Safety and Efficacy of Switching to BIC/FTC/TAF Plus DOR in HIV-Infected Patients With Multiclass-Resistant Virus

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Background

As a result of the continuous development of antiretrovirals (ARVs) with improved efficacy and tolerability, reduced pill burden, and lower potential for drug-drug interactions (DDIs), people living with HIV (PWH) for multiple decades often underwent numerous regimen changes.[1,2] Resistance to one or more ARVs occurred in some highly treatment-experienced (HTE) PWH due to the utilization of agents and regimens with lower resistance, administration of ARV monotherapy prior to combination antiretroviral therapy (ART) approaches, and/or reduced adherence resulting from poor tolerability or challenging dosing requirements of early agents.[1,3,4] Today, the medical management of HTE PWH often requires the use of complex multitablet regimens to achieve viral suppression, which can lead to increased pill burden and an increased risk for adverse events (AEs) and DDIs, especially in older patients with multiple comorbidities and concomitant medications.[5]

One currently available ARV regimen that may overcome multidrug resistant (MDR) virus and maintain viral suppression in HTE PWH (without the use of a booster) is coformulated rilpivirine/emtricitabine/tenofovir alafenamide (RPV/FTC/TAF) plus dolutegravir (DTG).[2] Following the approval of the integrase inhibitor (INSTI) bictegravir (BIC, available in the coformulated BIC/FTC/TAF tablet) and of the nonnucleoside reverse transcriptase inhibitor (NNRTI) doravirine (DOR), an attractive alternative option for HTE PWH with MDR virus is now available. Both BIC and DOR have high resistance, and a regimen that combines BIC/FTC/TAF and DOR confers low risk for AEs and DDIs.[6,7]

The current study sought to determine whether switching to BIC/FTC/TAF + DOR from RPV/FTC/TAF + DTG was safe and efficacious for HTE PWH with MDR virus. Quality of life (QOL), body mass index (BMI), and pharmacokinetics (PK) of BIC and DOR were also assessed.

Methods

This was a single center, open-label, prospective switch trial that evaluated maintenance of virologic suppression among 20 patients who changed their ARV regimen from RPV/FTC/TAF + DTG to BIC/FTC/TAF + DOR. Enrollment began in March 2020, just prior to the COVID-19 shelter-in-place ordinance in the city where the study was conducted. Study participants received orally administered BIC/FTC/TAF (50/200/25 mg) + DOR (100 mg) as a 2-tablet regimen, given together once a day. Outcomes related to QOL were measured by the Pittsburgh Sleep Quality Index (PSQI) and the Work Productivity and Activity Impairment Questionnaire (WPAI). Participant BMI was assessed at the Screening/Baseline and Week 48/End of Study visits, as were the QOL assessments (PSQI and WPAI). At the Week 4 visit (± 14 days), a subset of 10 study participants were separately consented to undergo a PK evaluation of BIC and DOR. The coprimary endpoints of the study were the percentage of participants with HIV viral loads <50 copies/mL and the percentage of participants with HIV viral loads <200 copies/mL at Week 48/End of Study. Secondary endpoints included descriptive measurements of CD4 count, safety and tolerability, PK parameters, changes in BMI, changes in sleep (PSQI), and changes in productivity (WPAI).

Eligible participants included cisgender men (no cisgender women at the site met eligibility criteria) living with HIV aged 45 years or older with prior ARV resistance who were stable on an ARV regimen of RPV/FTC/TAF + DTG for at least 9 months with at least 1 documented plasma HIV RNA level of ≤50 copies/mL in the previous 6 months. Inclusion criteria allowed for any genotypic or phenotypic resistance except K65R, T69 insertion, INSTI resistance, or resistance to RPV or DOR.

Study Participants

Table 1. Baseline Demographics

Characteristic [a]	Study participants (N=20)
Age, years	65 (46-74)
Sex, n (%)	
Male	20 (100)
Female	0
Gender nonconforming	0
Race, n (%)	
American Indian or Alaska Native	0
Asian	1 (5)
Black or African American	0
Native Hawaiian/other Pacific Islander	0
White	19 (95)
Other	0
Multiple	0
Ethnicity, n (%)	
Hispanic or Latino	1 (5)
Non-Hispanic or Latino	19 (95)
BMI, kg/m^2	24.4 (20-31)
Years since HIV diagnosis	37 (12-42[b])
HIV viral load, copies/mL	<20
Baseline CD4 count, cells/µL	623.5 (193-1273)

