Journal of Microbiology, Immunology and Infection 57 (2024) 760—770

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Twelve-month effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide in treatment-naïve and treatment-experienced people with HIV: Findings from the Asia cohort of the BICSTaR study

Yu-Ting Tseng [a], Chia-Jui Yang [b,c], Yeon-Sook Kim [d], Jun Yong Choi [e], Chen Seong Wong [f], Kuan-Yeh Lee [g], Jeong-a Lee [h], Jack Chang [g], Rebecca Harrison [i,1], Andrea Marongiu [i], Sun Hee Lee [j,**], Chien-Ching Hung [k,l,m,*]

[a] *Division of Infectious Diseases, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[b] *Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan*
[c] *School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan*
[d] *Division of Infectious Diseases, Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, Republic of Korea*
[e] *Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea*
[f] *Department of Infectious Diseases, National Centre for Infectious Diseases, Singapore*
[g] *Medical Affairs, Gilead Sciences, Taipei, Taiwan*
[h] *Medical Affairs, Gilead Sciences Korea Ltd, Seoul, Republic of Korea*
[i] *Real World Evidence, Gilead Sciences Europe Ltd, Uxbridge, United Kingdom*
[j] *Department of Internal Medicine, Pusan National University School of Medicine and Pusan National University Hospital, Busan, Republic of Korea*
[k] *Department of Internal Medicine, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan*
[l] *Department of Tropical Medicine and Parasitology, National Taiwan University College of Medicine, Taipei, Taiwan*
[m] *Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, Taipei, 10002, Taiwan.
** Corresponding author. Department of Internal Medicine, Pusan National University Hospital, Busan, 49241, Republic of Korea.
E-mail addresses: yttsengyttseng@gmail.com (Y.-T. Tseng), yangcj@ntu.edu.tw (C.-J. Yang), alice1777@naver.com (Y.-S. Kim), seran@yuhs.ac (J.Y. Choi), chen_seong_wong@ncid.sg (C.S. Wong), kuan-yeh.lee@gilead.com (K.-Y. Lee), jeong-a.lee@gilead.com (J.-a. Lee), jack.chang14@gilead.com (J. Chang), rebecca8harrison@gmail.com (R. Harrison), andrea.marongiu@gilead.com (A. Marongiu), zzanmery@gmail.com (S.H. Lee), hcc0401@ntu.edu.tw (C.-C. Hung).
[1] Rebecca Harrison was employed by Gilead at the time of writing the manuscript.

https://doi.org/10.1016/j.jmii.2024.07.003

Received 30 January 2024; received in revised form 17 June 2024; accepted 8 July 2024
Available online 14 July 2024

KEYWORDS
Antiretroviral therapy;
Integrase strand transfer inhibitor;
Nucleoside reverse transcriptase inhibitor;
Real-world evidence

Abstract *Background:* The ongoing, observational BICSTaR (BICtegravir Single Tablet Regimen) cohort study is evaluating real-world effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in people with HIV across 14 countries over 24 months. We present 12-month data from the BICSTaR Asia cohort.
Methods: Data were pooled from retrospective and prospective cohorts of antiretroviral therapy (ART)-naïve (hereafter, TN) and ART-experienced (hereafter, TE) people with HIV (aged ≥21 years) receiving B/F/TAF in routine clinical care in the Republic of Korea, Singapore, and Taiwan. Analyses included effectiveness (primary endpoint: HIV-1 RNA <50 copies/ml, missing = excluded analysis), CD4 count, CD4/CD8 ratio, safety, treatment persistence, and patient-reported outcomes (prospective group).
Results: The analysis population included 328 participants (80 retrospective, 248 prospective; 65 TN, 263 TE). Participants were predominantly male (96.9% TN, 93.2% TE) with ≥1 comorbidity (52.3% TN, 57.8% TE); median age (years) was 31 (TN) and 42 (TE). Following 12 months of B/F/TAF, HIV-1 RNA was <50 copies/ml in 98.2% (54/55) of TN and 97.0% (227/234) of TE participants. Median (Q1, Q3) CD4 cell count increased by +187 (119, 291) cells/μl in the TN group ($p < 0.001$) and remained stable (+8 [−91, 110] cells/μl) in the TE group. B/F/TAF persistence was high in the prospective group, with 1/34 (2.9%) TN and 5/214 (2.3%) TE participants discontinuing treatment within 12 months. Drug-related adverse events occurred in 5.8% (19/328) of participants, leading to treatment discontinuation in 0.6% (2/328).
Conclusions: Real-world evidence from BICSTaR supports the effectiveness, safety and tolerability of B/F/TAF in people with HIV in Asia.

Introduction

In 2022, there were 6.5 million people with human immunodeficiency virus (HIV) in Asia and the Pacific, including 300,000 people newly diagnosed that year.[1] Advances in HIV treatment have reduced mortality rates in the region,[2] and a growing proportion of people with HIV are aged ≥50 years.[3]

Given the life-long use of antiretroviral therapy (ART) by people with HIV, optimal treatment regimens need to maintain long-term viral suppression and have a favorable safety profile, a high resistance barrier, and low potential for drug—drug interactions.[4—6] With the increased multimorbidity and geriatric symptoms present in an aging population of people with HIV,[7] simplified treatment and reduced pill burden are also key attributes.[4,8]

For initial treatment of HIV, international[4,5] and local HIV guidelines in the Republic of Korea,[9] Singapore,[10] and Taiwan[11] recommend two- and three-drug ART regimens. Single-tablet formulations of multi-drug regimens have been associated with improved treatment adherence and persistence in comparison with multi-tablet regimens, including in real-world studies conducted in Asia,[12,13] and are recommended for people with HIV in Taiwan.[11,14]

Bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) is a three-drug regimen coformulated as a single tablet. The efficacy and safety of B/F/TAF have been demonstrated in clinical trials in ART-naïve (hereafter, TN) and ART-experienced (hereafter, TE) people with HIV,[15—19] including a pooled analysis of data from Asian people with HIV.[20] B/F/TAF is approved in multiple countries globally and across Asia, including the Republic of Korea, Singapore, and Taiwan, and is recommended as first-line treatment in international and regional Asian guidelines.[4,5,9,11,21]

The real-world effectiveness and safety of B/F/TAF have been confirmed in several small studies.[22—25] Within Asia, retrospective real-world analyses in specific populations of people with HIV have examined the use of B/F/TAF in Taiwan,[14,24,26,27] but real-world evidence in the broader population of people with HIV in Asia remains limited. As a number of sociodemographic differences exist between Asian and Western populations that may impact management of HIV and responses to therapy,[28,29] further real-world data for B/F/TAF within Asia is expected to be clinically valuable.

