Dolutegravir/lamivudine as a first-line regimen in a test-and-treat setting for newly diagnosed people living with HIV

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Objectives: Dolutegravir/lamivudine (DTG/3TC) is indicated for treatment-naive and experienced people with HIV; however, questions remain about its utility in a test-and-treat setting because of potential transmitted resistance and baseline hepatitis B virus (HBV) co-infection. We present feasibility and efficacy of DTG/3TC in newly diagnosed individuals in a test-and-treat setting.

Design: The single-arm STAT study evaluated DTG/3TC in a US test-and-treat setting.

Methods: Eligible adults initiated DTG/3TC 14 days or less after HIV-1 diagnosis without availability of baseline laboratory results. If baseline testing indicated DTG or 3TC resistance, HBV co-infection, or creatinine clearance less than 30 ml/min per 1.73 m^2, participants remained on study with treatment modification. Efficacy endpoints included proportions of participants with HIV-1 RNA less than 50 copies/ml at Week 24, regardless of antiretroviral regimen, among all participants (intention-to-treat exposed) and those with available HIV-1 RNA data (observed).

Results: Of 131 participants enrolled, 8% were female and 50% were non-white. Through Week 24, treatment was modified in eight participants [five with HBV co-infection, one with baseline M184V, one for adverse event (rash), one participant decision]. At Week 24, 78% (102/131) of all participants and 92% (102/111) of those with available data achieved HIV-1 RNA less than 50 copies/ml. Incidence of drug-related adverse events was low (7%); no drug-related serious adverse events occurred.

Conclusion: These data demonstrate the feasibility, efficacy, and safety of using DTG/3TC as a first-line regimen in a test-and-treat setting, with therapy adjustments for baseline resistance or HBV co-infection occurring safely via routine clinical care as needed [ClinicalTrials.gov, NCT03945981; see Supplemental Digital Content 1, video

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abstract (Video abstract summarizing the STAT study design and results), http://links.lww.com/QAD/C189].

Introduction

Timely access to care after initial HIV diagnosis is critical to successful HIV treatment [1]. Despite wide availability of antiretroviral therapy (ART), the US Centers for Disease Control and Prevention (CDC) reported that only 80% of people diagnosed with HIV in the United States in 2018 were linked to HIV medical care 1 month or less post-diagnosis [2].

One strategy to improve linkage of people living with HIV (PWH) to HIV care is initiation of ART immediately after a reactive HIV test, referred to as test–and–treat. The 2019 update to the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents also recommends initiating ART at diagnosis (when possible) or soon afterward to increase ART uptake, reduce time to linkage to care and virologic suppression, and improve virologic suppression rates in recently diagnosed individuals [3]. Despite these recommendations, several barriers can prevent rapid ART initiation, including clinical conditions requiring management beforehand and concerns regarding transmitted drug resistance [4,5].

Prevalence of transmitted integrase strand transfer inhibitor and lamivudine (3TC) resistance-associated mutations is low, occurring in up to 1% of ART-naive individuals [6–10]. These estimates are consistent with observations from the GEMINI-1/GEMINI-2 studies (conducted in 21 countries) in which three of 1974 (0.15%) participants failed screening because of transmitted M184V resistance [11].

Dolutegravir/3TC (DTG/3TC) is a two-drug fixed-dose combination (FDC) tablet regimen indicated for treatment-naive PWH or those who are virologically suppressed on a stable ART regimen with no history of treatment failure and no known or suspected resistance to the individual components [12]. Through 144 weeks of the identically designed, phase III GEMINI trials, DTG + 3TC demonstrated non-inferior virologic efficacy, similar numbers of participants meeting virologic failure criteria, and similar safety and tolerability profiles compared with the three-drug regimen DTG + tenofovir disoproxil fumarate/emtricitabine (FTC) in ART-naive PWH [13]. However, questions remain about its utility for rapid initiation due to potential transmitted resistance, baseline hepatitis B virus (HBV) co-infection, and high viral load.

In patients with HBV co-infection, 3TC is not recommended as monotherapy because of the risk of emergent resistance-associated HBV variants [14]. Although 3TC has antiviral activity against HBV, resistance rates of 15–32% after 1 year of treatment have been reported in patients taking 3TC monotherapy, with mutations rarely detected before 36 weeks [15].

