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ORIGINAL RESEARCH

Bictegravir/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed People with HIV Aged ≥ 65 Years: Week 48 Results of a Phase 3b, Open-Label Trial

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ABSTRACT

Introduction: We report the 48-week results of an ongoing study to assess the efficacy and safety of switching older people with HIV to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF).

Methods: This was a 96-week, phase 3b, open-label, single-arm study (GS-US-380-4449; NCT03405935). Virologically suppressed individuals aged ≥ 65 years receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide or a tenofovir disoproxil fumarate-based regimen were switched to B/F/TAF. Primary endpoint was the percentage of participants with HIV-1 RNA < 50 copies/ml at week 24.

Results: Eighty-six participants (median age 69 [range 65–80] years; 87% male; 95% white) were enrolled and treated in five European countries. Rates of virologic suppression were 97.7% at week 24 and 90.7% at week 48; none had HIV-1 RNA ≥ 50 copies/ml, and 100% had virologic suppression by missing = excluded analysis at both time points. No treatment-emergent resistance was observed. There were no grade 3–4 study drug-related adverse events (AEs) or study drug-related serious AEs or deaths. Three

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AEs led to premature discontinuation; one (moderate abdominal discomfort) was attributed to the study drug by the investigator. At week 48, median changes from baseline in weight and estimated glomerular filtration rate were + 0.1 kg (interquartile range [IQR] − 1.0, 2.3) and − 6.0 ml/min (IQR − 10.2, 0.0), respectively. There were no clinically relevant changes from baseline to week 48 in fasting lipid parameters. Treatment satisfaction improved, and health-related quality of life was maintained from baseline through week 48. Median adherence to the study drug was 98.6% (IQR 96.0, 100).

Conclusions: Switching to B/F/TAF was effective and well tolerated through 48 weeks in virologically suppressed adults aged ≥ 65 years.

Trial Registration: ClinicalTrials.gov identifier, NCT03405935.

Keywords: Age; Bictegravir; Clinical trial; Emtricitabine; HIV; Older; Safety; Tenofovir alafenamide

Key Summary Points

Why carry out this study?

People with HIV are living longer; older individuals with HIV are more likely to experience comorbidities and polypharmacy.

Ensuring the safety and tolerability of antiretroviral therapy in this population is crucial.

We assessed the virologic efficacy and safety of switching to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in virologically suppressed people living with HIV (PLWH) aged ≥ 65 years.

What was learned from the study?

Rates of virologic suppression were 97.7% at week 24 and 90.7% at week 48, and there were no grade 3–4 study drug-related adverse events (AEs) or study drug-related serious AEs or deaths.

Switching to B/F/TAF was effective and well tolerated through 48 weeks in virologically suppressed adults aged ≥ 65 years.

The findings represent an important addition to the evidence base in older PLWH.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14054402.

INTRODUCTION

Over the past 2 decades, people with HIV have been living longer [1]. Individuals aged ≥ 65 years comprised 16% of the HIV-positive population in the USA in 2015 [2], and globally the number of people living with HIV (PLWH) aged ≥ 50 years exceeded 4.2 million in 2013, with the highest burden reported in sub-Saharan Africa (2.5 million) followed by Western/Central Europe and North America (~ 800,000) and the Asia-Pacific region (~ 400,000) [3]. A recent analysis of the Swiss HIV Cohort found that PLWH aged ≥ 65 years took more additional medications and more complex antiretroviral therapy (ART) regimens than younger PLWH [4]. A French retrospective cohort study of > 9000 PLWH aged ≥ 65 years receiving combined ART found that drug–drug interactions (DDIs) were frequent (17% of individuals experienced ≥ 1 DDI), which substantially increased healthcare costs relative to propensity score-matched PLWH without DDIs [5]. As older individuals are at increased risk of comorbidities and may experience challenges with polypharmacy, ensuring the safety and tolerability of ART in this population is crucial [6].

First-line ART usually consists of two nucleoside reverse transcriptase inhibitors (NRTIs)

plus an integrase strand transfer inhibitor (INSTI) [7–9]. Guidelines recognize that a treatment switch may be considered in virologically suppressed PLWH to improve safety or tolerability, for regimen simplification, or to avoid DDIs [8, 9].