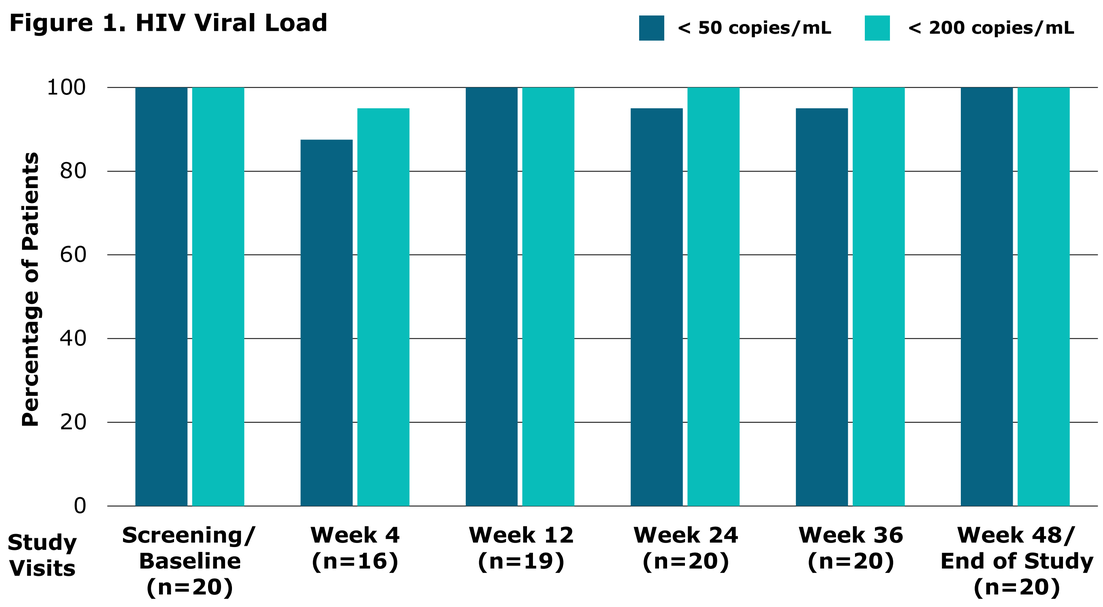
[a] *All data presented as median (range) unless otherwise noted*
[b] *Diagnoses >38 years ago were documented by stored blood samples from prior clinical trials.*

Results

HIV Viral Load and CD4 Count

All study participants reached the Week 48/End of Study visit. At the Week 48/End of Study visit, 100% of participants were virologically suppressed, with viral loads below both 50 and 200 copies/mL. CD4 counts stayed relatively stable, with a median (range) value of 623.5 (193-1273) cells/µL at Screening/Baseline and 589 (257-934) cells/µL at Week 48/End of Study.

