Treatment Outcomes in People With a Late HIV Diagnosis: A Pooled Analysis of Participants With Advanced HIV Disease at Diagnosis Randomized to Receive B/F/TAF

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ALLIANCE

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Conclusions

- In this pooled analysis of participants from three Phase 3 studies of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in treatment-naïve (TN) people with HIV (PWH), 18% had advanced HIV disease at diagnosis
- People with advanced HIV disease tended to be older, have a lower body weight and body mass index (BMI), and live outside of the US compared with those without advanced HIV disease
- Participants with advanced HIV disease achieved high virologic suppression (VS) rates with B/F/TAF through Week 240, with no safety concerns
- Consistent with previous studies,[1,2] participants with advanced HIV disease took longer to achieve VS and maintained lower CD4 cell counts than those without advanced HIV disease
  - Early diagnosis and treatment are, therefore, key to achieving positive treatment outcomes

Plain Language Summary

- People who have had human immunodeficiency virus (HIV) for a long time and have not had treatment are more likely to have more serious signs of HIV (called advanced HIV disease)
  - They may have more health problems and die sooner than those who find out they have HIV earlier and are treated earlier
- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is approved as a first-time treatment for people with HIV
  - It is a single tablet that contains three different HIV medicines: bictegravir (B), emtricitabine (F), and tenofovir alafenamide (TAF)
- Researchers wanted to find out how well B/F/TAF works in people with advanced HIV disease and if it has any side effects
- They found that B/F/TAF worked well to lower the level of HIV in the blood and had few side effects
- However, B/F/TAF took longer to lower the level of HIV (so that it could no longer be detected in the blood) in people with advanced HIV disease than in people who did not have advanced HIV disease
- These findings suggest that B/F/TAF is an effective treatment for people with advanced HIV disease, but that early diagnosis and treatment are important in achieving the best results

Introduction

- Despite improvements in access to HIV testing,[3] many PWH are still diagnosed late and often have advanced HIV disease at diagnosis[4-6]
- Late HIV diagnosis and advanced HIV disease are associated with increased morbidity and mortality[5,7]
- Early initiation of antiretroviral therapy is recommended to improve outcomes[8]
- B/F/TAF is a guideline-recommended regimen for TN PWH[8,9]
  - It has a high barrier to resistance, and is efficacious and well tolerated[10-12]
- This pooled analysis of three Phase 3 clinical trials aimed to assess the safety and efficacy of B/F/TAF in a large cohort of participants with advanced HIV disease

Objective

- To assess safety and efficacy outcomes with B/F/TAF as an initial regimen through Week 240 in TN PWH who had advanced HIV disease at diagnosis

Methods

Study Design

Adults with HIV-1 (N = 755) from B/F/TAF studies in TN participants:
- Randomized to receive B/F/TAF
- HIV-1 RNA ≥ 500 c/mL at screening

Definition of advanced HIV disease[a]:
CD4 count < 200 cells/μL and/or AIDS diagnosis at baseline

Clinical Studies Included in the Pooled Analysis

- **GS-US-380-1489 (NCT02607930)[10]**: n = 314, 240-week follow-up
- **GS-US-380-1490 (NCT02607956)[10]**: n = 320, 240-week follow-up
- **GS-US-380-4458 (ALLIANCE; NCT03547908)[11]**: n = 121, 144-week follow-up

→ **With advanced HIV disease[a]: CD4 count < 200 cells/μL and/or AIDS diagnosis at baseline (n = 135[b])**

→ **Without advanced HIV disease: CD4 count ≥ 200 cells/μL and no AIDS diagnosis at baseline (n = 620[c])**

Endpoints through Week 240:

Primary:
- Proportion of participants with HIV-1 RNA < 50 c/mL (M = E analysis)
- Change from baseline in CD4 cell count

Secondary:
- Proportion of participants with adverse events
- Grade 3/4 laboratory abnormalities
- Change from baseline in renal and metabolic parameters

[a]Based on World Health Organization definition.[13] [b]36, 49, and 50 from Studies 1489, 1490, and 4458, respectively. [c]278, 271, and 71 from Studies 1489, 1490, and 4458, respectively.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; CD4, cluster of differentiation 4; M = E, missing = excluded; TN, treatment-naïve.