We present results from the Week 24 primary analysis of the STAT study, evaluating DTG/3TC FDC as a first-line test-and-treat ART regimen. The strategy of allowing ART adjustment for identified HBV co-infection or underlying viral resistance was also assessed for efficacy without added risk of failure or emergent resistance due to these conditions.

Methods

Study design and population

STAT (ClinicalTrials.gov, NCT03945981) is a phase 3b, multi-center, open-label, single-arm, 52-week pilot study evaluating the feasibility, efficacy, and safety of using DTG/3TC FDC as a first-line regimen in a US test-and-treat setting. Eligible participants were ART-naive adults (aged ≥18 years) with a newly confirmed HIV-1 diagnosis (within 14 days of screening), no prior history of hepatic or renal impairment, and no known or suspected HBV co-infection. For a confirmed diagnosis, participants must have had positive results from two different HIV rapid tests or have had positive results using a US Food and Drug Administration (FDA)-approved fourth-generation assay antigen/antibody combination immunoassay or third-generation immunoassay that detects and differentiates HIV-1 and HIV-2 antibodies, confirmed by HIV western blot or an HIV-1 RNA. Participants who received previous post-exposure prophylaxis or pre-exposure prophylaxis were eligible to participate if the last dose was taken more than 6 months from HIV diagnosis or if HIV seronegativity was documented 2 months after the last prophylactic dose and before the date of HIV diagnosis.

The current study was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines, following the principles of the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, with approval of the protocol and all study-related documents and written informed consent obtained before study initiation.

Procedures

Participants were screened and enrolled on the same day (i.e. baseline) and started DTG 50 mg/3TC 300 mg FDC before availability of baseline laboratory results. Baseline laboratory results and baseline genotype for HIV-1 drug resistance mutations [assessed using standard PhenoSense and GenoSure testing methods (Monogram Biosciences, South San Francisco, California, USA)] were available at Week 1 or by Week 4. Participants with creatinine clearance less than 30 ml/min per 1.73 m^2, evidence of chronic HBV infection, or grade 3 or 4 laboratory abnormalities were evaluated for potential modification of their current DTG/3TC treatment. For participants with chronic HBV infection, testing for HBV 3TC resistance was performed using samples from Week 1 and Week 4 (depending on when ART modification occurred) as well as baseline samples. If baseline mutations associated with resistance to DTG or 3TC were detected, the ART regimen would be adjusted. Participants could also have their treatment modified for other intervention criteria such as pregnancy or safety considerations and remain on study.

Virologic non-response was defined as a confirmed decrease in baseline plasma HIV-1 RNA less than 2.0 log$_{10}$ copies/ml at Week 8 (unless plasma HIV-1 RNA is <200 copies/ml), confirmed plasma HIV-1 RNA at least 1000 copies/ml at Week 12, or confirmed plasma HIV-1 RNA at least 200 copies/ml on or after Week 24. Virologic rebound was defined as confirmed rebound in plasma HIV-1 RNA to at least 200 copies/ml after prior suppression to less than 200 copies/ml. For participants who met virologic failure criteria, plasma samples were analyzed for genotypic and phenotypic HIV-1 resistance testing using GenoSure and PhenoSense testing. Participants who met confirmed virologic failure criteria could remain on study; however, their ART regimen may have been modified based on resistance testing results. Lymphocyte subsets were assessed at baseline and Weeks 4, 12, and 24. Disease progression and HIV-associated conditions were assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults [16].

Safety was assessed throughout the study, including adverse events, serious adverse events (SAEs), adverse events leading to discontinuation of DTG/3TC, drug-related adverse events, and laboratory abnormalities. Clinical chemistry and weight were assessed at baseline and Weeks 4, 8, 12, and 24. Laboratory and vital signs data were summarized by visit for participants on treatment with DTG/3TC only. Adverse events were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, March 2017.