BICtegravir Single Tablet Regimen (BICSTaR) is an ongoing, multi-regional, observational cohort study which

aims to provide B/F/TAF effectiveness and safety data in a broad spectrum of people with HIV in routine clinical care. It has enrolled 2379 TN and TE people with HIV from 14 countries across five cohorts in Europe, Canada, Israel, Asia, and Japan, with a planned follow-up of 24 months. Its primary objective is effectiveness of B/F/TAF at 12 months and pooled prospective 12-month data from 12 countries have been published.[30]

Here, we report prospective and retrospective 12-month effectiveness and safety data for people with HIV in the BICSTaR Asia cohort, which enrolled participants across the Republic of Korea, Singapore, and Taiwan.

Methods

Study design

Detailed methodology for the observational BICSTaR study, which comprises five cohorts across multiple geographic regions, has been described.[30] For this 12-month analysis, data were collected between December 21, 2020 and March 1, 2023 in people with HIV receiving B/F/TAF in routine clinical care at 14 centers in the Republic of Korea (n = 7), Singapore (n = 1 center), and Taiwan (n = 6) (i.e., BICSTaR Cohort 4).

In the prospective cohort, data were collected in people who initiated/switched to B/F/TAF at study entry. Data were collected retrospectively and prospectively in those that initiated/switched to B/F/TAF before study entry (for simplicity referred to as "retrospective participants"). In an amendment (approved by site ethics committees between February 4 and July 26, 2021), the retrospective cohort was restricted to those on B/F/TAF for <3 months at study enrollment. Data were collected from clinical records, hospital files, clinic visits, electronic medical records, and (prospective cohort only) validated questionnaires for patient-reported outcomes (PROs). Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (v25.1). Follow-up visits were conducted according to standard practice at each site, based on the treating physician's decision.

Participants and treatment

Eligible participants were adults with HIV aged ≥21 years and receiving B/F/TAF in routine clinical care. Individuals who had previously participated in an interventional clinical trial (unless approved by the study sponsor) were excluded, as were those who had previously taken part in an observational B/F/TAF study. All participants provided written informed consent. Participants received B/F/TAF (50/200/25 mg) in accordance with approved local package information and local treatment guidelines in the Republic of Korea, Singapore, and Taiwan.[31–33]

Study endpoints and assessments

Endpoints and assessments have been described elsewhere.[30] The primary endpoint was viral suppression (HIV-1 RNA <50 copies/ml) at month 12. Secondary endpoints included HIV-1 RNA <50 copies/ml at months 3 and 6, changes from baseline in CD4 count and CD4/CD8 ratio at month 12, and the numbers and proportions of participants with AEs, serious AEs (SAEs), and drug-related AEs (DRAEs) at month 12. Additional exploratory endpoints included reasons for initiating ART in TN participants and for switching to B/F/TAF in TE participants; changes in weight and body mass index (BMI) at month 12; laboratory analyses including changes in lipid profile, renal function (estimated glomerular filtration rate [eGFR]) and blood glucose levels; persistence and reasons for discontinuation; and changes in several PROs from baseline to month 12. Overall bothersome symptom count was measured using the HIV-Symptom Index (HIV-SI) questionnaire. Physical and mental health–related quality of life was measured using the 36-item Short-Form Health Survey (SF-36) Mental Component Summary (MCS) and Physical Component Summary (PCS) scores. Treatment satisfaction was measured using the HIV Treatment Satisfaction Questionnaire–status (HIVTSQs) and –change (HIVTSQc) versions.

Statistical analysis

A detailed description of sample size determination and statistical analyses across the BICSTaR program is published elsewhere.[30] In brief, the primary endpoint analysis (viral suppression) at 12 months was measured using a missing-equals-excluded (M = E) analysis in participants with ≥1 HIV-1 RNA value within the 12-month visit window (defined as ≥275 days [9 months] to ≤548 days [18 months]). Participants with missing data or those who discontinued the study and/or B/F/TAF before the 12-month visit window were not included (no imputation). TN and TE cohorts were analyzed separately. A treatment discontinuation-equals-failure (D = F) analysis was also performed, which included participants with ≥1 HIV-1 RNA value within the 12-month visit window and those who discontinued B/F/TAF before the 12-month visit window; in the latter case, HIV-1 RNA was imputed as ≥50 copies/ml. Data from participants who discontinued B/F/TAF during the 12-month visit window were not imputed for the D = F analysis.

There was potential for overestimation of persistence in the retrospective cohort as individuals who discontinued prior to study initiation were excluded (i.e., immortal time bias). Virological effectiveness and AE incidence may also be associated with discontinuation and therefore potentially overestimated and underestimated respectively, in the retrospective cohort. This was mitigated by amending the retrospective cohort inclusion criteria to those on B/F/TAF for <3 months at study enrolment. To evaluate the presence of these biases, the above outcomes were stratified by cohort (retrospective vs prospective).

Descriptive statistics were used to analyze demographics and outcome data and 95% confidence intervals were calculated for categorical and continuous variables. Laboratory data and weight change were analyzed using the Student *t*-test or Sign test and

Wilcoxon signed rank test for groups with ≥20 participants, with the test for the null hypothesis that the mean/median is equal to zero. The Cockcroft—Gault equation was used to calculate eGFR. Statistical analyses were performed using SAS software, version 9.4.

Ethics approval

The BICSTaR protocol was approved by an independent ethics committee and the study was conducted in accordance with Good Pharmacoepidemiology Practice and the Heads of Medicines Agencies' Good Pharmacovigilance Practices.

Table 1 Baseline demographics and clinical characteristics.

