J Antimicrob Chemother 2023; **78**: 161–168
https://doi.org/10.1093/jac/dkac369 Advance Access publication 2 November 2022

Journal of Antimicrobial Chemotherapy

Bioavailability of dissolved and crushed single tablets of bictegravir, emtricitabine, tenofovir alafenamide in healthy adults: the SOLUBIC randomized crossover study

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Received 15 July 2022; accepted 10 October 2022

Background: Crushing or dissolving bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) tablets is not recommended because there are no data supporting this practice.

Methods: A crossover, randomized trial in healthy adults (NCT04244448) investigated the bioavailability of two off-label uses of BIC/TAF/FTC (50/200/25 mg), dissolved in water or crushed in apple compote, compared with the solid tablet. Pharmacokinetic (PK) parameters were estimated from sequential intensive plasma antiretroviral concentrations over a 72 h period post dose. Bioequivalence was met if the 90% CIs of the geometric least-squares means ratios comparing BIC/TAF/FTC exposures (AUC and C_{max}) from the experimental phases were within 80%–125% of the reference.

Results: Eighteen subjects participated in each of the three phases. Dissolved tablet C_{max} geometric mean ratio (90% CI) for BIC/TAF/FTC was 105% (93–119)/97% (87–108)/96% (74–124), respectively. Dissolved tablet AUC geometric mean ratio (90% CI) for BIC/TAF/FTC was 111% (100–122)/100% (94 to 105)/99% (81 to 120), respectively. Crushed tablet C_{max} geometric mean ratio (90%) CI for BIC/TAF/FTC was 110% (97 to 124)/70% (63–78)/66% (51–85), respectively. Crushed tablet AUC geometric mean ratio (90%) CI for BIC/TAF/FTC was 107% (96–118)/86% (82–91)/84% (69–103), respectively.

Conclusions: Crushing BIC/TAF/FTC tablets may lead to suboptimal emtricitabine and tenofovir alafenamide drug exposures. Dissolving BIC/TAF/FTC in water may be acceptable if the tablet cannot be swallowed whole.

Introduction

Development of single-tablet regimens (STRs) has considerably reduced antiretroviral pill burden.[1] Currently recommended antiretroviral combinations are almost exclusively dosed once daily with the majority available as an STR.[2,3] Some people living with HIV (PLWH) may be reluctant to take medications in standard oral dosage forms because of swallowing difficulties. For example, Kabeya *et al.*[4] found that 21 mm was the maximum threshold size of tablets and capsules; patients feel that larger tablets and capsules are too large to ingest. This can lead to reduced acceptability and adherence to treatment, because adherence is strongly conditioned by the perceived ease of swallowing, especially in the growing older population of PLWH.[5,6] In addition, oral ART administration will be challenging for any PLWH admitted to the ICU[7] and many hospitalized patients.

While the availability of long-acting injectable forms of antiretrovirals is emerging today, with more close to approval, developing alternatives to swallowing a whole tablet remains relevant to meet PLWH needs. In the absence of manufacturer recommendations, caregivers sometimes crush tablets to facilitate swallowing. However, disruption of the solid oral dosage form by

crushing or breaking tablets prior to ingestion may alter their pharmacokinetics.[7] Off-label alterations of the original formulation could modify absorption and metabolism.[7] Importantly, these alterations can compromise effectiveness (and potentially lead to virological failure and/or resistance) or toxicity.

Bictegravir/tenofovir alafenamide/emtricitabine (Biktarvy®, BIC/TAF/FTC) is currently one of the most frequently prescribed STRs amongst PLWH. Although it is a small tablet (15×8 mm), no separate, injectable or drinkable forms exist for it. The current recommendation from the EACS Guidelines[3] states: 'Tablets should be swallowed whole and should not be chewed, crushed or split'.[3] The objective of the SOLUBIC trial was to explore the bioavailability of dissolved or crushed BIC/TAF/FTC tablets compared with the whole tablet among healthy adult volunteers.

Patients and methods

Study design

We conducted a Phase I, open-label, single-dose, three-period crossover, randomized controlled trial in healthy adult volunteers. The study took place at Caen University Hospital's clinical research center (CRC) in France. BIC/TAF/FTC (50/200/25 mg) was administered in random sequences with directly observed therapy: crushed in apple compote (C phase), dissolved in water (D phase) and as a whole tablet (S phase) separated by a washout period of 14 to 28 days each. Participants were randomized equally to one of the following treatment sequences: C-D-S, C-S-D, D-C-S, D-S-C, S-C-D, S-D-C. All treatment phases were administered early in the morning following overnight fasting of 8 h.

