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Authors
Liu, Honghu
Daar, Eric
Wang, Yan
et al.

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Pharmacokinetics of Coencapsulated Antiretrovirals with Ingestible Sensors

Honghu Liu,[1–3] Eric Daar,[4] Yan Wang,[3,5] Lisa Siqueiros,[4] Kayla Campbell,[6] Jie Shen,[1] Mario Guerrero,[4] Meng-Wei Ko,[7] Di Xiong,[3] John Dao,[8] Todd Young,[8] Marc Rosen,[9] and Courtney V. Fletcher[6]

Abstract

We investigated the use of a system with an ingestible sensor (Proteus Digital Health Feedback system) coencapsulated with antiretrovirals (ARVs) to measure real-time adherence. To assess the safety and impact, if any, coencapsulation might have on ARV concentrations, we evaluated the pharmacokinetics of ARVs coencapsulated with an ingestible sensor for eight commonly used fixed-dose combination ARVs: emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF); FTC/tenofovir alafenamide (TAF); efavirenz (EFV)/FTC/TDF; abacavir (ABC)/lamivudine (3TC); dolutegravir (DTG)/ABC/3TC; rilpivirine (RPV)/TAF/FTC; elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF; and bictegravir (BIC)/FTC/TAF. The steady-state apparent peak plasma concentration (Cmax) and area under the concentration-time curve (AUC) were determined from plasma concentrations measured at predose, 1, 2, 4, and 6 h postdose, and compared with literature values. A total of 49 unique patients on stable regimens for at least 12 weeks with undetectable viral loads were recruited. Cmax and AUC values were not statistically significantly different from literature values for all of the formulations except the Cmax of FTC/TDF, Cmax of BIC, and the Cmax of RPV. In a subsequent evaluation of FTC/TDF and BIC/FTC/TAF using a crossover design, the geometric mean ratio (GMR) between the coencapsulated and the unencapsulated formulations for FTC/TDF were the following: FTC, 84.6% (90% confidence interval [CI] 66.6–107.4) for AUC and 77.5% (60.1–99.9) for Cmax. For tenofovir (TFV), the GMR was 96.2% (90% CI 89.2–103.8) for AUC and 87.3% (64.2–118.7) for Cmax. The GMR for BIC (from the BIC/FTC/TAF formulation) was 98.0% (90% CI 84.5–113.5) for AUC and 89.9% (84.5–95.7) for Cmax. The observed deviation in FTC/TDF (Truvada) may be due to participant characteristics, fasted/fed conditions, and/or random variation and may warrant further investigations with a larger sample size. These findings provide assurance for use of coencapsulated ARVs for future HIV treatment-adherence research.

Keywords: antiretroviral medication, bioavailability, pharmacokinetics, coencapsulated ARV, ingestible sensor, adherence

Introduction

Objective and accurate measurement of adherence to medication is critical for an understanding of the safety and efficacy of drugs.[1] Traditional measures of adherence, such as pharmacy refill records, pill counts, and medication event monitoring system,[2–4] provide only inferred measures of actual drug intake and most of them offer no real-time notification capability. Biosensor and digital medicine has created a new era in medical treatment and public health.[5–9] The Food and Drug Administration (FDA) approved the first digital medication in 2017[8] with a biosensor embedded with the medication to record the time medication was taken (Abilify MyCite®), although the ingestible sensor (Proteus) was approved for marketing as a medical device in 2012.[10] This allows the opportunity to provide immediate feedback

[1]Division of Public Health and Community Dentistry, University of California, Los Angeles (UCLA), Los Angeles, California.
[2]Department of Medicine, David Geffen School of Medicine, UCLA, Los Angeles, California.
[3]Department of Biostatistics, Fielding School of Public Health, UCLA, Los Angeles, California.
[4]Department of Medicine, Division of HIV Medicine, Lundquist Institute at Harbor-UCLA Medical Center, Torrance, California.
[5]Urban Health Collaborative, Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania.
[6]Center for Drug Discovery, University of Nebraska Medical Center, Omaha, Nebraska.
[7]Division of Oral Biology and Medicine, School of Dentistry, UCLA, Los Angeles, California.
[8]Proteus Digital Health, Redwood City, California.
[9]School of Medicine, Yale University, New Haven, Connecticut.