Characteristic	TN (n = 65)	TE (n = 263)
Sex,[a] n (%)		
Male	63 (96.9)	245 (93.2)
Female	2 (3.1)	18 (6.8)
Age		
Median (Q1, Q3), years	31.0 (28.0, 36.0)	42.0 (35.0, 49.0)
<50 years, n (%)	58 (89.2)	201 (76.4)
≥50 years, n (%)	7 (10.8)	62 (23.6)
Median (Q1, Q3) weight, kg	69.1 (60.8, 78.0)	69.1 (61.6, 77.4)
Median (Q1, Q3) BMI, kg/m^2	23.2 (21.1, 24.9)	23.8 (21.8, 25.9)
Race/ethnicity, n (%)		
Asian	65 (100)	263 (100)
Comorbidities, n (%)		
None	31 (47.7)	111 (42.2)
1	14 (21.5)	70 (26.6)
2	10 (15.4)	48 (18.3)
≥3	10 (15.4)	34 (12.9)
Most common		
Hyperlipidemia	2 (3.1)	52 (19.8)
Hypertension	4 (6.2)	21 (8.0)
Neuropsychiatric	3 (4.6)	19 (7.2)
Osteopathic	2 (3.1)	15 (5.7)
Chronic hepatitis B	1 (1.5)	37 (14.1)
Chronic hepatitis C	1 (1.5)	17 (6.5)
HIV-1 RNA load[b]		
Median (Q1, Q3), $\log_{10}$ copies/ml	4.5 (4.1, 5.4)	1.3 (1.3, 1.3)
<50 copies/ml, n (%)	0	167 (91.8)
>100,000 copies/ml, n (%)	18 (31.0)	6 (3.3)
Median (Q1, Q3) CD4 count,[c] cells/μl	296 (167, 476)	587 (440, 802)
Median (Q1, Q3) CD4/CD8 ratio[d]	0.34 (0.20, 0.49)	0.83 (0.60, 1.10)
Late HIV diagnosis,[e] n (%)		
CD4 <350 cells/μl[f]	36 (63.2)	—
CD4 <200 cells/μl[f]	23 (40.4)	—
Concomitant non-ART medications at baseline, n (%)[g]		
None	45 (70.3)	133 (51.8)
1	9 (14.1)	64 (24.9)
2	3 (4.7)	33 (12.8)
≥3	7 (10.9)	27 (10.5)
Median (Q1, Q3) number of previous ART regimens[h]	—	3.0 (2.0, 4.0)
Prior ART regimen (taken just prior to B/F/TAF),[i] n (%)		
INSTI	—	176 (67.7)
NNRTI	—	67 (25.8)
PI	—	20 (7.7)
F/TDF	—	57 (21.9)

(*continued on next page*)

Table 1 (*continued*)

Characteristic	TN (n = 65)	TE (n = 263)
F/TAF	–	170 (65.4)
History of prior virologic failure,[j] n (%)	–	40 (15.2)
Time from HIV diagnosis to B/F/TAF initiation,[k] median (Q1, Q3), days	7.0 (0.0, 21.0)	–

[a] Sex was defined by the participant.
[b] Sample size: 58 TN, 182 TE.
[c] Sample size: 55 TN, 156 TE.
[d] Sample size: 54 TN, 152 TE.
[e] Missing in eight participants.
[f] And/or ≥1 AIDS-defining event at baseline.
[g] Data were missing for one TN and six TE participants; out of a total of 126 TE participants reporting ongoing concomitant medication use, data on the number of medications was available for 124.
[h] Missing in four participants.
[i] Sample size: n = 260.
[j] Unknown in seven TE participants.
[k] Sample size: 61 TN.
Abbreviations: ART, antiretroviral treatment; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; CD, cluster of differentiation; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q, quartile; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; TE, treatment-experienced; TN, treatment-naïve.

Results

Baseline demographics and disease characteristics

In total, 337 people with HIV were enrolled in the BICSTaR Asia cohort, of whom 328 (80 retrospective, 248 prospective; 65 TN and 263 TE) were eligible for analysis at the time of data cutoff (March 1, 2023; Supplementary Figure S1).

Overall, 85 participants were residents of the Republic of Korea, 11 of Singapore, and 232 of Taiwan. Participant demographics and baseline characteristics are summarized in Table 1. Participants were predominantly male (96.9% TN, 93.2% TE) and all were Asian. More than half (52.3% TN, 57.8% TE) had a comorbidity, hyperlipidemia being the most common, and 44.2% were receiving concomitant non-ART medications. TE participants were older than TN participants (median: 42.0 vs. 31.0 years). Retrospective and prospective cohorts were generally similar regarding baseline demographics and disease characteristics (Supplementary Table S1).

Among TN participants, the main reason for starting B/F/TAF was related to local treatment guidelines (84.6%); among TE participants, the most common reason for switching to B/F/TAF from another regimen was to simplify ART (65.8%) (Supplementary Table S2). Overall, 4.3% (14/328) of participants who underwent testing had a documented primary resistance mutation at baseline (nucleoside reverse transcriptase inhibitor [NRTI], 3.0%; non-NRTI, 2.7%; protease inhibitor, 0.9%), with K103 N/S (1.8%; 6/328) and M184V/I (2.7%; 9/328) being the most common (Supplementary Table S3).

Effectiveness

Virologic outcomes for months 3, 6 and 12 are summarized in Fig. 1. In the primary endpoint analysis, high rates of viral suppression were seen at month 12, with 98.2% (54/55) of TN and 97.0% (227/234) of TE participants achieving HIV-1 RNA <50 copies/ml (M = E analysis) (Fig. 1). The D = F analysis presented similar results, with 96.4% (54/56) of TN and 93.8% (227/242) of TE participants achieving viral suppression at month 12 (Supplementary Figure S2). One TN participant and five TE participants had HIV-1 RNA ≥50 copies/ml at month 12 (M = E analysis). Of these, the TN participant had HIV-1 RNA >200 copies/ml at month 12 (HIV-1 RNA load: 238 copies/ml); the five TE participants had HIV-1 RNA ≥50 but <100 copies/ml. HIV-1 RNA load and the proportions of participants with HIV-1 RNA <50 copies/ml at 12 months were similar between retrospective and prospective cohorts (Supplementary Figure S3). There was no evidence of immortal time bias (i.e., where effectiveness could be overestimated in the retrospective cohort due to exclusion of participants with treatment failure before study entry).

Immunological outcomes

Median CD4 cell counts and CD4/CD8 ratios increased from baseline to 12 months in TN participants and remained stable in TE participants (Fig. 2). Median (Q1, Q3) change in CD4 count from baseline to 12 months was +187 (119, 291) cells/μl in TN ($p < 0.001$) and +8 (−91, 110) cells/μl in TE participants ($p = 0.712$). Median (Q1, Q3) change in CD4/CD8 ratios from baseline to 12 months was +0.24 (0.13, 0.36) in TN ($p < 0.001$) and +0.04 (−0.03, 0.13) in TE participants ($p = 0.001$). Changes in CD4 count and CD4/CD8 ratio were generally similar between retrospective and prospective cohorts at 12 months.

