Bictegravir/emtricitabine/tenofovir alafenamide plus doravirine in highly treatment-experienced men with multidrug-resistant HIV

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Objective: To evaluate the safety and efficacy of switching highly treatment-experienced people with HIV (HTE PWH) from rilpivirine/emtricitabine/tenofovir alafenamide (RPV/FTC/TAF) plus dolutegravir (DTG) to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) plus doravirine (DOR). A pharmacokinetic (PK) analysis was conducted to assess the potential interaction between BIC and DOR.

Design and methods: This open-label switch trial enrolled HTE PWH from a primary care private practice in the United States. Eligible participants were male, aged ≥45 years, with documented viral resistance to protease inhibitors, nucleoside reverse transcriptase inhibitors, and/or nonnucleoside reverse transcriptase inhibitors but no resistance to RPV or DOR, and no K65R or T69 insertion mutations. Virologic suppression (≤50 copies/ml) while on RPV/FTC/TAF plus DTG for ≥6 months was required prior to enrollment. The primary endpoint of the study was virologic suppression (<50 and <200 copies/ml) at 48 weeks. Secondary endpoints included safety, tolerability, changes in body mass index (BMI), and identification of PK parameters of BIC and DOR.

Results: Twenty males [median age: 65 years (range, 46–74), median time since HIV diagnosis: 37 years (range, 12–42)] completed the study. BIC/FTC/TAF plus DOR was well tolerated with no serious or treatment-related adverse events reported and no appreciable changes in BMI from baseline to Week 48. At Week 48, 100% of participants had <50 viral copies/ml. PK parameters for BIC and DOR ($n = 10$) were consistent with published data.

Conclusions: Switching from RPV/FTC/TAF plus DTG to BIC/FTC/TAF plus DOR was well tolerated and efficacious in HTE men aged ≥45 years with HIV.

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AIDS 2023, **37**:1057–1064

Keywords: antiretroviral agents, Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide), HIV, multidrug-resistant virus, optimizing HIV treatment, Pifeltro (doravirine)

Introduction

Over the past 35 years, improvements in antiretroviral therapy (ART) have transformed HIV infection from a largely fatal disease into a manageable chronic condition [1]. There are now more than 40 medicines approved by the US Food and Drug Administration to treat HIV infection [2,3]. For those who have been living with HIV

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Received: 30 September 2022; revised: 6 February 2023; accepted: 8 February 2023.

DOI:10.1097/QAD.0000000000003513

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for multiple decades, the evolving treatment landscape prompted numerous regimen changes as new antiretrovirals with improved efficacy and tolerability, reduced pill burden, and lower potential for drug-drug interactions (DDIs) became available [4,5]. The development of antiretroviral resistance occurred in some highly treatment-experienced (HTE) people with HIV (PWH) due to the utilization of agents and regimens with lower resistance barriers, administration of antiretroviral monotherapy prior to combination ART approaches, and/or reduced adherence resulting from the poor tolerability or challenging dosing requirements of early agents [6–8]. For HTE PWH with multidrug-resistant (MDR) virus, effective treatment options are limited and it can be difficult to achieve or maintain virologic suppression.

As such, the medical management of HTE PWH can be challenging for providers and often requires the use of complex multitablet regimens to achieve virologic suppression, taking into consideration individual treatment and resistance profiles, antiretroviral tolerability, past adherence, and potential for DDIs [5,6,9]. Current guidelines recommend that treatment-experienced PWH with confirmed virologic failure receive at least two fully active agents, as long as at least one of the agents has a high resistance barrier; otherwise, three fully active drugs are recommended to achieve an optimal virologic response [5]. Multitablet and/or coformulated combinations may be necessary to ensure that HTE PWH receive two or three fully active agents. In addition, agents with only partial activity may be maintained in a regimen to provide clinical benefit despite resistance [10]. These management steps can potentially lead to an increased pill burden and an increased risk for adverse events (AEs) and DDIs among HTE PWH, especially in older individuals with multiple comorbidities and concomitant medications [5,11].

