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Original Article

Patient-reported outcomes among virally suppressed people living with HIV after switching to Co-formulated bictegravir, emtricitabine and tenofovir alafenamide

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Abstract *Background:* While some evidence has suggested the benefits of co-formulated bictegravir, emtricitabine and tenofovir alafenamide (B/F/TAF) in improving the quality of life of people living with HIV (PLWH), patient-reported outcome studies that focus on Asian population remain scarce. We aimed to determine the changes in HIV-related symptom burden in virally-suppressed PLWH switching to B/F/TAF in a real-world setting.
Methods: PLWH on stable antiretroviral therapy (ART) for ≥6 months with plasma HIV RNA <200 copies/mL who decided to switch to B/F/TAF were eligible for the study. Participants' experience with 20 symptoms were assessed using HIV Symptom Index at baseline and weeks 24 and 48. Responses were dichotomized in two ways: 1) present vs. not present; and 2) bothersome vs. not bothersome, and compared across time points.
Results: Six hundred and thirty participants (prior regimen, 94.4% integrase inhibitor-based) who completed week 48 visit were included in the analysis. Forty-eight weeks after switching to B/F/TAF, six symptoms were significantly less prevalent, and seven symptoms were significantly less bothersome. Improvement was more pronounced in participants whose prior

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regimen was elvitegravir-based versus dolutegravir-based. Logistic regression results showed that prior dolutegravir-based ART and pre-existing diabetes independently predicted improvement in diarrhea/loose bowels and muscle aches/joint pain, respectively. Despite the overall improvement, some symptoms persisted in a substantial proportion of participants.
Conclusions: Virally-suppressed PLWH might benefit from a regimen switch to B/F/TAF to reduce the prevalence and level of bother of HIV-related symptoms. Nevertheless, additional multidisciplinary interventions are warranted to further alleviate the symptom burden of PLWH.

Introduction

Advances in antiretroviral therapy (ART) in the past decades have greatly extended the life expectancy of people living with HIV (PLWH) and turned HIV infection into a manageable chronic disease. However, living longer does not necessarily translate to improved quality of life (QoL). In addition to stigma and discrimination, PLWH face challenges with comorbidities and adverse events arising from HIV infection and its life-long treatment, all of which have a negative impact on their QoL.[1] As PLWH effectively treated with ART are now able to achieve and maintain viral suppression, the goal of HIV management is broadened from viral suppression to include patient-centered chronic care.[2] This shift is reflected in the emergence of a fourth 90 on top of the Joint United Nations Program on HIV/AIDS (UNAIDS) 90-90-90 targets (90% diagnosed, 90% on treatment and 90% virally suppressed) —ensuring that 90% of people with viral suppression have good health-related QoL (HRQoL).[2,3]

In order to help achieve the fourth 90 target, it is of utmost importance to choose the optimal ART regimen for PLWH that demonstrates not only durable efficacy but also ability to improve their HRQoL. Two- and three-drug integrase strand-transfer inhibitor (INSTI)-based regimens are recommended as a preferred treatment for HIV infection by major international guidelines.[4–7] Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) is a novel, INSTI-based, complete regimen. It has been proven to be potent and well-tolerated in previous studies and was approved by the U.S. Food and Drug Administration in 2018.[8–12] To align with international guidelines, B/F/TAF has been recommended as a first-line therapy for PLWH in Taiwan since September 2019.[13] A retrospective cohort study in Taiwan between November 2019 and November 2020 showed that 97.3% of virally-suppressed PLWH maintained suppression after switching to B/F/TAF.[14] Similarly, a recent study reported that the incidence of virologic failure was low (0.69 per 100 person-years of follow-up) among Taiwanese PLWH who switched to B/F/TAF from predominantly other INSTI-based regimens,[13] which together with the aforementioned study support the use of B/F/TAF as a switch regimen for Asian PLWH who have been on stable treatment. While evidence has suggested the advantages of B/F/TAF in improving the lives of PLWH beyond viral suppression,[15] studies that focus on Asian population remain scarce.

One of the most efficient ways to evaluate the HRQoL is by collecting and analyzing patient-reported outcomes (PROs).[16] PROs are measurements of any aspects of a patient's well-being reported directly by the patient without interpretation from physicians and others.[17] PROs can be used to support HIV management in a multitude of ways, including capturing patients' experience with ART more accurately, evaluating and differentiating treatment strategies, and predicting clinical outcomes such as hospitalization and mortality.[16] In this study, we aimed to survey virally-suppressed PLWH in Taiwan who switched to B/F/TAF about their experiences with symptoms commonly associated with HIV infection and treatment and to gain a more holistic view of their well-being to enhance patient-centered care.

Methods

Study design and participants

This was a prospective cohort study conducted at the outpatient clinics of National Taiwan University Hospital from October 2019 to September 2021. Eligible participants were PLWH aged 20 years or older with at least six months of ART experience and viral suppression (plasma HIV RNA load [PVL] <200 copies/mL). The option of switching to B/F/TAF, a regimen recommended by the national HIV treatment guidelines, was discussed with every eligible patient in the clinics. The decision of switching was made jointly by the treating physician and the patient. After the switch, clinical visits occurred at an interval of 12 weeks until week 48, with PROs collected at baseline and weeks 24 and 48. Participants were provided with life-style instructions and counselling throughout the study and were referred to specialists if needed.