in the event of missed doses and improve medication adherence.[11]

The ingestible sensor has been developed with elements that are consumed in the human diet from dietary minerals: copper, magnesium, and silicon in minute quantities.[12] Research has already demonstrated that the ingestible sensor has no risk of mechanical injury or toxicology concern.[7,11,13] The ingestible sensor technology has been used in monitoring different diseases such as diabetes,[14] hypertension,[15] mental health disorder,[16] and tuberculosis[13,17] as well as care for kidney transplant patients,[11,13,17–20] and has been well-accepted.[21,22]

To use the ingestible sensor to monitor medication taking and measure adherence, the medication must be coencapsulated with the sensor. There is limited research to date about using an ingestible sensor monitoring system for measuring and monitoring adherence to antiretroviral (ARV) drugs in HIV/AIDS research and treatment. Higher levels of adherence to ARVs are associated with better viral suppression and prevention of resistance and disease progression.[23] Currently, the Proteus Discover® system (Proteus Digital Health Feedback, Redwood City, CA) is the only system that is FDA-approved for safety and also met European Union safety requirements.[20] The system includes an ingestible sensor for ingestible event marker and the wearable sensor (patch with a microchip and a tiny battery). The ingestible sensor is activated by gastric fluid and is sensed by the adhesive sensor patch that is placed on the torso and replaced weekly.[24] A Bluetooth signal is sent to the patient's mobile device (tablet or smartphone) and then an encrypted message is sent to the central server with all of the transmitted data. Hence, a real-time signal is received once the medication has been taken by the patient.

The objective of this study was to confirm that coencapsulation does not affect the pharmacokinetics (PK) of eight commonly used ARV fixed dose combination tablets. All these ARVs are well absorbed across a spectrum of HIV-infected people ranging from otherwise healthy to those with more advanced coinfections. Some of these ARVs, such as elvitegravir (EVG) and rilpivirine (RPV) are recommended to be given with food. We therefore hypothesized that coencapsulation would not negatively affect the PK parameters of the ARVs, as primarily assessed by maximum concentration (Cmax) and the 24-h area under the concentration-time curve (AUC) in plasma.

Materials and Methods

In this PK trial, we recruited six HIV-infected individuals for each of the ARV formulations to be tested. All participants were at least 18 years of age and were on a stable ARV regimen with no detectable plasma HIV RNA levels for at least the last 3 months. All the participants indicated the ability to take coencapsulated ARVs at the time of screening and were able to provide informed consent. In addition, participants were required to have either >90% self-reported adherence or be estimated as having a similar level of adherence by their medical providers, to meet the assumption of steady state conditions.

Based on findings that bioavailability was not affected by the ingestible sensor system in other studies, we did not expect to observe a difference with the coencapsulation of ARVs.[24–26] Therefore, rather than a classical bioequivalence crossover design with participants serving as their own controls, we performed a PK study that compared the PK parameters of each of the coencapsulated ARVs to those reported in the manufacturer's package insert (or other published literature if necessary). If we observed a significant deviation in this comparison, then a repeat PK study with crossover design was conducted.

The eight commonly used fixed-dose combination ARV tablets studied included the following: emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF); FTC/tenofovir alafenamide (TAF); efavirenz (EFV)/FTC/TDF; abacavir (ABC)/lamivudine (3TC); ABC/3TC/dolutegravir (DTG); TAF/FTC/RPV; EVG/cobicistat (COBI)/FTC/TAF; and bictegravir (BIC)/FTC/TAF. Coencapsulation was performed by pharmacists in the Investigational Drug Pharmacy using an appropriately sized capsule (Capsugel®, Greenwood, SC) in manner consistent with guidelines from the sensor manufacturer and as summarized by Browne *et al.* (26). All participants came to the clinic after an overnight fast to take the coencapsulated ARV at the clinic in the morning. After a predose blood draw, they were witnessed to take the coencapsulated ARV medications with breakfast provided 5–20 min after medication. The breakfast consisted of the same food for each participant unless they had a special diet (e.g., diabetes, vegetarian). Another four blood samples were obtained at 1, 2, 4, and 6 h postdose.