Outcomes and statistical analyses

This is a single-arm study with no formal hypothesis testing. Therefore, the sample size was not statistically powered and was determined to require approximately 120 participants to allow estimation of the primary endpoint with sufficient precision [95% confidence interval (CI) width ≤15% assuming proportion of participants with HIV-1 RNA < 50 copies/ml ≥80%]. All enrolled participants who received at least one dose of DTG/3TC formed the intention-to-treat exposed (ITT-E) and safety populations. The primary endpoint was the proportion of participants in the ITT-E population with plasma HIV-1 RNA less than 50 copies/ml at Week 24; treatment modifications were not penalized (ITT-E missing = failure analysis). Missing HIV-1 RNA data for any reason (e.g. study withdrawal or missing data while on study) at Week 24 was considered HIV-1 RNA at least 50 copies/ml. Other key efficacy endpoints included the proportion of participants with plasma HIV-1 RNA less than 50 copies/ml among those with available HIV-1 RNA at Week 24 (treatment modifications were not penalized; observed analysis) and the proportion of participants in the ITT-E population with HIV-1 RNA less than 50 copies/ml at Week 24 still on DTG/3TC (treatment modifications were penalized; FDA Snapshot algorithm). Other secondary endpoints included the proportion of participants with modification from the first-line regimen, time to suppression from enrollment, and change from baseline in CD4$^+$ cell count and CD4$^+$/CD8$^+$ cell count ratio at Week 24. Exploratory endpoints included the proportion of participants with plasma HIV-1 RNA less than 50 copies/ml summarized by participant subgroups and change from baseline in overall symptom bother score [17]. Non-parametric Kaplan−Meier method was used to estimate median time to virologic suppression (i.e. HIV-1 RNA < 50 copies/ml) regardless of treatment modification.

The Symptom Distress Module [17], a 20-item questionnaire that evaluates patient-reported distress linked to symptoms associated with HIV or treatment, was administered at baseline and Weeks 4, 8, 12, and 24. Symptom bother score was calculated as the sum of the bothering level of each symptom (0 = does not have symptom, 1 = it doesn't bother me, up to 4 = it bothers me a lot) and ranged from 0 to 80. Missing values or values after participants switched from DTG/3TC were imputed using last observation carried forward (LOCF).

Results

Study participants

Of 133 participants screened, 131 were enrolled and included in the ITT-E and safety populations. Demographics and baseline characteristics are shown in Table 1. Fifty-five (42%) participants had a current psychiatric disorder and 11 (8%) reported previous psychiatric disorders. Fifteen (11%) participants discontinued study by Week 24: seven were lost to follow-up, five withdrew consent, and three discontinued based on physician decision (two had false-positive HIV tests at diagnosis, one missed several scheduled appointments). Through Week 24, eight (6%) participants switched from DTG/3TC but remained on study, five for baseline HBV co-infection, one for baseline M184V, and two for other reasons (adverse event of rash and participant decision). Two participants with baseline HBV co-infection did not modify their ART regimen, as their repeat HBV DNA tests came back unquantifiable, and investigators felt there was no evidence of active HBV replication. One additional participant switched from DTG/3TC after the Week 24 HIV-1 RNA assessment because of incident pregnancy.

Efficacy

At Week 24, 102 of 131 [78% (95% CI, 70–85%)] participants achieved HIV-1 RNA less than 50 copies/ml (ITT-E missing = failure analysis; Table 2); this includes five participants who had the initial DTG/3TC regimen modified before Week 24. Of the remaining 29 participants, nine (7%) had HIV-1 RNA at least 50 copies/ml at Week 24, 15 (11%) discontinued from study, and five (4%) missed the HIV-1 RNA assessment while on study (three due to the COVID-19 pandemic). Among participants with available HIV-1 RNA data under any ART at Week 24 ($n = 111$), 102 (92%) had HIV-1 RNA less than 50 copies/ml, and 109 (98%) had HIV-1 RNA less than 200 copies/ml (observed analysis; Table 2). Ninety-seven of 131 [74% (95% CI, 66–81%)] participants achieved HIV-1 RNA less than 50 copies/ml and were still on DTG/3TC at Week 24 (FDA Snapshot analysis; Table 2). Two participants met confirmed virologic failure criteria (virologic rebound) at Week 24, with both remaining on DTG/3TC at the discretion of the investigator until results of subsequent HIV-1 resistance testing became available. No treatment-emergent HIV resistance-associated mutations were detected. Of the nine evaluable participants with HIV-1 RNA at least 50 copies/ml at Week 24, all had baseline HIV-1 RNA more than 100 000 copies/ml (four of whom had baseline HIV-1 RNA > 500 000 copies/ml). Seven of these nine participants had HIV-1 RNA less than 200 copies/ml in the Week 24 window, and the other two had HIV-1 RNA 302 and 247 copies/ml at Week 24; these two participants met confirmed virologic failure criteria, and their baseline viral loads were 13 987 640 and 159 214 copies/ml, respectively. All nine participants had a decline at least $2.8 \log_{10}$ copies/ml from baseline HIV-1 RNA values (see Supplemental