Newer ART options have made it possible to simplify regimens and improve quality of life (QOL), even among those harboring MDR HIV [6]. One currently available antiretroviral regimen able to overcome MDR virus and maintain virologic suppression in HTE PWH (without the use of a booster) is coformulated rilpivirine/emtricitabine/tenofovir alafenamide (RPV/FTC/TAF) plus dolutegravir (DTG) [5]. With the approvals of the integrase strand transfer inhibitor (INSTI) bictegravir (BIC) (available in the combination product BIC/FTC/TAF) and the nonnucleoside reverse transcriptase inhibitor (NNRTI) doravirine (DOR), an alternative option for HTE PWH with MDR virus is also available. Although not simplifying pill count, advantages of BIC/FTC/TAF plus DOR over RPV/FTC/TAF plus DTG exist. Both BIC and DOR have higher resistance barriers than earlier generations of INSTIs and NNRTIs, and a regimen that combines BIC/FTC/TAF and DOR confers low risk for AEs and DDIs [12,13]. Furthermore, a BIC/FTC/TAF plus DOR regimen does not have food restrictions, unlike RPV/FTC/TAF plus DTG, which must be taken with a meal [12–14]. Also, DOR does not interact with agents that increase gastric pH, such as proton pump inhibitors (PPIs), while RPV concentrations are decreased in the presence of these agents [13,15].

Optimizing therapy and improving QOL in HTE PWH can be difficult for clinicians and places a heavy burden on healthcare resources, as limited antiretroviral regimens have been evaluated in this population [5,16]. The current study sought to determine whether switching to BIC/FTC/TAF plus DOR from RPV/FTC/TAF plus DTG was safe and efficacious for HTE PWH with MDR virus. Sleep and productivity QOL measures, body mass index (BMI), and pharmacokinetics (PK) of BIC and DOR were also assessed. To date, no data on the interaction between BIC and DOR have been published.

Methods

Study design

This was a single center, open-label, observational switch trial that evaluated maintenance of virologic suppression among 20 HTE PWH with MDR virus, including a nested PK arm of 10 patients, who changed their antiretroviral regimen from RPV/FTC/TAF plus DTG to BIC/FTC/TAF plus DOR. Of note, with evidence of multiclass antiretroviral resistance, switching these patients to a single-tablet, coformulated regimen was deemed insufficient by their established primary HIV healthcare provider. During the study period (commencing in early 2020 and finishing in early 2021, thus coinciding with the onset of the COVID-19 pandemic), QOL outcomes were measured by the Pittsburgh Sleep Quality Index (PSQI) and the Work Productivity and Activity Impairment Questionnaire (WPAI). In addition, changes in BMI were measured over the 48-week study period. Study participants received once-daily, orally administered BIC/FTC/TAF (50/200/25 mg) plus DOR (100 mg) as a two-tablet regimen. Eligible participants included PWH men (no cis-gender women at the primary care medical center would have met study eligibility criteria) aged 45 years or older. Participants were stable on an antiretroviral regimen of RPV/FTC/TAF plus DTG for at least 12 months with at least one documented plasma HIV RNA level of $\leq$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. All participants provided written informed consent prior to the conduct of any study procedures. The study was approved by the Advarra institutional review board and adhered to the International Council for Harmonisation good clinical practice guidelines, as well as to the provisions of the Declaration of Helsinki in its revised edition (Fortaleza, Brazil, 2013).

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The six study visits included Screening/Baseline and Weeks 4, 12, 24, 36, and 48/End of Study. All visits included a physical exam, complete blood count, serum chemistry, urinalysis, BMI assessment, HIV viral load testing, and review of AEs. Participant $CD4^+$ cell count 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 underwent a PK evaluation of BIC and DOR.

The co-primary endpoints of the study consisted of the percentage of participants with viral loads <50 copies/ml and the percentage of participants with HIV viral loads <200 copies/ml at Week 48/End of Study. Two viral load thresholds were measured to account for differences in international clinical guidelines as well as for transient episodes of viremia (blips), which have not been found to increase the risk of virologic and immunologic failure [5,17–20]. Secondary endpoints included descriptive measurements of $CD4^+$ cell count, safety and tolerability, PK parameters, changes in BMI, changes in sleep (PSQI), and changes in productivity (WPAI).