Demographics and clinical data collection

Participants' demographics (e.g., gender and age) and clinical characteristics (e.g., CD4 count, PVL, years since the diagnosis of HIV infection, years on ART, duration of HIV suppression, prior ART regimen, and the use of psychotropic medications) were collected from the electronic medical records. Blood and urine samples were collected at intervals of 3–6 months according to the national HIV treatment guidelines and were tested for fasting glucose, glycated hemoglobin (HbA1C), insulin, aminotransferases, lipids, anti-hepatitis C virus (HCV), serum and urine

creatinine, and urine proteins. Body weight was measured and recorded at every clinic visit.

Patient-reported outcome measure and instrument administration

HIV Symptom Index (HIV—SI) is a validated PRO instrument to evaluate the burden of 20 symptoms commonly associated with HIV infection or its treatment.[18] Participants were asked to rate their experiences with each of the 20 symptoms in the past month using a 5-point scale (0) I don't have this symptom; (1) I was not bothered; (2) I was a little bothered; (3) I was indeed bothered; (4) I was bothered a lot. The total score was calculated as the sum of scores for all symptoms ranging from 0 to 80, with a lower total score indicating less symptom burden. The HIV—SI questionnaire was self-administered in participants' native language (traditional Chinese) on paper. Participants who were illiterate, had presbyopia or trouble reading were interviewed by their HIV case managers instead.

Statistical analysis

All analyses were performed using SPSS 15. Baseline demographic and clinical characteristics were summarized using descriptive statistics. Between-visit comparisons of clinical characteristics were performed with the Fisher exact test for categorical data and a two-sided Wilcoxon rank sum test for continuous data.

To better capture changes in the occurrence of HIV symptoms and their associated burden after regimen switch, responses to each HIV—SI item were dichotomized in two different ways as previously reported: 1) absent (score of 0) vs. present (scores of 1—4); 2) not bothersome (scores of 0—1) vs. bothersome (scores of 2—4).[15,19—21] The percentages of participants reporting each symptom to be present vs. absent and bothersome vs. not bothersome were summarized, and changes from baseline were evaluated using the McNemar test. The total scores at baseline and week 48 were presented using descriptive statistics. PRO data from a participant were included in this study if the participant had filled in the HIV—SI questionnaire at both baseline and week 48. If a participant had a missing response to an item on the questionnaire at either baseline, week 24 or week 48, data on that particular item were excluded from the cross-time comparisons (i.e., baseline vs. week 24, and baseline vs. week 48).

Logistic regression was used to identify determinants of improvement for each significantly less bothersome symptom, reporting odds ratios with 95% confidence intervals (CI). A change from being bothered (scores of 2—4) to not being bothered (scores of 0—1), or from being bothered a lot (a score of 4) to being bothered a little (a score of 2) was considered as clinically significant improvement. Conversely, a change from not being bothered (scores of 0—1) to being bothered (scores of 2—4), or from being bothered (scores of 2—4) to being bothered (scores of 2—4) was considered as worsening/persistence. Participants who were not bothered at neither baseline nor week 48 were excluded from the analysis. A set of demographic variables (age and gender) and clinical variables (CD4 count, PVL<50 copies/mL, diabetes mellitus (DM) status, hypertension (HTN) status, hepatitis B virus (HBV) status, HCV status, years since HIV infection diagnosed, years on ART, and use of psychotropic medications) were selected as covariates. All significant covariates with $p < 0.05$ in the univariate analysis were selected for subsequent multivariate logistic regression unless otherwise stated. Prior ART regimens were forced into the multivariate models regardless of the univariate analysis results to evaluate their associations with symptom improvement.

Results

Participant disposition and baseline characteristics

A total of 673 PLWH were enrolled in the study. Forty-three (6.4%) discontinued B/F/TAF early due to adverse effects (26, 3.9%), death (2, 0.3%), and transfer of care or loss to follow-up (15, 2.2%). The detailed reasons for discontinuation are shown in Supplementary Table 1. The remaining 630 participants who completed the visit at week 48 were included in the analysis.

As shown in Table 1, the study population was predominantly male (97.0%) with a median age of 39.3 years; and 39.8% of the participants had been diagnosed with AIDS before. The median CD4 count was 651 cells/mm^3, and 97.6% had a CD4 count higher than 200 cells/mm^3 before switch. Prior to enrolment, the participants had been on ART for a median of 6.64 years with a median of 5.56 years on HIV suppression. Overall, 94.4% were using INSTI-based regimens (mostly dolutegravir [DTG]-based and elvitegravir [EVG]-based) before switching to B/F/TAF. It is worth noting that, at baseline, nearly a quarter of the participants were on psychotropic medications and 54.0% were overweight (body-mass index [BMI] $\geq$24 kg/m^2, as defined by the Ministry of Health and Welfare in Taiwan).[22]

Changes in clinical characteristics at week 48

Changes in clinical characteristics at week 48 are summarized in Supplementary Table 2. Briefly, viral suppression was maintained in 95.6% of the 602 participants with HIV PVL data available at the end of follow up. Improvement in immunological status was observed after switching to B/F/TAF for 48 weeks, as the median CD4 count increased significantly compared to baseline (667 vs. 651 cells/mm^3, $p = 0.018$). When stratified by years on ART (Supplementary Tables 3a—c), a significant increase in CD4 count after switch was shown in the participants who were on ART for less than three years (681 vs. 611 cells/mm^3, $p = 0.001$), but not in those who were on ART for three years or longer.