Bictegravir (BIC, B) is a potent INSTI and has a high barrier to resistance and in vitro activity against most INSTI-resistant variants [10]. Its pharmacokinetic properties enable once-daily dosing without a boosting agent [11]. Tenofovir alafenamide (TAF) is a prodrug of tenofovir that is associated with 90% lower plasma tenofovir levels than tenofovir disoproxil fumarate (TDF), reducing renal and bone toxicity [12]. BIC has been co-formulated with the guideline-recommended NRTI backbone, emtricitabine (FTC, F) and TAF for once-daily, single-tablet treatment of HIV-1 infection [13]. The combination is associated with low potential for DDIs [14]. The efficacy and safety of B/F/TAF have been demonstrated in both treatment-naïve and virologically suppressed PLWH switching from another treatment regimen [13, 15–18]. Although these trials were carried out in adult participants (≥ 18 years) with no other entry restriction based on age, clinical trial entry criteria (e.g., restricting comorbidities) increase the likelihood that older PLWH may be excluded from trials. Thus, older PLWH are generally underrepresented in ART trials [19].

Here we report the 48-week results of an ongoing study to assess the virologic efficacy and safety of switching to B/F/TAF in virologically suppressed PLWH aged ≥ 65 years.

METHODS

Study Design and Participants

This ongoing phase 3b, multicenter, open-label, single-arm study (GS-US-380-4449; NCT03405935) is being conducted in Belgium, France, Italy, Spain, and the UK. The study was approved by the institutional review boards or independent ethics committees at each participating site and was performed in accordance with Good Clinical Practice and the Declaration of Helsinki. Study-related procedures were conducted with the understanding and informed consent of each participant.

Key inclusion criteria were age ≥ 65 years, treatment with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) or F/TDF plus a third agent (if they were participating in or had participated in study GS-US-292-1826 [NCT02616783; a study examining a switch from TDF to E/C/F/TAF in PLWH aged ≥ 60 years]) for ≥ 3 months, plasma HIV-1 RNA < 50 copies/ml before and at screening (transient detectable viremia ≥ 50 and < 400 copies/ml before screening was acceptable) and an estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 30 ml/min. Principal exclusion criteria were opportunistic illness indicative of stage 3 HIV infection, resistance to any of the three components of B/F/TAF, clinically significant electrocardiogram abnormalities, decompensated cirrhosis and serious infections other than HIV-1 (e.g., acute hepatitis/active tuberculosis).

Study participants switched from their preceding therapy to receive oral B/F/TAF (50/200/25 mg) once daily for 96 weeks. Clinic visits were scheduled at baseline (day 1) and at the end of weeks 4, 12, 24, 36 and 48.

Outcomes and Assessments

The primary endpoint was the percentage of participants with HIV RNA < 50 copies/ml at week 24 as defined by the US Food and Drug Administration Snapshot algorithm (Snapshot) [20]. Secondary endpoints included the proportion of participants with HIV RNA < 50 copies/ml at week 48 (Snapshot) and the safety and tolerability of B/F/TAF, as assessed by adverse events (AEs), through week 48. Other pre-specified endpoints were: the proportion of participants with HIV RNA < 50 copies/ml at weeks 24 and 48, whereby missing data were treated as treatment failures ("missing = failure"); the proportion of participants with HIV RNA < 50 copies/ml at weeks 24 and 48, whereby missing data were excluded ("missing = excluded"); the change from baseline in CD4+ cell count and percentage at weeks 24

and 48. The percentages of participants with HIV RNA < 20 copies/ml (Snapshot) were evaluated as a supportive endpoint. Additional assessments included: patient satisfaction after switching to B/F/TAF, as assessed by HIV Treatment Satisfaction Questionnaire Status (HIVTSQs) and HIV Treatment Satisfaction Questionnaire Change (HIVTSQc); health-related quality of life through week 48, as assessed by EuroQol 5 Dimensions (EQ-5D) patient questionnaire (visual analog scale [VAS] and index score), Short Form 36 Health Survey (SF-36) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F); and adherence to study treatment through week 48, calculated based on pill counts for participants who returned ≥ 1 bottle and using the VAS adherence questionnaire.

Plasma HIV-1 RNA, CD4+ cell count, patient-reported outcomes (PROs), adherence, AEs (coded using the Medical Dictionary for Regulatory Activities), $eGFR_{CG}$, standard laboratory parameters and vital signs were assessed at each clinic visit. Safety data were collected for 30 days after the last dose of study drug for participants who permanently discontinued the study drug.