This sampling and PK analysis strategy was designed to make it feasible for the study participants, persons living with HIV-infection, to complete the study in the course of a single, ~6-h study visit; to capture Cmax that ranges from 1 to 5 h for these ARVs formulations in the literature; and to obtain an estimate of elimination half-life. Plasma was shipped from the Harbor-University of California at Los Angeles Medical Center to the Antiviral Pharmacology Laboratory (APL) at the University of Nebraska Medical Center (UNMC) once all six patients for a given formulation completed the trial. ARV concentrations were quantified with validated, quality-controlled, published liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. Cmax was taken as the maximum observed plasma concentration. AUC was determined by the linear up/log down trapezoidal method (Phoenix WinNonlin; Certara[27]) taking the predose concentration to be the 24 h postdose concentration under the assumption of steady-state PK and the principle of superposition.

We used package insert values (transformed data summary information in Table 2) for each ARV drug as reference to conduct a one-sided independent two-sample *t*-test.[28–30] We did not expect that coencapsulation will reduce Cmax and/or AUC of the ARV formulations, therefore did not design the study to assess whether coencapsulation would increase Cmax or AUC. Given this situation, a one-sided *t*-test, rather than a two-sided *t*-test, was selected, and it gave us stronger power to detect any potential difference. The null hypothesis was that the mean values of Cmax or AUC from coencapsulated ARVs were equal to the reference values for each component of the selected ARV formulations, and the alternative hypothesis was that the mean values of Cmax or AUC from coencapsulated ARVs were smaller than referenced ARVs at the significant level of 0.05.[31,32]

As described in the results, a significant difference was found for the Cmax of FTC and tenofovir (TFV) of coencapsulated

FTC/TDF, and for the Cmax of BIC of coencapusulated BIC/FTC/TAF when compared with the package insert values. Thus, a classical crossover trial was conducted with six participants for each of FTC/TDF and BIC/FTC/TAF. Participants in this crossover trial had similar inclusion criteria as the main study described above. In the crossover trial, participants, who had been on the above ARVs for at least 12 weeks, came in for a baseline PK blood draw. Participants had their blood drawn predose, took a regular dose of ARVs (i.e., without overencapsulation), and then had their blood drawn at 1, 2, 4, and 6 h postdose. Within 1 week of the first visit, the participants came back for a second PK-blood draw where they had their blood drawn predose, took a dose of coencapsulated ARVs, and then had their blood drawn at 1, 2, 4, and 6 h postdose. PK parameters were calculated as described. The geometric mean ratios (GMRs) of Cmax and AUC (coencapsulated to not-encapsulated) were calculated and a nonsignificant difference was defined as the 90% confidence interval (CI) of each ratio being within 80%–125%.

Results

A total of 49 unique participants (6 patients for each of the 8 ARV formulations, 2 patients were taking both Truvada and Descovy or Odefsey, 3 new participants were recruited for the FTC/TDF crossover trial, and for the crossover BIC/FTC/TFV trial, 4 were from the original Biktarvy PK trial and 2 switched from Atripla to Biktarvy) were recruited from the Harbor-UCLA Medical Center. A majority of the patients were males (92%) and half of the patients were Latinos (50%). The mean age ranged from 46 to 56 years across the eight ARV formulations. The overall mean body mass index was 30.4 (standard deviation [SD] 4.57), ranging from 26.5 (SD 5.0) of Atripla to 35.3 (SD 10.1) of Triumeq. Table 1 shows the demographic information for these 48 subjects in PK study and 12 patients in crossover trial. Concomitant medications are shown in Supplementary Table S1.

Table 2 gives the AUC and Cmax (mean and SD) for each component of the coencapsulated ARVs evaluated in this study. In addition, detailed information on the reference values for each of the eight formulations, including the sample size, mean and SD values of AUC and Cmax for each component of the ARVs with fasted or fed information, and website links of the online references for each package insert/reference values are also listed in Table 2. If the coefficient of variation (CV) was reported for the reference values, it was converted to SD by multiplying the CV by the mean.

