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MAJOR ARTICLE

Effectiveness and Safety of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Patients With HIV-1 Infection and Ongoing Substance Use Disorder: The BASE Study

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Background. People with human immunodeficiency virus (HIV) and substance use disorder (PWH/SUD) are at higher risk of nonadherence to antiretroviral therapy. Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) exhibits high rates of efficacy with a favorable adverse event profile. The BASE study (NCT03998176) is a phase 4, single-arm study evaluating the effectiveness and safety of B/F/TAF among PWH/SUD.

Methods. Viremic (HIV RNA >1000 copies/mL) PWH/SUD initiated B/F/TAF once daily for 48 weeks (W). The primary endpoint was proportion of participants with HIV RNA <50 copies/mL at W24. Secondary endpoints were proportion of participants with HIV-1 RNA <50 copies/mL at W48, safety, B/F/TAF adherence (dried blood spot [DBS] concentrations of emtricitabine triphosphate and tenofovir diphosphate [TFV-DP]), substance use (NIDA-ASSIST), and quality of life (SF-12).

Results. Forty-three participants were enrolled; 95% reported methamphetamine use. Median age was 38 (range, 21–62) years; 21% were female, 81% White, 14% Black, and 16% Hispanic. Thirty-two (74%) and 21 (49%) participants had HIV RNA <50 copies/mL (intention-to-treat) at W24 and W48, respectively. Seven participants (16%) experienced confirmed virologic failure through W48; 1 developed emergent drug resistance (M184V). Fifteen participants (35%) experienced grade ≥3 adverse events. Five participants (12%) reported suicidal ideation; none resulted in discontinuation. Median DBS concentrations were representative of 5–6 doses/week (TFV-DP, 1603 fmol/punches). NIDA-ASSIST scores declined from baseline to W48 with methamphetamine use decreasing most (−7.9 points; −29%), and SF-12 physical/mental scores increased 1.2 and 7.6 points, respectively.

Conclusions. B/F/TAF among a high-risk population of PWH/SUD resulted in an initial 72% viral suppression rate at W24 before dropping to 49% at W48 as retention declined. One participant developed emergent drug resistance (M184V).

Keywords. bictegravir/emtricitabine/tenofovir alafenamide; HIV; substance use disorder.

Use of substances such as cocaine, heroin, methamphetamine, prescription opioids, and stimulants, among others, has become a growing concern across nearly all regions of the United States (US) [1]. In 2017, 6.8% of new human immunodeficiency virus (HIV) infections occurred in people who injected drugs and 4% were in gay/bisexual men who injected drugs [2]. Furthermore, injection of substances and "chemsex" (ie, combining substance use with sexual activity) has been associated with outbreaks of HIV and viral hepatitis acquisition [3–5].

Of the 1.2 million people with HIV (PWH) in the US, an estimated 48% also have a substance use disorder (SUD) [6]. Poor antiretroviral therapy (ART) adherence and inconsistencies in retention in HIV care have been observed among PWH with SUD (PWH/SUD) [7–14]. Gaps in ART coverage and lack of retention in HIV care are factors that complicate the successful management of HIV infection among PWH/SUD, increasing risk of poor treatment outcomes and HIV transmission [13, 15, 16]. As a result, ART choice in PWH/SUD can prove challenging and often requires the selection of a regimen with a high barrier to drug resistance such as protease inhibitor (PI)–based ART [17–19]. However, concerns about drug–drug interactions between illicit substances and ART regimens containing a pharmacokinetic enhancer, such as a boosted PI-based regimen, have been raised [20–22].

Integrase strand inhibitor (INSTI)–based ART regimens are currently the preferred treatment option for most PWH in the US [17]. The INSTI-based regimen bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is generally well-tolerated, available in a single-tablet formulation that does not require a pharmacokinetic enhancer, and provides a high genetic barrier

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to resistance. In clinical trials among treatment-naive and treatment-experienced patients with virologic suppression, B/F/TAF exhibited efficacy of 89%–96%, without any cases of newly emergent treatment resistance [23–26].

However, little is known about the effectiveness and safety of B/F/TAF in PWH/SUD, as active SUD is often exclusionary from clinical trials and data from cohort studies are limited. Therefore, we aimed to prospectively evaluate the effectiveness and safety of B/F/TAF among viremic PWH/SUD through 48 weeks at the Nebraska Medicine Specialty Care Center (SCC) in Omaha, Nebraska, USA.

