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Original article

Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, non-inferiority, open-label, Phase IIIb study

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Background: Simplified dosing regimens are important for patients who face challenges in adhering to HIV-1 therapy. We investigated the safety and virological efficacy of switching to once-daily abacavir/dolutegravir/lamivudine (ABC/DTG/3TC).

Methods: The STRIIVING study was a randomized, open-label, Phase IIIb study in adults with HIV-1 RNA <50 copies/ml on antiretroviral therapy (ART) at enrolment (ClinicalTrials.gov identifier, NCT02105987). Subjects were randomly assigned to switch to ABC/DTG/3TC once daily for 48 weeks (early-switch group) or continue current ART for 24 weeks and then switch to ABC/DTG/3TC (late-switch group). The primary end point was the proportion of subjects with HIV-1 RNA <50 copies/ml at week 24.

Results: Of 553 subjects enrolled, 275 were randomly assigned to switch immediately to ABC/DTG/3TC and 278 continued on current ART. At week 24, 85% and 88% of subjects who switched to ABC/DTG/3TC or remained on current ART, respectively, were virologically suppressed, indicating that ABC/DTG/3TC was non-inferior (difference in proportion, -3.4%; 95% CI -9.1, 2.4). At week 48, 83% and 92% were virologically suppressed in the early- and late-switch groups, respectively. Adverse events were reported more frequently with ABC/DTG/3TC (66%) than with current ART (47%) by week 24, and in the late-switch group, 60% of subjects reported adverse events post-switch. Pharmacokinetic data supported immediate switch. HIV Treatment Satisfaction Questionnaire scores improved in participants switching to ABC/DTG/3TC versus current ART.

Conclusions: Data demonstrating non-inferiority of switching to ABC/DTG/3TC versus continuing current ART support ABC/DTG/3TC as an option when considering switch regimens in HIV-1-infected adults with stable viral suppression.

Introduction

Combination antiretroviral therapy (ART) has facilitated effective management of HIV infection for over two decades. New challenges in HIV therapy are emerging, including an ageing population of patients and the associated risks of comorbid conditions and multiple drug interactions [1]. A large-scale survey from 1 January 2002 to 30 June 2009 showed that within 3 years of ART initiation, treatment was modified or interrupted for more than half of patients, largely because of side effects, desire for dosing simplification or treatment non-compliance [2]. Therefore, despite the success of existing ART regimens, there is a continued need for novel

therapeutic agents with improved tolerability and simplified dosing regimens.

Dolutegravir (DTG) is a novel integrase inhibitor (INI) with low-to-moderate between-person pharmacokinetic variability and a 14-h plasma half-life, which supports once-daily dosing and avoids the need for pharmacokinetic boosters, thereby avoiding the risks of many booster-related drug–drug interactions [3]. DTG has little effect on drug-metabolizing enzymes and poses minimal drug-interaction risk or need for dose adjustments for medications such as oral contraceptives, anti-mycobacterial agents, statins and antiviral hepatitis agents, although antacids and multivitamins can reduce DTG exposure if taken at the same time [4,5]. DTG presents a higher barrier to genetic resistance compared with raltegravir and elvitegravir and is known to be effective against mutations selected by other antiretroviral therapies [6–10]. When combined with the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir and lamivudine in the SINGLE study, DTG demonstrated a superior rate of virological suppression (HIV-1 RNA <50 copies/ml) in ART-naive subjects compared with a regimen of efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) [10]. The frequency of adverse events (AEs) was lower with abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) than with EFV/TDF/FTC, leading to better treatment-related outcomes with ABC/DTG/3TC. On the basis of the results of the SINGLE study and other Phase III trials [8,10–13], ABC/DTG/3TC fixed-dose combination (FDC) was approved for marketing in the United States and Canada in 2014 under the brand name Triumeq® (ViiV Healthcare, Research Triangle Park, NC, USA) [14].

The effectiveness of ABC/DTG/3TC in stably suppressed ART-experienced adults has not been investigated. Establishing ABC/DTG/3TC as an option for regimen switching in these subjects may improve treatment satisfaction, facilitate treatment adherence and improve therapeutic outcomes.

Methods

Subject population

Subjects were HIV-1-positive men and women ≥18 years of age who had achieved and maintained virological suppression (HIV-1 RNA <50 copies/ml) on an ART regimen that had been stable for ≥6 months prior to screening. The inclusion criteria required that subjects have achieved plasma HIV-1 RNA level <50 copies/ml within 6 months of starting an initial ART regimen with no plasma HIV-1 RNA level >200 copies/ml following initial suppression. Allowable ART regimens at baseline included dual NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), an INI (raltegravir or elvitegravir) or a protease inhibitor (PI) with or without pharmacokinetic boosting. Subjects who were pregnant or breastfeeding, had hepatic impairment, were positive for hepatitis B surface antigen, had an anticipated need for hepatitis C treatment, were human leukocyte antigen (*HLA)-B*5701* positive, had a history of only mono- or dual-NRTI therapy prior to starting current ART or had active disease defined under Category C from the Centers for Disease Control and Prevention (CDC; except for Kaposi's sarcoma and historic $CD4^+$ T-cell count <200 cells/mm^3) were not eligible. All subjects gave written informed consent before the study.