The comparisons of AUC and Cmax between the averaged values from the six participants and the reference values are listed in Table 3. The one-sided *t*-test for the independent two-sample *t*-test with specific *p* value for each of the ARV component is presented and the significance level 0.05 is used to determine statistical significance. The degrees of freedom vary across different ARVs because different sample sizes were used in the package inserts. The *p* values of the *t*-tests indicated whether the coencapsulated formulation and reference formulation are similar. All *p* values were greater than .05, except for Cmax of RPV in the RPV/FTC/TAF formulation ($p = .01$), the Cmax of FTC and TFV from FTC/TDF ($p = .03$ and .01, respectively, for Cmax), and the Cmax of BIC in the BIC/FTC/TAF formulation ($p = .04$). The

TABLE 1. CHARACTERISTICS OF PATIENTS

ARVs	*Male*	*Female*	*NH White*	*NH AA*	*Hispanic*	*Asian*	*Other*	*Age (mean ± SD)*	*BMI (mean ± SD)*
TDF/FTC/EFV (Atripla)	6	0	1	2	2	1	0	56 ± 7	26.5 ± 4.96
FTC/TDF (Truvada)	6	0	0	2	4	0	0	50 ± 9	34.2 ± 11.21
FTC/TAF (Descovy)	5	1	0	3	3	0	0	47 ± 10	29.6 ± 8.52
FTC/RPV/TAF (Odefsey)	6	0	0	2	4	0	0	46 ± 7	27.2 ± 2.87
EVG/COBI/FTC/TAF (Genvoya)	5	1	0	2	4	0	0	48 ± 15	30.1 ± 4.64
ABC/3TC (Epzicom)	5	1	1	4	1	0	0	54 ± 9	30.5 ± 9.33
ABC/3TC/DTG (Triumeq)	5	1	1	2	3	0	0	53 ± 10	35.3 ± 10.09
BIC/FTC/TAF (Biktarvy	6	0	0	2	3	1	0	46 ± 12	30.1 ± 4.14
Summary ($N = 48$)[a]	44	4	3	19	24	2	0	50 ± 10	30.4 ± 7.57
FTC/TDF (Truvada)—crossover[b]	6	0	0	4	2	0	0	52 ± 5	28.5 ± 3.82
BIC/FTC/TAF (Biktarvy)—crossover[c]	6	0	1	1	3	0	1	50 ± 12	27.0 ± 3.03
Summary ($N = 12$)	12	0	1	5	5	0	1	51 ± 9	29.3 ± 7.27

[a]We actually only have a total 46 unique patients since two patients were taking both Truvada and Descovy or Odefsey.
[b]In crossover design of Truvada, three patients are newly recruited.
[c]No new patients are recruited in crossover design of Biktarvy, two patients switched from Atripla to Biktarvy.
ABC, abacavir; ARV, antiretroviral; BIC, bictegravir; BMI, body mass index; COBI, cobicistat; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; RPV, rilpivirine; 3TC, lamivudine; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 2. Reference Antiretrovirals and Components from Package Inserted Value