Assessments

A PK assessment of BIC and DOR was undertaken as no published data existed on the interaction between the agents. To assess PK parameters of BIC and DOR, blood was collected from a subset of 10 study participants at the Week 4 visit (± 14 days), with sampling occurring at the following time points: predose (−0.5 h) and 0.5, 1, 2, 4, 6, 8, 12, and 24 h after dosing. Validated liquid chromatography/tandem mass spectrometry methods were used to quantify plasma BIC and DOR concentrations. Individual participant plasma concentration-time data of BIC and DOR were analyzed using a noncompartmental model (Watson LIMS version 7.5) with calculated PK parameters including area under the curve from time 0 to 12 h, 0 to 24 h, and 0 to infinity (AUC_{0-12}, AUC_{0-24}, and AUC_{0-inf}, respectively), as well as maximum concentration (C_{max}), time to maximum concentration (T_{max}), and elimination half-life ($T_{1/2}$).

AEs were continuously monitored from study enrollment (date of signed informed consent) up to 30 days after the last dose of the study drug. AEs were graded using Common Terminology Criteria for Adverse Events version 5.0 and assessed for relationship to study drug. Tolerability was determined by the number of AEs and serious AEs (SAEs) that occurred during the study.

The PSQI and WPAI assessments were included in the study to evaluate potential impacts on QOL factors among this unique, virologically suppressed patient population undergoing a switch in ART. The PSQI is an instrument used to measure sleep quality and patterns [21]. The survey contains 19 self-rated questions and five questions rated by a bed partner or roommate (if applicable). Only the self-rated questions were included in the scoring for this study. The PSQI consists of seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. The seven component scores are added to calculate the global PSQI score, with a score of 5 or greater indicating poor sleep quality.

The WPAI questionnaire measures health-related work productivity via patient-reported responses to questions surrounding work-related absenteeism and general daily activity impairment [22]. The survey contains six questions: the first asks about current employment status, questions 2 through 5 are targeted toward employed individuals, and question 6 is focused on regular daily activities outside of work.

Statistical analyses

Analyses for efficacy, safety, PK, BMI, and QOL measurements were descriptive and did not include formal statistical tests. The changes in values from Screening/Baseline to Week 48/End of Study are presented for BMI, PSQI, and WPAI.

Results

Participant demographics at baseline are listed in Table 1. The majority of participants were white, non-Hispanic males. Notably, all participants in the study had been living with HIV for a decade or more, with a mean time since HIV diagnosis of 34.8 years. Concomitant

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)
Body mass index, kg/m^2	24.4 (20–31)
Years since HIV diagnosis	37 (12–42[b])
HIV viral load, copies/ml	<20
$CD4^+$ cell 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.

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Table 2. Number of agents with reduced activity per antiretroviral class[a].

Antiretroviral class	Median (range) number of agents with reduced activity ($N = 16$)[b]
NRTI	4 (0–7)
NNRTI	1 (0–3)
PI	4 (1–9)

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
[a]Results are based on a single resistance test for each participant and may not accurately represent the extent of archived resistance mutations.
[b]Resistance profiles were available for 16/20 study participants.

medication information was available for those who underwent the PK assessment; among those 10 participants, a median of 6 (range, 0–18) medications were taken in addition to BIC/FTC/TAF plus DOR.

Resistance data were reviewed by the principal investigator for enrollment purposes, and all participants met eligibility criteria with resistance to two or three classes of antiretroviral drugs. All study participants had been previously prescribed RPV/FTC/TAF plus DTG for reasons of regimen simplification and multiclass resistance per their HIV healthcare provider. Participant resistance profiles are summarized in Table 2 as median number of agents with reduced activity per antiviral class, according to available records from 16 of 20 participants. Importantly, these values likely underestimate the full resistance profiles of study participants, as single-time-point resistance tests provide information about a snapshot in time and may not capture all archived resistance mutations [23].

There were a total of eight missed visits and/or assessments throughout the study. Starting at Week 4, virtual visits were offered to study participants in response to the COVID-19 pandemic. A total of 44 visits were conducted virtually, corresponding to 31% of visits overall (44/140).