The median estimated glomerular filtration rate (eGFR) decreased from 92.0 mL/min/1.73 m^2 at baseline to 84.4 mL/min/1.73 m^2 at the end of follow up, which might be attributed to the known effect of bictegravir as an inhibitor of renal transporters (organic cation transporter 2 and multidrug and toxin extrusion 1) on reducing eGFR (but not the actual GFR).[11] Urine beta-2-microglobulin-to-creatinine ratio was significantly lower after regimen switch (162.0 vs. 193.2 mcg/g, $p < 0.001$), but urine

Table 1 Baseline characteristics of 630 participants.

Variable		n (%) or median (IQR)
Male		611 (97.0)
Age, years		39.3 (33.3–48.1)
>50 years		132 (21.0)
Men who have sex with men		571 (90.6)
Baseline CD4 count, cells/mm^3		651 (482.8–826.0)
<200 cells/mm^3		15 (2.4)
Baseline HIV viral load, copies/mL		
50–<200 copies/mL		21 (3.3)
<50 copies/mL		609 (96.7)
Ever having had an AIDS diagnosis		251 (39.8)
Years since HIV infection diagnosis		8.05 (5.0–12.2)
Years on ART		6.64 (4.2–10.0)
Duration of HIV suppression (PVL <200 copies/mL), years		5.56 (3.1–8.5)
Previous ART before switching to B/F/TAF		
By the third agent	INSTI-based	595 (94.5)
	DTG-based	115 (18.3)
	EVG-based	480 (76.2)
	NNRTI-based	26 (4.1)
	PI-based	9 (1.4)
By the NRTI backbone	TDF-based	51 (8.1)
	TAF-based	480 (76.2)
	Non-TFV-based	99 (15.7)
HBsAg positivity		75 (11.9)
Anti-HCV positivity		86 (13.7)
Hypertension		79 (12.5)
Diabetes mellitus		53 (8.4)
Use of lipid-lowering agents		109 (17.3)
Use of psychotropic medications[a]		157 (24.9)
Ever been diagnosed with insomnia		144 (22.9)
BMI, kg/m^2		24.4 (22.1–26.8)

[a] Psychotropic medications used by participants at baseline included zolpidem, estazolam, trazodone, clonazepam and alprazolam.

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; DTG, dolutegravir; EVG, elvitegravir; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; PI, protease inhibitor; PVL, plasma HIV RNA load; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV: tenofovir.

albumin-to-creatine ratio (ACR) remained similar (7.6 vs. 7.9 mg/g, $p = 0.404$).

Significant improvement was observed in participants' lipid profiles after switching to B/F/TAF: median values of triglyceride, total cholesterol, low-density lipoprotein cholesterol and total cholesterol:high-density lipoprotein cholesterol ratio all decreased significantly at week 48 compared with baseline ($p < 0.001$). However, it is worth noting that the proportion of the participants using lipid-lowering agents was significantly higher at week 48 (24.4% vs. 17.6%, $p < 0.001$). The median HbA1C remained similar throughout the study period; however, a higher proportion of the participants were diagnosed with DM at week 48 (9.0% vs. 8.4%, $p < 0.001$). The median body weight of the participants increased by 1 kg over the 48 weeks ($p < 0.001$); and 15.6% of them had weight gain of 5% or more. More detailed analysis of the clinical data collected in this study will be reported and discussed in another article which is currently under preparation.

Changes in patient-reported outcomes at week 48

Symptoms being present vs. absent

Overall, participants experienced fewer HIV-related symptoms after switching to B/F/TAF (a median of 4 [1–8] at week 48 vs. 5 [1–9] at baseline, $p < 0.001$). Out of the 20 symptoms investigated, six physical symptoms were significantly less reported: fevers/chills/sweats, nausea/vomiting, diarrhea/loose bowels, headaches, loss of appetite and muscle aches/joint pain (Fig. 1a). Of these, nausea/vomiting, diarrhea/loose bowels and muscle aches/joint pain each had more than 5% reduction; nausea/vomiting, diarrhea/loose bowels and loss of appetite appeared to improve at as early as week 24 (Supplementary Fig. 1). No cognitive and psychological symptoms or body image symptoms had significant improvement (Fig. 1b and c). Nevertheless, none of the 20 symptoms became more prevalent after 48 weeks.