Study design

STRIIVING was a 48-week, Phase IIIb, randomized, open-label, active-controlled, multicentre, parallel-group, non-inferiority study conducted at 96 sites in the United States and Canada. After a screening period of up to 28 days, eligible subjects were randomly assigned 1:1 to receive a single tablet containing ABC 600 mg/DTG 50 mg/3TC 300 mg once daily (early-switch group) or continue their current ART regimen for 24 weeks (late-switch group). Randomization was stratified by third-agent class (PI, INI or NNRTI) in the subjects' entry ART regimens. After 24 weeks, all subjects in both treatment arms were treated with ABC/DTG/3TC. Data from initiation of the trial (6 May 2014) through a cutoff date of 17 April 2015 were included in the week 24 analysis. The study was completed on 29 December 2015. The study was conducted under approval from national, regional or investigational site ethics committees in accordance with the 2008 Declaration of Helsinki. Protocol summaries were posted to www.clinicaltrials.gov (NCT02105987) and the GSK Clinical Study Register (201147).

Procedures

The primary efficacy end point was the proportion of subjects who maintained plasma HIV-1 RNA levels <50 copies/ml at 24 weeks (US Food and Drug Administration Snapshot [missing, switch or discontinuation equals failure] algorithm) [15]. Analysis of plasma HIV-1 RNA was done using the Abbott RealTime HIV-1 assay (Abbott Molecular, Des Plaines, IL, USA). Secondary end points included change from baseline to 24 weeks in $CD4^+$ T-cell count, frequency and severity of AEs, proportion of subjects who discontinued because of AEs, treatment satisfaction and analysis of specific biomarker analytes associated with renal function and bone turnover. Plasma concentrations of DTG, EFV and nevirapine (NVP) were evaluated in a subgroup of participants who switched to ABC/DTG/3TC from the latter two agents.

Clinical, laboratory and safety assessments were made during study visits at screening, day 1, and weeks

4, 8, 16, 24, 28, 32, 40 and 48. Procedures for analysing virological end points, lymphocyte counts, renal function, bone biomarkers, serum lipids and plasma drug concentrations are available in Additional file 1.

The HIV Treatment Satisfaction Questionnaire (HIVTSQ) [16] was administered at day 1, week 4, week 24, week 28, week 48 and at the withdrawal visit to assess general satisfaction/clinical and lifestyle/ease subscores. Change from baseline in HIVTSQ scores was based on analysis of variance with treatment, baseline score and stratification; missing data were imputed using the last observation carried forward method.

Statistical analysis

Preset criteria for non-inferiority of ABC/DTG/3TC at 24 weeks stipulated that the lower bound of the 95% CI for the difference in the primary end point had to be greater than a margin of -10%. Assuming a response rate of 85% at week 24 for both treatment groups, the study required 269 evaluable subjects per group to have 90% power with a one-sided significance level of 2.5%.

Both the intent-to-treat exposed (ITT-E) and safety populations included all subjects who had received ≥1 dose of ABC/DTG/3TC and subjects who remained on their current ART regimens. Efficacy and treatment satisfaction analyses were conducted using data from the ITT-E population and were assessed according to their randomized treatment. Safety analyses were conducted using data from the safety population and were analysed according to their actual treatment. The primary end point was analysed using the Cochran-Mantel-Haenszel test stratified by original ART third-agent class. Statistical methods for other laboratory and health outcomes analyses are available in Additional file 1. Data manipulations, tabulations and calculations were performed using SAS software version 9.1.3 or higher (SAS Institute, Inc, Cary, NC, USA).

Subjects were considered virological failures in the ITT-E analysis if the last dose of investigational product was not within the week 48 FDA Snapshot window. However, it was documented that 10 subjects were considered virological failures because they had been prescribed and were taking commercial ABC/DTG/3TC (Triumeq®; ViiV Healthcare, Research Triangle Park, NC, USA) instead of the ABC/DTG/3TC tablets provided as the study drug prior to their week 48 clinic visit. Thus, the week 48 viral load collections were taken within the week 48 FDA Snapshot window while these subjects were taking ABC/DTG/3TC in the form of commercial tablets instead of study drug. The HIV-1 RNA data for these subjects at week 48 were considered to be on treatment and were included in the Snapshot analysis (commercial ABC/DTG/3TC population).

After the week 48 analysis was completed, the sponsor of the study (ViiV Healthcare) became aware of issues of non-compliance to good clinical practice (GCP) at 1 site where 20 subjects (ABC/DTG/3TC, *n*=13; current ART, *n*=7) were enrolled. These subjects were excluded from the week 24 and week 48 sensitivity analyses to have an objective evaluation of any potential effect on overall study results.