HIV viral load and CD4$^+$ cell 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 <50 copies/ml (Fig. 1). At Week 4, COVID-19 lockdown measures were imposed resulting in four missed blood draws. Three of the 16 participants who had their blood drawn at Week 4 had viral load values >50 copies/ml (100 copies/ml, 190 copies/ml, and 596 copies/ml), and one participant had a viral load >200 copies/ml (596 copies/ml). One participant had a viral load >50 copies/ml at both Week 24 (143 copies/ml) and Week 36 (113 copies/ml). CD4$^+$ cell count stayed relatively stable, with a median (range) value of 623.5 cells/μl (193–1273) at Screening/Baseline and 589 cells/μl (257–934) at Week 48/End of Study.

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 removal). All AEs were assessed as unlikely to be related to the study drug, and none were considered an SAE. Intermittent headache was the only AE reported by more than one participant (reported by two participants).

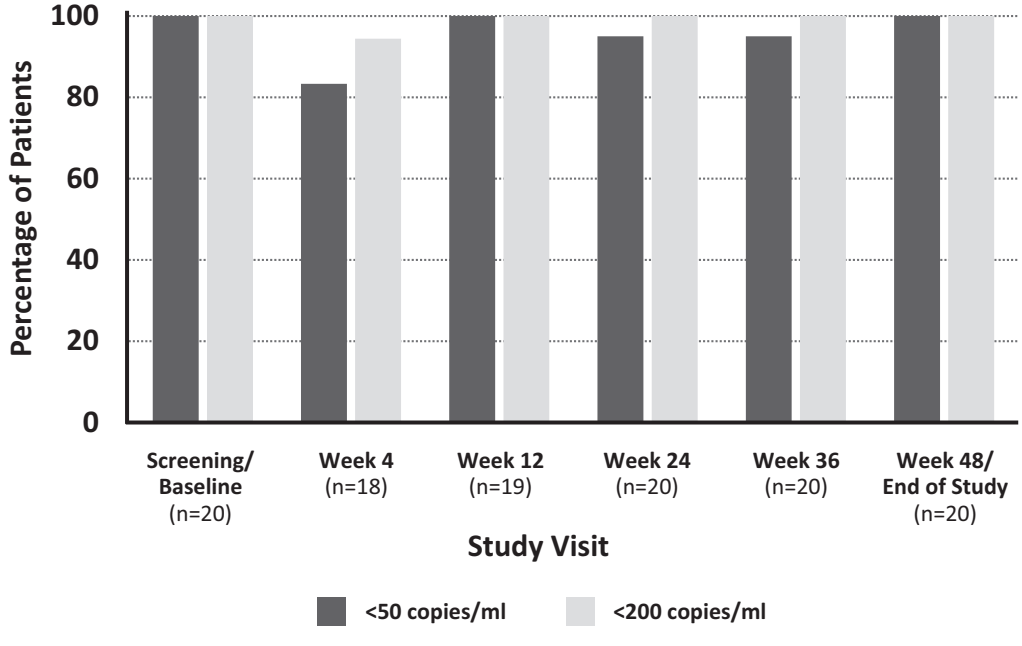

Fig. 1. HIV viral load.

