Working together in HIV

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

Charlotte-Paige Rolle,[1] Mezgebe Berhe,[2] Tulika Singh,[3] Roberto Ortiz,[4] Anson Wurapa,[5] Moti Ramgopal,[6] Peter A. Leone,[7] Jessica E. Matthews,[7] Marybeth Dalessandro,[8] Mark R. Underwood,[7] Konstantinos Angelis,[9] Brian R. Wynne,[7] Deanna Merrill,[7] Christopher Nguyen,[7] Jean van Wyk[10]

[1]Orlando Immunology Center, Orlando, FL, USA; [2]Baylor University Medical Center, Dallas, TX, USA; [3]Desert AIDS Project, Palm Springs, CA, USA; [4]Bliss Healthcare Services, Orlando, FL, USA; [5]Infectious Disease Specialists of Atlanta, Decatur, GA, USA; [6]Midway Immunology and Research Center, Fort Pierce, FL, USA; [7]ViiV Healthcare, Research Triangle Park, NC, USA; [8]GlaxoSmithKline, Upper Providence, PA, USA; [9]GlaxoSmithKline, Uxbridge, UK; [10]ViiV Healthcare, Brentford, UK

14th Annual ACTHIV Conference; August 20-22, 2020; Virtual

Date of preparation: September 2020 PM-IE-DLL-PPT-200005

Introduction

- Rapid initiation of ART increases ART uptake, improves virologic suppression rates, and reduces onward HIV transmission[1-3]
- DTG/3TC is indicated for the treatment of HIV-1 in adults and adolescents above 12 years weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine
- Questions remain about its use in a test-and-treat setting due to potential transmitted resistance and BL HBV co-infection
  - Globally, the estimated prevalence of transmitted M184V mutations is 1%[4]
  - Although 3TC has activity against HBV infection, it is not recommended for use as monotherapy because of the risk of developing resistance[5]
- 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 the United States

1. Koenig et al. *PLoS Med*. 2017;14:e1002357. **2.** Rosen et al. *PLoS Med*. 2015;13:e1002015. **3.** Cohen et al. *N Engl J Med*. 2011;365:493-505. **4.** Vannappagari et al. *Antivir Ther*. 2019;24:393-404. **5.** Iser et al. *J Gastro Hepatol*. 2008;23:699-706.

Methods

- Eligible participants were ART-naive adults aged ≥18 years diagnosed with HIV within 14 days of study entry for whom laboratory results were not available at BL
- 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 with treatment adjustments remained on study
- Key efficacy analyses
  - **Observed:** Proportion of participants with plasma HIV-1 RNA <50 c/mL, regardless of ART regimen, among those with available HIV-1 RNA at Week 24
  - **ITT-E missing = failure:** Proportion of **all** participants with plasma HIV-1 RNA <50 c/mL at Week 24, regardless of ART regimen
    - Participants with HIV-1 RNA ≥50 c/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 c/mL
  - **FDA Snapshot:** Proportion of **all** participants with plasma HIV-1 RNA <50 c/mL at Week 24 still taking DTG/3TC
- Safety of DTG/3TC was assessed as incidence and severity of AEs, drug-related AEs, discontinuation of DTG/3TC due to AEs, and laboratory abnormalities

Renal impairment: Dovato is not recommended for use in patients with a creatinine clearance <50 mL/min*

Participant Characteristics

- Overall, 131 participants were enrolled in the study across 16 sites
- Through Week 24, DTG/3TC treatment was adjusted in 8 participants; 15 (11%) participants discontinued study before Week 24
  - 2 participants met the inclusion criteria for 2 positive HIV tests and enrolled in the study, but later they were found to be HIV negative and withdrew from study