ARVs			Observed data					Package insert values				
				AUC (ng×h/mL)		Cmax (ng/mL)			AUC (ng×h/mL)		Cmax (ng/mL)		
Drug	*Fasted/Fed*	*Component*	N	*Mean*	*SD*	*Mean*	*SD*	N	*Mean*	*SD*	*Mean*	*SD*	*References*
Atripla	Fasted	EFV	6	106812	67219.3	6027.17	3149.23	35	58085	23044	4072	1168	https://www.accessdata.fda.gov/drugsatfda_
		FTC	6	11024.8	1791.08	1467.33	423.52	35	10000	3100	1800	700	docs/label/2008/021937s007lbl.pdf
		TFV	6	3134.33	1385.68	299.98	55.34	35	2287	685	296	90	
Descovy	Fed	FTC	6	13680.7	4025.29	2238.67	689.86	48	11700	1940	2100	424	https://www.accessdata.fda.gov/drugsatfda_
		TFV	6	725.5	409.91	41.06	18.51	48	290	79.5	20	5.22	docs/label/2016/208215s000lbl.pdf
Epzicom	Fasted	3TC	6	16092.2	4163.02	1851.5	242.15	11	8870	1830	2040	540	https://www.accessdata.fda.gov/drugsatfda_
		ABC	6	15173.8	3994.94	3972.67	2090.93	11	11950	2510	4260	1190	docs/label/2012/021652s015lbl.pdf
Genvoya	Fed	COB	6	11173.7	5019.85	1721.28	672.1	19	9500	3220.5	1500	426	https://www.accessdata.fda.gov/drugsatfda_
		EVG	6	17216.8	5343.2	1562.67	449.78	19	22800	7910	2100	707.7	docs/label/2016/207561s002lbl.pdf
		FTC	6	11976.8	4703.11	1918.67	372.15	19	11700	1942.2	2100	424.2	
		TFV	6	290	123.99	18.67	7.97	19	290	79.46	20	5.22	
Odefsey	Fed	FTC	6	11221.3	4106.61	1890	546.5	19	11700	1942	2100	424.2	https://www.accessdata.fda.gov/drugsatfda_
		RPV[a]	6	2779.33	1206.04	145.17	63.62	19	3238	941.5	211.5	54.69	docs/label/2016/208351s000lbl.pdf
		TFV	6	261.5	82.49	17.11	3.46	19	290	79.46	20	5.22	
Triumeq	Fasted	3TC	6	15905	4799.11	1902.67	412.37	11	8870	1830	2040	540	https://www.accessdata.fda.gov/drugsatfda_
		ABC	6	12363.5	2685.53	3352.83	1661.73	11	11950	2510	4260	1190	docs/label/2014/205551s000lbl.pdf
		DTG	6	50384.8	14959.3	3650.17	847.84	11	53600	14472	3670	734	
Truvada	Fasted	FTC	6	9285.67	1561.09	1228.85	281.39	39	10000	3120	1800	720	https://www.accessdata.fda.gov/drugsatfda_
		TFV	6	2217.83	510.66	193.97	85.3	39	2287	690	296	90	docs/label/2016/021752s047lbl.pdf
Biktarvy	Fasted	BIC[b]	6	54831.67	21939.34	4292.83	1443	4	87538	28625	6080	1325	https://www.accessdata.fda.gov/drugsatfda_
	Fed	FTC	6	10812.33	3009.67	1898.88	645.61	19	11700	1942.2	2100	424.2	docs/label/2018/210251s000lbl.pdf
		TAF	6	242.5	214	18.52	12.87	19	290	79.46	20	5.22	

[a]We also compare the RPV with the most updated published results, Kakuda *et al.*[33]
[b]Reference for Biktarvy: Gallant *et al.*[43]
AUC, area under the concentration-time curve; TFV, tenofovir.

Table 3. Two Sample One-Sided t-test on AUC and Cmax

ARVs		*AUC*			*Cmax*		
Drug	*Component*	*T-stats*	*DF*	p	*T-stats*	*DF*	p
Atripla	EFV	3.42	39	1.00	2.82	39	1.00
	FTC	0.78	39	.78	−1.12	39	.13
	TFV	2.37	39	.99	0.10	39	.54
Descovy	FTC	2.05	52	.98	0.70	52	.76
	TFV	6.80	52	1.00	6.41	52	1.00
Epzicom	3TC	5.03	15	1.00	−0.80	15	.22
	ABC	2.06	15	.97	−0.37	15	.36
Genvoya	COB	0.97	23	.83	0.96	23	.83
	EVG	−1.61	23	.06	−1.74	23	.05
	FTC	0.21	23	.58	−0.94	23	.18
	TFV	0.00	23	.50	−0.48	23	.32
Odefsey	FTC	−0.40	23	.35	−0.99	23	.17
	RPV	−0.97	23	.17	−2.43	20	**.01**
	TFV	−0.76	23	.23	−1.26	23	.11
Triumeq	3TC	4.40	15	1.00	−0.54	15	.30
	ABC	0.32	15	.62	−1.31	15	.11
	DTG	−0.43	15	.34	−0.05	15	.48
Truvada	FTC	−0.55	43	.29	−1.91	43	**.03**
	TFV	−0.23	43	.41	−2.60	43	**.01**
Biktarvy	BIC	4.69	8	1.00	−1.98	8	**.04**
	FTC	−0.85	23	.20	−0.89	23	.19
	TFV	−0.83	23	.21	−0.42	23	.34