Table 1. Baseline demographics and participant characteristics (intention-to-treat exposed 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)[a]
Enrolled on day of diagnosis, n (%)	34 (26)
HIV-1 RNA, median (range) (copies/ml[b])	63 056 (<40–68 706 840)[c]
<100 000, n (%)	79 (60)
100 000 to <500 000, n (%)	32 (24)
500 000 to <1 000 000, n (%)	9 (7)
≥1 000 000, n (%)	10 (8)
CD4$^+$ cell count, median (range) (cells/µl)	389.0 (<20–1466)[d]
<200, n (%)	37 (28)
HBV co-infection, n (%) (95% CI)[e,f]	7 (5) [2–11]
M184V resistance mutation, n (%)[e]	1 (<1)
Major INSTI resistance mutation, n (%)[e]	0

DTG/3TC, dolutegravir/lamivudine; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor.
[a]One participant joined the study past the 14-day window after diagnosis (15 days).
[b]One (<1%) participant had missing plasma HIV-1 RNA results at baseline.
[c]Lower limit of quantification is <40.
[d]Lower limit of quantification is <20.
[e]Baseline resistance was identified at Week 4 and HBV co-infection was identified at Week 1 from samples taken at baseline.
[f]Two participants with HBV co-infection remained on DTG/3TC.

Table 2. Summary of virologic outcomes at Week 24.

	DTG/3TC, *n/N* (%)
Observed analysis	
Participants with available HIV-1 RNA	111/131 (85)
HIV-1 RNA < 50 copies/ml[a]	102/111 (92)
On DTG/3TC	97/102 (95)
On modified ART	5/102 (5)
ITT-E missing = failure analysis	
HIV-1 RNA < 50 copies/ml[a]	102/131 (78)
HIV-1 RNA ≥ 50 copies/ml	29/131 (22)
Data in window and HIV-1 RNA ≥ 50 copies/ml	9/131 (7)[b]
On study but missing data in window	5/131 (4)[c]
Discontinued study due to lost to follow-up/withdrew consent	12/131 (9)[d]
Discontinued study for other reasons	3/131 (2)[e]
FDA Snapshot analysis	
HIV-1 RNA < 50 copies/ml[f]	97/131 (74)
HIV-1 RNA ≥ 50 copies/ml	23/131 (18)
Data in window and HIV-1 RNA ≥ 50 copies/ml	9/131 (7)
Discontinued for lack of efficacy	0 (0)
Discontinued study for other reason and HIV-1 RNA ≥ 50 copies/ml	6/131 (5)
Change in ART	8/131 (6)
No virologic data	11/131 (8)

ART, antiretroviral therapy; COVID-19, coronavirus disease 2019; DTG/3TC, dolutegravir/lamivudine; ITT-E, intention-to-treat exposed.
[a]Includes participants on DTG/3TC (*n* = 97) or modified ART (*n* = 5).
[b]All nine participants were on DTG/3TC.
[c]Three participants missed HIV-1 RNA assessment at Week 24 due to COVID-19.
[d]Seven due to lost to follow-up; five withdrew consent (three relocations, one incarceration, one no subreason).
[e]Three due to physician decision (two HIV negative, one did not show up to several scheduled appointments).
[f]Includes participants on DTG/3TC only.

Digital Content 2, http://links.lww.com/QAD/C190, table showing viral load during study for participants with HIV-1 RNA ≥ 50 copies/ml at Week 24).