Interventions

Phase S: a tablet was dispensed in a labelled, transparent packet by the study staff. The entire tablet was administered orally with 360 mL of water to the participant. Phase D: the tablet was extemporaneously dissolved in a plastic bottle containing 240 mL of sterile room temperature drinking water by the study pharmacist using a magnetic mixer (Video S1, available as Supplementary data at *JAC* Online). Typically, complete tablet dissolution took 6 to 7 min. The dissolved tablet was then administered orally to the participant. Once administered, the content of the bottle was rinsed with 120 mL of sterile drinking water and administered to the participant. Phase C: the tablet was extemporaneously crushed by the study pharmacist using a mortar and pestle (Video S2). The powder obtained was poured into commercially available apple compote and was administered orally to the participant. Once administered, the container of the compote was rinsed with 360 mL of water and its contents were administered to the participant.

Study participants

Subjects eligible for inclusion in the study were adult volunteers aged 18 to 55 years, with a BMI of 18–30 kg/m^2, no previous intolerance to the study drugs, and were able and willing to sign the informed consent form before the preliminary evaluations. Participants were examined by study investigators (J.-J.P., A.F., S.D.), which included physical examination, clinical laboratory tests (no evidence of HIV or active hepatitis) and a normal ECG. Participants had to be non-smokers and non-consumers of nicotine-containing products for 90 days before taking the first treatment in the study.

The primary exclusion criteria were creatinine clearance below 90 mL/min, pregnancy or breastfeeding, not using adequate contraception when appropriate, any treatment during the 2 weeks before the first administration of BIC/TAF/FTC that could interfere with the study medications, any relevant medical history (including drug, alcohol or solvent abuse) or current illnesses that were likely to interfere with the absorption, distribution, metabolism or excretion of the study drugs, liver abnormalities ≥1.5 times the upper normal value, serum albumin <35 g/L, serum total protein <65 g/L, QTc <450 ms, or participation in a study with a medication in the 60 days before the first administration of BIC/TAF/FTC.

Sample collection

For each of the three phases, participants were confined at the CRC during the first 24 h and then returned three times over next 48 h to carry out the intensive pharmacokinetic study. Venous blood samples were collected once before dosing (0 h) and at prespecified times (0.5, 1, 1.5, 2, 2.5, 3, 4, 8, 12, 24, 36, 48 and 72 h) after administration of each phase of the study intervention. The samples were centrifuged at 1300 g for 10 min at 4°C to separate the plasma. The plasma samples were stored at −20°C until analysis.

Pharmacokinetic analysis

The primary endpoints of the study were C_{max} and AUC, used to assess the bioequivalence of each of the three active drugs contained in a tablet of BIC/TAF/FTC when administered crushed and suspended in apple compote or dissolved in water, as compared with the whole tablet.

Plasma concentrations of BIC/TAF/FTC were quantified using an internally and externally validated LC-MS method (QTRAP 5500, SCIEX, Les Ulis, France) at Orléans Regional Hospital (France). The limit of quantification for bictegravir, emtricitabine and tenofovir alafenamide was 0.04–4, 0.01–1 and 0.002–0.2 mg/L, respectively. The values below the lower limit of quantification were removed from the pharmacokinetic analysis.

The pharmacokinetic parameters were determined for each subject through a non-compartmental analysis using Phoenix WinNonlin 7.0 (Pharsight Corporation, Certara, NJ, USA). Key pharmacokinetic parameters that were derived included peak plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) and elimination half-life ($t_{½}$).

Safety and tolerability

Secondary endpoints of the study were to evaluate safety and tolerability of the three modalities of BIC/TAF/FTC administration. Safety and tolerability was assessed for all randomized participants who received at least one dose of the study drug. Clinical and biological adverse events at all grades [Common Terminology Criteria for Adverse Events (CTCAE) scale, version 5.0] were systematically collected from consent form signature to 1 month after the last administration of the study drug. We also measured the acceptability (taste, ease of taking) of the three phases after each administration by using the mean of visual analogue scales (ranging from 0 to 10). Participants' preferred phases were classified after the third intake of the study drug.

Statistical analyses

The sample size was not computed based on a statistical hypothesis. We empirically considered including 18 volunteers (9 men and 9 women) to account for potential withdrawals and analyse the data of at least 15 participants. The two primary endpoints of the study were C_{max} and AUC to assess the bioequivalence of each of the three active drugs contained in a tablet of BIC/TAF/FTC when administered crushed and suspended in apple compote or dissolved in water, as compared with a whole tablet.