METHODS

Study Design and Participants

The BASE study (Bictegravir/Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected Patients With Active Illicit Substance Use; NCT03998176) was a phase 4, open-label, single-arm, prospective 48-week trial evaluating the use of B/F/TAF in PWH/SUD at the SCC. Inclusion criteria included age ≥19 years; ART treatment naive or experienced; HIV-1 RNA ≥1000 copies/mL; any documented substance use other than nicotine, alcohol, or marijuana within the past 6 months (assessed by verbal acknowledgment or drug screening assays); creatinine clearance (Cockcroft-Gault) >30 mL/minute; and liver aminotransferases <5 times the upper limit of normal. Exclusion criteria included resistance mutations reducing susceptibility to the components of B/F/TAF (previously documented or baseline INSTI or tenofovir-related resistance-associated mutations [RAMs] as defined by the International Antiviral Society–USA [27]; presence of thymidine analogue mutations or the M184V/I mutation were allowed), pregnancy, current concomitant use of cytochrome P450-inducing medications, or serious illness requiring systemic treatment and/or hospitalization within 30 days of study entry. Concomitant hepatitis B or C infections was not exclusionary.

Procedures

Patients were recruited for study participation by convenience sampling and screening occurred within the constructs of a scheduled HIV care visit. If inclusion/exclusion criteria were met, participants were able to enroll in the study, including the start of B/F/TAF, the same day prior to the availability of laboratory results, or within 30 days of screening. Sociodemographic information was collected at the screening visit.

Study visits were conducted at weeks 0, 6, 12, 24, 36, and 48. Complete blood count, comprehensive metabolic panel, CD4 cell count, and quantitative HIV-1 RNA (Cobas HIV-1 Test; Roche Diagnostics, Indianapolis, Indiana), were completed at weeks 0, 6, 24, and 48, and urine pregnancy screening, if applicable, was completed at each study visit. Adherence to B/F/TAF was assessed by emtricitabine triphosphate (FTC-TP) and tenofovir diphosphate (TFV-DP) levels in dried blood spots (DBSs) at weeks 6, 24, and 48 (see Pharmacokinetic Sampling). Additionally, subjective adherence was assessed at each study visit using the AIDS Clinical Trials Group Brief Adherence Report [28] and refill histories were collected at weeks 24 and 48 to calculate a percentage of days covered (PDC). Patient-reported outcomes, including ongoing substance use (modified National Institute on Drug Use, Alcohol, Smoking, and Substance Involvement Screening Test [NIDA-ASSIST]) [29] and quality of life (12-Item Short-Form Survey [SF-12]) [30, 31], were collected longitudinally throughout the study. Participants were offered referral to substance use counseling and/or treatment at each visit through referral and linkage to an Omaha, Nebraska (Nebraska Medicine Intensive Outpatient Treatment, HERO Addiction Recovery, Campus for Hope) or Lincoln, Nebraska (CenterPointe, Houses for Hope) SUD treatment program. Transportation support and compensation via Visa cash cards ($20/hour) were provided for each study visit completed.

Safety was assessed by physical examinations, laboratory tests, B/F/TAF discontinuation, and reported adverse events (AEs). AEs were assessed at each study visit and graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [32]. Any grade ≥3 AE was evaluated by the study team for relationship to B/F/TAF. Study withdrawal criteria included protocol-defined confirmed virologic failure (CVF; see Outcomes), pregnancy, or a B/F/TAF-related grade 4 event.

Pharmacokinetic Sampling

Blood for pharmacokinetic studies was collected by random postdose sampling at weeks 6, 24, and 48. The time of last B/F/TAF dose and whether it was taken with food were collected for each sampling. Four milliliters of K2 ethylenediaminetetraacetic acid (EDTA) whole blood was collected by venipuncture to assess TFV-DP and FTC-TP concentrations in DBSs. Using a Whatman 903 Protein Saver card (DBS card), 25 µL of whole blood from the K2 EDTA was spotted on each circle on the card and allowed to dry for at least 3 hours. Dried DBS cards were stored at −80°C in plastic bags until analysis. TFV-DP and FTC-TP were quantified from the DBS card using two 7-mm punches via a validated liquid chromatography–tandem mass spectrometry assay [33–35]. All pharmacokinetic assays were processed at the University of Nebraska Medical Center Antiretroviral Pharmacology Laboratory.

Outcomes

The primary endpoint was the proportion of participants with HIV-1 RNA <50 copies/mL at week 24 by the US Food and Drug Administration (FDA) Snapshot analysis for the intention-to-treat (ITT) population. Subgroup analyses by participant characteristics were performed for the ITT population.

Per-protocol analyses, excluding participants with missing data, were completed for HIV-1 RNA cut points of <50 and <200 copies/mL. Protocol-defined CVF was defined as HIV-1 RNA >400 copies/mL on 2 consecutive readings at week 24 or later. Genotypic resistance testing for reverse transcriptase inhibitors, PIs, and INSTIs (GenoSure PRIme; Monogram Biosciences, San Francisco, California) was performed on all participants meeting CVF criteria.

Secondary analyses included the proportion of participants with HIV-1 RNA <50 copies/mL at week 48, grade ≥3 AEs, proportion of participants completing each study visit (retention in care), and changes from baseline in CD4 cell counts and percentage, adherence metrics, and patient-reported outcome evaluations for substance use and mental component score (MCS)/physical component score (PCS).