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

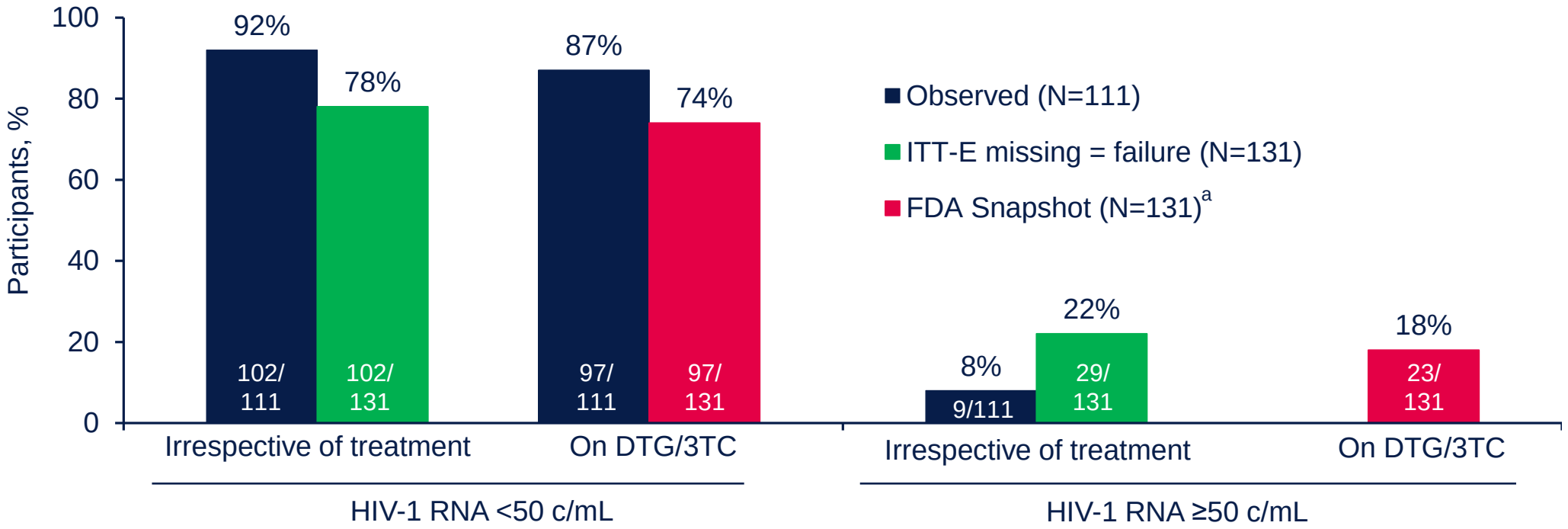
Characteristic	DTG/3TC (N=131)
Age, median (range), years	31 (18-63)
≥50 years, n (%)	20 (15)
Cisgender female, n (%)	10 (8)
Transgender female, n (%)	1 (<1)
Ethnicity, n (%)	
Hispanic/Latino	38 (29)
Not Hispanic/Latino	93 (71)
Race, n (%)	
Black/African American	61 (47)
White	65 (50)
Other	5 (4)
Time to enrollment since diagnosis, median (range), days	5 (0-15)
HIV-1 RNA, median (range), c/mL, n (%)[a,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[b]	389.0 (<20 to 1466)[d]
<200, n (%)	37 (28)
HBV co-infection, n (%)[b,e]	7 (5)
M184V resistance mutation, n (%)[b]	1 (<1)

[a]1 (<1%) participant had missing plasma HIV-1 RNA results at BL. [b]BL resistance was identified at Week 4, and HIV-1 viral load, CD4+ cell count, and HBV co-infection were identified at Week 1 from samples taken at BL. [c]Lower limit of quantification is <40. [d]Lower limit of quantification is <20. [e]2 participants with HBV co-infection remained on DTG/3TC.

Virologic Outcomes at Week 24

- Per observed analysis, among participants with available HIV-1 RNA assessment at Week 24 (N=111), 92% achieved HIV-1 RNA <50 c/mL and 98% achieved HIV-1 RNA <200 c/mL at Week 24, irrespective of ART
  - 87% achieved HIV-1 RNA <50 c/mL on DTG/3TC without a modified ART regimen
- Per ITT-E missing = failure analysis, among all participants, 78% achieved HIV-1 RNA <50 c/mL at Week 24, irrespective of ART
- ITT-E suppression rates were driven by non-virologic factors (ie, high withdrawal rate)
- At Week 24, median $\log_{10}$ decrease from BL in plasma HIV-1 RNA on any ART was 3.2 $\log_{10}$ c/mL (n=110)
- Per FDA Snapshot analysis, among all participants, 74% achieved HIV-1 RNA <50 c/mL at Week 24 and were still on DTG/3TC

Results of Efficacy Analyses: Virologic Outcomes at Week 24



[a]11 (8%) of 131 participants had no virologic data at Week 24.