Estimates of pharmacokinetic exposure parameters are presented as geometric mean [% coefficient of variation (CV)]. An average bioequivalence analysis using Phoenix WinNonlin 7.0 (Pharsight Corporation, Certara, NJ, USA) was performed on the ln-transformed C_{max}, AUC_{0-last} and $AUC_{0-\infty}$ values. Sequence, period and formulation were considered

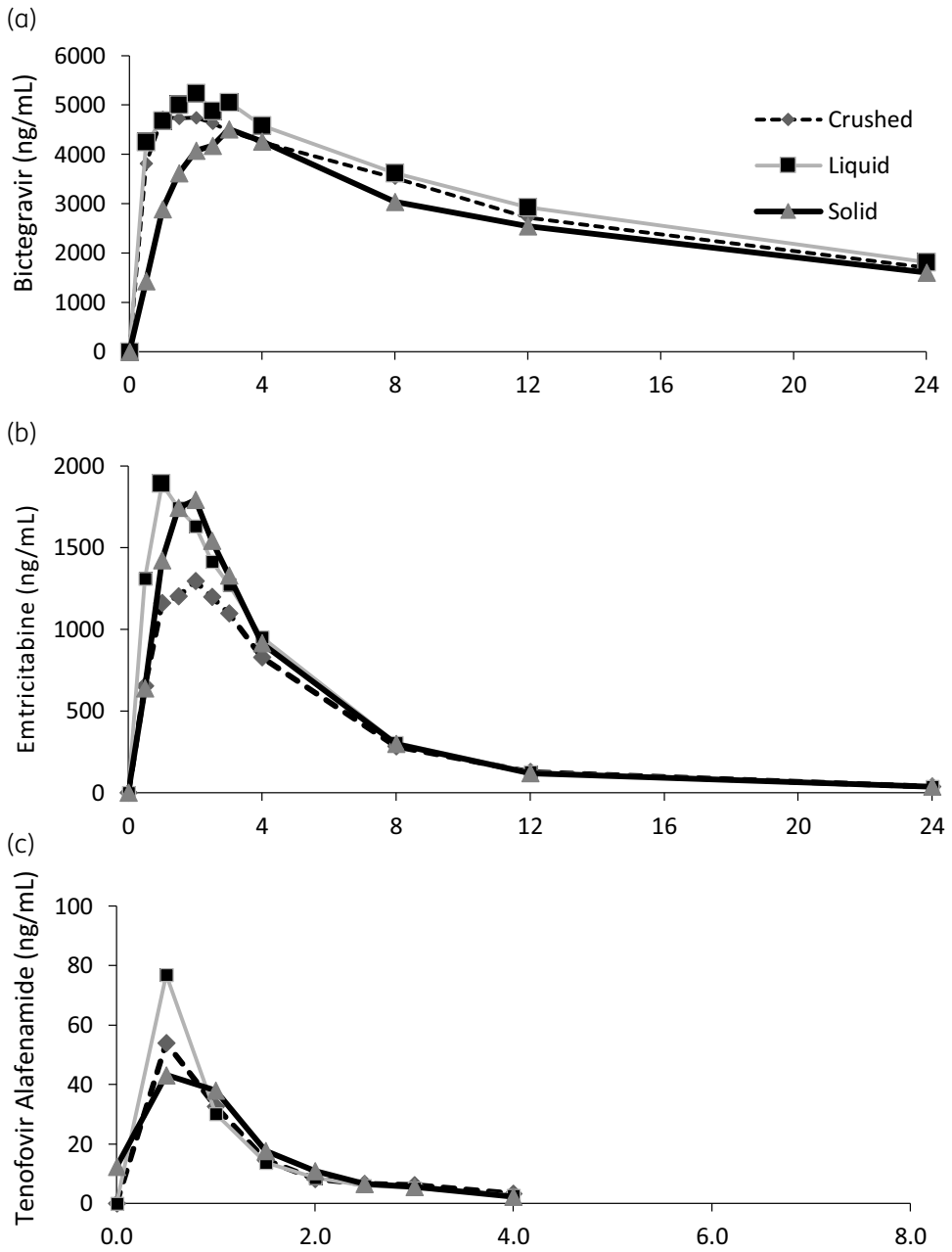

Figure 1. Concentration–time curves of bictegravir (a), emtricitabine (b) during the first 24 h and tenofovir alafenamide (c) during the first 8 h after a single dose of the BIC/TAF/FTC 50/200/25 mg tablet administered as solid whole tablet (S phase), dissolved in water (D phase) or crushed in apple compote (C phase).