Of the eight participants who switched from DTG/3TC before Week 24, five achieved HIV-1 RNA less than 50 copies/ml; the other three did not have available Week 24 data (Table 3). At Week 24, six of the seven participants with baseline HBV co-infection achieved HIV-1 RNA less than 50 copies/ml, two on DTG/3TC (who had no active HBV replication) and four on modified ART; the other participant was on study but missing data in the Week 24 window (a late Week 24 visit showed HIV-1 RNA less than 50 copies/ml in this participant). No treatment–emergent HBV resistance–associated mutations were detected through Week 24. The participant with baseline M184V mutation achieved HIV-1 RNA less than 50 copies/ml by Week 8, then switched to another regimen (DTG/rilpivirine FDC) and withdrew consent at Week 12 because of relocation.

Median time to suppression was 35 days (95% CI, 30–55). At Week 24, median change from baseline in $CD4^+$ cell count and $CD4^+/CD8^+$ cell count ratio under DTG/3TC treatment was 170 cells/μl [interquartile range (IQR), 90–255] and 0.26 (IQR, 0.12–0.42), respectively.

Table 3. Participants who switched from dolutegravir/lamivudine before the Week 24 HIV-1 RNA assessment.

Reason for switch	Visit window	Modified ART	Plasma HIV-1 RNA at Week 24
Baseline HBV	Week 1	DTG/3TC + TAF	<40 copies/ml
Baseline HBV	Week 1	BIC/FTC/TAF	NA[a]
Baseline HBV	Week 4	DTG + TDF/FTC	<40 copies/ml
Baseline HBV	Week 4	BIC/FTC/TAF or DTG + TDF/FTC[b]	49 copies/ml
Decision by participant or proxy	Week 4	BIC/FTC/TAF	NA[c]
Baseline HBV	Week 8	DTG/3TC + TAF	<40 copies/ml
Baseline M184V	Week 8	DTG/RPV	NA[d]
Adverse event (rash)	Week 12; Week 12	DRV/COBI/FTC/TAF; BIC/FTC/TAF[e]	<40 copies/ml

ART, antiretroviral therapy; BIC, bictegravir; COBI, cobicistat; DRV, darunavir; DTG/3TC, dolutegravir/lamivudine; FTC, emtricitabine; HBV, hepatitis B virus; NA, not available; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
[a]Participant on study but missing data in window. Participant had HIV-1 RNA < 40 copies/ml at Week 36.
[b]Participant participates in another double-blind clinical trial with a tenofovir-based regimen; switched to either Biktarvy (Gilead Sciences, Inc, Foster City, California, USA) or Truvada (Gilead Sciences, Inc) + Tivicay (ViiV Healthcare, Research Triangle Park, North Carolina, USA).
[c]Participant withdrew consent after switch from DTG/3TC.
[d]Participant had HIV-1 RNA 18 752 copies/ml at baseline, <40 copies/ml on Day 47, switched to DTG/RPV on Day 49, and had last HIV-1 RNA 54 copies/ml on Day 57; participant withdrew consent (due to relocation) on Day 106.
[e]Participant switched ART twice.