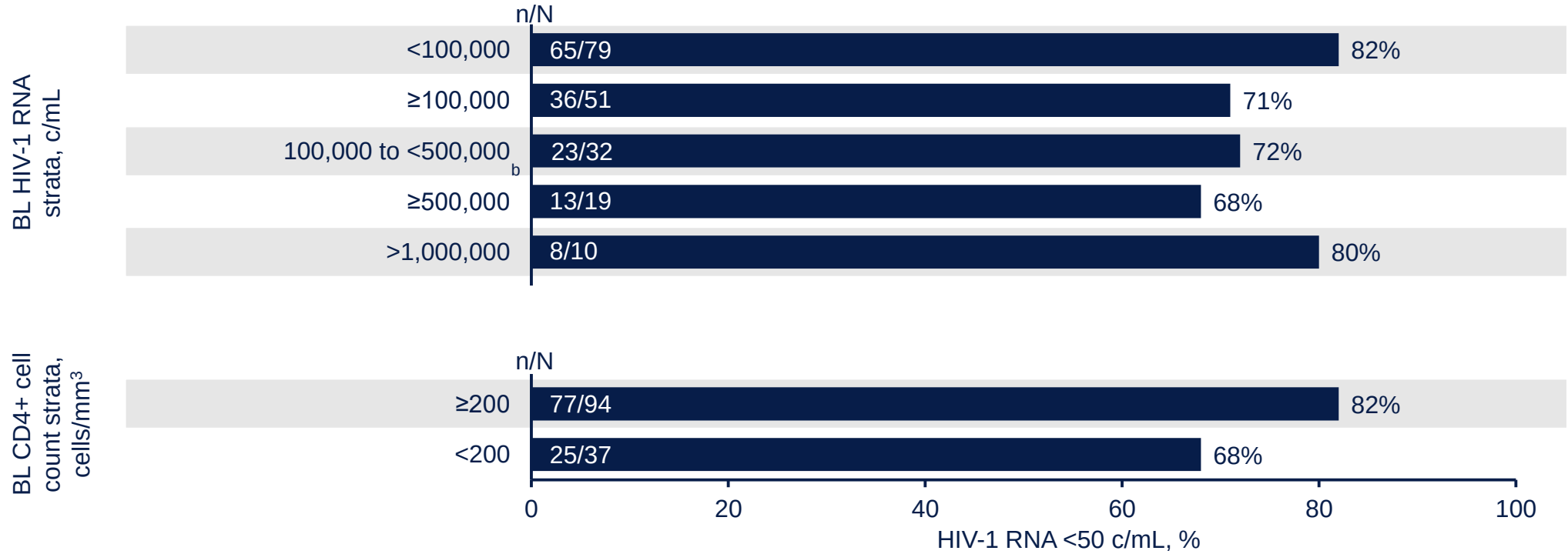
Summary of Virologic Outcomes at Week 24

	DTG/3TC, n/N (%)
Observed analysis	
HIV-1 RNA <50 c/mL	102/111 (92)
On DTG/3TC	97/111 (87)
On modified ART	5/111 (5)
ITT-E missing = failure analysis	
HIV-1 RNA <50 c/mL	**102/131 (78)**
HIV-1 RNA ≥50 c/mL	**29/131 (22)**
Data in window and HIV-1 RNA ≥50 c/mL	9/131 (7)
On study but missing data in window	5/131 (4)[a]
Discontinued study due to lost to follow-up/withdrew consent	12/131 (9)[b]
Discontinued study for other reasons	3/131 (2)[c]
FDA Snapshot analysis	
HIV-1 RNA <50 c/mL	**97/131 (74)**
HIV-1 RNA ≥50 c/mL	**23/131 (18)**
Data in window and HIV-1 RNA ≥50 c/mL	9/131 (7)
Discontinued for lack of efficacy	0
Discontinued study for other reason and HIV-1 RNA ≥50 c/mL	6/131 (5)
Change in ART	8/131 (6)
No virologic data	**11/131 (8)**

[a]3 participants missed HIV-1 RNA assessment at Week 24 due to COVID-19. [b]7 due to lost to follow-up; 5 withdrew consent (3 relocations, 1 incarceration, 1 no sub-reason). [c]3 due to physician decision (2 HIV negative, 1 did not show up to several scheduled appointments).

Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 24 by BL HIV-1 RNA[a] and CD4+ Cell Count (ITT-E Missing = Failure Analysis)

- Most participants with very high viral load at BL (>1,000,000 c/mL) achieved HIV-1 RNA <50 c/mL by Week 24
- No treatment-emergent HIV or HBV resistance-associated mutations were detected



[a]1 (<1%) participant had missing plasma HIV-1 RNA results at BL. [b]Of the 19 participants with BL viral load ≥500,000 c/mL, 13 (68%) were suppressed to <50 c/mL, 4 remain on study with viral load >50 c/mL (3 <200 c/mL), and 2 discontinued.

Participants Who Switched From DTG/3TC at Any Time Point by Week 24

- All participants with available data who had an ART adjustment and remained on study at Week 24 had HIV-1 RNA <50 c/mL

Reason for switch	Visit window
BL HBV	Week 1
BL HBV	Week 1
BL HBV	Week 4
BL HBV	Week 4
Decision by participant or proxy	Week 4
BL HBV	Week 8
BL M184V	Week 8
AE (rash)	Week 12; Week 12

AEs Reported Under Treatment With DTG/3TC

- DTG/3TC was well tolerated, with low rates of grade 2-5 drug-related AEs (2%) and serious AEs (2%)
- Median (IQR) percent change from BL in weight was 5.2% (1.4%-8.4%) with DTG/3TC at Week 24
- Absolute median increase in weight was 4.6 kg

Characteristic, n (%)	DTG/3TC (N=131)
Any AE	85 (65)
AEs occurring in >5% of participants	
Headache	10 (8)
Diarrhea	8 (6)
Fatigue	8 (6)
Drug-related AEs	9 (7)
Grade 2-5 AEs	2 (2)[a]
AEs leading to discontinuation of DTG/3TC	1 (<1)[b]
Any SAE	2 (2)[c]

[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. AEs were coded using MedDRA v23.0.