as fixed effects and subject (sequence) as random effect. The C_{max} and AUC ratios (test C or D/ref S) for the two experimental formulations and their 90% CIs were calculated from the least-squares means square (LMS) of each treatment. We tested the absence of sequence or period effects and none was found to be significant. A 90% CI within the range 80%–125% was considered to denote bioequivalence. Secondary endpoints were compared between phases using non-parametric Wilcoxon or Mann–Whitney tests, Fisher's exact test or chi-squared test according to the data.

We also conducted a *post hoc* meta-analysis of our PK ratio parameters obtained: (i) with emtricitabine and tenofovir alafenamide dissolved in 240 mL of water combined with a similar experiment[8] in 12 healthy volunteers investigating the bioequivalence of elvitegravir (EVG)/cobicistat (CBT)/FTC/TAF dissolved in 120 mL of water; and (ii) with emtricitabine and tenofovir alafenamide crushed in apple compote combined with a similar experiment[9] in 30 healthy volunteers investigating the bioequivalence of darunavir (DRV)/CBT/FTC/TAF crushed with a mortar and pestle and mixed with 4 ounces of apple compote.

Mixed models were computed with random intercepts using Review Manager Software (RevMan 5.3; The Cochrane Collaboration, Copenhagen, Denmark).

Table 1. Pharmacokinetic parameters over 72 h for bictegravir, emtricitabine and tenofovir alafenamide after each oral intake, according to the administration modality of the tablet (whole, dissolved or crushed)

	Bictegravir			Emtricitabine			Tenofovir alafenamide		
Parameter	Solid	Dissolved	Crushed	Solid	Dissolved	Crushed	Solid	Dissolved	Crushed
C_{max} (mg/L)	5.0 (42)	5.2 (62)	5.5 (84)	2.0 (24)	2.0 (38)	1.4 (27)	0.065 (130)	0.062 (133)	0.043 (116)
T_{max} (h)	2.3 (0.5–4)	2.5 (0.5–4)	2 (0.5–8)	1.5 (1–2.5)	1.5 (0.5–2.5)	2 (1–3)	1 (0.5–2)	0.5 (0.5–1)	0.5 (0.5–2)
AUC_{0-last} (h*mg/L)	100.0 (39)	111.9 (30)	106.2 (35)	10.2 (18)	10.2 (20)	8.7 (18)	0.053 (98)	0.053 (102)	0.047 (91)
$AUC_{0-\infty}$ (h*mg/L)	107.9 (39)	119.4 (31)	115.0 (36)	10.5 (18)	10.5 (20)	9.1 (19)	0.058 (90)	0.056 (96)	0.052 (80)
$t_{½}$ (h)	19.1 (20)	18.2 (18)	19.1 (25)	14.2 (46)	14.4 (65)	19.2 (45)	0.415 (180)	0.383 (55)	0.458 (45)

$AUC_{0-\infty}$, AUC_{0-last}, C_{max} and $t_{½}$ are shown as geometric mean (%CV).
T_{max} is shown as median (range).

Ethics

The protocol was approved by the national ethics committee of Sud-Ouest et Outre-Mer 1 on 15 July 2019 and has been registered at ClinicalTrials.gov (NCT04244448). All participants provided written informed consent. The study was conducted in accordance with the Good Clinical Practice and ethical principles of the Declaration of Helsinki.

Results

Participants

Between December 2019 and February 2021, encompassing a 6 month interruption due to the COVID-19 pandemic lockdown, nine males and nine females, all of whom were Caucasian, were included and completed the three phases of the study. The median (IQR) age was 30 years (20–36) and the median (IQR) BMI was 21 (20–27). The median (IQR) interval between each phase of the study was 21 days (14–28).

Pharmacokinetics

Pharmacokinetic plasma profiles of bictegravir, emtricitabine and tenofovir alafenamide when administered as whole, crushed and dissolved forms are presented in Figure 1. Pharmacokinetic parameters (C_{max}, $AUC_{0-\infty}$, AUC_{0-last}, $t_{½}$ and T_{max}) are summarized in Table 1.