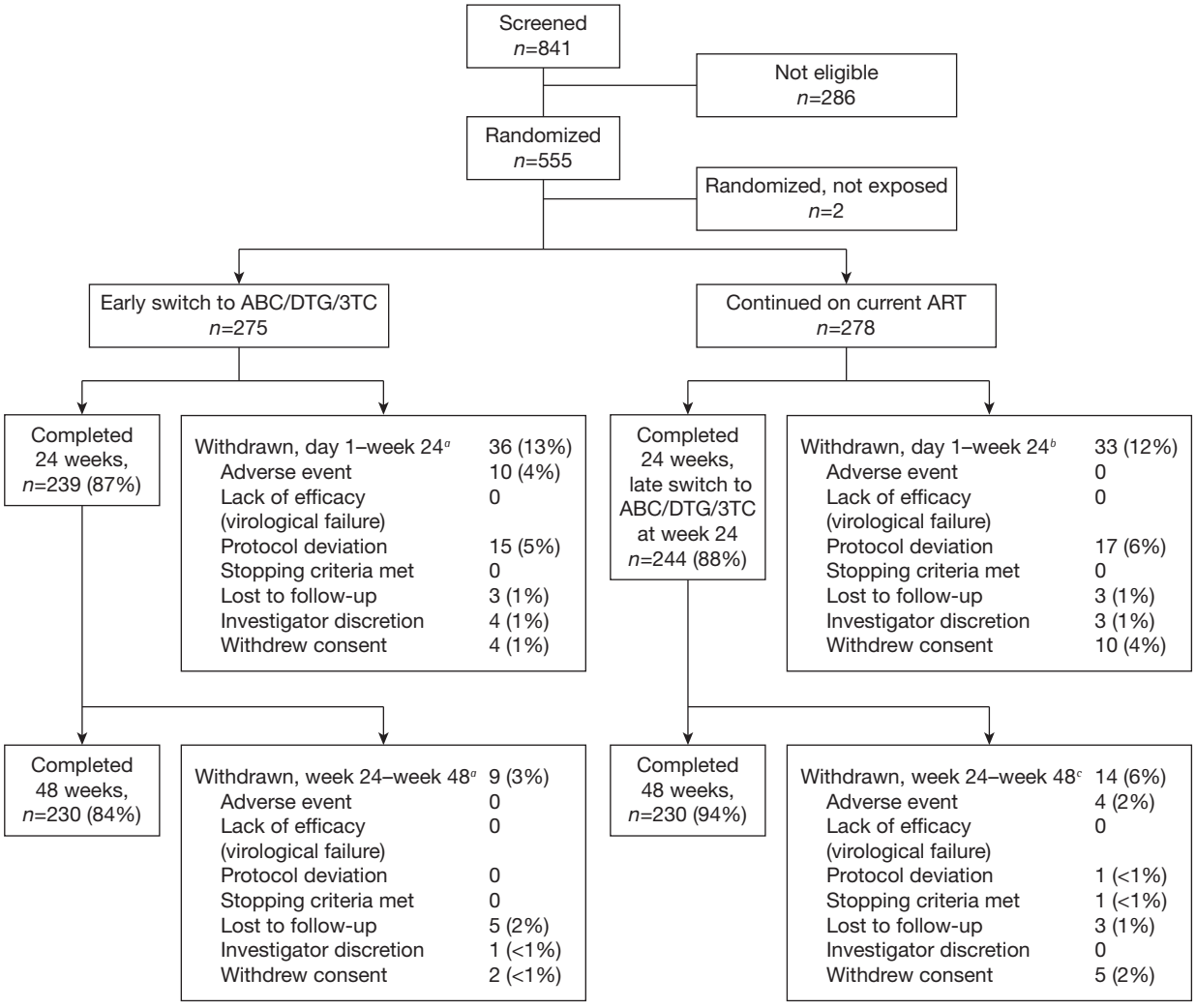
Results

Study population

Of 841 subjects screened, 553 were included in the ITT-E population and randomly assigned to treatment with either ABC/DTG/3TC (*n*=275, early-switch group) or current ART (*n*=278, late-switch group) for 24 weeks followed by 24 weeks of treatment with ABC/DTG/3TC (late-switch period; Figure 1). Median age was 45 years and 47 years in the early-switch group and the late-switch group, respectively (Table 1). Subjects were predominantly male (86% in both groups) and white (ABC/DTG/3TC, 65%; current ART, 66%). At enrolment, subjects were on stable suppressive (for at least 6 months, with no evidence of treatment failure) ART regimens comprising 2 NRTIs plus an NNRTI (both groups, 31%), an INI (ABC/DTG/3TC, 25%; current ART, 27%) or a PI (ABC/DTG/3TC, 43%; current ART, 42%). Median time on ART was 54 months in the early-switch group and 51 months in the late-switch group. Subjects randomized to ABC/DTG/3TC switched to a single-tablet, once-daily regimen of ABC/DTG/3TC from other single-tablet, multi-tablet or twice-daily regimens. Both groups had similar disease characteristics (that is, $CD4^+$ T-cell counts, Centers for Disease Control and Prevention symptom category and hepatitis tests) and HIV-1 risk factors (data not shown). At 24 weeks, protocol deviations were identified in 116 subjects (total cohort, 21%; ABC/DTG/3TC, *n*=54 [20%]; current ART, *n*=62 [22%]), most of which were attributed to administrative errors, reflecting stringent viral inclusion criteria (Additional file 1). Protocol deviations resulted in permanent discontinuation of study medication for 5% and 6% of subjects in the early-switch and current-ART groups, respectively. The most frequent protocol deviations were subjects who lacked documentation of achieving plasma HIV-1 RNA <50 copies/ml within 6 months of starting their initial ART regimen and plasma HIV-1 RNA >200 copies/ml after initial suppression (12% in each treatment group).

A total of 483 subjects completed the week 24 study visit (ABC/DTG/3TC, *n*=239; current ART, *n*=245, one of whom completed week 24 but did not make the switch to ABC/DTG/3TC) and 69 subjects withdrew before the week 24 study visit (ABC/DTG/3TC, *n*=36; current ART, *n*=33). By week 48, 230 subjects in each group had completed the study and 92 had withdrawn.