Safety and tolerability

By month 12, 52.1% (171/328) of participants had experienced an AE; 63.1% (41/65) of TN and 49.4% (130/263) of TE participants (Table 2). The proportion of participants

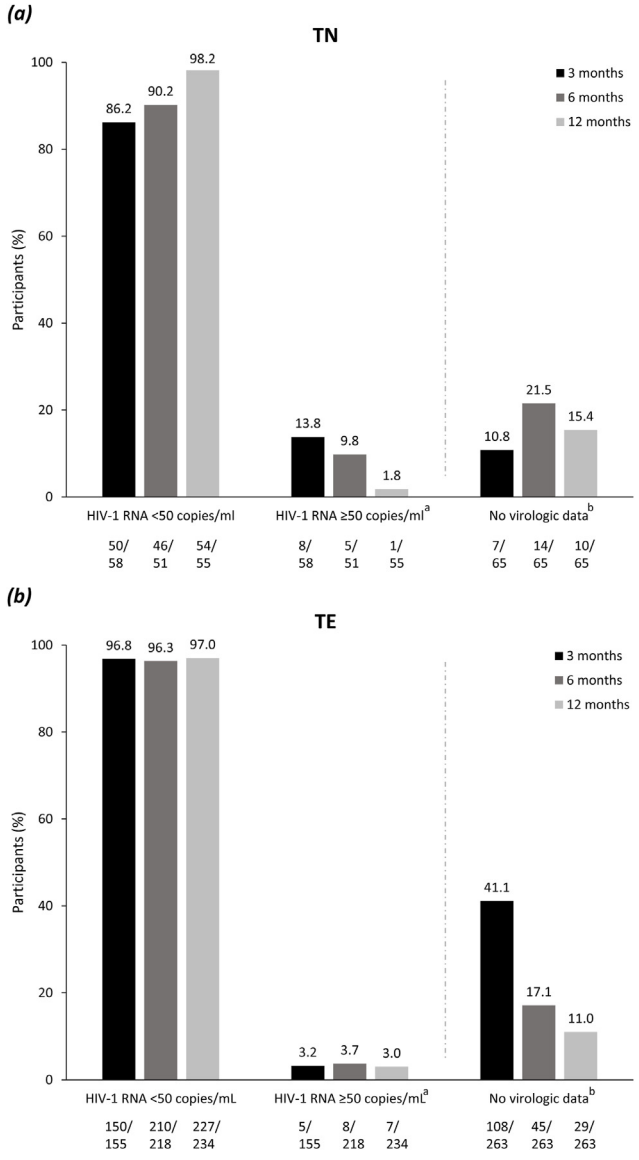

Figure 1. Virologic outcomes at 3, 6, and 12 months (M = E analysis) in (a) TN participants and (b) TE participants. [a]Of the 1/55 TN and 7/234 TE participants with HIV-1 RNA ≥50 copies/ml at month 12, only one TN participant had HIV-1 RNA >200 copies/ml; [b]For the "No virologic data category", numerators include participants with missing data and those who discontinued the study and/or B/F/TAF before the 12-month visit window (denominators represent the total analysis population of TN and TE participants). Abbreviations: M = E, missing-equals-excluded; TE, treatment-experienced; TN, treatment-naïve.

experiencing AEs was generally similar in retrospective and prospective cohorts and there was no evidence that the retrospective cohort experienced fewer AEs. No SAEs or deaths occurred.

Most AEs were unrelated to B/F/TAF. DRAEs occurred in 5.8% (19/328) of participants, all of which were mild or moderate. DRAEs mostly occurred among TE participants (n = 17) and in the prospective cohort (TN, n = 2; TE, n = 15). The most common DRAEs were gastrointestinal disorders (n = 8), weight gain (n = 4), and psychiatric disorders (n = 4).

Among the four TE participants experiencing a DRAE of weight gain, three had taken tenofovir disoproxil fumarate (TDF) or efavirenz as part of their ART regimen immediately before B/F/TAF initiation (Table 2). Baseline median (Q1, Q3) weight was 60.1 (57.1, 68.0) kg and BMI was 22.2 (21.3, 23.7) kg/m^2 in three participants with available data; at month 12, median weight was 65.7 (63.2, 74.8) kg and BMI was 24.3 (23.7, 26.0) kg/m^2 in these participants.

Of the four participants experiencing a psychiatric DRAE, only one had ongoing neuropsychiatric disorder(s) at baseline.

Overall, 2/328 (0.6%; 0 TN, 2 TE) participants discontinued B/F/TAF because of a DRAE (weight gain) (Table 2). There were no B/F/TAF discontinuations due to renal, bone, or hepatic DRAEs. TN and TE participants gained a median (Q1, Q3) of +3.3 (1.1, 5.8) kg ($p < 0.001$) and +0.9 (−1.3, 3.0) kg ($p < 0.005$), respectively, through month 12 (Fig. 3). BMI also increased slightly from baseline (+1.2 and + 0.3 kg/m^2) in TN and TE participants, respectively (Fig. 3). Weight- and BMI-related findings were generally similar in retrospective and prospective participants (Supplementary Figure S4). Changes in weight and BMI were greater in TE participants with prior TDF use than in those with no prior TDF use (Supplementary Figure S5). There were small but statistically significant changes from baseline in some lipid parameters (Supplementary Figure S6) and eGFR (Supplementary Figure S7) at month 12, none of which were considered clinically relevant. For TE participants, there was a small but statistically significant reduction in blood glucose level at month 12 versus baseline (median [Q1, Q3] change: −0.1 [−0.5, 0.2] mmol/l; $p < 0.05$); however, this was not considered clinically relevant (Supplementary Figure S8). There was no statistically significant change from baseline in glucose levels for TN participants.

Persistence and study drug discontinuations

Treatment persistence in prospective participants was high at 12 months; 2.9% (1/34) of TN participants and 2.3% (5/214) of TE participants discontinued B/F/TAF within 12 months of initiating B/F/TAF. Of the prospective participants discontinuing B/F/TAF, one TE participant discontinued due to lack of efficacy. This participant had an HIV-1 RNA load of 70 copies/ml at baseline, which reduced to 55 copies/ml at month 6, at which point the participant was switched to abacavir/dolutegravir/lamivudine; HIV-1 RNA load was <20 copies/ml at 12 months. A second prospective TE participant discontinued due to AEs. For the other three TE participants, discontinuation was due to participant decision. The proportions of participants who discontinued B/F/TAF were generally similar for retrospective and prospective participants (Supplementary Table S4).