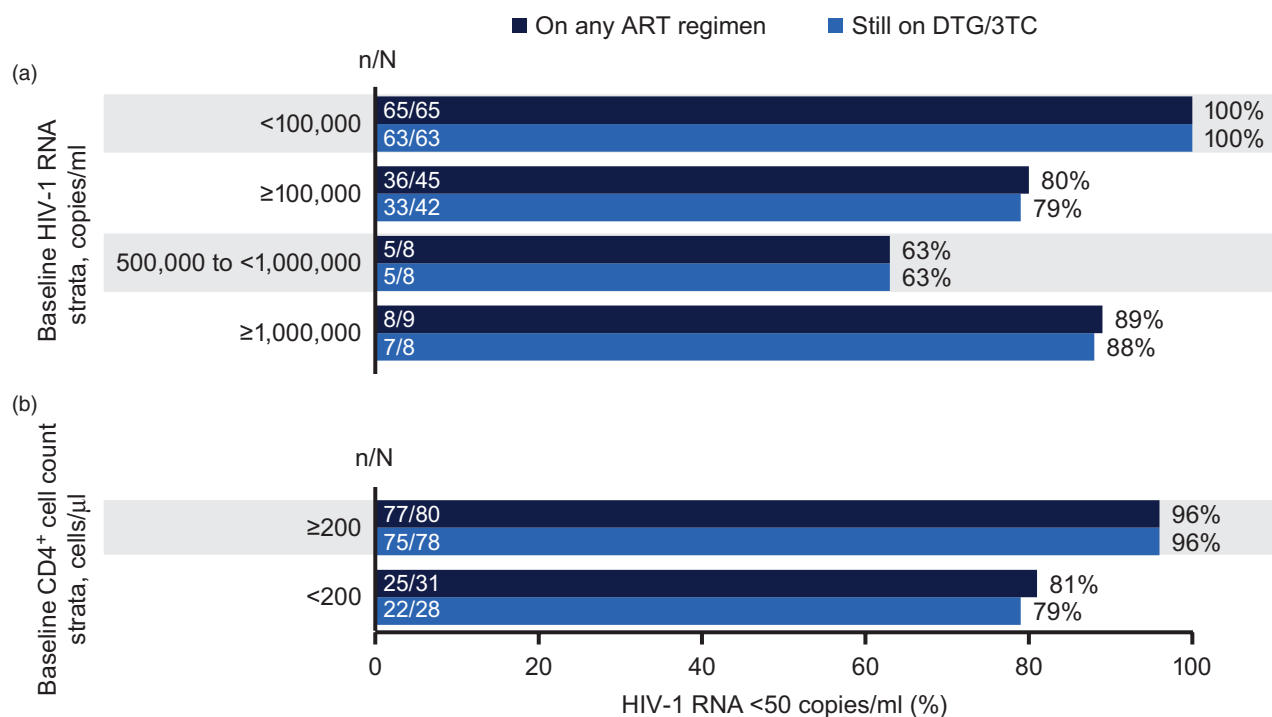■ On any ART regimen   ■ Still on DTG/3TC

Fig. 1. Proportion of participants with plasma HIV-1 RNA less than 50 copies/ml at Week 24 among participants with available HIV-1 RNA assessment by baseline (a) HIV-1 RNA[a] and (b) CD4+ cell count (observed analysis). [a]One (<1%) participant had missing plasma HIV-1 RNA results at baseline.

According to the ITT-E missing = failure analysis, the proportion of participants achieving HIV-1 RNA less than 50 copies/ml was consistent across baseline demographic subgroups including current sex [female, 9/11 (82%); male, 93/120 (78%)], age [<50 years, 86/111 (77%); ≥50 years, 16/20 (80%)], and race [white, 52/65 (80%); non-white, 50/66 (76%)]. Among participants with baseline HIV-1 RNA at least 1000 000 and those with CD4+ cell count less than 200 cells/μl, 8/10 (80%) and 25/37 (68%) achieved HIV-1 RNA less than 50 copies/ml at Week 24, respectively. Of the 12 participants with CD4+ cell count less than 200 cells/μl who did not reach HIV-1 RNA less than 50 copies/ml at Week 24, seven remained on study with HIV-1 RNA at least 50 copies/ml at Week 24 and five discontinued (three lost to follow-up, one physician decision, one participant decision). Among the 19 participants with baseline HIV-1 RNA at least 500 000 copies/ml, 13 (68%) were suppressed to less than 50 copies/ml at Week 24, four remain on study with HIV-1 RNA at least 50 copies/ml at Week 24 (three achieved HIV-1 RNA < 200 copies/ml), and two discontinued.

Among nine participants with available viral load assessment at Week 24 under any ART regimen and baseline HIV-1 RNA at least 1000 000 copies/ml, eight (89%) achieved HIV-1 RNA less than 50 copies/ml (observed analysis; Fig. 1).

Safety

Eighty-five (65%) participants experienced an adverse event on DTG/3TC through Week 24 (Table 4). The most commonly reported adverse events (occurring in

Table 4. Adverse events reported under treatment with dolutegravir/lamivudine.

n (%)	DTG/3TC, N = 131[a]
Any AE	85 (65)
AEs occurring in >5% of participants	
Headache	10 (8)
Diarrhea	8 (6)
Fatigue	8 (6)
Most common AEs by SOC occurring in >15% of participants	
Infections and infestations	39 (30)
Gastrointestinal disorders	29 (22)
Nervous system disorders	22 (17)
Skin and subcutaneous tissue disorders	21 (16)
Drug-related AEs	9 (7)
Grade 2–5 AEs	2 (2)[b]
AEs leading to discontinuation of DTG/3TC	1 (<1)[c]
Any SAE	2 (2)[d]
AEs of special interest	
Psychiatric disorders	19 (15)

AE, adverse event; DTG/3TC, dolutegravir/lamivudine; SAE, serious AE; SOC, system organ class.
[a]Reported values indicate the number of participants with AEs.
[b]All AEs were grade 2.
[c]Rash. The event resolved.
[d]Two SAEs occurred (cellulitis, streptococcal bacteremia). No fatal SAEs occurred. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v23.0.