The presence of pre-existing resistance-associated mutations (RAMs) in protease (PR), reverse transcriptase (RT) and integrase (IN) genes was evaluated by historical genotypes, if available, and by HIV-1 proviral DNA genotype testing (GenoSure® Archive, Monogram Biosciences, San Francisco, CA, USA), which was performed retrospectively using baseline samples. The GenoSure Archive assay utilizes next-generation sequencing (NGS) technology but generates a consensus sequence from the NGS data and reports a population-like genotype (the report cut-off is unknown). APOBEC3G-induced hypermutations were removed by bioinformatics filters.

Resistance analysis for emergent mutations was performed in participants with virologic failure (defined as a rebound in HIV-1 RNA ≥ 50 copies/ml that was subsequently confirmed and ≥ 200 copies/ml at the next scheduled/unscheduled visit or as HIV-1 RNA ≥ 200 copies/ml at study drug discontinuation or week 48). Testing included the genotype and phenotype of HIV PR, RT and IN genes (PhenoSense® GT, GeneSeq® IN, and PhenoSense® IN; Monogram Biosciences) at the time point when virologic failure was confirmed.

Statistical Analysis

Sample size was based on the feasibility of conducting a study in individuals aged ≥ 65 years. Efficacy analyses were based on the full analysis set, which comprised all enrolled participants who received ≥ 1 dose of study drug and did not have any major protocol violations (defined as ART regimen at study entry other than E/C/F/TAF fixed-dose combination [or FTC/TDF + third agent if currently or previously participated in study GS-US-292-1826] and ART regimen at study entry for < 3 months). The safety analysis set included all enrolled participants who received ≥ 1 dose of study drug.

Statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA). The Clopper-Pearson exact method was used to calculate 95% confidence intervals (CIs) for the proportion of participants with HIV-1 RNA < 50 copies/ml. Descriptive statistics were used to summarize changes from baseline in CD4+ cell count, percentage of CD4+ cells at each visit, AEs and clinical laboratory data. Changes from baseline in fasting lipids and glucose were tested using the two-sided Wilcoxon signed-rank test.

RESULTS

A total of 90 participants were screened, of whom 86 were enrolled and treated (see Fig. S1 in the electronic supplementary material). Three participants discontinued treatment early (before week 48) because of AEs, two of which were considered unrelated to the study drug. Table 1 shows the baseline demographics for the treated participants (safety analysis set). The median age of participants was 69 (range 65–80) years. Most participants were male (87%) and white (95%), and the median body mass index was 26.6 (range 17.5–35.9) kg/m^2. Most (92%)

Table 1 Participants' baseline demographics and disease characteristics (safety analysis set, $N = 86$)

Parameter	Value
Median age, years (range)	69 (65–80)
Female, *n* (%)	11 (12.8)
Race, *n* (%)	
White	82 (95.3)
Black	1 (1.2)
Not permitted to be disclosed	3 (3.5)
Hispanic/Latino ethnicity, *n* (%)	12 (14.5)
Median weight, kg (range)	78.3 (49.0–110.0)
Median body mass index, kg/m^2 (range)	26.6 (17.5–35.9)
Median $eGFR_{CG}$, ml/min (range)	76.2 (39.6–130.2)
HIV RNA < 50 copies/ml, *n* (%)	84 (97.7)
HIV RNA < 20 copies/ml, *n* (%)	80 (93.0)
CD4+	
Median CD4+ count, cells/mm^3 (range)	676 (132–1385)
Median CD4+ percentage (range)	35.3 (11.1–59.6)
Renal markers	
Median RBP:Cr, μg/g (IQR)	139.3 (92.3–218.5)
Median β-2 m:Cr μg/g (IQR)	72.0 (26.8–194.6)
Lipids	
Median total fasting lipids, mg/dl (IQR)	191 (167–227)
Median low-density lipoprotein, mg/dl (IQR)	117 (95–140)
Median high-density lipoprotein, mg/dl (IQR)	51 (44–58)
Median triglycerides, mg/dl (IQR)	131 (99–173)
Total cholesterol:high-density lipoprotein	3.9 (3.3–4.5)
Glucose, mg/dl (IQR)	102 (91–119)
Antiretroviral therapy, *n* (%)	
E/C/F/TAF	79 (91.9)
RPV/F/TDF	4 (4.7)
EFV/F/TDF	1 (1.2)
E/C/F/TDF	1 (1.2)
NVP + F/TDF	1 (1.2)
Chronic[a] non-ARV medications, median (IQR)	3.0 (2–5)
Chronic[a] non-ARV medications by system organ class, *n* (%)	