Symptoms being bothersome vs. not bothersome

In addition to assessing whether the regimen switch resulted in fewer symptoms, we also assessed whether these symptoms became less bothersome. Overall, the median total score given to all 20 symptoms decreased from 7 (2–14) to 5 (2–12) after 48 weeks on B/F/TAF ($p < 0.001$), suggesting a lower symptom burden. There was significant reduction in the proportion of the participants bothered by five physical symptoms (pain/numbness/tingling in hands/feet, diarrhea/loose bowels, headaches, muscle aches/joint pain, and problems with sex), one cognitive and psychological symptom (trouble remembering), and one body image symptom (changes in body composition/weight gain) (Fig. 2). More than 50% of the participants who were bothered by these seven symptoms at baseline were no longer bothered at week 48 (Fig. 2). Nevertheless, intriguingly, 4.3%–9.3% of the participants became bothered by these symptoms after the switch (Fig. 2). Among the 13 symptoms of which the overall levels of bother remained unchanged, fatigue/loss of energy had the highest proportion of the participants changing from not being bothered to being bothered (11.3% [data not shown]).

Subgroup analysis by prior regimen: DTG-based vs. EVG-based

INSTI-based regimens with DTG or EVG as the third drug were the most common treatments participants had been receiving before enrolment (Table 1). To explore the level of benefits derived from switching to B/F/TAF from different INSTI-based regimens, we performed a subgroup analysis by participants' prior INSTI before switch. At baseline, numerically fewer participants on prior DTG-based regimens (the DTG group) were bothered by 16 out of 20 symptoms compared with participants on prior EVG-

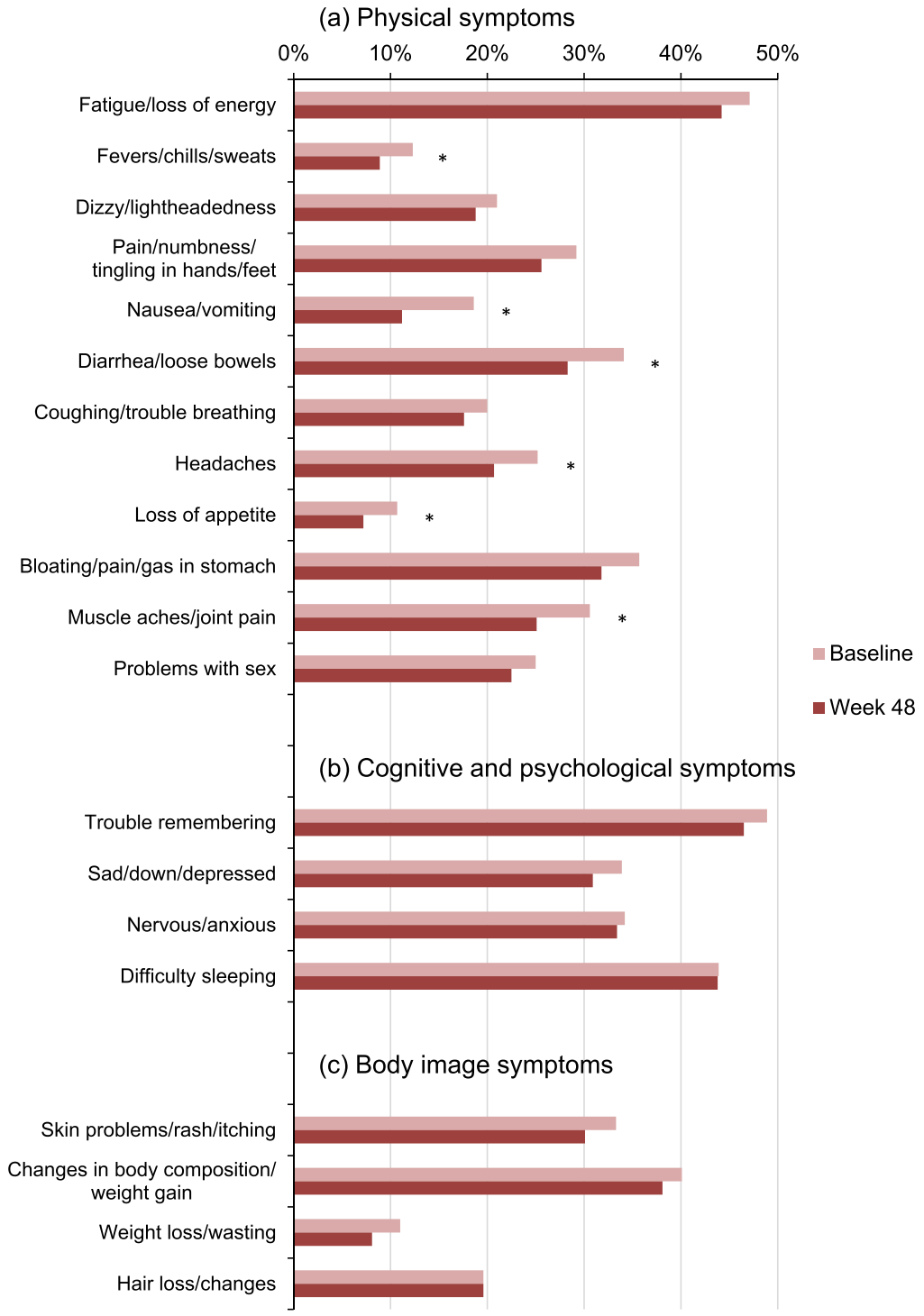

Figure 1. Percentages of participants reporting the presence of symptoms at baseline and week 48. Six physical symptoms were reported to be present by significantly lower percentages of participants 48 weeks after switching to B/F/TAF. Asterisk (*) indicates statistically significant difference with $p < 0.05$.