Figure 1. Subject disposition in the ITT-E population through week 48

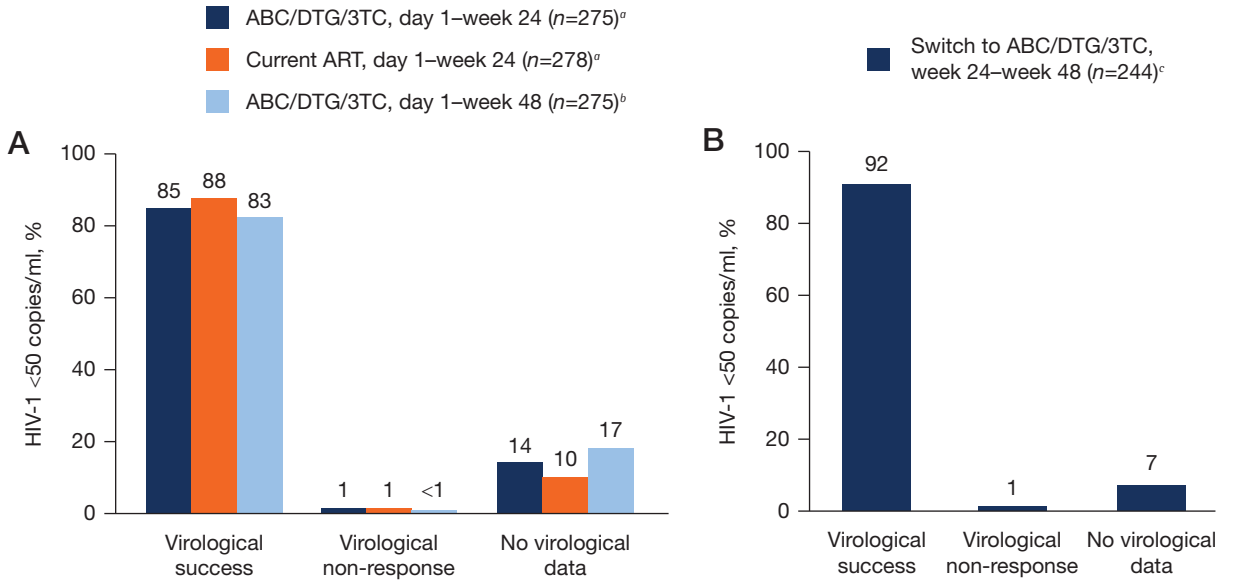


[a]Reported as proportions of patients randomized to early switch to abacavir/dolutegravir/lamivudine (ABC/DTG/3TC; *n*=275). [b]Reported as proportions of patients randomized to continue current antiretroviral therapy (ART; *n*=278). [c]Reported as proportions of patients who underwent late switch to ABC/DTG/3TC (*n*=244). ITT-E, intent-to-treat exposed.

Efficacy in virological suppression

At week 24, 233 subjects (85%) assigned to ABC/DTG/3TC at baseline (early-switch group) and 245 subjects (88%) who continued current ART (late-switch group) exhibited plasma HIV-1 RNA levels <50 copies/ml (Figure 2A). The lower bound of the 95% CI for the adjusted treatment difference was -9.1%, which demonstrated that switching to ABC/DTG/3TC was non-inferior to continuing ART in accordance with the primary efficacy end point at week 24. This result was supported by the week 24 per protocol population in which 93% of subjects in each treatment group (ABC/DTG/3TC, 205/221; current ART 201/216) had HIV-1 RNA <50 copies/ml (adjusted treatment difference; 95% CI [-0.2; -5.0, 4.6]). A GCP sensitivity analysis, which excluded subjects from site 209994, supported the original week 24 result (Additional file 1). The test for evidence against homogeneity of the treatment difference across original ART was not statistically significant (P=0.203). The proportion of virological non-responders, defined as those with HIV-1 RNA levels >50 copies/ml, those who discontinued because of lack of efficacy or other reasons while above the viral load threshold, or those who changed ART regimens, was 1% in each treatment group at week 24. No subjects met the confirmed virological withdrawal

Figure 2. Proportion of subjects with HIV-1 RNA <50 copies/ml after 24 and 48 weeks of treatment



(A) After 24 weeks of treatment. **(B)** After 48 weeks of treatment. [a]Intent-to-treat exposed (ITT-E) analysis. [b]Includes eight patients who were originally considered to have virological non-response in the ITT-E analysis but were found to have received commerical abacavir/dolutegravir/lamivudine (ABC/DTG/3TC; Triumeq®) instead of study drug. [c]Includes two patients who were originally considered to have virological non-response in the ITT-E analysis but were found to have received commercial ABC/DTG/3TC (Triumeq®) instead of study drug. ART, antiretroviral therapy.

criteria (plasma HIV-1 RNA samples ≥400 copies/ml on 2 successive visits separated by at least 2 weeks). In the early-switch group 83% of subjects (*n*=227) maintained virological suppression at week 48 (non-response subjects were cumulative from day 1). In the late-switch group, which at week 48 comprised subjects who had received ABC/DTG/3TC for 24 weeks and excluded subjects who withdrew prior to week 24, 92% of subjects (*n*=224) were virologically suppressed at week 48.