Bold figures are statistically significant.
AUC, area under the concentration-time curve; DF, degrees of freedom.

comparison of EVG from the EVG/COBI/FTC/TAF formulation showed marginal differences compared with literature values in Cmax ($p = .05$) and AUC ($p = .06$). The Cmax and AUC values for the other four coencapsulated combination tablets were comparable with those published package insert and/or literature values, including EFV/FTC/TDF where no difference for any component was seen.

Based upon results described above, crossover trials were conducted for the FTC/TDF tablet and BIC/FTC/TAF tablet. In the crossover analysis, the GMR of the coencapsulated to not-encapsulated formulations of TFV (in the FTC/TDF formulation) was 96.2% (90% CI 89.2–103.8) for AUC and 87.3% (64.2–118.7) for Cmax. The GMR for FTC was 84.6% (90% CI 66.6–107.4) for AUC and 77.5% (60.1–99.9) for Cmax. Thus, the coencapsulated formulation of FTC/TDF did not meet the bioequivalence criteria. The plots of concentration curves for FTC/TDF are shown in Figures 1 and 2. The GMR for BIC was 98.0% (90% CI 84.5–113.5) for AUC and 89.9% (84.5–95.7) for Cmax, which indicates that BIC in the crossover trial did meet the bioequivalence definition, as did FTC and TAF from the BIC/FTC/TAF formulation. The plots of the concentration curves for BIC/FTC/TAF formulation are shown in Figures 3–5.

Discussion

The PK characteristics of the coencapsulated commercial combination ARV tablets, EFV/TDF/FTC, FTC/TAF, ABC/3TC, and ABC/3TC/DTG (four of the eight evaluated), were comparable with historical data taken from the package inserts or the literature. There was evidence for a marginal influence of coencapsulation (an approximate 25% reduction) on the AUC and Cmax of the EVG component EFG/COBI/FTC/TAF. Due to a lack of stated package insert values for the Cmax of RPV, we compared both the AUC and Cmax with published literature values.[33] There was no significant difference in the AUC of RPV with the reference value, but Cmax of RPV was significantly different; the AUC and Cmax of the FTC and TAF components of the RPV/FTC/TAF coencapsulated tablet were not different from package insert values. When compared in a crossover design, we found that coencapsulation of FTC/TDF tablet reduced the Cmax of both TFV and FTC and the AUC of FTC. The Cmax of BIC (from the BIC/FTC/TAF tablet) was significantly different when compared with historical values;