Overall, the shape of the plasma concentration–time curves is shown for the two experimental and reference phases in Figure 1. As expected, bictegravir exhibited rapid absorption in all three phases, with the median T_{max} ranging from 2 to 2.5 h. Compared with the whole tablet, the plasma concentrations of bictegravir were slightly higher with the crushed and dissolved tablets. The mean AUCs of bictegravir were also slightly increased with the crushed and dissolved tablets. Compared with the whole tablet, the T_{max} observed for emtricitabine concentrations was comparable to that of the crushed and dissolved tablets [Figure 1(b)], but the median C_{max} observed with the crushed tablet was lower (1.4 versus 2.0 mg/L). Similarly, the AUCs were slightly lower with the crushed tablet. Emtricitabine pharmacokinetics were fairly comparable for the whole and dissolved tablets. As anticipated, tenofovir alafenamide was short-lived in plasma, with concentrations falling rapidly below the limit of quantification (Figure 1c) and were only measurable for 4 h ($t_{½}$ = 30 min) post dose. During this period, inter-individual variability was important, and concentrations, both in terms of C_{max} and AUC, were lower with the crushed tablet than with the whole or dissolved tablets.

Relative bioavailability

The bioequivalence results of the SOLUBIC trial are summarized in Figure 2.

Dissolved versus solid tablet

After ingestion of the dissolved tablet, the relative AUCs (90% CI) of bictegravir, emtricitabine and tenofovir alafenamide (as compared with the whole tablet) were 111% (100–122), 100% (94–105) and 99% (81–120), respectively, and the relative C_{max} (90% CI) values were 105% (93–119), 97% (87–108), and 96% (74–124), respectively [Figure 2(a)]. Therefore, the dissolved