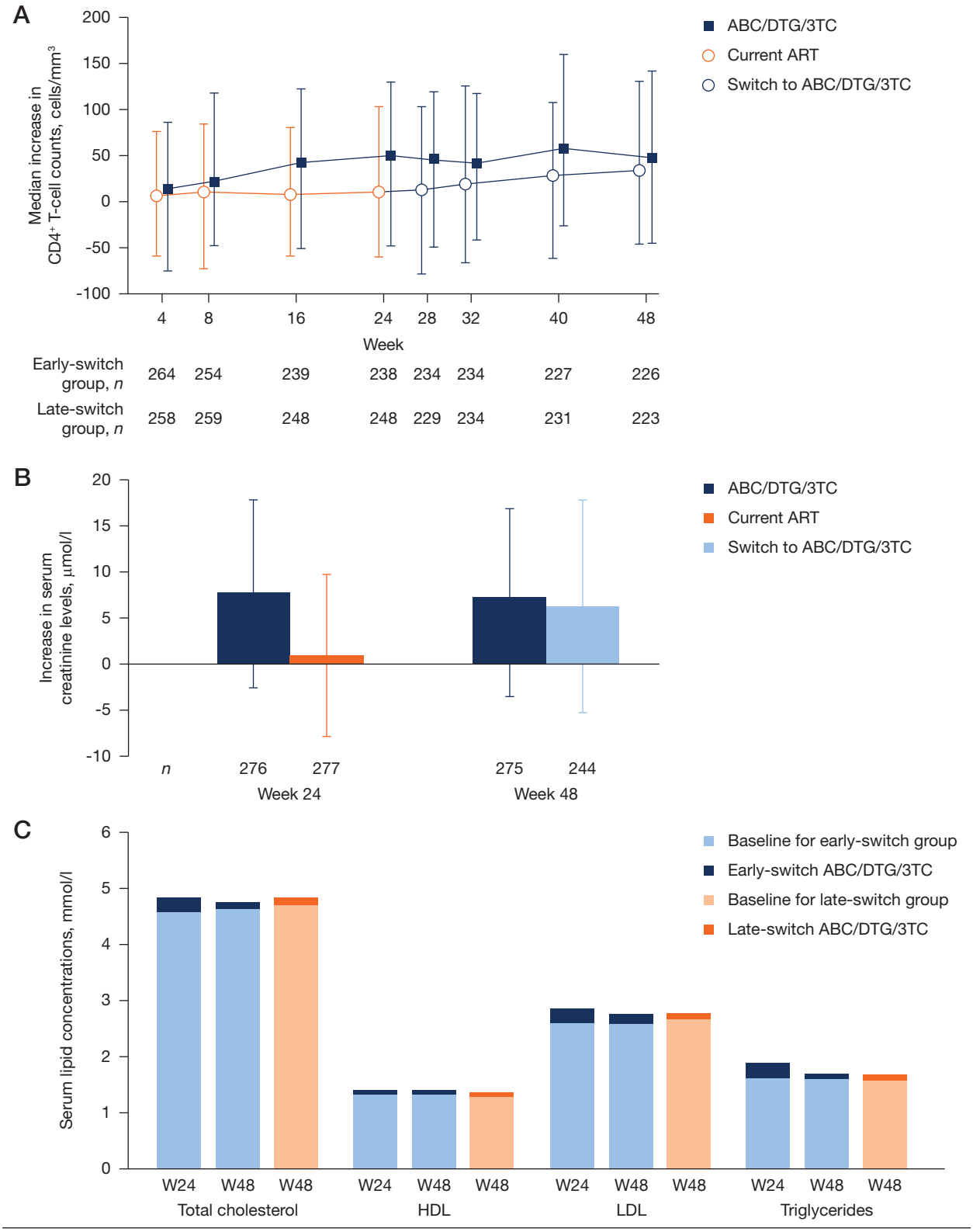
At week 24, the median increase in CD4+ T-cell count was 50 cells/mm^3 in the ABC/DTG/3TC early-switch group and 11 cells/mm^3 in the current-ART late-switch group. At week 48, the median increase in CD4+ T-cell count was 48.5 cells/mm^3 among subjects in the early-switch group and 34.0 cells/mm^3 among subjects in the late-switch group (Figure 3A).

Safety and tolerability

At week 24, the rate of AEs reported in the early-switch group was 66% and increased to 75% by week 48 (Table 2). Similarly, by week 48, 60% of subjects in the current-ART late-switch group reported AEs after switching to ABC/DTG/3TC at week 24. Subjects in the ABC/DTG/3TC treatment group were more likely to develop nausea (*n*=27 [10%]), fatigue (*n*=19 [7%]), diarrhoea (*n*=17 [6%]) and headache (*n*=13 [5%]) compared with subjects in the current ART treatment group (1% for each; the lower bound of the 95% CI for relative risk was >1). The majority of AEs were recorded as mild (Grade 1) or moderate (Grade 2), with a low, comparable incidence of severe (Grade 3) or life-threatening/disabling (Grade 4) adverse events. Grade 4 events through week 48 were reported in 2 subjects (<1%) in the early-switch group, each with increased lipase, and 4 subjects in the late-switch group, 1 with increased alanine aminotransferase, 1 with aortic thrombosis (while receiving current ART), 1 with pulmonary embolism and 1 with myocardial infarction (all <1%). These events were not considered to be related to the study medication.

Psychiatric disorder AEs were reported more frequently in the ABC/DTG/3TC group compared with the current ART group (ABC/DTG/3TC, *n*=35 [13%]; current ART, *n*=8, [3%]) through week 24. The rate of psychiatric AEs in the ABC/DTG/3TC group through 24 weeks was similar to that of the late-switch group between weeks 24 and 48 (*n*=22 [9%]). At week 48, most psychiatric AEs were grade 1 and grade 2. In the ABC/DTG/3TC group, 1 subject experienced a grade 3 event of depression (occurring on day 14). In the late-switch group, 2 subjects reported grade 3 AEs of insomnia and suicidal ideation. No grade 4 psychiatric AEs were reported in either group.