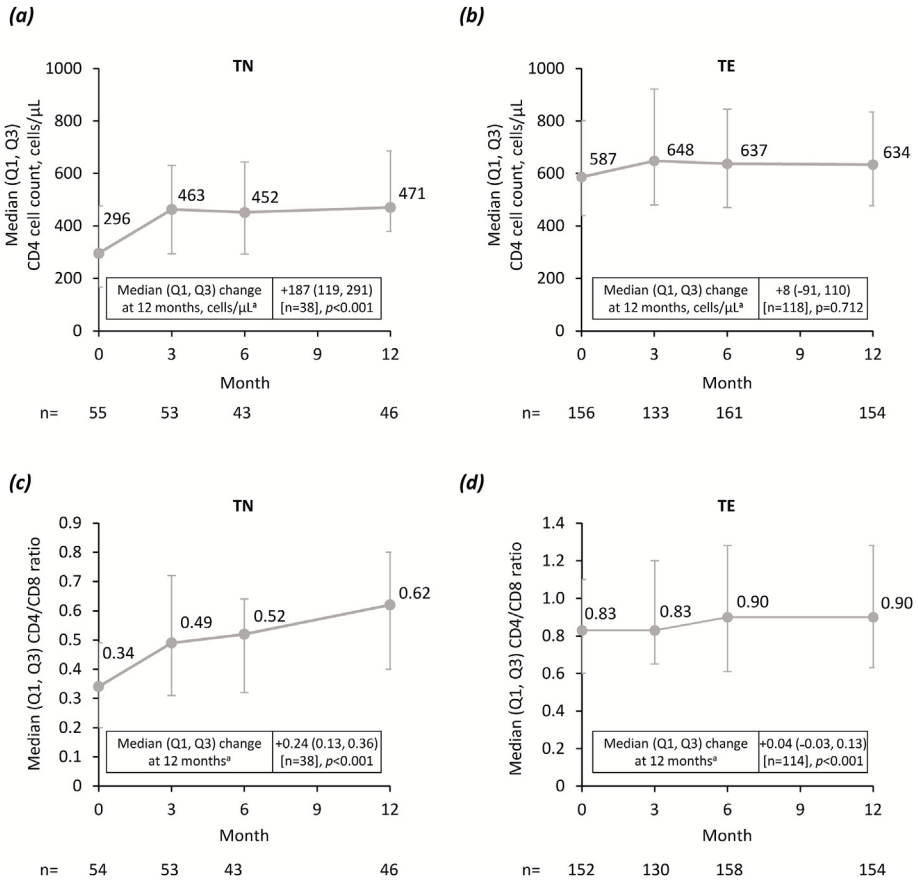

Figure 2. Change in CD4 count (a and b) and CD4/CD8 ratio (c and d) from baseline to 12 months in TN and TE participants.
[a]Median change was calculated in participants with data at baseline and 12 months. *P*-values were calculated using the Sign test.
Abbreviations: Q, quartile; TE, treatment-experienced; TN, treatment-naïve.

Table 2 Adverse events reported through 12 months.

Summary of AEs, n (%)	All (N = 328)	TN (n = 65)	TE (n = 263)
Participants with ≥1 AE	171 (52.1)	41 (63.1)	130 (49.4)
Participants with ≥1 DRAE	19 (5.8)	2 (3.1)	17 (6.5)
Gastrointestinal disorders	8 (2.4)	1 (1.5)[a]	7 (2.7)[b]
Weight gain	4 (1.2)	0	4 (1.5)[c]
Psychiatric disorders	4 (1.2)	1 (1.5)[d]	3 (1.1)[e]
Dizziness	2 (0.6)	0	2 (0.8)
Headache	1 (0.3)	0	1 (0.4)
COVID-19	2 (0.6)	0	2 (0.8)
Hiccups	1 (0.3)	0	1 (0.4)
Urticaria	1 (0.3)	1 (1.5)	0
Any SAE related to B/F/TAF	0	0	0
Discontinued B/F/TAF due to DRAEs	2 (0.6)	0	2 (0.8)
Weight gain	2 (0.6)	0	2 (0.8)
Deaths	0	0	0

[a] Diarrhea.
[b] Diarrhea, abdominal distension, abdominal pain, hard feces, flatulence, gastroesophageal reflux disease, irritable bowel syndrome, salivary gland calculus.
[c] ART regimen just prior to B/F/TAF initiation: AZT/3TC + LPV/r (n = 1), EFV/F/TDF (n = 2), and F/TDF + NVP (n = 1).
[d] Insomnia.
[e] Depressed mood, depression, sleep disorder.
Abbreviations: 3TC, lamivudine; AE, adverse event; ART, antiretroviral therapy; AZT, zidovudine; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DRAE, drug-related adverse event; EFV, efavirenz; F, emtricitabine; LPV/r, lopinavir-ritonavir; NVP, nevirapine; SAE, serious adverse event; TDF, tenofovir disoproxil fumarate; TE, treatment-experienced; TN, treatment-naïve.

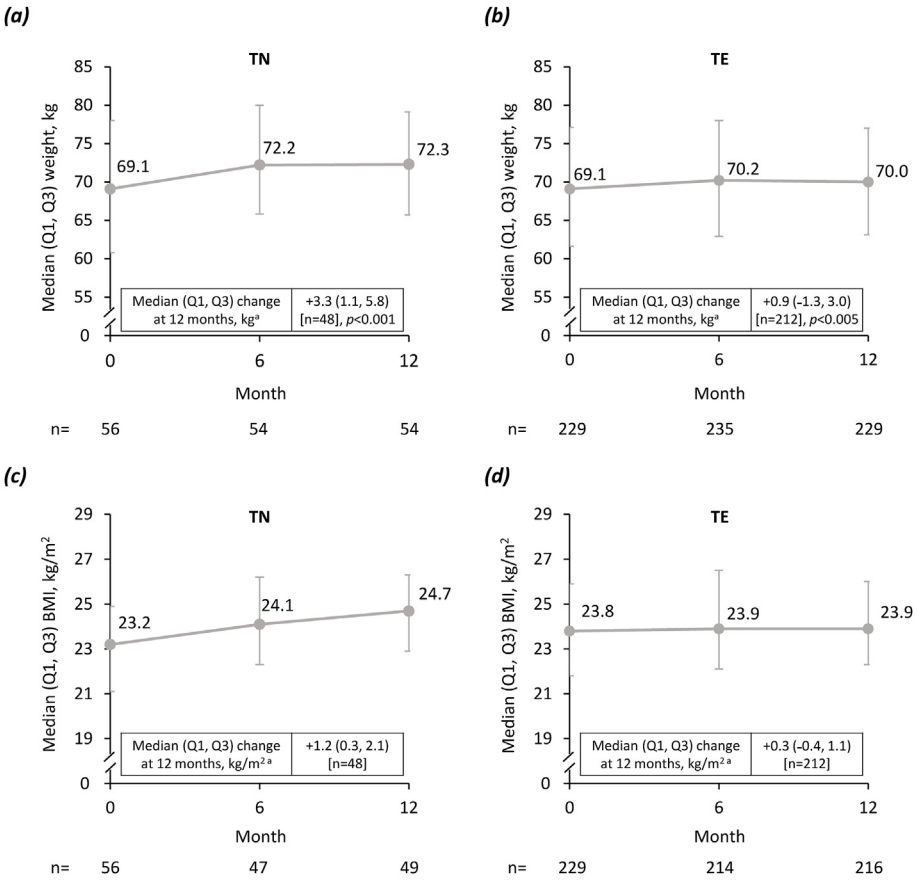

Figure 3. Change in weight (a and b) and BMI (c and d) analyses from baseline to 12 months in TN and TE participants. [a]Median change was calculated in participants with data at baseline and 12 months. *P*-values were calculated using the Sign test. Abbreviations: BMI, body mass index; Q, quartile; TE, treatment-experienced; TN, treatment-naïve.