Table 1 continued

Parameter	Value
Cardiovascular system	55 (64.0)
Gastrointestinal tract	54 (62.8)
Nervous system	38 (44.2)
Blood and blood-forming organs	23 (26.7)
Musculoskeletal system	20 (23.3)
Genitourinary system and sex hormones	18 (20.9)

ARV antiretroviral, *β-2 m:Cr* beta-2-microglobulin to creatinine ratio, *C* cobicistat, *E* elvitegravir, *EFV* efavirenz, $eGFR_{CG}$ estimated glomerular filtration rate calculated with the Cockcroft-Gault equation, *F* emtricitabine, *IQR* interquartile range, *NVP* nevirapine, *RBP:Cr* retinol-binding protein to creatinine ratio, *RPV* rilpivirine, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate

[a] Oral or inhaled medications taken for ≥ 30 days

were receiving E/C/F/TAF before switching to B/F/TAF.

In the primary efficacy analysis, the rate of virologic suppression (HIV-1 RNA < 50 copies/ml) was 97.7% (95% CI 91.9–99.7) at week 24 and 90.7% (95% CI 82.5–95.9) at week 48 (Fig. 1). The difference was mainly attributable to virologic data being unavailable in more participants at week 48 than week 24, including for one participant who discontinued treatment between weeks 24 and 48 (see Fig. S1 in the electronic supplementary material). No participants had HIV-1 RNA ≥ 50 copies/ml at either time point (Fig. 1). Results of the missing = failure and missing = excluded analyses were consistent with the primary analysis. When missing data were treated as failures, the rate of virologic suppression remained at 97.7% at week 24 and 90.7% at week 48. When missing data were excluded, the rate of virologic suppression was 100.0% at weeks 24 and 48.

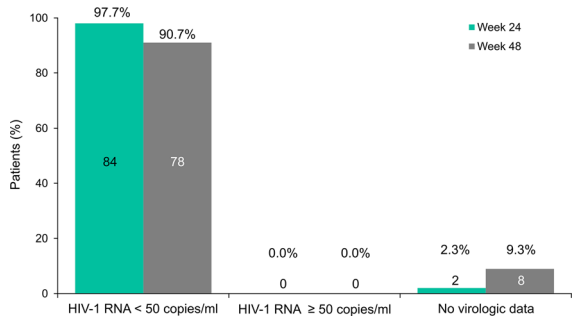

Fig. 1 Virologic outcomes at weeks 24 and 48 (primary efficacy endpoint: proportion of participants with HIV RNA < 50 copies/ml at week 24) (full analysis set, $N = 86$). Annotated numbers show the number of patients

The percentages of participants with HIV-1 RNA < 20 copies/ml were 94.2% (95% CI 87.0–98.1) and 88.4% (95% CI 79.7–94.3) at weeks 24 and 48, respectively. Both the number and percentage of CD4+ cells were maintained during 48 weeks' treatment with B/F/TAF (see Table S1 in the electronic supplementary material). None of the 86 participants who received the study drug exhibited virologic failure, and no treatment-emergent resistance occurred through week 48.

Baseline proviral DNA and/or historical genotype results were available for 84/86 (97.7%) participants for the PR/RT genes and 83/86 (96.5%) for the IN gene. Pre-existing RAMs were observed in the study population (see Table S2 in the electronic supplementary material). In total, five participants had protocol-defined exclusionary mutations in their proviral DNA genotypes that were captured retrospectively using the baseline visit sample. Primary NRTI-associated resistance mutations were observed in nine (10.7%) participants: of these, two had ≥ 3 thymidine analog mutations

Table 2 Summary of treatment-emergent adverse events (safety analysis set, $N = 86$)