based regimens (the EVG group) (Supplementary Table 4). After switching to B/F/TAF for 48 weeks, greater improvement in PROs was demonstrated in the EVG group overall, where the participants reported significantly fewer symptoms (median [IQR]: 4 [1–8] at week 48 vs. 5 [1–9] at baseline, $p < 0.001$) and a lower total score (median [IQR]: 5 [2–12] at week 48 vs. 7 [2–14] at baseline, $p < 0.001$). In particular, the EVG group was significantly less bothered by six physical symptoms and two body image symptoms, among which the greatest improvement was observed in

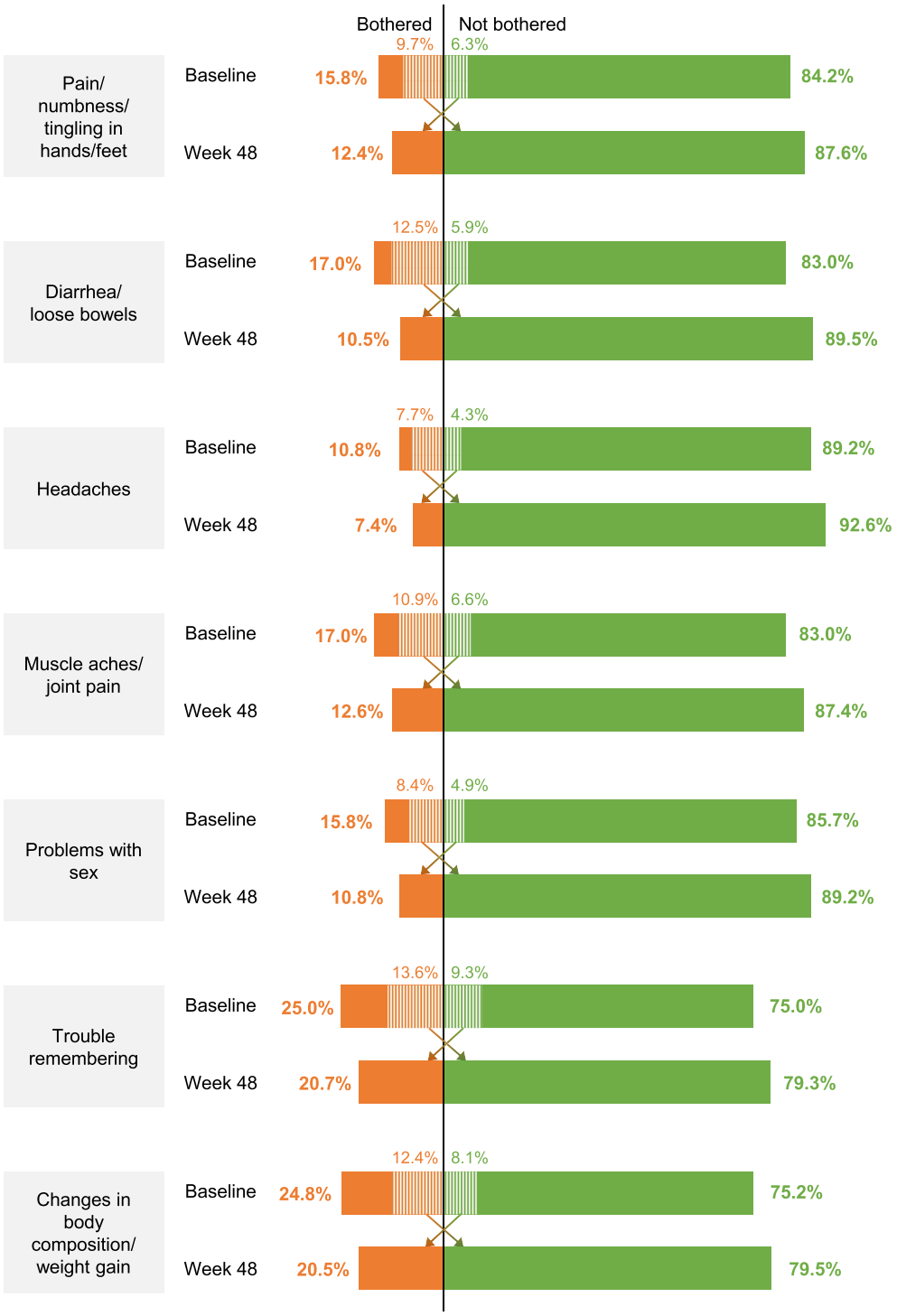

Figure 2. Percentages of participants bothered by each symptom at baseline and week 48. Each of the seven symptoms presented here was reported to be bothersome by a significantly lower percentage of participants. The area shaded with orange lines indicated the proportion of participants who changed from being bothered at baseline to not being bothered on week 48. The area shaded with green lines indicated the proportion of participants who changed from not being bothered at baseline to being bothered on week 48.

diarrhea/loose bowels with a notable 7.0% reduction (Fig. 3). In contrast, in the DTG group, neither the median total number of symptoms (median [IQR]: 3 [1—7] at week 48 vs. 3 [1—7] at baseline, $p = 0.222$) nor the median total score (median [IQR]: 4 [1—10] at week 48 vs. 5 [0—11] at baseline, $p = 0.181$) was significantly reduced. Participants switching from DTG-based regimens to B/F/TAF were only less bothered by diarrhea/loose bowels (Fig. 3).