Statistical Analysis

Descriptive statistics were used to summarize patient demographics and baseline characteristics. Counts and percentages were used for categorical data, and median (range) or mean (standard deviation [SD]) for continuous data. HIV-1 RNA was dichotomized at ≥50 or <50 copies/mL. The ITT (participants receiving ≥1 dose of B/F/TAF) and observed, per-protocol analyses were performed for viral suppression (VS) endpoints.

A sample size of 30 participants produced a 2-sided 95% confidence interval (CI) with a width equal to 0.35 when the sample proportion of patients who achieved HIV-1 RNA <50 copies/mL at week 24 was 0.70. The target sample size was increased to 45 to allow for 50% attrition. Fisher exact test was used to compare the proportion of participants achieving an HIV-1 RNA <50 copies/mL among subgroups. Wilcoxon rank-sum test was used to compare the continuous data with treatment status and suppression status. Paired *t* tests were used to compare mean FTC-TP and TFV-DP concentration in DBSs at weeks 6, 24, and 48. Linear mixed models were used to compare NIDA-ASSIST for substance use and SF-12 (MCS and PCS) between the 3 time points. Pairwise comparisons, when performed, were adjusted using Tukey method. All analyses were done using SAS version 9.4 (SAS Institute, Cary, North Carolina). A *P* value of <.05 was considered statistically significant.

Patient Consent Statement

The University of Nebraska Medical Center Institutional Review Board (IRB) approved the protocol (IRB number 471-19-FB). All participants provided written informed consent. An independent safety monitoring committee provided study oversight.

RESULTS

Study Population

Between 1 October 2019 and 1 April 2021, 49 patients were screened for BASE study entry with 43 participants meeting study inclusion/exclusion criteria for enrollment. All 43 participants were included in the ITT population. Median age was 38 (range, 21–62) years. The majority were male (79.1%) and White (81.4%). Black and Hispanic participants were 14.0% and 16.3% of the study population, respectively. Median HIV-1 RNA and CD4 count at screening were 55 800 (range, 1212–2 280 000) copies/mL and 460 (range, 40–1653) cells/μL, respectively. Methamphetamine use was most frequent, with 95.3% of participants reporting use within 6 months of entry.

Thirty-one participants (72.1%) were ART experienced. Median time since last HIV care clinic visit was 10.0 (range, 1–44) months and the average time since HIV diagnosis was 12.7 (range, 0.5–27) years. A little over half (n = 18 [58.0%]) of the treatment-experienced participants had any RAMs. Nonnucleoside reverse transcriptase inhibitor (NNRTI) RAMs were most common (35.5%), and 5 participants (16.1%) had an archived M184V/I. Baseline transmitted resistance in the 12 treatment-naive participants was rare, with only 1 participant exhibiting a single NNRTI RAM (K103N). Baseline characteristics are summarized in Table 1.

Participant Disposition

Participant disposition through week 48 is outlined in Figure 1. Overall, a total of 37 (86.0%) and 31 (72.1%) participants completed week 24 and 48, respectively. Two participants relocated after week 6, 2 participants were incarcerated during study, and 8 participants were lost to follow-up at week 48. Retention in care initially diverged at week 6 by prior treatment status (naive, 58.3% vs experienced, 87.1%) before converging to similar retention rates after week 6 through week 48, with a mean proportion of participants completing each visit of 80.0% (Supplementary Figure 1).

Effectiveness

Thirty-two participants (74.4%) achieved VS with an HIV-1 RNA <50 copies/mL at week 24. Seven participants (16.3%) missed the week 24 visit window and did not provide HIV-1 RNA or other clinical data. At week 48, 21 participants (48.8%) achieved VS as participant loss to follow-up increased (n = 12 [27.9%]) (Figure 2). In per-protocol analyses, 86.1% and 67.7% of participants achieved VS at weeks 24 and 48. In subgroup analyses, significant differences in VS were observed based on treatment experience at week 48 (naive, n = 9/9 [100.0%] vs experienced, n = 12/22 [54.5%]; $P = .029$). No other differences in VS were observed across other subgroups (Supplementary Table 1).

Seven participants (16.3%) experienced CVF through week 48. The median HIV-1 RNA of participants with CVF was 3410 (range, 202–452 000) copies/mL. Three participants returned for repeat HIV-1 RNA and genotyping, 3 were lost to follow-up, and 1 had an HIV-1 RNA too low to perform genotypic