Patient-reported outcomes (prospective cohort only)

HIV-SI bothersome symptom counts showed a statistically significant decrease from baseline in TN participants, with a median (Q1, Q3) reduction of −2.0 (−6.0, −1.0) at 12 months ($p < 0.001$); HIV-SI bothersome symptom counts remained stable in TE participants (Supplementary Table S5). Median (Q1, Q3) SF-36 MCS scores at baseline were 40.4 (30.3, 50.8) in TN and 47.7 (42.1, 52.4) in TE participants (scores <50 indicate worse than average function). MCS scores showed a statistically significant improvement, with a median (Q1, Q3) change from baseline of +6.9 (−0.5, 15.9) in TN participants ($p = 0.001$) and +1.3 (−3.0, 5.1) in TE participants ($p = 0.026$) at 12 months. Median (Q1, Q3) SF-36 PCS scores at baseline were 56.0 (47.3, 58.7) in TN and 57.3 (53.5, 59.9) in TE participants; PCS scores remained stable at 12 months (Supplementary Table S5). Baseline HIVTSQs scores showed high satisfaction with current ART among TE participants. Satisfaction improved after switching to B/F/TAF, with a median (Q1, Q3) total HIVTSQc score of +26.0 (16.0, 30.0; n = 205) at month 12 ($p < 0.001$), where a score of +30 represents the maximum possible increase in treatment satisfaction (Supplementary Table S5).

Discussion

Twelve-month data from the BICSTaR Asia cohort support previously published pooled, multi-regional data from BICSTaR,[30] providing evidence for the real-world use of B/F/TAF in people with HIV in Asia.

Some baseline differences were observed between the Asian cohort and the population from the pooled analysis, which included 1509 prospective participants from cohorts in Europe, Canada, Israel, Japan and Taiwan.[30] For example, the Asian cohort had a younger median age, a greater proportion of males, a lower median baseline CD4 count, and lower median body weight compared with the pooled analysis. Despite these baseline differences, effectiveness and safety results from the Asian cohort were generally consistent with those of the pooled analysis. In the Asian cohort, levels of viral suppression at 12 months were ≥97% across TN and TE participants, demonstrating the consistently high effectiveness of B/F/TAF, and supporting previous clinical trial data.[15–19] CD4 cell counts increased in the TN group and remained stable in the TE group. These improvements in the TN group suggest a restoration of immune function, as also indicated by results of previous controlled clinical trials[15,34] and a real-world observational cohort (BICTEL).[35] Safety and

tolerability findings were consistent with the known profile of B/F/TAF[34] and were reflected by the high level of persistence and low frequency of drug-related discontinuations, which occurred in 2/328 patients (0.6%) due to weight gain. Improvements in already high treatment satisfaction rates among TE participants were also observed.

Median changes in body weight among TN and TE participants were +3.3 and +0.9 kg, respectively, over 12 months. The median weight gain for TE participants was in line with the average annual weight gain of 0.5–1 kg reported in the general (non-HIV) adult population.[36] Observations in TE participants were also consistent with a study in virologically suppressed people with HIV in Taiwan, which reported that switching to B/F/TAF resulted in minimal weight gain (+0.6 kg at week 48).[37] Others have reported that weight gain associated with ART initiation in TN individuals may be partly due to a return to health,[38] while switches from ART associated with weight-suppressive effects can lead to reported weight gain in TE individuals.[39] Additionally, reduced physical activity and change in eating habits during the COVID-19 pandemic may have contributed to weight gain in the present cohort,[40] although these were not specifically evaluated. Notably, weight gain as a DRAE was only reported for TE participants: three of four participants who had a DRAE of weight gain had switched to B/F/TAF from ART regimens that included both TDF and efavirenz, which are associated with suppressive effects on weight.[39]

Our study population includes people with HIV receiving treatment in routine clinical care in the Republic of Korea, Singapore, and Taiwan. Current real-world evidence for B/F/TAF in people with HIV in Asia is sparse, typically based in Taiwan, and mostly retrospective.[14,24,26,27,41] One retrospective cohort study in Taiwan that compared B/F/TAF and dolutegravir/abacavir/lamivudine concluded that participants on B/F/TAF were 80% less likely to discontinue treatment due to adverse reactions.[26] Another study in Taiwan demonstrated that 81.5% of individuals who had experienced virologic failure on previous ART subsequently achieved viral suppression after switching to B/F/TAF.[24] An additional retrospective study confirmed the effectiveness of B/F/TAF in virologically suppressed TE individuals with archived K65 N/R mutation (which confers resistance to NRTIs).[27]

As an observational cohort study, our analyses were subject to the limitations inherent in this study type. These include lack of randomization and potential for selection and information bias. There were also some missing data, potentially confounded by missing visits due to the COVID-19 pandemic[42]; however, this information was not recorded. To minimize the effects of bias, eligibility criteria for participants were clearly defined and standardized electronic case report forms were used by trained staff. Participants from the retrospective cohort were selected in a consecutive manner to reduce the limitations associated with retrospective data, and comparison of retrospective and prospective data showed that data in the two groups were generally similar. The retrospective cohort was, by definition, persistent on ART before study entry, and therefore, drug discontinuation data must be interpreted with caution to avoid potential immortal time bias, although we found no evidence of this in our analyses.

Most participants (70.7%) were enrolled in Taiwan; the sample from Singapore was small (n = 11; 3.4%). While our findings may not be representative of all three participating countries, the populations of Taiwan and the Republic of Korea are considered largely ethnically homogenous and, therefore, our findings may be considered generalizable. The use of a common protocol across all BICSTaR cohorts also enables comparison of these data with a larger and more diverse global population.[30] Although the number of TN participants was relatively small (n = 65), our findings are consistent with those from the larger multi-national program.[30] The 12-month observation period reported herein is relatively short for evaluation of persistence, safety, and tolerability. However, findings are consistent with the results of a 48-week prospective PRO study in 630 virologically suppressed people with HIV in Taiwan, in which symptoms were substantially less prevalent and bothersome after switching to B/F/TAF.[43]

Conclusions

This 12-month analysis demonstrated that B/F/TAF was associated with high levels of effectiveness, treatment persistence, and satisfaction among people with HIV in the Republic of Korea, Singapore, and Taiwan receiving routine clinical care. B/F/TAF was well tolerated, with a favorable safety profile, and no new safety signals or emergence of resistance were observed. These findings support the use of B/F/TAF for people with HIV in Asia. The BICSTaR study is ongoing and will provide longer-term (24-month) follow-up data.

Funding

The BICSTaR program was funded by Gilead Sciences Inc. (Foster City, CA, USA). Funding for medical writing support for this article was provided by Gilead Sciences. The study sponsor, Gilead Sciences, played a role in the study design, data collection and analysis, decision to publish, and preparation of the manuscript.

