 RNA <50 c/mL (Figure 1)
- ITT-E non-suppression rates were driven by non-virologic factors (ie, high withdrawal rate); Snapshot non-suppression rates were driven by study withdrawals and ART modifications
- 18 (14%) participants discontinued study before Week 48 (Table 2)
- At Week 48, median $\log_{10}$ decrease from BL in plasma HIV-1 RNA on any ART was 3.2 $\log_{10}$ c/mL (n=109)
- 2 participants with confirmed virologic failure had no evidence of treatment-emergent resistance and both remained on DTG/3TC in study (1 suppressed to HIV-1 RNA <50 c/mL and 1 had HIV-1 RNA 70 c/mL at Week 48)

Figure 1. Results of Efficacy Analyses: Virologic Outcomes at Week 48



[a]For Snapshot HIV-1 RNA <50 c/mL analysis, 103/131 participants were on DTG/3TC; for Snapshot HIV-1 RNA ≥50 c/mL analysis, 19/131 participants were on any ART regimen (12/131 participants had no virologic data at Week 48).

Table 2. Summary of Virologic Outcomes at Week 48

	DTG/3TC, n/N (%)
Observed analysis	
Participants with available HIV-1 RNA	110/131 (84)
HIV-1 RNA <50 c/mL	**107/110 (97)**
On DTG/3TC	100/107 (93)
On modified ART	7/107 (7)
ITT-E missing = failure analysis	
HIV-1 RNA <50 c/mL	**107/131 (82)**
HIV-1 RNA ≥50 c/mL	**24/131 (18)**
Data in window and HIV-1 RNA ≥50 c/mL	3/131 (2)
On study but missing data in window	3/131 (2)[a]
Discontinued study due to lost to follow-up/withdrew consent	14/131 (11)[b]
Discontinued study for other reasons	4/131 (3)[c]
FDA Snapshot analysis	
HIV-1 RNA <50 c/mL	**100/131 (76)**
HIV-1 RNA ≥50 c/mL	**19/131 (15)**
Data in window and HIV-1 RNA ≥50 c/mL	3/131 (2)
Discontinued for lack of efficacy	0
Discontinued study for other reason and HIV-1 RNA ≥50 c/mL	6/131 (5)
Change in ART	10/131 (8)
No virologic data	**12/131 (9)**

[a]1 participant missed HIV-1 RNA assessment at Week 48 due to COVID-19. [b]8 due to lost to follow-up; 6 withdrew consent (3 relocations, 2 incarcerations, 1 no sub-reason). [c]All due to physician decision (2 HIV negative, 2 did not show up to several scheduled appointments).

- Among the 3 of 7 participants with HBV co-infection with successful resistance tests, there was no evidence of treatment-emergent resistance in HBV at time of switch off DTG/3TC (when HBV infection was confirmed at BL testing)
- By Week 48, DTG/3TC treatment was adjusted in 10 participants (Table 3)
- All participants with available data who had an ART adjustment and remained on study at Week 48 had HIV-1 RNA <50 c/mL
  - 2 participants switched after the Week 48 HIV-1 RNA assessments

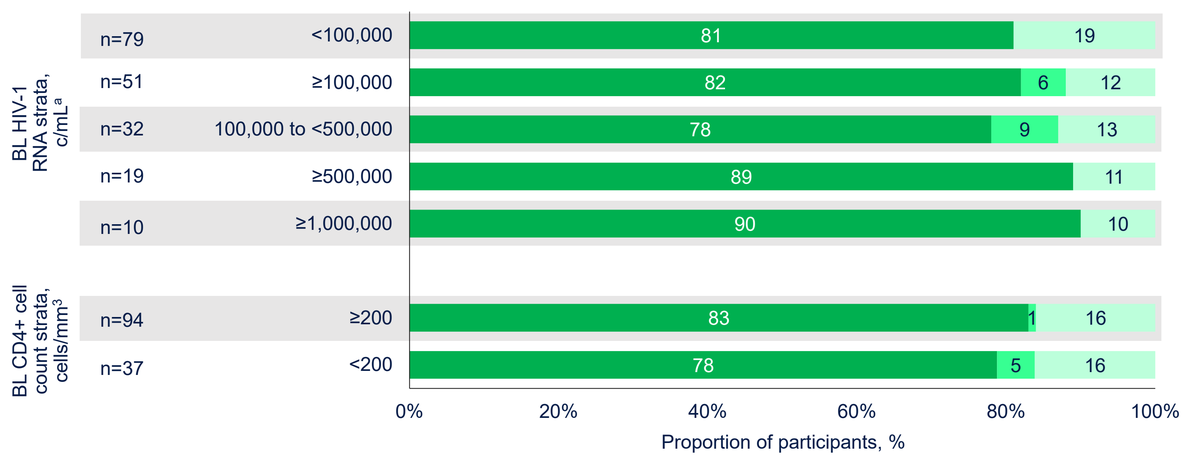
Table 3. Participants Who Switched From DTG/3TC at Any Time Point by Week 48