Table 1. Baseline Characteristics

Characteristic	B/F/TAF		
	Total Population (N = 43)	ART-Naive (n = 12)	ART-Experienced (n = 31)
Age, y, median (range)	38.0 (21.0–62.0)	32.0 (27.0–62.0)	40.0 (21.0–61.0)
Sex[a]			
Male	34 (79.1)	10 (83.3)	24 (77.4)
Female	9 (20.9)	2 (16.7)	7 (22.6)
Race			
White	35 (81.4)	11 (91.7)	24 (77.4)
Black	6 (14.0)	1 (8.3)	5 (16.1)
Asian/Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Native American	2 (4.6)	0 (0.0)	2 (6.5)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity			
Hispanic	7 (16.3)	4 (33.3)	3 (9.7)
Not Hispanic	36 (83.7)	8 (66.7)	28 (90.3)
Housing status			
Stable	23 (53.5)	7 (58.4)	16 (51.6)
Marginal	13 (30.2)	4 (33.3)	9 (29.0)
Homeless	7 (16.3)	1 (8.3)	6 (19.4)
Annual income level, USD			
<$15 000	33 (76.7)	9 (75.0)	24 (77.4)
$15 000-$40 000	8 (18.6)	2 (16.7)	6 (19.4)
$40 001-$70 000	2 (4.7)	1 (8.3)	1 (3.2)
>$70 000	0 (0.0)	0 (0.0)	0 (0.0)
Insurance coverage			
Commercial	5 (11.6)	2 (16.7)	3 (9.7)
Medicaid	9 (20.9)	1 (8.3)	8 (25.8)
Medicare	5 (11.6)	1 (8.3)	4 (12.9)
Uninsured/ADAP	24 (55.9)	8 (66.7)	16 (51.6)
HIV acquisition risk factor			
MSM	16 (37.2)	4 (33.3)	12 (38.7)
MSM/IVDU	13 (30.3)	4 (33.3)	9 (29.0)
IVDU	3 (7.0)	2 (16.7)	1 (3.2)
Heterosexual	9 (20.9)	1 (8.3)	8 (25.8)
Unknown	2 (4.6)	1 (8.3)	1 (3.2)
Substance use, NIDA-ASSIST	43 (100.0)	12 (100.0)	31 (100.0)
Cannabis	27 (62.8)	8 (66.7)	19 (61.3)
Cocaine	9 (20.9)	1 (8.3)	8 (25.8)
Hallucinogens	9 (20.9)	2 (16.7)	7 (22.6)
Opiates/heroin	8 (18.6)	1 (8.3)	7 (22.6)
Sedatives	4 (9.3)	0 (0.0)	4 (12.9)
Stimulants/methamphetamine	41 (95.3)	12 (100.0)	29 (93.6)
Substance use, UDS	10 (23.3)	1 (8.3)	9 (29.0)
Amphetamines	9 (90.0)	1 (8.3)	8 (25.8)
Benzodiazepines	1 (10.0)	0 (0.0)	1 (3.2)
Cannabis	3 (30.0)	1 (8.3)	2 (6.5)
Opiates	1 (10.0)	0 (0.0)	1 (3.2)
IVDU			
Never	14 (32.6)	5 (41.7)	9 (29.0)
Yes, not within last 3 mo	8 (18.6)	2 (15.7)	6 (19.4)
Yes, within last 3 mo	21 (48.8)	5 (41.7)	16 (51.6)
Weight, kg, median (range)	81.1 (50.9–176.9)	81.9 (57.6–106.0)	80.0 (50.9–176.9)
BMI, kg/m^2, median (range)	25.9 (18.7–48.8)	25.7 (19.9–30.0)	25.9 (18.7–48.7)
CD4 count, cells/μL, median (range)	460 (40–1653)	453 (44–841)	489 (40–1653)
CD4%, median (range)	22.9 (3.2–43.3)	21.4 (3.2–29.7)	22.9 (4.9–43.3)
HIV RNA, copies/mL, median (range)	55 800 (1212–2 280 000)	82 400 (19 400–835 000)	43 700 (1212–2 280 000)

Table 1. Continued

Characteristic	B/F/TAF		
	Total Population (N = 43)	ART-Naive (n = 12)	ART-Experienced (n = 31)
Genotypic drug resistance			
Any	19 (44.2)	1 (8.3)	18 (58.0)
NNRTI-based	12 (28.0)	1 (8.3)	11 (35.5)
PI-based	1 (2.3)	0 (0.0)	1 (3.2)
Any TAMs	1 (2.3)	0 (0.0)	1 (3.2)
M184V/I	5 (11.6)	0 (0.0)	5 (16.1)
Previous ART regimen			
INSTI + 2 NRTIs	…	…	22 (71.0)
PI + 2 NRTIs	…	…	9 (29.0)
NNRTI + 2 NRTIs	…	…	0 (0.0)
Other	…	…	0 (0.0)
Time since diagnosis, y, median (range)	…	…	12.7 (0.5–27.0)
Time since last visit, mo, median (range)	…	…	10.0 (1.0–44.0)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ADAP, AIDS Drug Assistance Program; ART, antiretroviral therapy; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IVDU, intravenous drug use; MSM, men who have sex with men; NIDA-ASSIST, National Institute on Drug Use, Alcohol, Smoking, and Substance Involvement Screening Test; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAM, thymidine analogue mutation; UDS, urine drug screening; USD, United States dollars.