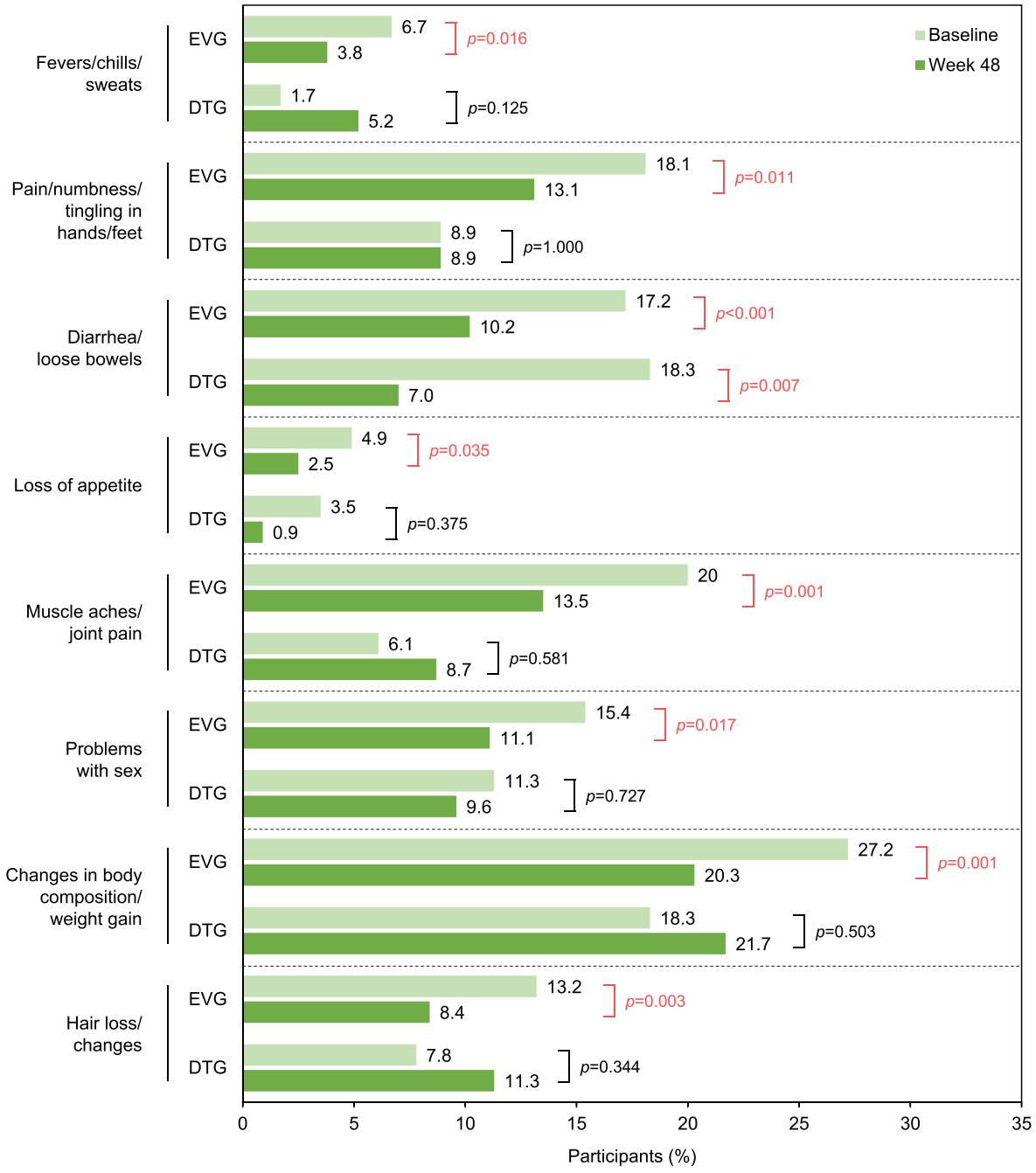

Figure 3. Percentages of participants bothered by each symptom at baseline and week 48 by prior INSTI-based regimen. Each of the eight symptoms presented here was reported to be bothersome by a significantly lower percentage of participants in either the EVG group or the DTG group. *P* values < 0.05 were colored in red. Abbreviation: DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor.

Predictors of symptom improvement

To determine variables that could predict symptom improvement, logistic regression analysis was conducted for the seven symptoms reported above to be significantly less bothersome at week 48. The results of multivariate analysis showed that the improvement of four symptoms were significantly associated with specific clinical variables (Table 2): (1) receiving DTG-based ART prior to the switch significantly predicted improvement in diarrhea/loose bowels; (2) pre-existing diabetes at baseline significantly predicted improvement in muscle aches/joint pain; (3) psychotropic medications at baseline significantly predicted worsening/persistence of pain/numbness/tingling in hands/feet; and (4) BMI $>30\ kg/m^2$ at baseline and change in weight at week 48 were associated with decreased odds of improvement in body composition/weight gain. Full logistic regression results could be found in Supplementary Tables 5a—g.