Results

Baseline Demographic and Clinical Characteristics

	With Advanced HIV Disease n = 135	Without Advanced HIV Disease n = 620
Age, years, median (Q1, Q3)	34 (28, 45)	31 (26, 42)
Male sex assigned at birth, n (%)	117 (87)	560 (90)
Race, n (%)		
Asian[a]	50 (37)	71 (11)
Black	38 (28)	175 (28)
White	36 (27)	337 (54)
Other	10 (7)	36 (6)
Not permitted[b]	1 (1)	1 (< 1)
Ethnicity, n (%)		
Hispanic or Latine	22 (16)	140 (23)
Not Hispanic or Latine	113 (84)	478 (77)
Not permitted[b]	0	2 (< 1)
HIV-1 RNA, $\log_{10}$ c/mL, median (Q1, Q3)	5.0 (4.6, 5.3)	4.4 (4.0, 4.8)
HIV-1 RNA > 100,000 c/mL, n (%)	66 (49)	91 (15)
CD4 count, cells/μL, median (Q1, Q3)	111.0 (49.0, 173.0)	463.0 (344.0, 602.5)
$eCrCl_{CG}$, mL/min, median (Q1, Q3)	112.1 (93.3, 134.0)	121.1 (102.7, 143.5)
Absolute body weight, kg, median (Q1, Q3)	70.0 (58.2, 81.0)	75.8 (67.0, 87.3)
BMI, kg/m², median (Q1, Q3)	23.3 (20.7, 25.6)	25.0 (22.1, 28.3)
BMI < 25 kg/m², n (%)	95 (70)	313 (50)
BMI ≥ 25 kg/m², n (%)	40 (30)	307 (50)

With advanced HIV disease[13]: CD4 count < 200 cells/μL and/or AIDS diagnosis at baseline; without advanced HIV disease: CD4 count ≥ 200 cells/μL and no AIDS diagnosis at baseline. [a]Of the Asian participants, 47 and 61 of those with and without advanced HIV disease, respectively, were from Study 4458; 89% of participants from this study were of Asian race; all of these participants had hepatitis B virus coinfection. [b]Local regulators did not allow collection of race or ethnicity data.
BMI, body mass index; c, copies; CD4, cluster of differentiation 4; $eCrCl_{CG}$, estimated creatinine clearance by Cockcroft-Gault equation; Q, quartile.

Baseline Factors Associated With Advanced HIV Disease

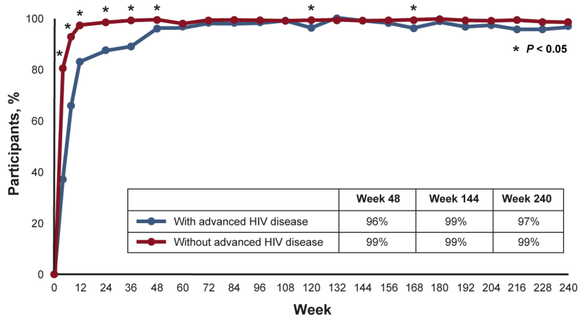
Baseline Factor	With Advanced HIV Disease n = 135	Without Advanced HIV Disease n = 620	*P* Value[a]
Age, years > 30 vs ≤ 30, n (%)	86 (64) vs 49 (36)	321 (52) vs 299 (48)	**0.012**
Sex assigned at birth Female vs male, n (%)	18 (13) vs 117 (87)	60 (10) vs 560 (90)	0.206
Race[b] Black vs non-Black, n (%)	38 (28) vs 96 (72)	175 (28) vs 444 (72)	0.984
Region Non-US vs US, n (%)	70 (52) vs 65 (48)	263 (42) vs 357 (58)	**0.046**
Absolute body weight, kg Median (Q1, Q3)	70.0 (58.2, 81.0)	75.8 (67.0, 87.3)	**<0.001**
BMI, kg/m² < 25 vs ≥ 25, n (%)	95 (70) vs 40 (30)	313 (50) vs 307 (50)	**< 0.001**
HIV-1 RNA, $\log_{10}$ c/mL Median (Q1, Q3) > 100,000 c/mL vs ≤ 100,000 c/mL, n (%)	5.0 (4.6, 5.3) 66 (49) vs 69 (51)	4.4 (4.0, 4.8) 91 (15) vs 529 (85)	**< 0.001** **< 0.001**
$eCrCl_{CG}$, mL/min Median (Q1, Q3)	112.1 (93.3, 134.0)	121.1 (102.7, 143.5)	**< 0.001**
HIV disease status Symptomatic or AIDS diagnosis vs asymptomatic, n (%)	71 (53) vs 64 (47)	29[c] (5) vs 591 (95)	**< 0.001**

With advanced HIV disease[13]: CD4 count < 200 cells/μL and/or AIDS diagnosis at baseline; without advanced HIV disease: CD4 count ≥ 200 cells/μL and no AIDS diagnosis at baseline. [a]*P* values were calculated using the Cochran-Mantel-Haenszel test for categorical data (using the general association statistic for nominal data and the row mean scores differ statistic for ordinal data) and the two-sided Wilcoxon rank sum test for continuous data; significant *P* values are shown in **bold**. [b]Race was not permitted for one participant in each group. [c]All 29 participants were symptomatic.
BMI, body mass index; c, copies; CD4, cluster of differentiation 4; $eCrCl_{CG}$, estimated creatinine clearance by Cockcroft-Gault equation; Q, quartile.