[a]No transgender or nonbinary people were enrolled in the BASE study.

resistance testing. Treatment-emergent resistance was observed in 1 participant (M184V). A summary of participants evaluated for CVF can be found in Supplementary Table 2.

Immunologic outcomes from baseline through week 48 increased overall with mean increase in CD4 count and CD4% of 105 (SD, 203) cells/μL and 6.0% (SD, 7.0%), respectively.

Safety

Overall, 15 participants (34.9%) reported 27 grade ≥3 severe AEs (SAEs) through week 48. Suicidal ideation was most common, with 7 incidents among 5 participants (11.6%). Notably, all cases of suicidal ideation occurred during periods of methamphetamine intoxication and participants were immediately provided mental health services. None of the suicidal ideation cases were deemed attributable to B/F/TAF by the study team. Laboratory SAEs were relatively uncommon and occurred on 4 occasions among 3 participants. Three laboratory SAEs were transient elevations in creatinine that were attributed to hypertension. No SAEs led to withdrawal of B/F/TAF. A summary of SAEs is described in Table 2. Mean weight and body mass index (BMI) change from baseline to week 48 was 2.4 (SD, 7.6) kg and 0.5 (SD, 5.0) kg/m^2, respectively. No significant differences were observed based on participants' treatment experience for changes in both weight (naive, 1.5 kg vs experienced, 2.8 kg; $P = .627$) and BMI (naive, 0.9 kg/m^2 vs experienced, 0.9 kg/m^2; $P = .916$) through week 48.

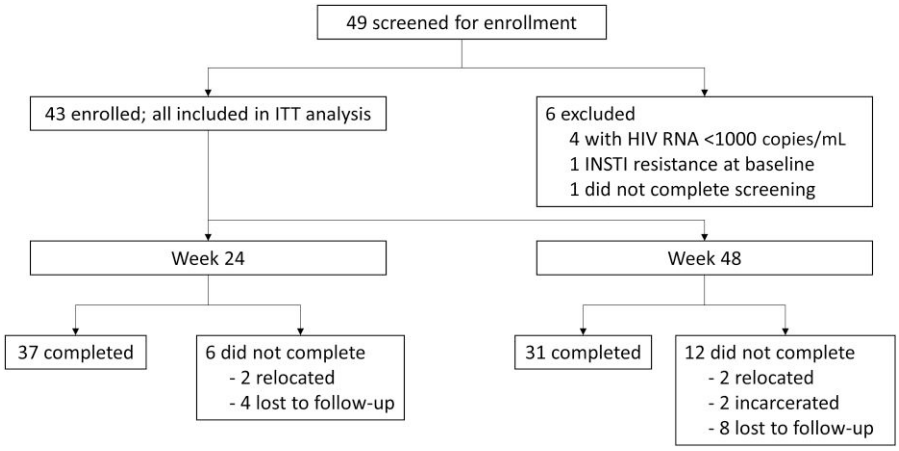

Figure 1. Participant disposition. Abbreviations: HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; ITT, intention-to-treat analysis.

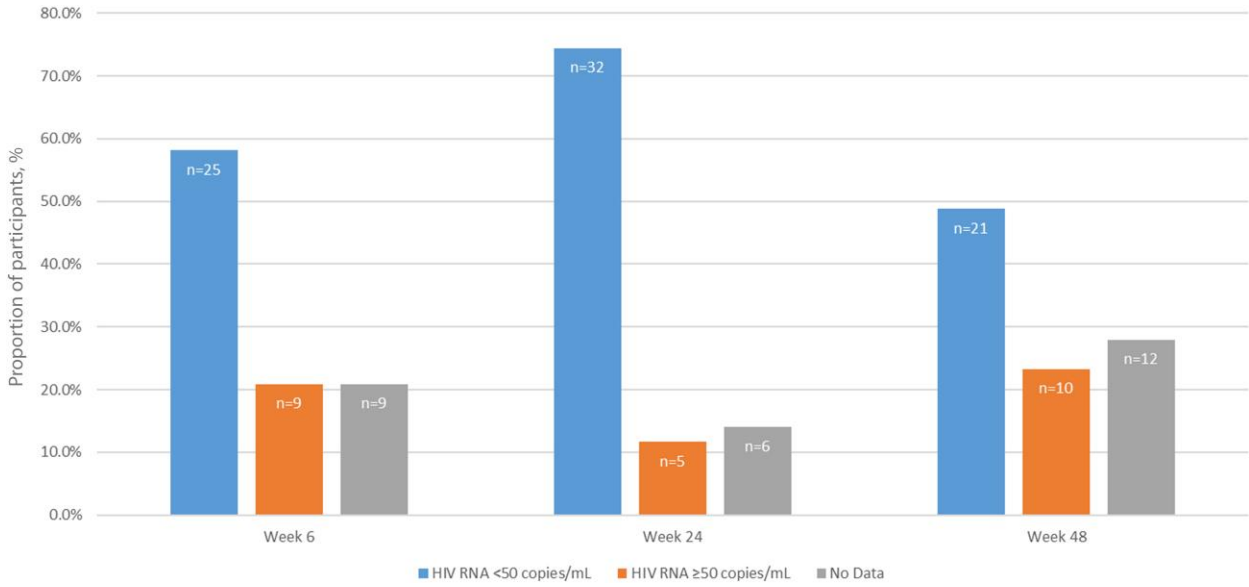

Figure 2. Virologic outcomes through week 48 by intention-to-treat (N = 43) analysis. Abbreviation: HIV, human immunodeficiency virus.