Table 2 Factors independently associated with improvement of the 7 significantly less bothersome symptoms.

Symptom	Associated Factors	OR[a] (95% CI), *p* value
Pain/numbness/tingling in hands/feet[b]	Use of psychotropic medications	0.4 (0.2—1.0), 0.039
Diarrhoea/loose bowels[d]	Prior ART (DTG vs. non-INSTI)	4.8 (1.1—20.3)[c], 0.034
Headaches	—	—
Muscle aches/joint pain[e]	DM	2.8 (1.0—7.8), 0.049
Problems with sex	—	—
Trouble remembering	—	—
Changes in body composition/weight gain[f]	Weight change at week 48 (kg)	0.8 (0.8—0.9), <0.001
	BMI>30 kg/m^2 vs. BMI<24 kg/m^2	0.3 (0.1—1.0), 0.043

[a] OR was obtained from multivariate analysis unless otherwise stated.
[b] Other covariates included in the multivariate model were: age, DM, DTG as prior ART, and EVG/c as prior ART.
[c] OR was obtained from a univariate model as this is the only significant factor.
[d] Other covariates included in the multivariate model were: HCV, EVG/c as prior ART.
[e] Other covariates included in the multivariate model were: DTG as prior ART, and EVG/c as prior ART.
[f] Other covariates included in the multivariate model were: DTG as prior ART, EVG/c as prior ART, BMI 24—27, and BMI 27—30.
Abbreviation: ART, antiretroviral therapy; BMI, body mass index; DM, diabetes mellitus; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; OR, odds ratio.

Discussion

To the best of our knowledge, this was the first large, longitudinal, real-world PRO study that prospectively evaluated a switch to B/F/TAF in PLWH who were virally suppressed on their previous regimens. This study focused on assessing the burden of 20 symptoms associated with HIV disease or treatment by directly surveying PLWH about their experiences using the HIV—SI instrument. It was encouraging to find that the switch to B/F/TAF from previous regimens (mostly DTG- or EVG-based) led to improvement in half of the 20 symptoms investigated, which were reported as absent and/or not bothersome by a significantly higher proportion of the participants 48 weeks after the switch. Considering that all participants were virally suppressed for a median of 5.56 years and over 95% remained so after the switch, the changes in symptom burden could be more related to the treatments than HIV per se, though more studies are warranted to confirm our findings.

The comparisons between the presence of symptoms at baseline and that at week 48 showed that six physical symptoms significantly improved. The notable 7.4% reduction in nausea/vomiting might be attributed to the fact that nausea is a known adverse effect associated with both DTG- and EVG/c-based regimens.[6] Diarrhea, another common adverse effect of EVG/c-based regimen,[6] was reduced by 7.0% after switching to B/F/TAF. The comparisons of bothersome symptoms between baseline and week 48 revealed improvement in two additional physical symptoms plus one cognitive and psychological symptom, and one body image symptom. It is interesting to note that while participants gained a median of 1 kg over the 48 weeks, they felt significantly less bothered by changes in body composition/weight gain. Collectively, these results demonstrated burden-reducing benefits on ten symptoms prevalent in PLWH after the regimen switch.

While the overall analysis suggested a potential advantage of switching to B/F/TAF from other regimens, the relative improvement was found to be more pronounced in those who were on EVG-based regimens vs. DTG-based regimens before switch. DTG has previously demonstrated advantages over EVG with respect to high resistance barrier and minimal drug—drug interactions, whereas bictegravir exhibited similar profiles to DTG.[23] Though significantly fewer drug-related adverse events on B/F/TAF versus DTG + F/TAF were observed in treatment-naïve patients,[24] a multicenter, double-blinded clinical trial showed that these regimens had comparable efficacy and safety profiles in virally-suppressed PLWH.[25] Therefore, it is reasonable to expect that switching to B/F/TAF may be more beneficial for virally-suppressed individuals previously on EVG-based regimens compared with those on DTG-based regimens.

Multivariate analysis showed that individuals with pre-existing diabetes might predict improvement in muscle aches/joint pain, and those on psychotropic medications and those with BMI >30 kg/m^2 at baseline had lower odds of achieving improvement in pain/numbness/tingling in hands/feet and body composition/weight gain, respectively, after switching to B/F/TAF. In addition to the effect of baseline clinical characteristics on the changes of PROs, there might be interesting association between the changes of clinical characteristics and the changes of PROs as well. For instance, the prevalence of DM and the use of lipid-lowering agents both increased significantly on week 48. While these clinical changes did not result in greater overall symptom burden, their association with specific symptoms in the long-term needs to be further explored in a larger study population.