Reason for switch	Visit window	Modified ART	Plasma HIV-1 RNA at Week 48, c/mL
BL HBV	Week 1	DTG/3TC + TAF	<40
BL HBV	Week 1	BIC/FTC/TAF	<40
BL HBV	Week 4	DTG + TAF/FTC	<40
BL HBV	Week 4	BIC/FTC/TAF or DTG + TDF/FTC[a]	NA[b]
Decision by participant or proxy	Week 4	BIC/FTC/TAF	NA[c]
BL HBV	Week 8	DTG/3TC + TAF	<40
BL M184V	Week 8	DTG/RPV	NA[d]
AE (rash)	Week 12; Week 12	DRV/COBI/FTC/TAF; BIC/FTC/TAF[e]	<40
Decision by participant or proxy	Week 24	BIC/FTC/TAF	<40
Pregnancy	Week 24	DTG/ABC/3TC	327; <40
Participants who switched after Week 48 HIV-1 RNA assessment			
Lack of efficacy	Week 48	DTG + 3TC[f]	223; 182; 831
Non-adherence	Post-Week 48	Off treatment[g]	NA

[a]Participant modified ART by subsequently joining a double-blind clinical trial and was switched to either BIC/FTC/TAF or DTG + TDF/FTC. [b]Week 36 HIV-1 RNA was 57 c/mL. [c]Participant withdrew consent after switch from DTG/3TC. [d]Participant had HIV-1 RNA 18,752 c/mL at baseline, <40 c/mL on Day 47, switched to DTG/RPV on Day 49 due to M184V (despite viral load <40 c/mL), and had last HIV-1 RNA 54 c/mL on Day 57; participant withdrew consent (due to relocation) on Day 106 (Week 12). [e]Participant switched ART twice. [f]Participant switched to BIC/FTC/TAF post-Week 48 HIV-1 RNA assessment (after the 831 c/mL assessment); HIV-1 RNA was 51 c/mL at last follow-up visit. [g]Participant stopped DTG/3TC due to non-adherence and re-started DTG/3TC ~4 months later; last HIV-1 RNA was 104 c/mL at last follow-up visit on modified ART.

- 90% of participants with very high viral load at BL (≥1,000,000 c/mL) achieved HIV-1 RNA <50 c/mL by Week 48 (Figure 2)

Figure 2. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 48 by BL (A) HIV-1 RNA and (B) CD4+ Cell Count (ITT-E Missing = Failure Analysis)



[a]1 (<1%) participant had missing plasma HIV-1 RNA results at BL.

Safety

- DTG/3TC was well tolerated, with low rates of grade 2-5 drug-related AEs (2%) and serious AEs (2%; Table 4)
- Median (IQR) percent change from BL in weight was 6.1% (0.5%-11.7%), and absolute median increase in weight was 4.9 kg on DTG/3TC at Week 48
- Median (IQR) change from BL in BMI was 1.6 kg/m^2 (0.1-2.9) on DTG/3TC

Table 4. AEs Reported Under Treatment With DTG/3TC

AEs, n (%)	DTG/3TC (N=131)
Any AE	100 (76)
AEs occurring in ≥7% of participants	
Headache	12 (9)
Diarrhea	10 (8)
Depression	9 (7)
Nausea	9 (7)
Drug-related AEs	10 (8)
Grade 2-5 drug-related AEs	3 (2)[a]
AEs leading to discontinuation of DTG/3TC	1 (<1)[b]
Any SAE	2 (2)[c]
Psychiatric disorders[d]	24 (18)

[a]All AEs were grade 2. [b]1 AE leading to discontinuation of DTG/3TC occurred (rash). The event resolved. [c]2 SAEs occurred (cellulitis, streptococcal bacteremia). No fatal SAEs occurred. [d]All psychiatric AEs were grade 1 or 2. AEs were coded using MedDRA v23.1.

Conclusions

- In participants with newly diagnosed HIV-1 and rapid DTG/3TC initiation, high virologic suppression rates were observed at Week 48, including in those with very high baseline viral load
- Few participants required modification to their ART regimen due to baseline resistance or HBV co-infection
- Only 2 participants met criteria for confirmed virologic failure, and none had evidence of treatment-emergent resistance; both participants remained on DTG/3TC
- No participants with available genotyping developed treatment-emergent HBV resistance
- DTG/3TC was well tolerated, with only 1 AE leading to discontinuation of study drug
- These data demonstrate the feasibility, good safety profile, and high barrier to resistance of DTG/3TC as a first-line regimen in a test-and-treat setting. Therapy adjustments for baseline resistance or HBV co-infection occurred safely via routine clinical care as needed

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References: 1. Centers for Disease Control and Prevention. Understanding the HIV Care Continuum. 2019. **2.** Rolle et al. *AIDS*. 2021 [Epub ahead of print].

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