Adherence

Overall, mean adherence by subjective reporting and PDC across participants through week 48 was 82.2% and 78.4%, respectively. Observed median intracellular FTC-TP (3934 [range, below the limit of quantification {BLQ} to 11 775] fmol/punches) and TFV-DP (1603 [range, BLQ to 4816] fmol/punches) through week 48 were reflective of 5–6 doses/week based on previously published ranges [36]. The proportion of participants taking <4, 4–6, and >6 doses weekly was steady across study time points (Supplementary Figure 2). Significant differences in DBS concentrations were observed based on participant virologic status at week 24 (FTC-TP) and week 48 (FTC-TP and TFV-DP) (Figure 3). Participants with detectable FTC-TP DBS concentrations had higher odds of VS at week 24 (odds ratio [OR], 14.5 [95% CI, 1.7–121.5]; $P = .0139$) and week 48 (OR, 11.3 [95% CI, 1.7–73.0]; $P = .0111$) compared to participants with undetectable FTC-TP DBS concentrations in exploratory analyses. Roughly 30% of participants had an adherence/virologic status mismatch (Supplementary Figure 3), with an increasing proportion of participants displaying mismatches of high adherence in the setting of viremia (n = 5 [16.1%]) and low adherence in the setting of viremia (n = 5 [16.1%]) through week 48.

Longitudinal adherence descriptions according to all adherence metrics used and virologic outcome status at weeks 6, 24, and 48 are summarized in Supplementary Table 3. In general, across all study time points, higher mean subjective adherence reports were observed among participants achieving HIV-1 RNA <50 copies/mL (range, 83.8%–91.5%) compared to participants with HIV-1 RNA ≥50 copies/mL (range, 59.0%–72.5%). Similarly, adherence by PDC was higher for

Table 2. Summary of Severe Adverse Events Through Week 48

Severe Adverse Event	B/F/TAF	
	Participants, No. (%)[a]	SAE, No. (%)
Any SAE	15 (34.9)	27 (100.0)
SAE		
Grade 3	12 (27.9)	23 (85.2)
Suicidal ideation	5 (11.6)	7 (25.9)
COVID-19 infection	2 (4.7)	2 (7.4)
Intractable headache	2 (4.7)	2 (7.4)
Neurosyphilis	2 (4.7)	2 (7.4)
Acute kidney injury	2 (4.7)	2 (7.4)
Acute mental status change	1 (2.3)	1 (3.7)
Epididymitis	1 (2.3)	1 (3.7)
Sepsis	1 (2.3)	1 (3.7)
Hypertension	1 (2.3)	1 (3.7)
Chest pain	1 (2.3)	1 (3.7)
Vallecular cyst	1 (2.3)	1 (3.7)
Cellulitis	1 (2.3)	1 (3.7)
Acute mania	1 (2.3)	1 (3.7)
Grade 4	0 (0.0)	0 (0.0)
Laboratory SAE		
Grade 3	3 (7.0)	4 (14.8)
Elevated creatinine, 1.4 × ULN	2 (4.7)	2 (7.4)
Elevated creatinine, 1.8 × ULN	1 (2.3)	1 (3.7)
Hyperglycemia, >250–500 mg/dL, nonfasting	1 (2.3)	1 (3.7)
Grade 4	0 (0.0)	0 (0.0)
Drug-related SAE	0 (0.0)	0 (0.0)
AEs leading to withdrawal	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; COVID-19, coronavirus disease 2019; SAE, severe (grade ≥3) adverse event; ULN, upper limit of normal.

[a]All percentages are calculated based on total number of participants in the intention-to-treat analysis (N = 43).