Summary of adverse events	Incidence, *n* (%)
Any adverse event	70 (81.4)
Grade 3–4 adverse event	7 (8.1)
Any drug-related adverse event	9 (10.5)
Grade 3–4 drug-related adverse event	0
Any serious adverse event	7 (8.1)
Drug-related serious adverse event	0
Adverse event leading to premature discontinuation of study drug	3 (3.5)[a]
Treatment-emergent adverse events reported in ≥ 3% of participants	
Bronchitis	8 (9.3)
Arthralgia	6 (7.0)
Hypertension	5 (5.8)
Nasopharyngitis	5 (5.8)
Back pain	3 (3.5)
Depression	3 (3.5)
Diarrhea	3 (3.5)
Dizziness	3 (3.5)
Hypercholesterolemia	3 (3.5)
Myalgia	3 (3.5)
Sciatica	3 (3.5)
Upper respiratory tract infection	3 (3.5)
Visual impairment	3 (3.5)

[a] One participant had an adverse event of abdominal discomfort (grade 2), considered related to study drug; one had a serious adverse event of alcohol withdrawal (grade 3), considered not related to study drug; one had an adverse event of benzodiazepine withdrawal (grade 2), considered not related to study drug

(TAMs) and three had M184V (two of whom also had ≥ 3 TAMs that included M41L). Primary non-nucleoside reverse transcriptase inhibitor (NNRTI)-associated resistance mutations were observed in 10 (11.9%) participants. Primary IN mutations were observed in one (1.2%) participant. All participants with exclusionary mutations maintained HIV-1 RNA < 50 copies/ml through week 48.

AEs were reported in 70/86 participants (81.4%) (Table 2). Serious AEs (SAEs) were reported in seven participants (8.1%); all were considered unrelated to study medication. AEs that led to study drug discontinuation were abdominal discomfort (moderate, attributed to study drug by the investigator), alcohol withdrawal and benzodiazepine withdrawal ($n = 1$ for each; not considered related to study drug). No deaths were reported. There were no grade 3–4 study drug-related AEs.

The most common AEs (≥ 3% of participants) were bronchitis, arthralgia, hypertension and nasopharyngitis (Table 2). AEs attributed to treatment by the investigator occurred in nine participants (10.5%): abdominal discomfort, abnormal feces, constipation, dizziness, gamma-glutamyl transferase increased, insomnia, myalgia, pruritus and weight increase ($n = 1$ [1.2%] for each). The median change in weight at week 48 was + 0.1 kg (interquartile range [IQR] − 1.0, 2.3). In seven participants who switched from a TDF-based regimen to B/F/TAF, four had a weight increase (+ 3 to + 4.5 kg) and three had a weight decrease (− 2.5 to − 3 kg).

As anticipated based on the known effects of BIC, $eGFR_{CG}$ decreased by week 4 but changed little thereafter (Fig. 2a). The median change from baseline in $eGFR_{CG}$ at week 48 was − 6.0 ml/min (IQR − 10.2, 0.0). No participants developed proximal tubulopathy, including Fanconi syndrome. Retinol-binding protein/creatinine decreased by a median of 15.1%, and β-2-microglobulin/creatinine increased by a median of 31.6% at week 48 (see Fig. S2 in the electronic supplementary material). There were no hepatic SAEs, and no hepatic, bone or renal AEs resulted in discontinuation of the study drug.

Median total cholesterol, low-density lipoprotein, high-density lipoprotein (HDL), total cholesterol:HDL ratio and triglyceride levels all declined from baseline to week 48, but only total cholesterol and triglyceride changes