Data sharing statement

Gilead Sciences shares anonymized individual participant 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 DataSharing@gilead.com.

Ethics statement

The protocol was approved by the independent ethics committee at each center, and the study was conducted

following Good Pharmacoepidemiology Practice and the Heads of Medicines Agencies' Good Pharmacovigilance Practices. Participants provided signed informed consent.

CRediT authorship contribution statement

Yu-Ting Tseng: Investigation, Writing — review & editing. **Chia-Jui Yang:** Investigation, Writing — review & editing. **Yeon-Sook Kim:** Investigation, Writing — review & editing. **Jun Yong Choi:** Investigation, Writing — review & editing. **Chen Seong Wong:** Investigation, Writing — review & editing. **Kuan-Yeh Lee:** Conceptualization, Writing — review & editing. **Jeong-a Lee:** Writing — review & editing. **Jack Chang:** Writing — review & editing. **Rebecca Harrison:** Formal analysis, Writing — review & editing. **Andrea Marongiu:** Conceptualization, Formal analysis, Writing — review & editing. **Sun Hee Lee:** Investigation, Writing — review & editing. **Chien-Ching Hung:** Investigation, Writing — review & editing.

Declaration of competing interest

CSW has received advisory board and speaking fees from Gilead Sciences, Janssen, and ViiV Healthcare, and research funding from Gilead Sciences.
K-YL, J-aL, JC, and AM are employees of Gilead Sciences and own shares in Gilead Sciences.
RH was an employee of Gilead Sciences and owned shares in Gilead Sciences at the time of writing.
C-CH has received research support and speaker honoraria from Gilead Sciences, and has served on advisory boards for Gilead Sciences.
SHL has received speaker honoraria from and served on advisory boards for Gilead Sciences Korea and GSK Korea.
Y-TT, C-JY, Y-SK and JYC declare no conflicts of interest.

Acknowledgments

The authors thank all participants and investigators involved in the BICSTaR Asia cohort (see Supplementary Information for the list of investigators). Medical writing support, including development of a draft outline and subsequent drafts in consultation with the authors, collating author comments, copyediting, fact checking, and referencing, was provided by Josh Lilly at Aspire Scientific Limited (Bollington, UK).

References

1. UNAIDS. *Global HIV & AIDS statistics — fact sheet*. 2023. Available at: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. [Accessed 1 May 2024].
2. Jung IY, Rupasinghe D, Woolley I, O'Connor CC, Giles M, Azwa RI, et al. Trends in mortality among ART-treated HIV-infected adults in the Asia-pacific region between 1999 and 2017: results from the TREAT Asia HIV observational database (TAHOD) and Australian HIV observational database (AHOD) of IeDEA Asia-Pacific. *J Int AIDS Soc* 2019;**22**:e25219.
3. Puhr R, Kumarasamy N, Ly PS, Ng OT, Van Nguyen K, Merati TP, et al. HIV and aging: demographic change in the Asia-Pacific region. *J Acquir Immune Defic Syndr* 2017;**74**:e146—8.
4. Gandhi RT, Bedimo R, Hoy JF, Landovitz RJ, Smith DM, Eaton EF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 recommendations of the International Antiviral Society-USA Panel. *JAMA* 2023;**329**:63—84.
5. European AIDS Clinical Society (EACS). *Guidelines version 12.0*. 2023. Available at: https://www.eacsociety.org/guidelines/eacs-guidelines/. [Accessed 1 May 2024].
6. U.S. Department of Health and Human Services, Office of AIDS Research. *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV*. 2024. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. [Accessed 1 May 2024].
7. Sangarlangkarn A, Yamada Y, Ko FC. HIV and aging: overcoming challenges in existing HIV guidelines to provide patient-centered care for older people with HIV. *Pathogens* 2021;**10**:1332.
8. Nachega JB, Parienti JJ, Uthman OA, Gross R, Dowdy DW, Sax PE, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. *Clin Infect Dis* 2014;**58**:1297—307.
9. The Korean Society for AIDS. Summary of 2021 clinical guidelines for the diagnosis and treatment of HIV/AIDS in HIV-infected Koreans. *Infect Chemother* 2021;**53**:592—616.
10. National Centre for Infectious Diseases. *National HIV programme: recommendations for the use of antiretroviral therapy (ART) in adults living in Singapore*. 2023. Available at: https://www.ncid.sg/About-NCID/OurDepartments/Documents/NHIVP%20ART%20Recommendations%202023_final.pdf. [Accessed 1 May 2024].
11. Taiwan AIDS Society. *Guidelines for diagnosis and treatment of HIV/AIDS. Sixth edition (2020 revision)*. 2023. Available at: http://www.aids-care.org.tw/journal/treatment.php. [Accessed 1 May 2024].
12. Wang X, Schmerold L, Naito T. Real-world medication persistence among HIV-1 patients initiating integrase inhibitor-based antiretroviral therapy in Japan. *J Infect Chemother* 2022;**28**:1464—70.
13. Oh KS, Han E. A comparison of medication adherence and viral suppression in antiretroviral treatment-naive patients with HIV/AIDS depending on the drug formulary. *PLoS One* 2021;**16**:e0245185.
14. Chen GJ, Sun HY, Chen LY, Hsieh SM, Sheng WH, Liu WD, et al. Low-level viraemia and virologic failure among people living with HIV who received maintenance therapy with co-formulated bictegravir, emtricitabine and tenofovir alafenamide versus dolutegravir-based regimens. *Int J Antimicrob Agents* 2022;**60**:106631.
15. Orkin C, DeJesus E, Sax PE, Arribas JR, Gupta SK, Martorell C, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. *Lancet HIV* 2020;**7**:e389—400.
16. Sax PE, Rockstroh JK, Luetkemeyer AF, Yazdanpanah Y, Ward D, Trottier B, et al. Switching to bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with human immunodeficiency virus. *Clin Infect Dis* 2021;**73**:e485—93.
17. Stellbrink HJ, Arribas JR, Stephens JL, Albrecht H, Sax PE, Maggiolo F, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind,

multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019;**6**:e364—72.
18. Sax PE, Arribas JR, Orkin C, Lazzarin A, Pozniak A, DeJesus E, et al. Bictegravir/emtricitabine/tenofovir alafenamide as initial treatment for HIV-1: five-year follow-up from two randomized trials. *EClinicalMedicine* 2023;**59**:101991.
19. Maggiolo F, Rizzardini G, Molina JM, Pulido F, De Wit S, Vandekerckhove L, et al. Bictegravir/emtricitabine/tenofovir alafenamide in older individuals with HIV: results of a 96-week, phase 3b, open-label, switch trial in virologically suppressed people ≥65 years of age. *HIV Med* 2023;**24**:27—36.
20. Avihingsanon A, Chetchotisakd P, Kiertiburanakul S, Ratanasuwan W, Siripassorn K, Supparatpinyo K, et al. Efficacy and safety of switching to bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed Asian adults living with HIV: a pooled analysis from three international phase III randomized trials. *HIV Med* 2023;**24**:290—300.
21. Choy CY, Wong CS, Kumar PA, Olszyna DP, Teh YE, Chien MFJ, et al. Recommendations for the use of antiretroviral therapy in adults living with HIV in Singapore. *Singapore Med J* 2024;**65**:259—73.
22. Ambrosioni J, Rojas Lievano J, Berrocal L, Inciarte A, de la Mora L, Gonzalez-Cordon A, et al. Real-life experience with bictegravir/emtricitabine/tenofovir alafenamide in a large reference clinical centre. *J Antimicrob Chemother* 2022;**77**:1133—9.
23. Armenia D, Forbici F, Bertoli A, Berno G, Malagnino V, Gagliardini R, et al. Bictegravir/emtricitabine/tenofovir alafenamide ensures high rates of virological suppression maintenance despite previous resistance in PLWH who optimize treatment in clinical practice. *J Glob Antimicrob Resist* 2022;**30**:326—34.
24. Chang HM, Chou PY, Chou CH, Tsai HC. Outcomes after switching to BIC/FTC/TAF in patients with virological failure to protease inhibitors or non-nucleoside reverse transcriptase inhibitors: a real-world cohort study. *Infect Drug Resist* 2021;**14**:4877—86.
25. Rolle CP, Nguyen V, Patel K, Cruz D, DeJesus E, Hinestrosa F. Real-world efficacy and safety of switching to bictegravir/emtricitabine/tenofovir alafenamide in older people living with HIV. *Medicine (Baltimore)* 2021;**100**:e27330.
26. Lee CY, Lee CH, Tang HJ, Tsai HC, Yang CH, Lin YP, et al. Comparison of virological efficacy of DTG/ABC/3TG and B/F/TAF regimens and discontinuation patterns in persons living with advanced HIV in the era of rapid ART: a retrospective multicenter cohort study. *Infect Dis Ther* 2023;**12**:843—61.
27. Tsai MS, Sun HY, Chen CP, Lee CH, Lee CY, Liu CE, et al. Switching to coformulated bictegravir, emtricitabine, and tenofovir alafenamide maintained viral suppression in adults with historical virological failures and K65N/R mutation. *Int J Infect Dis* 2023;**126**:39—47.
28. Choi JP, Seo BK. HIV-related stigma reduction in the era of undetectable equals untransmittable: the South Korean perspective. *Infect Chemother* 2021;**53**:661—75.
29. Ananworanich J, Avihingsanon A. HIV and noncommunicable diseases: the Asian perspective. *J Acquir Immune Defic Syndr* 2014;**67**(Suppl 1):S99—103.
30. Esser S, Brunetta J, Inciarte A, Levy I, D'Arminio Monforte A, Lambert JS, et al. Twelve-month effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide in people with HIV: real-world insights from BICSTaR cohorts. *HIV Med* 2024;25:440—53.
31. Gilead Sciences. *Biktarvy tablet product information (Korea)*. 2020. Available at: https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq=201900267aupdateTs2023-07-03%2017:55:00.0b. [Accessed 1 May 2024].
32. Gilead Sciences. *Biktarvy tablets prescribing information (Singapore)*. 2023. Available at: https://www.gilead.com/-/media/files/pdfs/other/Biktarvy_Singapore.pdf. [Accessed 1 May 2024].
33. Gilead Sciences. *Biktarvy tablets product information (Taiwan)*. 2023. Available at: https://mcp.fda.gov.tw/im_detail_1/%E8%A1%9B%E9%83%A8%E8%97%A5%E8%BC%B8%E5%AD%97%E7%AC%AC027570%E8%99%9F. [Accessed 1 May 2024].
34. Wohl DA, Yazdanpanah Y, Baumgarten A, Clarke A, Thompson MA, Brinson C, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019;**6**:e355—63.
35. Lazzaro A, Bianchini D, Gentilini Cacciola E, Mezzaroma I, Falciano M, Andreoni C, et al. Immune reconstitution and safe metabolic profile after the switch to bictegravir/emtricitabine/tenofovir alafenamide fumarate among virologically controlled PLWH: a 96 week update from the BICTEL cohort. *Viruses* 2023;**15**:1222.
36. Hutfless S, Maruthur NM, Wilson RF, Gudzune KA, Brown R, Lau B, et al. *Strategies to prevent weight gain among adults. Comparative effectiveness reviews. No. 97. AHRQ publication No. 13-EHC029-EF*. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
37. Hsu JY, Sun HY, Chen LY, Chang SY, Chuang YC, Huang YS, et al. Weight and metabolic changes among virally suppressed people with HIV who switched to co-formulated bictegravir/emtricitabine/tenofovir alafenamide. *J Glob Antimicrob Resist* 2024;**36**:426—35.
38. Kumar S, Samaras K. The impact of weight gain during HIV treatment on risk of pre-diabetes, diabetes mellitus, cardiovascular disease, and mortality. *Front Endocrinol* 2018;**9**:705.
39. Erlandson KM, Carter CC, Melbourne K, Brown TT, Cohen C, Das M, et al. Weight change following antiretroviral therapy switch in people with viral suppression: pooled data from randomized clinical trials. *Clin Infect Dis* 2021;**73**:1440—51.
40. Zachary Z, Brianna F, Brianna L, Garrett P, Jade W, Alyssa D, et al. Self-quarantine and weight gain related risk factors during the COVID-19 pandemic. *Obes Res Clin Pract* 2020;**14**:210—6.
41. Chen GJ, Sun HY, Chang SY, Hsieh SM, Sheng WH, Chuang YC, et al. Effectiveness of second-generation integrase strand-transfer inhibitor-based regimens for antiretroviral-experienced people with HIV who had viral rebound. *J Microbiol Immunol Infect* 2023;**56**:988—95.
42. Wu P-Y, Sun H-Y, Sheng W-H, Hsieh S-M, Chuang Y-C, Huang Y-S, et al. Impact of coronavirus disease 2019 on the HIV testing and health care delivery at a university hospital in Taiwan, 2020—2021. *J Microbiol Immunol Infect* 2022;**55**:1005—12.
43. Chen LY, Sun HY, Chuang YC, Huang YS, Liu WD, Lin KY, et al. Patient-reported outcomes among virally suppressed people living with HIV after switching to co-formulated bictegravir, emtricitabine and tenofovir alafenamide. *J Microbiol Immunol Infect* 2023;**56**:575—85.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.07.003.