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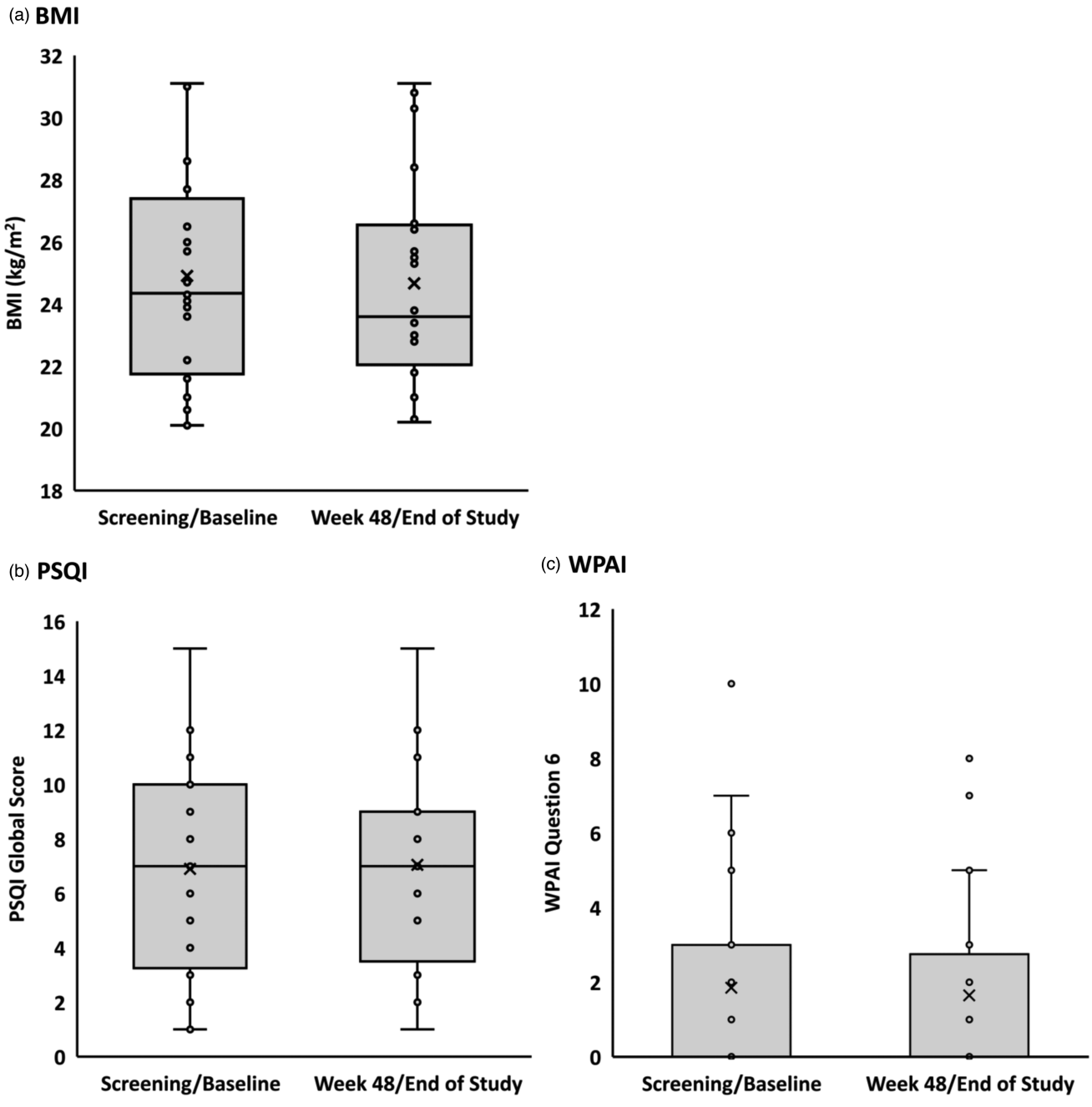

Fig. 2. Change in BMI, PSQI, and WPAI. The × inside the box represents the mean, the horizontal line inside the box represents the median, the box represents 50% of the data distributed between the 1st and 3rd quartiles, the whiskers represent variability outside of the upper and lower quartiles, and 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. BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; WPAI, Work Productivity and Activity Impairment Questionnaire.

Body mass index

The mean (standard deviation) change in BMI from baseline to Week 48 was −0.2 (0.85) kg/m^2. 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 (Fig. 2a).

Pittsburgh Sleep Quality Index

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 global score decreased between these time points in eight study participants, increased in eight, and stayed the same in four (Fig. 2b).

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Work Productivity and Activity Impairment questionnaire

Questions 2–5 of the WPAI questionnaire addressed health-related factors affecting work, whereas 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 five employed participants, two reported missing work due to health problems. Median (range) hours missed due to health problems remained unchanged and the maximum value decreased between Screening/Baseline and Week 48/End of Study visits from 0 (0–10) to 0 (0–0) among the five employed participants. The median (range) assessment of health problems affecting productivity while working also remained unchanged while the maximum value decreased between Screening/Baseline and Week 48/End of Study visits from 0 (0–5) to 0 (0–2) in the five participants who worked.