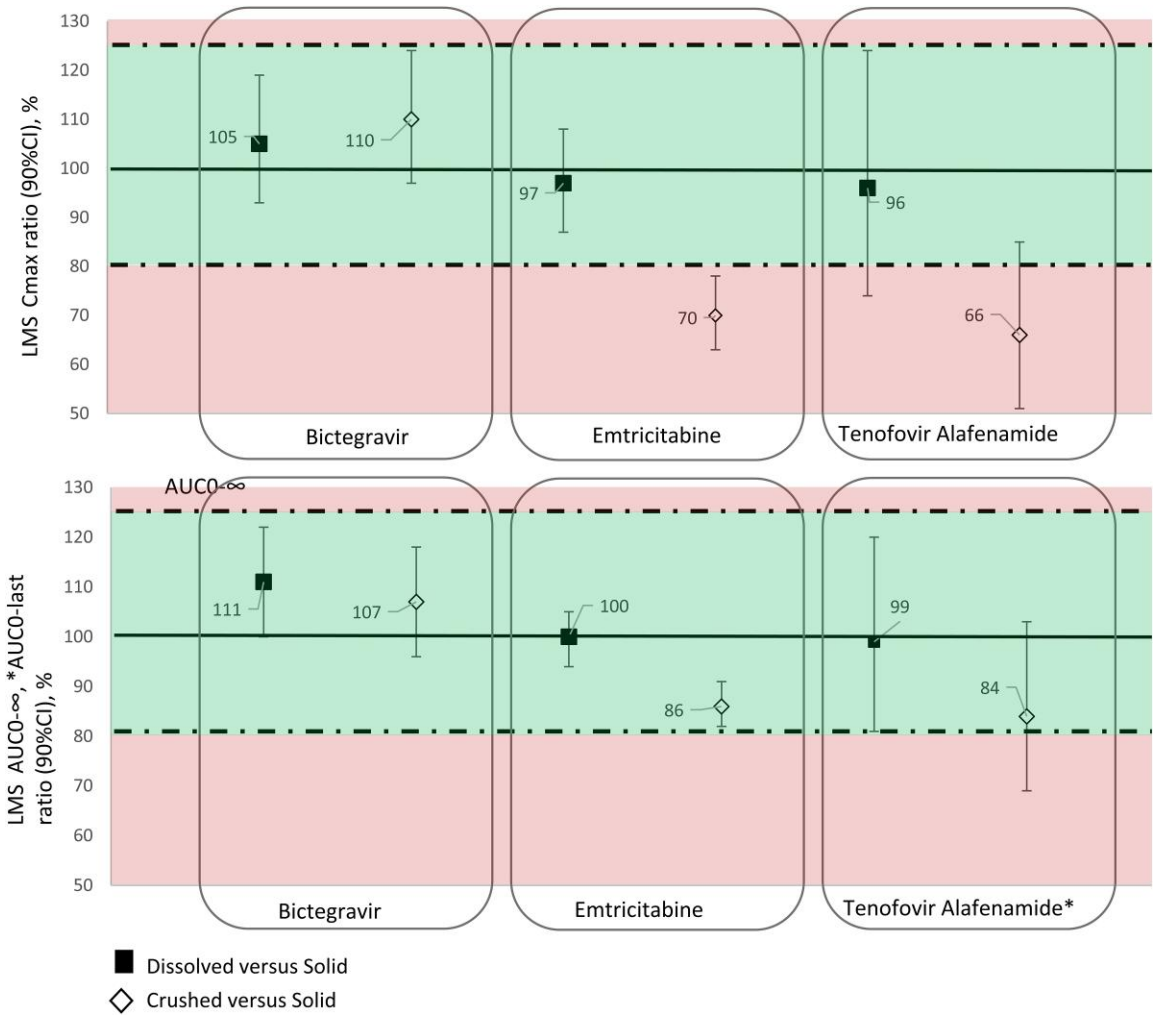

Figure 2. Main pharmacokinetic parameters ($AUC_{0-\infty}$, AUC_{0-last} and C_{max}) after administration of BIC/TAF/FTC either as dissolved in water (black square) or crushed in apple compote (empty square) as compared with the solid tablet. Results are expressed as geometric least squares means ratio (90% CI) for the experimental modality over reference administration. Area between the two dashed lines represents the bioequivalence zone.

tablet showed equivalent $AUC_{0-\infty}$ for bictegravir and emtricitabine and equivalent AUC_{0-last} for tenofovir alafenamide and equivalent C_{max} for bictegravir/emtricitabine, whereas the lower bound of 90% CI C_{max} for tenofovir alafenamide was 74%. T_{max} and $t_{½}$ were not significantly different, whether for bictegravir, tenofovir alafenamide or emtricitabine.

Crushed versus solid tablet

After the intake of the crushed tablet, the relative AUCs (90% CI) of bictegravir, emtricitabine and tenofovir alafenamide (as compared with the whole tablet) were 107% (96–118), 86% (82–91), and 84% (69–103), respectively, and the relative C_{max} values (90% CI) were 110% (97–124), 70% (63–78), and 66% (51–85), respectively [Figure 2(b)]. Therefore, the crushed tablet showed equivalent $AUC_{0-\infty}$ for bictegravir/emtricitabine and equivalent C_{max} for bictegravir, whereas all other parameters were not equivalent. T_{max} was not significantly different, whether for bictegravir, tenofovir alafenamide or emtricitabine. $t_{½}$ was not significantly different for bictegravir or tenofovir alafenamide but was significantly different ($P=0.0139$) for emtricitabine.

Meta-analysis

The results of the meta-analysis for emtricitabine and tenofovir alafenamide bioequivalence are shown in Table 2 and the corresponding Forest plots in Figure S1(a–h). The dissolved tenofovir alafenamide and emtricitabine components fulfilled all criteria for bioequivalence, while the crushed tenofovir alafenamide and emtricitabine components were not bioequivalent and fulfilled all criteria for potentially significant underdosing.

Acceptability, safety and tolerability

Overall, 5/18 (28%) participants experienced at least one adverse event (AE) during the study, and a total of seven AEs were reported: three during the S phase, two during the D phase, one during the C phase and one with drug not administered yet.

Table 2. Combination of pharmacokinetics parameters ratio for tenofovir alafenamide and emtricitabine dissolved (SOLUBIC, $n=18$; and Abdul Massih,[8] $n=12$) and crushed (SOLUBIC, $n=18$; and Brown,[9] $n=30$)

Pharmacokinetics parameter	GMR (90% CI)	Bioequivalence
Dissolved versus solid		
Tenofovir alafenamide		
C_{max}	1.01 (0.84–1.23)	Yes
AUC	1.05 (0.93–1.19)	Yes
Emtricitabine		
C_{max}	1.03 (0.97–1.09)	Yes
AUC	1.02 (0.98–1.07)	Yes
Crushed versus solid		
Tenofovir alafenamide		
C_{max}	0.69 (0.59–0.81)	No
AUC	0.81 (0.75–0.88)	No
Emtricitabine		
C_{max}	0.77 (0.67–0.88)	No
AUC	0.89 (0.84–0.94)	Yes

GMR, geometric mean ratio.

All AEs were moderate (grade 1, $n=1$; grade 2, $n=6$). According to the investigators, 3/7 (43%) AEs were possibly related to the study drug; all 3 were headache reported the day of administration (2 during phase D and 1 during phase C).