Despite the improvement observed after switching to B/F/TAF, most of our participants continued to experience at least one symptom, and several symptoms persisted in a substantial proportion of participants through the 48-week study period. The most prevalent symptoms, namely fatigue/loss of energy, trouble remembering, difficulty sleeping, and changes in body composition/weight gain, were reported by more than 40% of the participants at both baseline and week 48 (Fig. 1). These four symptoms were also the most bothersome as more than 20% of the participants scored ≥2 at both baseline and week 48 (Fig. 2), which were consistent with a previous phase III B/F/TAF switch study where more than 20% of virally-suppressed PLWH felt bothered by these symptoms both before and after regimen switch for 48 weeks.[15]

Considering that B/F/TAF is an effective and well-tolerated guideline-recommended regimen, the above findings reiterate the importance of patient-centered care beyond viral suppression, such as that provided through the multidisciplinary team (MDT) approach,[26] in order to further improve the HRQoL of PLWH. For example, the participants who experienced pain/numbness/tingling in hands/feet or muscle aches/joint pain at week 48 in this study could be at risk of chronic pain and analgesic dependence and might benefit from additional physical therapy if available from an MDT.[27,28] The limited improvements observed in non-physical symptoms in our study also warranted an MDT that addresses biological, behavioral and social concerns of PLWH. A meta-analysis based on 47 studies demonstrated that HIV interventions involving psychologists or psychotherapists had the largest pooled effect sizes on alleviating depression.[29] Community and public health campaigns to increase understanding of HIV treatment and prevention could also reduce HIV stigma and benefit mental health.[30]

With the wide acceptance of the fourth 90 target, PROs have become increasingly important in HIV care and shared treatment decision-making. Multiple groups of researchers have recently employed various instruments to evaluate PROs associated with ART among PLWH in real-life clinical settings.[31—33] However, challenges remain as no gold-standard or consensus set of measures has been established in HIV care.[16] HIV—SI is a widely used PRO instrument to assess HIV-related symptoms. The 20 symptoms included were selected based upon prior reports of symptom prevalence and bother and expert opinion,[18] providing holistic insight into the HIV-related symptom burden among PLWH. Based on our experience, the HIV—SI instrument, with its short list of specific and straightforward questions, was particularly easy to administer as part of routine practice in the setting of a busy outpatient clinic. Most participants were able to complete the questionnaire within 5 min. In addition, the results of HIV—SI were relatively easy to interpret and could be used directly in guiding treatment decisions and directing physicians' focus onto the bothersome symptoms identified. These merits collectively would support the integration of HIV-SI in routine practice to promote patient-centered care. Nonetheless, it should be noted that HIV—SI does not evaluate general aspects of life like HRQoL scales such as the Short Form Health Survey-36. If greater insights into the extent and impact of certain symptoms are desired, symptom-specific instruments including Beck Anxiety Inventory, Beck Depression Inventory, and Pittsburgh Sleep Quality Index could be considered.

This study has a few limitations. Firstly, due to the lack of blinding and a parallel control arm continuing with their previous treatment for 48 weeks, it was difficult to demonstrate that the changes in PROs observed after regimen switch was independently associated with B/F/TAF. Secondly, as PRO data of the small proportion of the participants who discontinued B/F/TAF (6.4%) early were not collected and excluded from the analysis, the benefits of switch might have been overestimated. Thirdly, given that HIV remains a socially complex disease, other factors, such as family life, career life and social discrimination, might have contributed to the improvement or worsening of HIV-related symptoms, which were not investigated in this study. Fourthly, we might not be able to provide scientifically sound explanations for the changes of level of bother for each symptom from the viewpoint of pharmacotoxicology, such as pain/numbness/tingling in hands and feet, headache, muscle aches/joint pain, problem with sex, loss of appetite and trouble remembering, given the fact that multiple factors could have been involved. Moreover, as answers to the questionnaire were entirely subjective, they might have been influenced by participants' states of mind at a specific timepoint. Lastly, generalizability of study findings must be done with caution as the participants included in this study were mostly stable and virally-suppressed male patients with few comorbidities.

In summary, with the high efficacy of modern ART, PROs have become increasingly important to inform therapeutic choices among antiretroviral regimens with otherwise similar virological response. This study demonstrated that over 48 weeks of follow-up after switching to B/F/TAF from predominantly EVG- or DTG-based regimens, the overall symptom burden on PLWH decreased significantly in both prevalence and severity, suggesting potential benefits of switching to B/F/TAF in virally-suppressed PLWH. Nevertheless, the study revealed that HIV-related symptom burden cannot be addressed by optimal ART alone. Additional multidisciplinary interventions and care services are warranted to further improve the long-term QoL of PLWH.

Ethics statement

The study was approved by the National Taiwan University Hospital Research Ethics Committee (NTUH REC No. 20200402RINA). All participants were required to provide written informed consent prior to participating in the study. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

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Author contributions

LYC, HYS, and CCH contributed to the study conception and design. Material preparation and data collection were performed by LYC, HYS, YCC, YSH, WDL, KYL, HYC, YZL, PYW, YCS and WCL. Analysis of the data was performed by LYC, HYS, and CCH. The first draft of the manuscript was written by LYC and CCH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

CCH declares that he has received honoraria for speaking at educational events or consulting from Gilead Sciences and ViiV Healthcare, and research funding from Gilead Sciences, Merck, and ViiV Healthcare by participating in clinical trials. HYS declares that she has received research funding from Gilead Sciences. The remaining authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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