>5% of participants) were headache, diarrhea, and fatigue. Nine (7%) participants experienced a drug-related adverse event; all drug-related adverse events were grade 1 except for grade 2 headache and pruritis, which occurred in one participant, and grade 2 increased weight in another. Only one adverse event led to discontinuation of DTG/3TC, a grade 1 rash that resolved after discontinuing study treatment. SAEs occurred in two (2%) participants under DTG/3TC treatment: cellulitis ($n = 1$) and streptococcal bacteremia ($n = 1$); none were fatal. Psychiatric disorders were reported in 19 (15%) participants under DTG/3TC treatment; the most common were anxiety ($n = 6$, 5%), insomnia ($n = 6$, 5%), and depression ($n = 5$, 4%). Thirteen of these 19 participants had current or prior psychiatric conditions at baseline. All psychiatric adverse events were grade 1 or 2.

At baseline, median (IQR) weight was 74.2 kg (66.0–86.7). At Week 24, median (IQR) weight under treatment with DTG/3TC was 78.8 kg (68.7–90.1) for a median (IQR) percentage increase in body weight from baseline of 5.2% (1.4–8.4%). Few grade 3 or 4 chemistry toxicities occurred under DTG/3TC treatment: decreased creatinine clearance using the Chronic Kidney Disease Epidemiology Collaboration equation ($n = 7$, 5%), increased creatinine ($n = 2$, 2%), increased aspartate aminotransferase ($n = 1$, <1%), increased bilirubin ($n = 1$, <1%), and increased glucose ($n = 1$, <1%).

Symptom bother score

At baseline, median (IQR) symptom bother score was 8 (3–21). At Week 24, median (IQR) decrease from baseline in symptom bother score under DTG/3TC treatment using LOCF data was 3 (10–0).

Discussion

Primary results from the STAT study demonstrate the feasibility, efficacy, and safety of using DTG/3TC as a first-line regimen in a test-and-treat approach. When using a test-and-treat approach, baseline genotypic and laboratory data are not available before therapy initiation; therefore, transmitted resistance and HBV co-infection are important considerations. In STAT with participants treated within 15 days of diagnosis, including same-day ART initiation in 34 (26%) participants, few required ART modifications for HBV co-infection ($n = 5$) or baseline 3TC resistance ($n = 1$). All participants who switched from the initial DTG/3TC regimen with available data at Week 24 achieved HIV-1 RNA less than 50 copies/ml. The one participant with baseline M184V achieved HIV-1 RNA less than 50 copies/ml by Week 8, before ART adjustment. Although the number of ART modifications was minimal, these results suggest that appropriate therapy adjustments in the presence of baseline resistance or HBV co-infection can be performed safely via

routine clinical care and careful follow-up in a test-and-treat setting with DTG/3TC and that this would be required in a small proportion of US patients.

The observed analysis, which included all 111 participants with available Week 24 HIV-1 RNA data, demonstrated achievement of HIV-1 RNA less than 50 copies/ml in 92% ($n = 102$), irrespective of ART received. The observed analysis is critical to answering the clinical practice question – whether a test-and-treat approach using DTG/3TC, which allowed for ART adjustment for identified HBV co-infection or underlying viral resistance, could provide efficacy without added risk of failure or de novo resistance due to these conditions.

The ITT-E missing = failure analysis evaluates the probability of a newly diagnosed individual with HIV-1 immediately initiating DTG/3TC, remaining in care, and being suppressed (HIV-1 RNA < 50 copies/ml) 24 weeks later regardless of ART regimen. Among all participants, 78% (102/131) had HIV-1 RNA less than 50 copies/ml at Week 24, irrespective of ART (ITT-E missing = failure). Seven (5%) participants were lost to follow-up, more than previous studies (GEMINI trials, 2%) [18] or other test-and-treat studies (DIAMOND, 3%) at Week 24 [19], but evaluation of these withdrawals showed no specific pattern. Two (2%) participants had false-positive HIV tests at diagnosis and therefore withdrew.