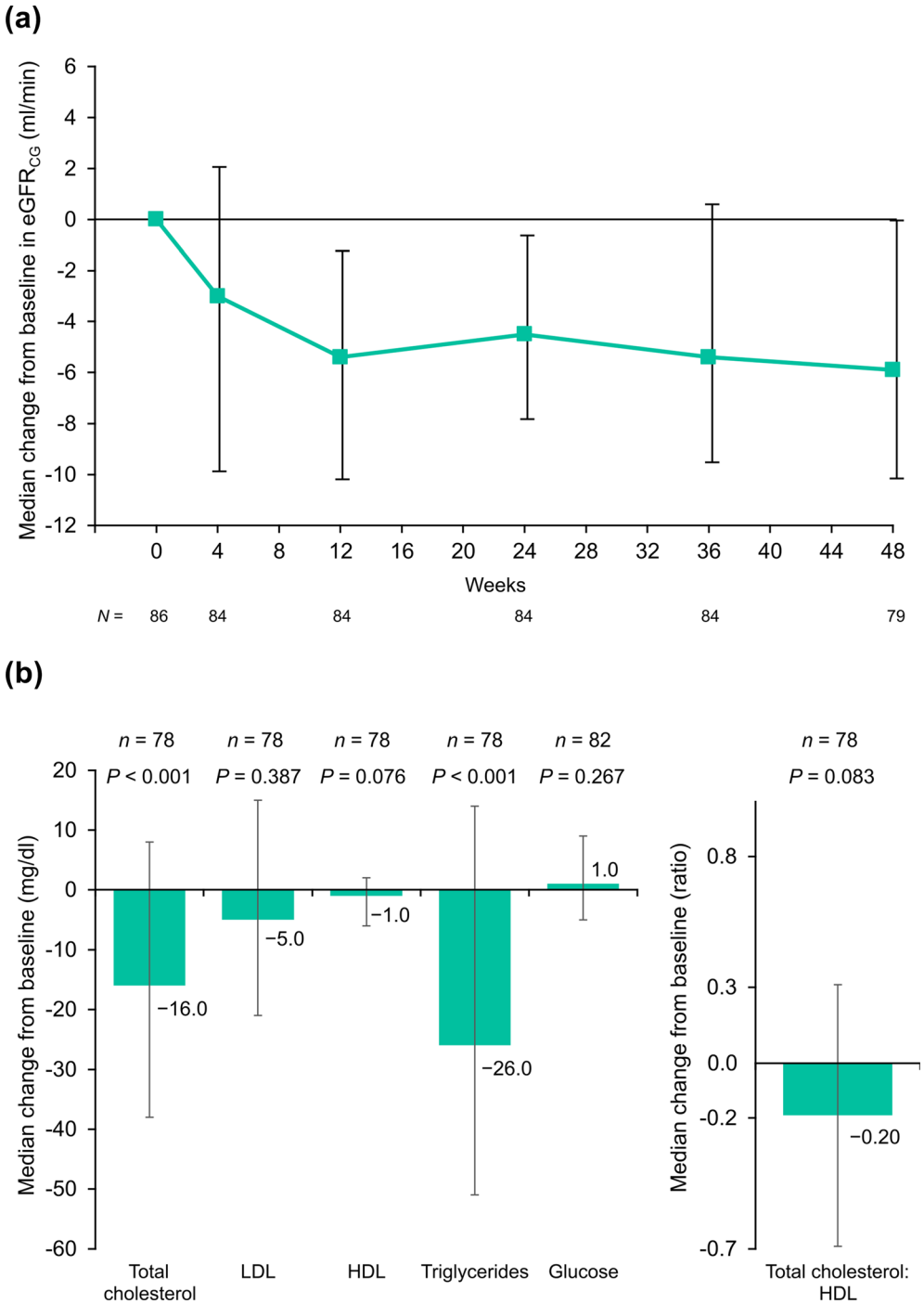

Fig. 2 Change from baseline in **a** the estimated glomerular filtration rate calculated with Cockcroft-Gault equation ($eGFR_{CG}$) and **b** fasting lipids and glucose at week 48 (safety analysis set). Error bars in part **a** represent interquartile range. Error bars in part **b** represent Q1 to Q3. *P* values calculated using the two-sided Wilcoxon signed-rank test. *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *Q* quartile

were statistically significant (Fig. 2b). Median plasma glucose increased by 1.0 mg/dl at week 48 (not statistically significant; Fig. 2b). Median values for hematology and clinical chemistry parameters were generally within reference ranges (data not shown).

An overall treatment satisfaction score was calculated as the sum of the responses to the questions in the HIVTSQ. At baseline, treatment satisfaction was high with a median total score of 58.0 (IQR 51.0, 60.0) (scored from 0 to 60; unfavorable to favorable). At week 48, treatment satisfaction improved as indicated by a median total score of 28.0 (IQR 14.0, 30.0) on the post-baseline change form (scored from − 30 to 30; unfavorable to favorable).