- Baseline factors significantly associated with advanced HIV disease were being > 30 years old, living outside of the US, lower body weight, lower BMI (< 25 kg/m²), higher HIV-1 RNA (> 100,000 c/mL HIV-1 RNA), lower estimated creatinine clearance ($eCrCl_{CG}$), and symptomatic HIV disease or an AIDS diagnosis

Efficacy Outcomes Through Week 240

Virologic Suppression (HIV-1 RNA < 50 c/mL; M = E Analysis)



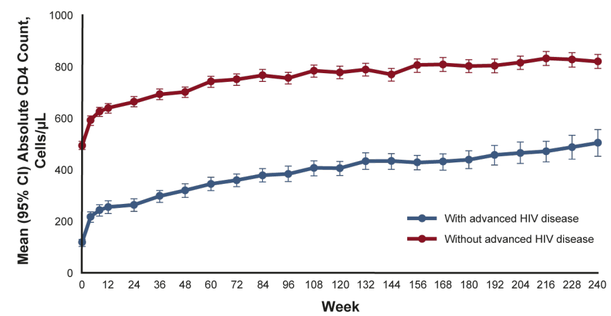
	Week 48	Week 144	Week 240
With advanced HIV disease	96%	99%	97%
Without advanced HIV disease	99%	99%	99%

n =	133	130	128	126	124	120	116	119	117	116	112	114	111	109	102	95	90	81	72	71	64
n =	620	603	598	585	582	566	558	552	547	546	536	530	525	523	492	468	454	396	415	408	390

With advanced HIV disease[13]: CD4 count < 200 cells/μL and/or AIDS diagnosis at baseline; without advanced HIV disease: CD4 count ≥ 200 cells/μL and no AIDS diagnosis at baseline. *P* values determined using Cochran-Mantel-Haenszel test (with vs without advanced HIV disease, stratified by baseline HIV-1 RNA [≤ 100,000 vs > 100,000 c/mL]).
c, copies; CD4, cluster of differentiation 4; M = E, missing = excluded.

- ≥ 96% of participants without advanced HIV disease achieved VS by Week 12; participants with advanced HIV disease reached this threshold by Week 48; VS remained high through Week 240

Absolute CD4 Cell Counts



n =	133	128	125	125	125	122	115	117	116	115	110	110	110	105	99	94	86	79	72	70	61
n =	620	601	591	584	576	558	549	545	540	538	522	514	513	507	480	463	448	394	407	408	373

With advanced HIV disease[13]: CD4 count < 200 cells/μL and/or AIDS diagnosis at baseline; without advanced HIV disease: CD4 count ≥ 200 cells/μL and no AIDS diagnosis at baseline. *P* < 0.001 at every timepoint (ANOVA adjusted by baseline HIV-1 RNA [≤ 100,000 vs > 100,000 c/mL]).
ANOVA, analysis of variance; c, copies; CD4, cluster of differentiation 4; CI, confidence interval.

- Increased CD4 cell counts were observed in participants with and without advanced HIV disease through Week 240 but remained significantly lower in those with advanced HIV disease

Safety Outcomes Through Week 240

Participants With AEs, n (%)	With Advanced HIV Disease n = 135	Without Advanced HIV Disease n = 620
Any AE	125 (93)	596 (96)
Grade 3/4 AEs	33 (24)	125 (20)
DRAEs	39 (29)	178 (29)
Grade 3/4 DRAEs	5 (4)[a]	12 (2)[b]
Serious DRAEs	1 (1)[c]	5 (1)[d]
AEs leading to study drug discontinuation	2 (1)[e]	9 (1)[f]
Grade 3/4 laboratory abnormalities	48 (36)[g]	211 (34)[h]
Immune reconstitution inflammatory syndrome (IRIS)	2 (1)	4 (1)
Deaths[i]	4 (3)[j]	7 (1)[k]