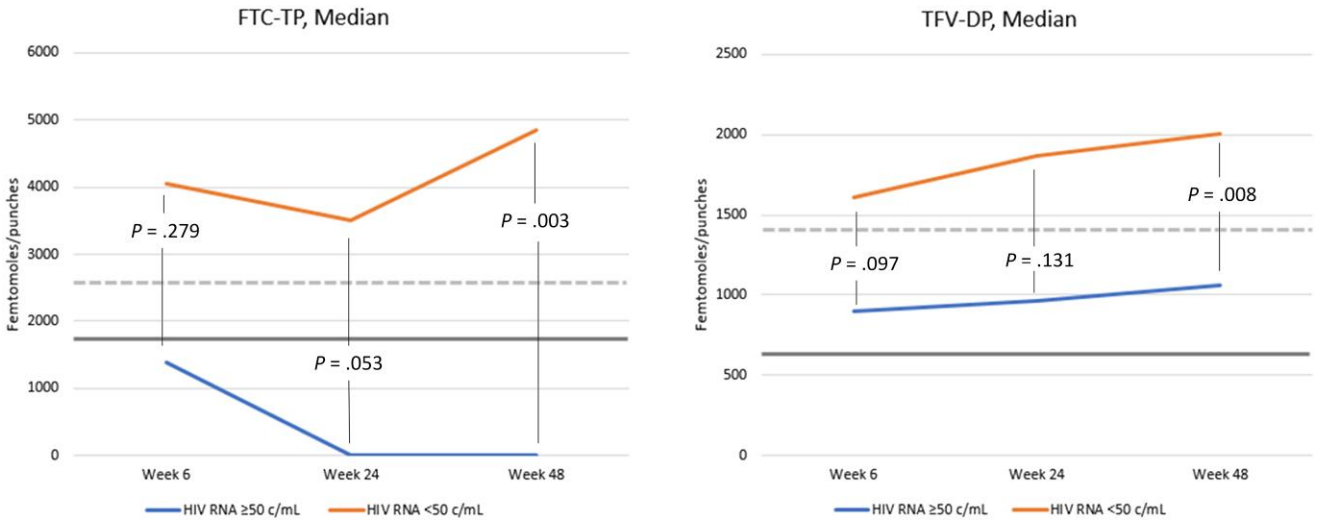

Figure 3. Bictegravir/emtricitabine/tenofovir alafenamide adherence based on intracellular tenofovir diphosphate (TFV-DP) in dried blood spots (DBSs) at weeks 6, 24, and 48, presented as dose per week. Thresholds for 2–3 doses per week (solid line) and 4–5 doses per week (dashed line) are noted for both emtricitabine triphosphate and TFV-DP based on tenofovir alafenamide DBS data [36]. Abbreviations: c/mL, copies/mL; FTC-TP, emtricitabine triphosphate; HIV, human immunodeficiency virus; TFV-DP, tenofovir diphosphate.

participants with HIV-1 RNA <50 copies/mL (81.7%) compared to participants with HIV-1 RNA ≥50 copies/mL (58.8%–66.0%).

Patient-Reported Outcomes

Methamphetamine and cannabis use were the most common substances reported. No participants were identified as having an opiate use disorder. Most substance use patterns remained consistent but in a downward trend through week 48. However, methamphetamine use declined most by a mean change from baseline of −7.9 points (−29%) by NIDA-ASSIST scoring. Seven participants (16.3%) entered intensive substance use treatment for methamphetamine SUD through week 48 (intensive outpatient SUD treatment program, 4 participants; inpatient SUD treatment program, 3 participants). Two participants (28.6%) received naltrexone as part of their methamphetamine use disorder treatment. Five participants (71.4%) reported substance use cessation. All 7 participants (100%) were virally suppressed at week 48 with HIV RNA <50 copies/mL. MCS and PCS for SF-12 generally trended upward through week 48. Mean change in MCS and PCS from baseline through week 48 were +7.6 ($P = .001$) and +1.2 ($P = .809$), respectively. Supplementary Figure 4 summarizes substance use and MCS/PCS through week 48.

DISCUSSION

This clinical trial evaluated the use of B/F/TAF among PWH/SUD through 48 weeks. We found B/F/TAF to be safe and effective despite suboptimal adherence and downward trending rates of retention in care through week 48. Our results found that 72% of participants reached the primary outcome of VS with HIV-1 RNA <50 copies/mL at week 24 (ITT) before declining to 49% at week 48. While this rate is lower than published clinical trial rates for B/F/TAF at 89%–96% [23–26], our population faces additional barriers to retention in care and is at a greater need for support services (eg, housing, transportation). Unlike previous clinical trials of B/F/TAF, which observed no treatment-emergent RAMs, 1 participant developed an emergent HIV-1 drug RAM (M184V) at week 48.

Ongoing SUD among PWH has been associated with lower rates of ART adherence [13, 14] and higher rates of HIV viremia [7, 9, 10]. Of note, nearly all BASE participants had methamphetamine use disorder, and methamphetamine use specifically has been associated with larger reductions in ART adherence and poorer HIV outcomes [8, 11]. Decreased rates of complete ART adherence (no use, 76.3%; moderate use, 21.7%; heavy use, 2.0%) and VS (no use, 74.6%; moderate use, 22.7%; heavy use, 2.7%) were observed based on methamphetamine use at 6 months in a study by the DRug use and Infections in ViEtnam (DRIVE) study team [8]. In contrast to the DRIVE study, we found a much higher rate of VS (72%) comparatively among our population with methamphetamine use patterns similar to DRIVE's moderate use description (methamphetamine use 1–19 days within the past 30 days) (Supplementary Table 4). Similarly, we observed higher adherence rates overall across all adherence metrics compared to DRIVE.