The median EQ-VAS score (scale 0 to 100, representing worst imaginable to best imaginable self-rated health, respectively) was 85 (IQR 75, 95) at baseline and 88 (IQR 80, 95) at week 48. Similarly, the EQ-5D index score responses (scale − 0.594 to 1.000; worst to best health status) indicated that "no problems" were reported in most participants' health status at baseline (median score 1.000 [IQR 0.796, 1.000]) and at week 48 (median change from baseline 0 [IQR –0.140, 0]). Scores for each of the EQ-5D dimensions remained consistent from baseline through week 48. There was no change in overall health at week 48 versus baseline in 53.2% of participants, worsened health in 29.1% and improved health in 17.7%. Week 48 scores for subdomains of the SF-36 and FACIT-F were consistent with those reported at baseline (data not shown).

Eighty-five of 86 participants returned ≥ 1 bottle and had calculable adherence. As of week 48, the median adherence to study drug was 98.6% (IQR 96.0, 100), and most participants (77.6%) had adherence of ≥ 95% up to the week 48 visit. For 19 participants who had < 95% adherence, 14 (73.7%) had a week 48 Snapshot result of HIV-1 RNA < 50 copies/ml and three (15.8%) discontinued the study (because of AE/death), but the last available HIV-1 RNA measurement was < 50 copies/ml, and two (10.5%) had missing data. Three participants (3.5%) had adherence < 80% up to week 48, with the minimum adherence 52.1%. Each of these three participants had a week 48 Snapshot result of HIV-1 RNA < 50 copies/ml. Median self-reported adherence based on the VAS adherence questionnaire was 100% for all post-baseline visits through week 48.

DISCUSSION

In the present study of B/F/TAF for the treatment of virologically suppressed PLWH aged ≥ 65 years, we observed high rates of viral suppression, no HIV-1 RNA values > 50 copies/ml and no treatment-emergent resistance. B/F/TAF was well tolerated, with no drug-related grade 3–4 AEs/SAEs and no discontinuations due to renal, hepatic or bone-related AEs. Positive PROs—including measures of health-related quality of life, patient satisfaction and treatment adherence—reflected the efficacy and safety results.

The rates of virologic suppression (HIV-1 RNA < 50 copies/ml) observed in PLWH aged ≥ 65 years in the present study (week 24, 98%; week 48, 91%) are consistent with previously reported rates in younger adults who switched to B/F/TAF [9, 13, 15], suggesting no difference in virologic response between older and younger patients. For example, Molina and colleagues reported that switching to B/F/TAF was non-inferior to remaining on dolutegravir/abacavir/lamivudine in virologically suppressed adults, with 94% of participants in the B/F/TAF group (median age 47 years) achieving virologic suppression at week 48 [16]. Similarly, Daar and colleagues reported that switching to B/F/TAF was non-inferior to continuing boosted protease inhibitor (PI)-based therapy in virologically suppressed adults, with 92% of participants who switched to B/F/TAF (median age 48 years) achieving virologic suppression at week 48 [13]. Finally, Kityo and colleagues reported that switching to B/F/TAF was non-inferior to remaining on a baseline regimen in virologically suppressed women, with 96% of women in the B/F/TAF group (median age 39 years) achieving virologic suppression at week 48 [15].

The similarity in virologic responses with B/F/TAF between older and younger patients has also been noted with other ART regimens

[21–24]. For example, in a pooled analysis of 19 prospective cohort studies in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), cumulative rates of HIV RNA $\leq$ 500 copies/ml in the first 2 years after ART initiation (NNRTI-based/boosted PI-based regimens) did not differ by age [21]. Additionally, a cross-sectional analysis of the French Dat'AIDS cohort reported that plasma HIV RNA was < 50 copies/ml in 90.6% and 90.9% of individuals receiving ART who were aged 50–74 years and $\geq$ 75 years, respectively [24].

Notably, 100% of individuals in the present study with pre-existing archived NRTI resistance by proviral DNA genotype ($n = 9$; none with K65R) achieved successful virologic outcomes with no emergent resistance. This is consistent with recent analyses of the efficacy of switching to B/F/TAF in studies GS-US-380-1878, GS-US-380-1844, GS-US-380-4030 and GS-US-380-4580 in PLWH with pre-existing resistance [25–28]. High rates of virologic suppression were observed in the overall population and in individuals with pre-existing resistance, indicating that B/F/TAF is an effective treatment option for virologically suppressed patients with archived NRTI resistance [25]. In addition, no emergent resistance has been observed in clinical trials of B/F/TAF to date [13, 15–18, 25, 28–30].