Figure 3. Changes in CD4+ T-cell count, serum creatinine and serum lipid levels in the ITT-E population



(A) Median increases ±IQR in CD4+ T-cell counts in the intent-to-treat exposed (ITT-E) population. Cell counts were 618 cells/mm³ for the early-switch group and 598 cells/mm³ for the current antiretroviral therapy (ART) late-switch group at baseline and 617.5 cells/mm³ for the late-switch group at week 24. **(B)** Changes in serum creatinine levels (µmol/l) reported as mean ± standard deviation. Creatinine levels were 84.66 µmol/l for the early-switch group and 83.87 µmol/l for the current ART late-switch group at baseline and 85.31 µmol/l for late-switch group at week 24. **(C)** Mean changes in serum lipid concentrations (mmol/l) associated with abacavir/dolutegravir/lamivudine (ABC/DTG/3TC). HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 1. Baseline demographics and disease characteristics

	Early-switch phase		Late-switch phase,
	ABC/DTG/3TC (*n*=275); day 1–week 24	Current ART (*n*=278); day 1–week 24	ABC/DTG/3TC (*n*=244); week 24–week 48
Median age, years (range)	45 (22–74)	47 (22–80)	47 (23–80)
Sex			
Male, *n* (%)	237 (86)	237 (86)	212 (87)
Female, *n* (%)	38 (14)	40 (14)	32 (13)
Ethnicity			
Hispanic/Latino, *n* (%)	55 (20)	59 (21)	51 (21)
Not Hispanic/Latino, *n* (%)	220 (80)	218 (79)	193 (79)
Race			
African-American/African heritage, *n* (%)	81 (29)	76 (27)	63 (26)
American Indian/Alaska native, *n* (%)	3 (1)	2 (<1)	2 (1)
Asian heritage, *n* (%)	4 (1)	8 (3)	8 (3)
White, *n* (%)	178 (65)	183 (66)	165 (68)
HBV surface antigen positive, *n* (%)	0	0	0
HCV positive, *n* (%)	21 (8)	15 (5)	15 (6)
CDC class C, *n* (%)	40 (15)	45 (16)	43 (18)
Median baseline CD4$^+$ T-cell count, cells/mm^3 (Q1/Q3)	618 (480/812)	597 (444/794)	618 (469/810)
<500 cells/mm^3, *n* (%)	83 (30)	91 (33)	66 (27)
≥500 cells/mm^3, *n* (%)	192 (70)	186 (67)	178 (73)
Median time on current ART, months	54	51	50
Current ART at baseline			
NNRTI, *n* (%)	87 (32)	85 (31)	NA
INI, *n* (%)	70 (25)	76 (27)	NA
PI, *n* (%)	118 (43)	117 (42)	NA
TDF/FTC backbone, *n* (%)	208 (76)	219 (79)	NA

ABC/DTG/3TC, abacavir/dolutegravir/lamivudine; ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; INI, integrase inhibitor; NA, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q1, 25th percentile; Q3, 75th percentile; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

At week 24, 11 subjects (4%) in the early-switch group had experienced AEs that led to discontinuation of ABC/DTG/3TC treatment, compared with no withdrawals in the current ART group. The majority of AEs leading to withdrawal were gastrointestinal disorders, general disorders, psychiatric disorders, and skin and subcutaneous tissue disorders. In the current-ART late-switch group, there were 6 AEs (2%) that led to withdrawal, all from the period following the switch to ABC/DTG/3TC. The majority of AEs that led to withdrawal were Grade 1 or 2, with the exceptions of 2 grade 3 events (insomnia, increased ALT) and 1 grade 4 event (myocardial infarction).

After treatment with ABC/DTG/3TC through week 24, the rate of drug-related AEs was 21% (*n*=59), and the rate of SAEs was 2% (*n*=6). In comparison, in the late-switch group (weeks 24 through 48) the rate of drug-related AEs was 13% (*n*=32) and the rate of SAEs was 2% (*n*=6). Twenty-three new subjects reported AEs (1 drug-related AE and 3 SAEs) in the early-switch group in weeks 24 through 48, with total rates through week 48 of 75% (*n*=206), 22% (*n*=60) and 3% (*n*=9), respectively. No subjects in the early-switch group withdrew from the study during weeks 24 through 48, compared with 6 subjects (2%) in the late-switch group.

At week 24, subjects in the early-switch group demonstrated an expected non-progressive mean increase in serum creatinine levels (7.65 µmol/l; standard deviation [SD], 10.20) that was greater than the increases observed in the current-ART late-switch group (0.91 µmol/l; SD, 8.74; Figure 3B). At week 48, mean increases over baseline were 7.29 µmol/l (SD, 9.44) in the early-switch group and 6.23 µmol/l (SD, 11.51) in the late-switch group. As expected, because GFR is a calculated value based on serum creatinine values, a greater decrease from baseline was observed at week 24 in subjects treated with ABC/DTG/3TC than in subjects in the current ART group according to both CKD-EPI (adjusted mean difference, -6.87 ml/min/1.73 m^2; 95% CI, -8.64, -5.11; *P*<0.001) and MDRD (adjusted mean difference, -0.13 ml/min/1.73 m^2; 95% CI, -0.17, -0.10; *P*<0.001) equations. Little change was observed in urine albumin/creatinine ratio (median change over baseline [IQR]: ABC/DTG/3TC, 0 g/mol [-0.20, 0.20]; current ART, 0 g/mol [-0.20, 0.30]) or urine protein/creatinine ratio (median change over baseline [IQR]:

Table 2. Adverse events

	Early-switch phase			Late-switch phase,
	ABC/DTG/3TC (*n*=276[a]), day 1–week 24; *n* (%)	Current ART (*n*=277), day 1–week 24; *n* (%)	ABC/DTG/3TC (*n*=275[a]), day 1–week 48; *n* (%)	ABC/DTG/3TC (*n*=244), week 24–week 48; *n* (%)
Any event	183 (66)	129 (47)	206 (75)	146 (60)
Common AE by type[b]				
URT infection	21 (8)	20 (7)	35 (13)	22 (9)
Nausea	27 (10)	3 (1)	28 (10)	15 (6)
Fatigue	19 (7)	3 (1)	22 (8)	6 (2)
Diarrhoea	17 (6)	4 (1)	20 (7)	9 (4)
Headache	13 (5)	4 (1)	17 (6)	10 (4)
Cough	14 (5)	8 (3)	17 (6)	6 (2)
Insomnia	10 (4)	1 (<1)	14 (5)	9 (4)
Nasopharyngitis	10 (4)	6 (2)	13 (5)	6 (2)
Psychiatric disorder AE	35 (13)	8 (3)	42 (15)	22 (9)
Any drug-related event	59 (21)	4 (1)	60 (22)	32 (13)
Any serious event	6 (2)	5 (2)	9 (3)	6 (2)
Any serious drug-related event	0	0	0	0
Any fatal event	1 (<1)	0	1 (<1)	1 (<1)
Any serious drug-related fatal event	0	0	0	0
Any event leading to withdrawal	11 (4)	0	11 (4)	6 (2)

[a]The difference in the number of subjects in the abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) treatment group for the early (*n*=276) and late switch (*n*=275) population is due to subject 958107. This subject was randomized to the current antiretroviral therapy (ART) group but was receiving ABC/DTG/3TC as current ART at study entry. For the week 24 analysis, based on the analysis populations defined in the reporting analysis plan (RAP), the subject was included in the ABC/DTG/3TC safety population (*n*=276). This subject withdrew from the study on day 79 and therefore did not satisfy the criteria for inclusion in the late-switch safety population (*n*=275). [b]Common adverse events (AEs) were those with ≥5% (with rounding) incidence for either treatment. URT, upper respiratory tract.

ABC/DTG/3TC, -0.20 g/mol [-2.60, 2.30]; current ART, 1.20 g/mol [-1.00, 3.30]) at week 24.

At week 24, mean increases (±SD) in total cholesterol were observed in subjects in the early switch group compared with baseline (3.52% ±18.36). At week 48, total cholesterol increased by 1.78% ±15.86 in the early-switch group and by 2.48% ±17.99 in the late-switch group (Figure 3C). Similar changes were observed in high- and low-density lipoprotein cholesterol. Triglycerides in the early-switch treatment group increased by 13.53% ±86.12 at week 24 and by 4.00% ±52.02 and 6.19% ±43.92 in the early-switch and late-switch groups, respectively, at week 48.

Mean levels (±SD) of 3 markers of bone formation were reduced in both treatment groups at week 24 and week 48 (Additional file 1). The ABC/DTG/3TC treatment group had larger decreases from baseline than the current ART treatment group at week 24 for all bone formation markers (bone-specific alkaline phosphatase, osteocalcin and procollagen type 1 N-propeptide). Little change was observed in the bone resorption marker collagen cross-linked C-telopeptide for either treatment group. The bone marker analyte changes were consistent across baseline ART third-agent class subgroups (PI, INI or NNRTI).

Pharmacokinetic analysis of the subset of participants who switched from EFV- or NVP-containing regimens to ABC/DTG/3TC showed plasma concentrations of DTG increased from week 1 through week 4 post-switch, reaching previously reported steady-state pre-dose concentrations and then remaining relatively constant through week 24. Mean plasma concentrations of DTG were maintained above the protein-adjusted concentration required for 90% viral inhibition (PA-IC_{90}) at all sample times (Additional file 1). After switching to ABC/DTG/3TC, residual concentrations of EFV or NVP rapidly decreased. No subjects in the PK substudy had quantifiable concentrations of EFV or NVP at week 4.

Treatment satisfaction

Baseline HIVTSQ scores were similar between early-switch (mean ±SD, 53.0 ±8.2) and late-switch (mean ±SD, 53.4 ±7.8) groups. At week 24, subjects in the early-switch group recorded significantly higher increases in total mean score than subjects in the current-ART late-switch group (3.2 versus 0.8; adjusted mean difference 2.4; 95% CI, 1.3, 3.5; $P<0.001$), general satisfaction/clinical subscore (1.3 versus 0.2; adjusted mean difference 1.0; 95% CI, 0.4, 1.7; $P=0.002$) and the lifestyle/ease subscore (1.8 versus 0.6; adjusted mean difference 1.3; 95% CI 0.7, 1.8; $P<0.001$). At week 48, total HIVTSQ scores (mean ±SD) increased in the early switch subjects by 4.1 ±10.2 and by 3.5 ±8.8 for the late-switch subjects.

Discussion

STRIIVING is a regimen-switching study comparing the efficacy, safety and tolerability of ABC/DTG/3TC with continuation of ART regimens in stably suppressed adults with HIV-1 infection. The primary analysis at week 24 demonstrated that switching to ABC/DTG/3TC FDC was non-inferior to staying on current ART. At week 48, after continuing ABC/DTG/3TC for an additional 24 weeks, virological suppression was maintained in this group. In the current-ART late-switch group, after switching from current ART to ABC/DTG/3TC at week 24, virological suppression was similar 24 weeks after switching compared with the early-switch group after 24 weeks. No subject met virological withdrawal criteria (verified viral load of >400 copies/ml). In addition, no ART resistance was noted in this study.