Conclusions

- These data demonstrate the feasibility and safety of using DTG/3TC as a first-line regimen in a test-and-treat (rapid ART) setting
- Among participants with available HIV-1 RNA assessment at Week 24, 92% achieved HIV-1 RNA <50 c/mL
- Few participants required modification to their ART regimen due to BL resistance or HBV co-infection; therefore, appropriate therapy adjustments in the presence of BL resistance or HBV co-infection can be performed safely via routine clinical care and careful follow-up care after rapid initiation of DTG/3TC

Prescribing Information
DOVATO dolutegravir 50mg/lamivudine 300mg tablets
See Summary of Product Characteristics (SmPC) before prescribing

Presentation: Film-coated tablet containing dolutegravir sodium equivalent to 50 mg dolutegravir and 300 mg lamivudine debossed with “SV-137” on one face.
Indication: HIV-1 in adults & adolescents above 12 years of age weighing ≥40kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine. **Dosing:** One tablet once daily with or without food. Use an additional 50mg tablet of dolutegravir approximately 12 hours after the dose of Dovato when co-administered with efavirenz, nevirapine, tipranavir/ritonavir, etravirine (without boosted PI), carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St John’s Wort or rifampicin. *Elderly:* Limited data in 65+ yrs. Not recommended in patients with creatinine clearance < 50 mL/min. Caution in severe hepatic impairment. **Contraindications:** Hypersensitivity to any ingredient. Co-administration with substrates of OCT-2 with narrow therapeutic windows, such as fampridine. **Special warnings/precautions:** Risk of hypersensitivity reactions. Discontinue dolutegravir and other suspect agents immediately. Risks of osteonecrosis, immune reactivation syndrome. Monitor LFTs in Hepatitis B/C co-infection and ensure effective Hepatitis B therapy. Caution with metformin: monitor renal function and consider metformin dose adjustment. Use with etravirine requires boosted PI or increased dose of dolutegravir. Use with Mg/Al-containing antacids requires dosage separation. Use with calcium, multivitamins or iron also requires dosage separation if not taken at the same time with food. Use with cladribine or emtricitabine not recommended. When possible, avoid chronic co-administration of sorbitol or other osmotic acting alcohols (see SmPC section 4.5). If unavoidable, consider more frequent viral load monitoring. **Fertility, pregnancy and lactation:** Human fertility - no data; animal fertility - studies indicate no effects. Women of childbearing potential (WOCBP) should be counselled about the potential risk of neural tube defects including consideration of effective contraceptive measures. If a woman plans pregnancy, the benefits and the risks of continuing treatment should be discussed with the patient. The safety and efficacy of a duel regime has not been studied in pregnancy. If a pregnancy is confirmed in the first trimester while on Dovato, the benefits and risks of continuing Dovato versus switching to another antiretroviral regimen should be discussed with the patient taking the gestational age and the critical time period of neural tube defect development into account (see SmPC section 4.6). There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. Do not breast-feed. **Side effects:** See SmPC for full details. Headache, GI disturbance, insomnia, abnormal dreams, depression, anxiety, dizziness, somnolence, rash, pruritus, alopecia, fatigue, arthralgia, myalgia, hypersensitivity, suicidal ideation or suicide attempt, hepatitis, blood dyscrasias, acute hepatic failure, pancreatitis, angioedema, rhabdomyolysis, lactic acidosis, peripheral neuropathy. Elevations of ALT, AST and CPK. **MA Nr:** EU/1/19/1370/001. **MA holder:** ViiV Healthcare BV, Van Asch van Wijckstraat 55H, 3811 LP Amersfoort, Netherlands. **Legal Category:** POM A. **Date of preparation of API:** July 2020. Code: PI-6305. Further information available from GlaxoSmithKline, 12 Riverwalk, Citywest, Business Campus, Dublin 24. Tel: 01-4955000.

Adverse events should be reported to the Health Products Regulatory Authority (HPRA) using an Adverse Reaction Report Form obtained either from the HPRA or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling (01) 6764971. Adverse events should also be reported to GlaxoSmithKline on 1800 244 255.

Working together in HIV

DOVATO is owned by or licenced to the ViiV Healthcare group of companies