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 (Fig. 2c). Participants were asked to circle a number between 0 and 10, with 0 indicating 'Health problems had no effect on my daily activities' and 10 indicating 'Health problems completely prevented me from doing my daily activities.'

Pharmacokinetics

The PK parameters for BIC and DOR were consistent with historical data, suggesting that no clinically significant interactions occurred between BIC and DOR (Table 3) [12,13]. Published PK data from the DOR product label report geometric mean [% coefficient of variation (CV)] values for C_{max} and AUC_{0-24} of 0.962 (19) μg/ml and 16.1 (29) μg·h/ml, respectively, as well as T_{max} and $T_{1/2}$ values of 2 h and 15 h, respectively [13]. In the BIC/FTC/TAF product label, the T_{max} for BIC is reported as 2.0–4.0 h and the median $T_{1/2}$ value as 17.3 h [12]. Multiple-dose PK parameters of BIC, per population PK analysis, indicate a mean (% CV) C_{max} and area under the curve from time zero to the end of the dosing interval (AUC_{tau}) of 6.15 (22.9) μg/ml and 102 (26.9) μg·h/ml, respectively [12].

Table 3. PK parameters for BIC (as a component of BIC/FTC/TAF) and DOR ($n = 10$).

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	1.5 (0.5–4)	2.0 (1–24)
$T_{1/2}$, h	18.3 (27.5)	15.4 (38.4)[a]

AUC, area under the curve; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CV, coefficient of variation; DOR, doravirine; PK, pharmacokinetic.
[a]Reported as geometric mean (geometric % CV).
[b]Reported as median (range).

Discussion

Treatment options for HIV infection have improved significantly over the last 35 years [2,3]. Early antiretroviral regimens had high pill burdens, challenging dosing schedules, treatment-limiting toxicities, and suboptimal efficacy [24]. Sequential monotherapy and incomplete virologic suppression resulted in the emergence of multiple resistance mutations for many PWH, with long-term treatment consequences due to cross-resistance to other agents in the same antiretroviral class [5,24]. Additionally, the majority of PWH who have undergone treatment for HIV for 30 or more years are now older adults with compounded age-related diseases, impairments, possible hepatitis B virus (HBV) coinfection, and concomitant medications that may collectively limit antiretroviral options [5,16,25].

This study found that switching HTE PWH with MDR virus from RPV/FTC/TAF plus DTG to BIC/FTC/TAF plus DOR maintained virologic 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 adherence or access to ART. Results from the PK analysis indicated that no clinically significant interactions occurred between BIC and DOR, with PK parameters for both agents similar to previously published values. Switching from RPV/FTC/TAF plus DTG to BIC/FTC/TAF plus DOR did not lead to substantial changes in sleep or work productivity in this HTE patient population, and there was also no appreciable change in BMI. While weight gain has been reported in treatment-naive patients initiating antiretroviral therapy with an INSTI, it would not be expected in a population switching from one INSTI-based regimen to another [26,27].

Our study did have limitations. Participants were mostly white and all male, and the total study population was small ($N = 20$). Also, we did not have viral clade information available for all participants. As such, our study findings may not be generalizable to all HTE PWH with MDR virus.

Compared with non-HTE and treatment-naive PWH, HTE PWH are older and have a higher daily pill burden [16]. In addition to extensive antiretroviral treatment histories and high numbers of resistance mutations, participants in this study had a median age of 65 years and most had multiple health conditions and concomitant medications. These factors led their HIV healthcare provider to consider simplified regimens such as DTG/RPV or BIC/FTC/TAF as too risky and unlikely to result in continued virologic suppression. To date, no studies have demonstrated treatment success with DTG/RPV or BIC/FTC/TAF among MDR PWH similar in age and complexity to those represented in this study.