This study sought to enrol subjects who were virologically suppressed and stable on their current ART regimens and had no history of virological failure. Entry criteria required that subjects demonstrate an HIV-1 viral load <50 copies/ml prior to enrolment and maintain suppression without significant viral load increases. Documentation of prior treatment regimens and dates of viral load collection were used to satisfy the inclusion criteria. In some instances, however, protocol deviations occurred when source documents were not available to demonstrate that all study eligibility criteria were met before the subject was randomly assigned. Protocol deviations of any type detected after randomization did not automatically result in discontinuation unless the deviation was deemed to pose a safety risk to the subject or potentially affect the efficacy analyses. Thus, several subjects with missing prior documentation whose personal safety was not deemed at risk and who would not potentially affect the efficacy analyses were retained in the study and included in the ITT-E population. Subjects who had a significant protocol deviation were not included in the per-protocol analyses of efficacy. Notably, no difference in virological failure rate was observed between the treatment groups in either the ITT-E or per-protocol populations, suggesting that the entry criteria successfully selected for subjects with little risk of viral resistance or that any antiviral resistance that developed prior to enrolment had little or no effect on the efficacy analyses.

A single site was noted to have not maintained full GCP compliance during the study. The study data were analysed both including and then excluding the subjects from this site, with no change in efficacy findings between the 2 analyses. Safety data from the site were included in the final safety analysis to allow for capture of all possible related adverse events.

HIVTSQ scores for general satisfaction and lifestyle/ease were significantly higher in subjects taking ABC/DTG/3TC at week 24, possibly reflecting a preference for a simplified single-tablet regimen and other aspects of this DTG-based regimen such as the absence of food restrictions related to dosing and relatively few restrictions regarding concomitant medications [17].

Overall, ABC/DTG/3TC FDC demonstrated a safety profile that was consistent with that observed in previous studies of DTG, ABC and 3TC and are reflected in the labels of these drugs, including the ABC/DTG/3TC single tablet. No new safety issues were identified. As expected, with time on the new treatment regimen, subjects established tolerability to ABC/DTG/3TC after switching from their current regimen. The similar safety profile in the early-switch participants at week 48 compared with week 24 demonstrated that once initial tolerability issues were resolved during the first 24 weeks of treatment, subjects experienced few AEs related to drug regimen tolerability. The observed imbalance between the 2 groups in incidence of AEs observed at the week 24 analysis reflected that, unlike subjects in the current-ART late-switch arm who had been on stable therapeutic regimens for ≥6 months before enrolment, subjects in the early-switch arm may have been exposed to as many as 3 new drugs. Therefore, the relatively high number of AEs reported in the early-switch group through week 24 was not unexpected because AEs would be expected to be more frequent when switching to new medications compared with staying on a stable regimen that has been presumably well tolerated for some time. This imbalance in reported AEs was demonstrated in a previous study in subjects who switched to FTC/TDF-containing regimens from regimens containing ABC/3TC [18]. The pattern of AEs reported by the late-switch subjects was similar to the early-switch subjects at week 24, though the overall rate was modestly lower, suggesting that subjects and providers may have become more familiar with both the study itself or with the use the novel ABC/DTG/3TC fixed-dose tablet, which became available for prescribing in the study countries during the time this study was conducted.

Despite both groups having few virological failures at week 24 (≤1% in each group), a small difference (3%) in the overall Snapshot algorithm outcome was observed and is likely attributed to a greater number of AEs leading to withdrawal associated with ABC/DTG/3TC compared with current ART, a finding consistent with the challenge of a new treatment regimen being compared with a current (previously determined to be tolerable) stable regimen. Another noteworthy difference between the 2 study arms is observed in the rates of subject withdrawal due to AEs during their respective first 24 weeks of ABC/DTG/3TC therapy. The relatively low rate of

withdrawals in the late-switch group compared with the early-switch group may reflect an effect of familiarity with clinical trial participation in the late-switch subjects. Also, for these subjects, participation in the trial for 24 weeks while on their baseline treatment regimen may have conferred an incentive to remain in the study long enough to switch to ABC/DTG/3TC despite encountering AEs.

There are limitations to this study. First, this was an open-label study, which can be more vulnerable to bias. This design was necessary to assess treatment satisfaction related to the single-tablet formulation of ABC/DTG/3TC compared with the current ART, which included multi-tablet regimens. Second, the composition of the study sample, 65% white and 86% male adults in high-income countries (that is, the United States and Canada), may not accurately represent the global population of patients with HIV-1. The limited proportion of women enrolled may be partially attributable to enrolment restrictions based on birth control and pregnancy. Finally, the study may be limited by the higher-than-expected rate of discontinuations, which was driven in large part by protocol deviations. However, non-inferiority was concluded in both the ITT-E and per-protocol populations in accordance with prespecified criteria.

In summary, the efficacy, safety and pharmacokinetic data from the STRIIVING study support the use of the once-daily, single-tablet regimen of ABC/DTG/3TC as an attractive option to switch therapy for long-term use in ART-experienced adults who are virologically suppressed.

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Additional file

Additional file 1: Supplementary material can be found at https://www.intmedpress.com/uploads/documents/3972_Trottier_Addfile1.pdf

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