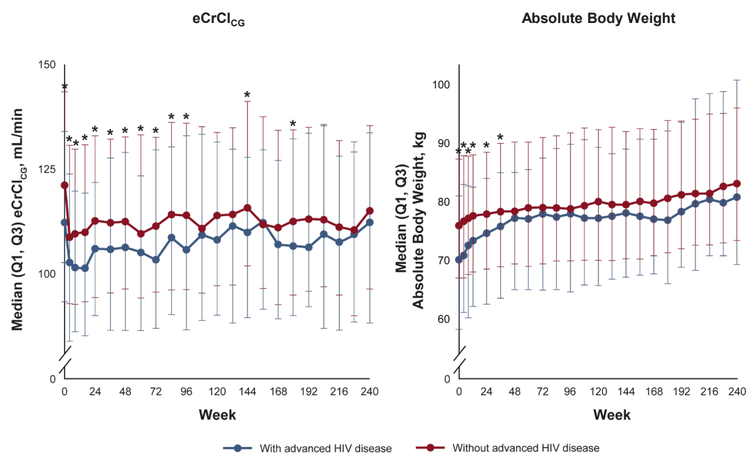
With advanced HIV disease[13]: CD4 count < 200 cells/μL and/or AIDS diagnosis at baseline; without advanced HIV disease: CD4 count ≥ 200 cells/μL and no AIDS diagnosis at baseline. Multiple AEs were counted only once per participant for the highest severity grade for each System Organ Class and Preferred Term. Participants were counted once for the maximum postbaseline severity for each laboratory abnormality.
[a]Increased GGT, increased ALT, increased AST, major depression, cryptococcal meningitis, increased weight, hypomagnesemia, and increased blood triglycerides (n = 1 each); participants could have ≥ 1 event. [b]Abdominal pain, osteoporosis, grand mal seizure, chest pain, atrial flutter, dizziness, acute pancreatitis, suicide attempt, diarrhea, abdominal distension, increased ALT, increased blood creatinine (n = 1 each), and abnormal weight gain (n = 2); participants could have ≥ 1 event. [c]Cryptococcal meningitis (n = 1). [d]Atrial flutter, dizziness, and acute pancreatitis (all reported in a single participant); grand mal seizure, spontaneous abortion, chest pain, and suicide attempt (n = 1 each). [e]Obesity and toxicity to various agents (n = 1 each). [f]Sleep disorder, dyspepsia, tension headache, depressed mood, and insomnia (all reported in a single participant); chest pain, depression, abdominal distension, cardiac arrest, COVID-19, intervertebral discitis, hepatocellular carcinoma, and paranoia (n = 1 each). [g]One participant had no postbaseline data and was excluded from the denominator for the percentage. [h]Six participants had no postbaseline data and were excluded from the denominator for the percentage. [i]Treatment-emergent death (defined as death occurring between the first and last dose dates plus 30 days [inclusive]). [j]Poorly differentiated gastric adenocarcinoma, sudden cardiac arrest, ischemic heart disease, and unknown cause (n = 1 each; none were considered related to study drug). [k]COVID-19, combined toxicity of chloroethane and methamphetamine, self-inflicted wrist wound, cardiac arrest, congestive heart failure, metastatic squamous cell carcinoma from epiglottis, and unknown cause (n = 1 each; none were considered related to study drug).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD4, cluster of differentiation 4; DRAE, drug-related adverse event; GGT, gamma-glutamyl transferase.

- The incidences of adverse events (AEs), drug-related AEs (DRAEs), serious DRAEs, discontinuations due to AEs, Grade 3/4 laboratory abnormalities, IRIS, and deaths through Week 240 were similar for participants with and without advanced HIV disease

Impact of CD4 Cell Count and AIDS Diagnosis

- Of the 135 participants with advanced HIV disease, 85 had CD4 count < 200 cells/μL and no AIDS diagnosis at baseline, 41 had CD4 count < 200 cells/μL and an AIDS diagnosis at baseline, and 9 had CD4 count ≥ 200 cells/μL and an AIDS diagnosis at baseline
  - Excluding the nine participants with CD4 count ≥ 200 cells/μL and an AIDS diagnosis at baseline from the group with advanced HIV disease had little effect on the efficacy and safety outcomes

$eCrCl_{CG}$ and Absolute Body Weight Through Week 240



With advanced HIV disease[13]: CD4 count < 200 cells/μL and/or AIDS diagnosis at baseline; without advanced HIV disease: CD4 count ≥ 200 cells/μL and no AIDS diagnosis at baseline. Baseline value was defined as the last non-missing value obtained on or prior to the first dose of B/F/TAF.
*P < 0.05, with advanced HIV disease vs without advanced HIV disease (two-sided Wilcoxon rank sum test).
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CD4, cluster of differentiation 4; $eCrCl_{CG}$, estimated creatinine clearance by Cockcroft-Gault equation; Q, quartile.

- Baseline eCrCl was slightly lower in participants with advanced HIV disease than in those without advanced HIV disease; these differences generally reduced after Week 96, and participants in both groups showed similar fluctuations through Week 240
- Absolute body weight was lower at baseline and through Week 36 in participants with advanced HIV disease than in those without advanced HIV disease, but was similar in both groups from Week 48 through Week 240 as a result of a greater weight increase in those with advanced HIV disease, consistent with return to health[14,15]

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