The four AEs not related were two headaches (one 4 weeks after the last administration; the other before drug had been administered), one sinusitis (12 days after phase S administration) and one genital wart (3 months after the last administration). No AE led to study discontinuation. All AEs resolved. There were no significant or clinically relevant changes in any vital signs or laboratory tests from baseline to the last visit of follow-up.

All 18 participants evaluated the taste and the ease of swallowing at each phase just after the oral challenge, using a visual scale (0 corresponded to the worse taste/most complicated administration modality, whereas 10 was the best taste/easiest administration). The score for the taste was significantly higher for the whole-tablet phase [median (IQR): 10 (9–10)] than for the dissolved and crushed phases [3.5 (2–4) and 3 (2–4), respectively; $P<0.001$). The ease-of-taking score was significantly higher for the solid and crushed phases [median (IQR): 10 [10–10] and 9.5 (9–10), respectively], than for the dissolved phase [6.5 (6–9); $P<0.005$]. Participants ranked the three phases as follows (by decreasing preference): solid > crushed > dissolved.

Discussion

Our hypothesis of bioequivalence was generally met for the dissolved tablet form. While the tenofovir alafenamide C_{max} did not achieve bioequivalence, this pharmacokinetic parameter is not as clinically important as AUC, because C_{max} is a transient measurement. In addition, tenofovir alafenamide concentrates within the cells, while we measured only plasma pharmacokinetics. More importantly, the large 90% CI for C_{max} is possibly due to a lack of statistical power, as suggested by our *post hoc* meta-analysis. In contrast, the crushed tablet taken in apple compote deviated greatly from the bioequivalence criteria for emtricitabine and tenofovir alafenamide, providing a strong argument against crushing BIC/TAF/FTC tablets. Obviously, this cannot result from residual drug left in the mortar pestle used for crushing, as demonstrated by Video S2.

The internal validity of the pharmacokinetics results is strengthened by the experimental crossover randomized design including the whole-tablet control phase. In addition, total ingestion of the formulations was ensured by directly observed therapy. Moreover, the pharmacokinetics estimates of the BIC/TAF/FTC whole-tablet formulation are consistent with the data from the BIC/TAF/FTC registration dossier.

Although not recommended by the manufacturer due to lack of data at the time of drug approval, the use of crushed BIC/TAF/FTC has been described in several case reports.[10–13] A recent publication even reported its use in a dissolved form at the initiative of the patient herself.[14] By demonstrating the low AUC for emtricitabine and tenofovir alafenamide as components of crushed BIC/TAF/FTC, the SOLUBIC trial provides a pharmacological explanation of the several observations reporting virological failure with potential emerging mutations[12] (M184V, R263K) of the crushed BIC/TAF/FTC tablet, namely the increased risk of bictegravir monotherapy. The low AUC and C_{max} of tenofovir alafenamide and emtricitabine [Table 2 and Figure S1(e–h)] if the tablet is crushed may also be concerning when this combination is used as pre-exposure prophylaxis.

Although widely used, SOLUBIC is the only study evaluating crushed and dissolved BIC/TAF/FTC tablets in a significant number of participants. Of note, we dissolved the intact BIC/TAF/FTC tablet (Video S1) to administer it in an easily drinkable form. Only four other trials have evaluated the bioequivalence of a modified antiretroviral STR in healthy volunteers: crushed EVG/CBT/FTC/TDF (Stribild®),[15] crushed dolutegravir (DTG)/abacavir (ABC)/3TC (Triumeq®),[16] crushed DRV/CBT/FTC/TAF (Symtuza®)[9] and dissolved EVG/CBT/FTC/TAF (Genvoya®).[8] STRs were crushed and then swallowed orally with either a standardized breakfast, apple compote, liquid enteral nutrition or water. Overall, only EVG/CBT/FTC/TDF crushed and suspended in enteral nutrition liquid was found to be bioequivalent to the solid tablet. The other attempts were not bioequivalent, mainly because of a lower C_{max} and occasionally lower AUC. Overall, the integrase inhibitor or PI concentrations were correct (darunavir) or overexposed (dolutegravir, elvitegravir), while NRTIs were often underexposed (tenofovir alafenamide > tenofovir disoproxil fumarate, abacavir > emtricitabine). Our study confirmed these trends, especially when combined with the study by Brown *et al.*[9] showing that crushing tenofovir alafenamide/emtricitabine led to underexposure of these drugs compared with the whole tablet.