Associations between adherence and VS were notable through the course of 48 weeks. Stable adherence rates >80% by subjective reporting and PDC were observed among VS

participants, in comparison to viremic participants, who had steady declines in adherence to roughly 59% at week 24 (Supplementary Table 3). Similarly, this was also reflected in intracellular FTC-TP and TFV-DP concentrations in DBS, which have been shown to be representative of short-term (half-life, ~1.5 days) and intermediate-term (half-life, ~17 days) adherence, respectively [33, 34]. Overall, we found FTC-TP and TFV-DP concentrations to be consistent with dosing of 5–6 doses of B/F/TAF weekly using previously defined ranges specified by the TAF-DBS study [36]. However, when comparing participants based on virologic status at study time points, lower intracellular FTC-TP and TFV-DP levels were observed among viremic participants (Figure 3), suggesting that viremic participants were taking between 3 and 4 doses (~50%) weekly and rarely taking any B/F/TAF on a shorter-term adherence timeframe prior to study visits. Furthermore, 30% of our study population displayed mismatches [37] in adherence by TFV-DP in DBS and virologic status (Supplementary Figure 3), highlighting the importance of early ART adherence interventions to prevent the development of drug resistance and poor treatment outcomes. Importantly, 1 participant with CVF and emergent drug resistance (M184V) at week 48 had FTC-TP and TFV-DP concentrations of BLQ and 400.0 fmol/punches, respectively, despite VS at week 24. However, development of the M184V mutation has not constituted a lack of B/F/TAF efficacy in other studies [38]. Yet, no emergent INSTI drug resistance was observed, which supports current data regarding B/F/TAF's high barrier to resistance [39].

Similar to randomized clinical trial results [23–26], B/F/TAF was well-tolerated with low rates of AEs. However, suicidal ideation was relatively common (n = 5 [11.6%]) in our study population. All of these instances of suicidal ideation were in conjunction with acute methamphetamine intoxication and deemed by study investigators not related specifically to B/F/TAF. While suicidality was rare in previous clinical trials [23–26], the relative risk of suicide among people with SUD is high, as demonstrated in a recent case-control study by Lynch and colleagues [40] where the adjusted odds of suicide increased with each additional substance used, ranging from 2.0 (tobacco only) to 11.2 (tobacco, alcohol, and multiple substances). Importantly, most BASE participants used multiple substances in addition to tobacco and alcohol and thus represent a population at high baseline risk for mental health disorders and suicidality. However, BASE participants reported declines in overall substance use and improvements in mental health scores (Supplementary Figure 4).

A large portion of our population was treatment experienced (72%) and had not had an HIV care visit in roughly 1 year prior to BASE entry, demonstrating a lack of retention in care. Gaps in HIV care are common among PWH/SUD [41] and have been associated with higher risk of viral failure [12]. We had planned for 50% attrition, yet, BASE enrollment was generally positive for retention in care (mean adherence to study visits of 80%). However, transportation assistance and financial incentives likely contributed to study visit completion, as these factors have been associated with better VS rates among PWH [42, 43] and PWH/SUD [7]. These factors were also noted by participants of the BASE qualitative substudy in helping them come to study visits (unpublished data). Additionally, incarceration has been noted as a common barrier to retention in HIV care among PWH/SUD [44]. Only 2 participants (5%) experienced incarceration during the study period; however, both were considered lost to follow-up at week 48 and their virologic status was unknown. Improvements in retention in care also provide the healthcare team the opportunity to offer social support, develop patient trust, and encourage linkage for mental health and substance use treatment services. This is evidenced by the observed declines in substance use, participant entry into substance use treatment (n = 7), and improvements in overall quality of life by mental and physical SF-12 component scores among our study participants. Importantly, all participants linked to substance use treatment achieved VS at week 48, highlighting the importance of concurrent HIV and SUD treatment [45]. While encouraging, these results likely reflect the secondary benefits of study participation for this vulnerable population.

While this study was designed to embody a "real-world" representation, it is not without limitations. Most notably, our sample size was small, and the single-arm study design among a single cohort at 1 site limits the generalizability of the results. Larger studies would be needed to thoroughly evaluate the validity of our findings.

In the BASE study, the use of B/F/TAF in a high-risk population of PWH/SUD resulted in an initial 72% VS rate at week 24 before dropping to 49% at week 48 as retention declined. While our data generally support B/F/TAF's high barrier to resistance, it is important to note that 1 participant with incomplete adherence developed emergent reverse transcriptase drug resistance. Study participation was associated with reductions in substance use and improvements in mental and physical health.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. P. H., E. L., and S. S. designed the study. J. P. H. contributed to the data collection. A. T. P. and K. K. S. designed and conducted the pharmacokinetic analyses. E. L. performed the statistical analyses. All authors analyzed and interpreted the data. J. P. H. drafted the manuscript. All authors reviewed, critically revised, and approved the final manuscript.

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