The safety profile, including overall incidence and types of drug-related AEs, was consistent with that expected with B/F/TAF based on previous studies [9, 13, 15, 31]. There were no indicators of bone- or kidney-related toxicity, which are of special concern in older patients, who experience loss of glomerular function and bone mineral density as they age. No participants developed proximal tubulopathy, and changes in renal biomarkers were consistent with the known renal safety profile of TAF. The observed decline in $eGFR_{CG}$ is consistent with the known effect of BIC as an inhibitor of the renal transporters, organic cation transporter 2 (OCT2) and multidrug and toxin extrusion 1 (MATE1; noting the effect is on the estimated measurement of GFR and not the actual GFR). However, as most participants had been receiving E/C/F/TAF before switching to B/F/TAF, and cobicistat is also an inhibitor of cation transporters, predominantly MATE1 [32, 33], it is difficult to draw direct conclusions on the effect of BIC on renal transporters in this older patient population.

The lack of weight gain is an interesting finding, as INSTI treatment has been associated with weight gain [34, 35]. The lack of additional weight gain following the switch to B/F/TAF is reassuring given that most participants were on an elvitegravir-containing therapy at baseline, and elvitegravir appears to be associated with the least amount of weight gain among the INSTIs [35]. However, most patients in this study were taking TAF. Unlike TDF, which has been associated with weight loss or suppression of expected weight gain, there is no weight-suppressive effect of TAF [34]. Thus, patients switching from TDF might be expected to gain weight after a switch to B/F/TAF; however, we did not see any trend in the small number of patients studied. Furthermore, the lack of observed weight gain should also be considered in the context of the predominantly white male study population; weight gain with INSTI therapy has been reported to be greater in female and black PLWH [34, 35].

Patient-reported treatment satisfaction was higher at week 48 with B/F/TAF versus the pre-switch baseline regimens. While this is an encouraging result, without a true control group, it is difficult to reach firm conclusions around treatment satisfaction. Although not directly assessed, potential explanations for the suggested greater treatment satisfaction with B/F/TAF could include the small pill size, fewer DDIs or reduced gastrointestinal side effects. The use of unboosted INSTIs as third agents has been shown to be associated with a lower risk of experiencing "red-flag" and "orange-flag" DDIs [36]. On this basis, it was proposed that unboosted INSTI-based regimens should be considered for patients at a high risk of experiencing harm from DDIs, e.g., those with organ dysfunction, comorbidities and polypharmacy [36]. However, we did not measure the occurrence of DDIs when switching regimens in this study. The present findings suggest that B/F/TAF is an appropriate ART regimen for virologically

suppressed PLWH aged ≥ 65 years who wish to switch.

A strength of the study is that it specifically and prospectively investigated the effects of B/F/TAF in PLWH aged ≥ 65 years, a patient group underrepresented in ART trials. Additionally, the study design included a breadth of outcome measures, including PROs as well as conventional efficacy and safety assessments.

Limitations of the study include the open-label, uncontrolled design, which increases the risk of bias, particularly for subjective measures such as the PROs. A formal sample size calculation was not performed, as recruitment was based on the feasibility of enrolling elderly patients within a reasonable time scale. Finally, participants were mainly white men, which may be representative of the current older population of PLWH in many resource-rich regions [37], but does not necessarily reflect changing demographics or the characteristics of older populations in other regions. Additionally, most participants had been previously taking E/C/F/TAF, so observed changes from baseline in outcome measures might not be applicable to patients switching from other regimens. Thus, the generalizability of the findings to clinical practice should be considered in the context of the population studied. Nevertheless, the present findings represent an important addition to the evidence base, as over half of participants were > 69 years of age, meaning that the study cohort was truly an elderly population, in contrast to other studies in "elderly" patients that have often included much younger patients (e.g., aged > 50 years).

CONCLUSION

Switching to B/F/TAF was effective and well tolerated in virologically suppressed adults aged ≥ 65 years through 48 weeks. Treatment satisfaction was higher with B/F/TAF than with baseline treatment, although there were no changes in other PROs in response to the switch. The study is ongoing and will continue through 96 weeks, providing additional data on the long-term efficacy, safety and tolerability of B/F/TAF in this age group.

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Data Availability. Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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