The tablet-crushing procedure can lead to a loss of material or even hydrolysis of the destructured tablet on contact with its carrier, leading to an alteration of the pharmacological properties.[5,7] For these reasons, we collected carefully all the crushed material (Video S2) and we administered the crushed tablet within half an hour of its preparation. These experimental conditions may not be generalizable to crushing a tablet at home or in the hospital, increasing the concern about underdosing of the crushed BIC/TAF/FTC tablet. The preparation in liquid form offers the advantage of being completely contained in its carrier solution, which does not risk loss of material, provided the bottle is rinsed well.

Nevertheless, some PLWH are fluid restricted and may find it a challenge to ingest 360 mL of water. It that situation, the 120 mL volume of water used to rinse the bottle may be in our opinion reduced.

Our study has several limitations. First, it was conducted in HIV-negative volunteers taking no chronic medications, not in PLWH with polypharmacy. However, BIC/TAF/FTC is not associated with significant drug–drug interaction liability.[17] Second, the liquid phase was taken fasting and the crushed phase with apple compote; therefore, our results may not be applicable to non-fasting conditions. Third, the study participants took only three doses of BIC/TAF/FTC separated by at least 14 days, whereas patients take BIC/TAF/FTC daily, which leads to accumulation of the individual components and their associated metabolites (as applicable). Finally, the meta-analysis results should be interpreted with caution since tenofovir alafenamide dosing was 25 mg in SOLUBIC but 10 mg in the other studies as a result of which agent tenofovir alafenamide was combined with.[8,9] Nevertheless, the study-level effect size synthesized a pharmacokinetic ratio with the same dosing, and there was no evidence of between-study heterogeneity.

Our work may have important implications for future research. The specific formulation of BIC/TAF/FTC dosed for administration to children (30/120/15 mg) may require a similar bioequivalence trial. For the purposes of this assessment, we would recommend dissolving BIC/TAF/FTC in water. Additionally, because of the large variability of tenofovir alafenamide C_{max}, we would recommend enrolling at least 25 participants based on our power analysis. Our work may also have important implications for clinical practice. The study findings are directly relevant for people with swallowing difficulties who are still able to drink the dissolved tablet. For people who have nasogastric tubes, we recommend the following steps: flush the tube with 30 mL of water; administer the dissolved BIC/TAF/FTC formulation in 240 mL of water; and flush the tube with 30 mL of water. If case of enteral feeding, we suggest separating the administration of BIC/TAF/FTC from enteral feeds by 4 h because of the risk of interaction with polyvalent metal cations.

In conclusion, the results of the SOLUBIC trial and the available evidence on tablet modifications suggest that crushing BIC/TAF/FTC should be avoided. If the BIC/TAF/FTC tablet cannot be swallowed whole, dissolving it in water and taking it immediately may be an acceptable option.

Acknowledgements

Results of the SOLUBIC study were presented in part at the European AIDS Conference Society 2021 in London (Abstract PE2/76).

We warmly thank all volunteers who participated in the trial and Gregoire Rist from EXPEO for the video footage showing how to prepare experimental modalities.

Funding

The SOLUBIC trial (study number CO-FR-380-5442) was funded by a grant from Gilead Sciences to Caen University hospital. Medication was donated by Gilead Sciences. The funder provided advice regarding the study design, drug preparation, data analysis and interpretation.

Transparency declarations

L.H. reports personal fees and non-financial support from Gilead Sciences, personal fees and non-financial support from Janssen, personal fees and non-financial support from MSD, personal fees and non-financial support from ViiV Healthcare, outside the submitted work. I.M. is an employee and stockholder of Gilead Sciences. J.-J.P. reports grants and personal fees from ViiV Healthcare, personal fees from Gilead, grants and personal fees from MSD, outside the submitted work. All other authors: none to declare.

Author contributions

L.H., T.P., I.M. and J.-J.P. participated in the conception and design of the study. S.D., A.F., J.-J.P. included volunteers. A.A. prepared soluble and crushed tablets. C.V., S.B. and F.F. supervised volunteer's care and blood sampling. L.P.-S.-P. oversaw pharmacovigilance. S.L., J.B. and L.G. carried out the pharmacological dosages. S.L., N.G. and J.-J.P. analysed and interpreted the data. L.H., S.L. and J.-J.P. wrote the manuscript. All authors reviewed, revised for consent, and approved the final version of this manuscript. All authors had full access to the data and are responsible for the veracity and completeness of the data reported. The corresponding author had final responsibility for the decision to submit for publication.

Supplementary data

Figure S1 and links for Videos S1 and S2 are available as Supplementary data at *JAC* Online.

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