Thirteen of 19 participants with HIV-1 RNA at least 500 000 copies/ml at baseline (including 8/10 with ≥1 000 000 copies/ml) were suppressed to less than 50 copies/ml at Week 24, and two discontinued. Of the four remaining on study with HIV-1 RNA at least 50 copies/ml at Week 24, three achieved HIV-1 RNA less than 200 copies/ml. The relatively short observation period may not have allowed adequate time for virologic suppression in some participants with very high baseline viral loads. These results are consistent with those in participants with high baseline viral load from the pooled GEMINI trials, in which 13 of 716 (2%) participants had HIV-1 RNA more than 500 000 copies/ml at baseline, with eight (62%) suppressed to HIV-1 RNA less than 50 copies/ml by Week 24 [20].

Another recent phase 3 prospective study with a test-and-treat approach was the DIAMOND trial (NCT03227861), which assessed darunavir/cobicistat/FTC/TAF (DRV/COBI/FTC/TAF) [21]. However, in DIAMOND, participants discontinuing DRV/COBI/FTC/TAF also discontinued from study, not allowing for efficacy evaluation in those requiring treatment modification for any reason. DIAMOND participants had a median age of 28 years, 87% were male, 40% were non-white, and median (range) baseline viral load was 38 700 (19–144 000 000) copies/ml. Overall, 90% (88/98) of participants with available 24-week assessments in DIAMOND achieved HIV-1 RNA less than 50

copies/ml, and 92% (97/106 on DTG/3TC) achieved HIV-1 RNA less than 50 copies/ml in STAT [19].

A limitation of STAT is that it only evaluated DTG/3TC in a test-and-treat approach in the United States, and results may not be generalizable to other geographic regions with greater HIV burden, increased prevalence of transmitted resistance and HBV co-infection, and fewer healthcare resources. Generalizability may also be limited by the single-arm, non-comparative study design; however, this trial was primarily intended to assess the feasibility of using DTG/3TC in a rapid ART initiation approach. The primary evaluation of efficacy in treatment-naive adults comes from the GEMINI studies, but STAT provides additional data.

Conclusion

These data offer further evidence that DTG/3TC is an effective, well tolerated, two-drug single-tablet option that offers newly diagnosed PWH the ability to start effective therapy using fewer antiretroviral agents. Based on prior studies, advantages of initiating DTG/3TC include reduced short-term and long-term toxicity secondary to reduced cumulative ART exposure, fewer drug−drug interactions, and possible metabolic advantages. In addition, DTG/3TC may be a cost-effective option for PWH. Considering the high lifetime costs associated with ART [22], DTG/3TC has been associated with cost savings when compared with three-drug or four-drug regimens [23]. Despite questions about its utility, primary results from STAT support the feasibility of rapid DTG/3TC initiation and provide preliminary evidence that ART modifications can be performed safely via routine clinical care in the presence of baseline resistance or HBV co-infection to achieve virologic efficacy, thus providing the potential advantages of DTG/3TC as soon as the day of diagnosis.

Conflicts of interest

C.-P.R. has received grants from ViiV Healthcare, Gilead, and Janssen and has served on advisory boards/speakers bureaus for ViiV Healthcare, Gilead, and Theratechnologies. T.S. has received grants from Gilead, ViiV Healthcare, GlaxoSmithKline (GSK), and Anchor and has served on advisory boards/speakers bureaus for ViiV Healthcare and Gilead. M.R. has received grants and served on advisory boards/speaker bureaus for Gilead, ViiV Healthcare, Janssen, and Merck. P.A.L., J.E.M., M.D., M.R.U., B.R.W., D.M., C.N., J.v.W., and A.Z. are employees of ViiV Healthcare and shareholders in GSK; M.R.U. has a patent WO2011/094150 pending. K.A. is an employee of and shareholder in GSK. M.B., R.O., and A.W. have nothing to disclose. This study was funded by ViiV Healthcare.

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