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In general, selecting an efficacious and well tolerated antiretroviral regimen for older PWH can be challenging. Age-related decreases in renal and liver function influence choice of antiretroviral medications, and potential interactions between antiretroviral medications and drugs used to manage comorbidities must be considered [5]. A study of PWH in France found that 62% of older patients whose HIV was diagnosed before 2000 had one or more comorbidities, and 71% were receiving at least 1 co-medication [28]. In a cross-sectional study in PWH aged ≥65 years, the prevalence of comorbidities and polypharmacy increased with both older age and longer duration of HIV infection; those infected for 10 or more years had a higher probability of comorbidities compared with HIV-uninfected controls, and independent predictors for the presence of comorbidities included age ≥75 years, male gender, and HIV duration above 20 years [29]. There is also evidence that PWH ≥50 years old are more likely to be prescribed an antiretroviral/non-antiretroviral combination that is either explicitly contraindicated or known to have moderate to high evidence of interaction relative to PWH <50 years [30]. Accordingly, an antiretroviral regimen with a low potential for DDIs may provide significant advantages in aging PWH. As BIC/FTC/TAF plus DOR does not interact with PPIs or H2 blockers, it could be a beneficial regimen in older populations of HTE PWH with MDR virus.

Many providers proactively switch their aging patients away from older nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs). This practice preemptively reduces the risk for certain antiretroviral-related DDIs and AEs involving renal, liver, cardiovascular, central nervous system, metabolic, and bone health [5]. Previous studies have established an association between some PI-based regimens and increased risk for cardiovascular events [31–33]. Additionally, expert guidance now recommends switching older PWH with high risk for fragility fractures off of tenofovir disoproxil fumarate (TDF) and/or boosted PIs due to the association of these agents with decreases in bone mineral density relative to regimens containing other NRTIs and INSTIs [5,34,35]. There is a continued need for establishing the safety and efficacy of regimens that do not contain a PI, booster, or TDF in aging PWH.

Clinicians often have a wide variety of antiretroviral combinations to consider for maximizing long-term treatment success in HTE PWH. The management of HTE PWH harboring MDR virus includes not only avoiding virologic failure, preserving immunologic function, and minimizing the development of further resistance but also optimizing ART to improve QOL, including tolerability, avoidance of DDIs, and minimization of non-HIV-related complications [5,30]. Long-term treatment success in this patient population includes good health-related QOL, a goal that some in the field have called 'the 4th 90', referring to the previous '90–90–90' targets developed by the Joint United Nations Programme on HIV/AIDS (UNAIDS) to improve HIV diagnosis and treatment worldwide [36,37]. Updated '95–95–95' UNAIDS targets now aim for 95% of those living with HIV worldwide to know their status, 95% of those who know their status to be on treatment, and 95% of those on treatment to be virologically suppressed by 2025 [38]. Results from a recent survey found that PWH ranked the reduction of viral transmissibility and emotional well being as the most important factors to achieving good long-term QOL [39]. HTE PWH with MDR virus face unique challenges that must be addressed by informed providers to ensure access to both HIV-related and non-HIV clinical services, in addition to any needed social support, to optimize treatment outcomes and patient QOL [36].

Conclusion

This study found that switching older HTE PWH with MDR virus from a stable regimen of RPV/FTC/TAF plus DTG to BIC/FTC/TAF plus DOR was safe and efficacious, providing a treatment option for this patient population that is compatible with PPIs and H2 blockers, is active against HBV coinfection, has a low pill burden, is well tolerated, and can be taken without food restrictions. Additionally, participants in this study showed no evidence of concerning effects on BMI or QOL measures assessed.

Acknowledgements

We would like to thank everyone who contributed to the success of the study: all study participants and their families, as well as the staff at Quest Clinical Research. Medical writing assistance was provided by Sharon Morjig, PharmD, in collaboration with R&R Healthcare Communications.

Authors' contributions: F.L.S. and J.P.L. critically reviewed the manuscript. All coauthors contributed to the interpretation of study findings and provided approval of the final manuscript.

Funding statement: This investigator-initiated study was authored by F.L.S. with funding from Gilead Sciences provided to Quest Clinical Research.

Conflicts of interest

F.L.S. is a current employee of Gilead Sciences and owns stock or stock options in the company. Prior to full-time employment. F.L.S. served as a consultant and researcher for Gilead Sciences. F.L.S. has sat on the Community Advisory Board of Directors for the San Francisco AIDS Foundation since 2015. All other study authors reported no conflicts of interest.

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