Figure 1. HIV Viral Load



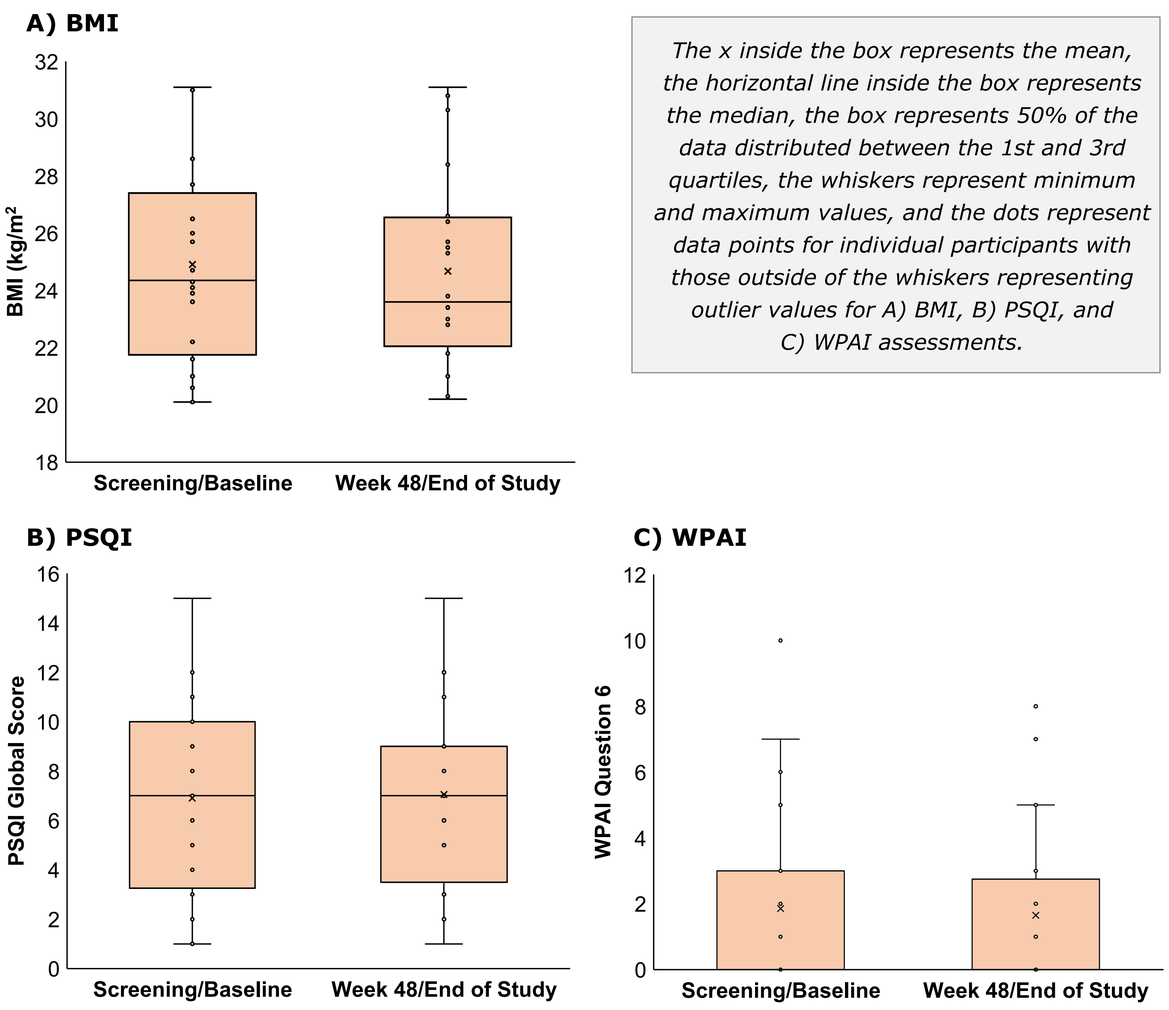
Safety and Tolerability

A total of 16 AEs were reported throughout the study: 14 mild, 1 moderate (new onset diabetes mellitus), and 1 severe (renal cell carcinoma, resected). All AEs were assessed as unlikely to be related to the study drug. Intermittent headache and urinary tract infection were the only AEs reported by more than 1 participant (each was reported by 2 participants).

BMI, PSQI, and WPAI

The median (range) BMI was 24.4 (20-31) kg/m^2 at Screening/Baseline and 23.6 (20-31) kg/m^2 at Week 48/End of Study. The median (range) global score on the PSQI was 7 (1-15) at both the Screening/Baseline and Week 48/End of Study visits. The first 5 questions of the WPAI questionnaire addressed health-related factors affecting work, while the final question asked about health-related impacts on normal daily activities. Five of the 20 participants reported current employment at both the Screening/Baseline and Week 48/End of Study visits. Of the 5 employed participants, 2 reported missing work due to health problems. The median (range) response to Question 6 ("How much did health problems affect regular daily activities over the past 7 days?") was 0 (0-10) and 0 (0-8) at Screening/Baseline and Week 48/End of Study, respectively.

Figure 2. Change in BMI, PSQI, and WPAI



The x inside the box represents the mean, the horizontal line inside the box represents the median, the box represents 50% of the data distributed between the 1st and 3rd quartiles, the whiskers represent minimum and maximum values, and the dots represent data points for individual participants with those outside of the whiskers representing outlier values for A) BMI, B) PSQI, and C) WPAI assessments.

Pharmacokinetic Parameters

The PK parameters for BIC and DOR were consistent with historical data, suggesting that no clinically significant interactions occurred between BIC and DOR.[6,7]

Table 2. Pharmacokinetic Parameters

PK parameter, mean (% CV)	Plasma BIC (n=10)	Plasma DOR (n=10)
C_{max}, µg/mL	8.55 (33)	1.2 (34)[a]
AUC_{0-24}, µg·h/mL	138 (32.2)	17.7 (39)[a]
T_{max} , h[b]	1.5 (0.5-4)	2.0 (1-24)
$T_{1/2}$, h	18.3 (27.5)	15.4 (38.4)[a]

[a] *Reported as geometric mean (geometric % CV).*
[b] *Reported as median (range).*

Conclusion

This study found that switching HTE PWH with MDR virus to BIC/FTC/TAF + DOR maintained viral suppression and was well tolerated. Of note, viremia occurred in 19% (3/16) of participants who had their blood drawn at the Week 4 study visit. The timing of this visit coincided with initial local COVID-19 lockdown measures; these circumstances may have affected patient adherence or access to ART. BIC/FTC/TAF + DOR was well tolerated and did not lead to significant changes in this study population in BMI, sleep, or work productivity. Results from the PK analysis indicated that no clinically significant interactions occurred between BIC and DOR, with PK data for both agents similar to values previously published in the US Food and Drug Administration labels for BIC/FTC/TAF and DOR.[6,7]

Treatment options for HIV infection have improved significantly over the last 35 years.[8,9] Early ARV regimens had high pill burdens, challenging dosing schedules, treatment-limiting toxicities, and suboptimal efficacy that, when coupled with sequential monotherapy and incomplete virologic suppression, led to the development of multiple resistance mutations for many PWH.[10] Furthermore, most PWH who have undergone treatment for HIV for 30 or more years are now older adults with compounded age-related diseases, impairments, and concomitant medications that may also limit ARV options.[2,11]

The management of HTE PWH with MDR virus includes not only preventing and avoiding virologic failure but also optimizing ART to improve QOL, including tolerability, avoidance of DDIs, and minimization of non–HIV-related complications.[2,12] This study found that switching HTE PWH with MDR virus to BIC/FTC/TAF + DOR had a favorable safety profile, was efficacious, and provided a treatment option with few DDIs, a low pill burden, and no impact on BMI or QOL.

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