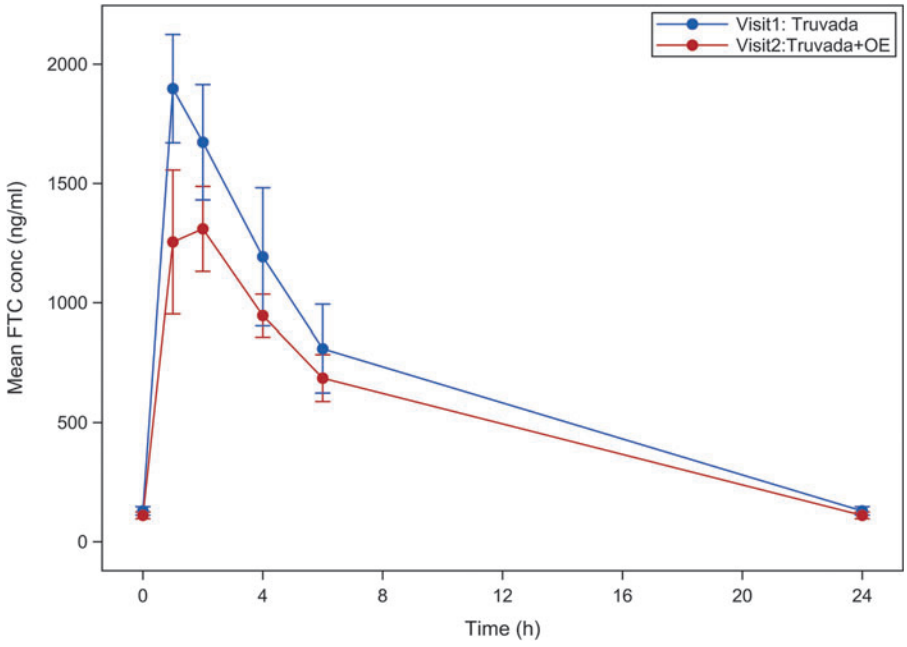

FIG. 1. Mean concentration-time curves for emtricitabine (FTC) in Truvada.

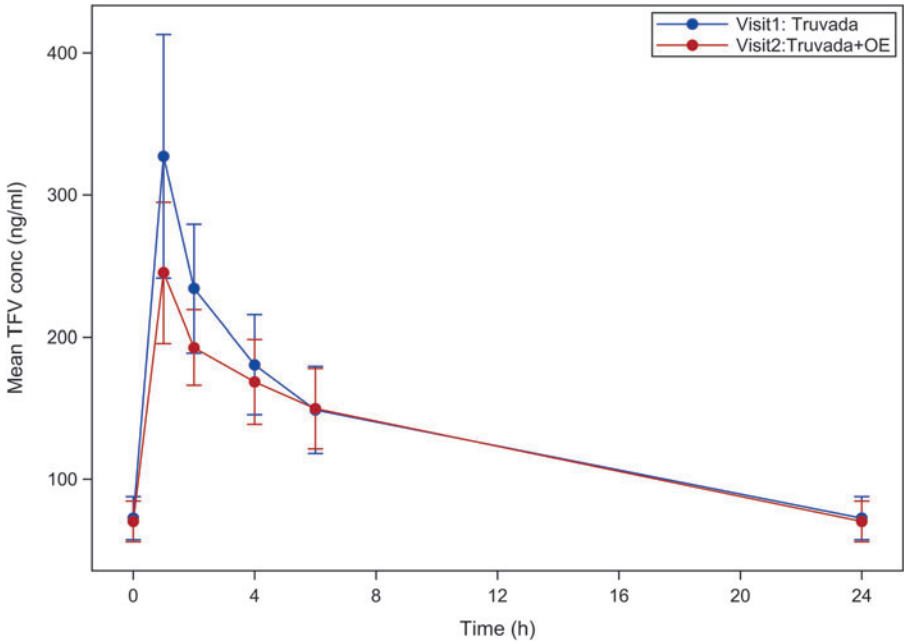

FIG. 2. Mean concentration-time curves for tenofovir (TFV) in Truvada.

however, in the crossover trial, the Cmax and AUC of BIC, FTC, and TFV (from TAF) met the bioequivalence criteria.

In literature, there are two different capsules commonly used for coencapsulation, plant-derived polymer hydroxypropyl methylcellulose and hard gelatin capsules.[34] Prior studies indicated comparable bioavailability for both of the two capsules when used for overencapsulation. The drug release and absorption from the two capsules meet the PK criteria for bioequivalence. However, there is at least one study that found that the encapsulation process affected the bioavailability of sumatriptan, a drug used for migraine treatment.[35] Encapsulation was shown to delay sumatriptan absorption about 0–2 h and to reduce the AUC by 21%–27% in healthy volunteers and patients suffering a migraine.

We used the common level of 0.05 as significance level for our two-sample one-sided *t*-test when comparing with historical data. For one-sided *t*-test (which has a larger power compared with a two-sided test for the same data), our approach is quite conservative and tends to identify significant differences when it could not be significantly different otherwise. The purpose of this study was to evaluate the PK of eight commonly used ARVs when coencapsulated with the Proteus sensor and to compare those values with historical data. Our objective was to make sure that the process of

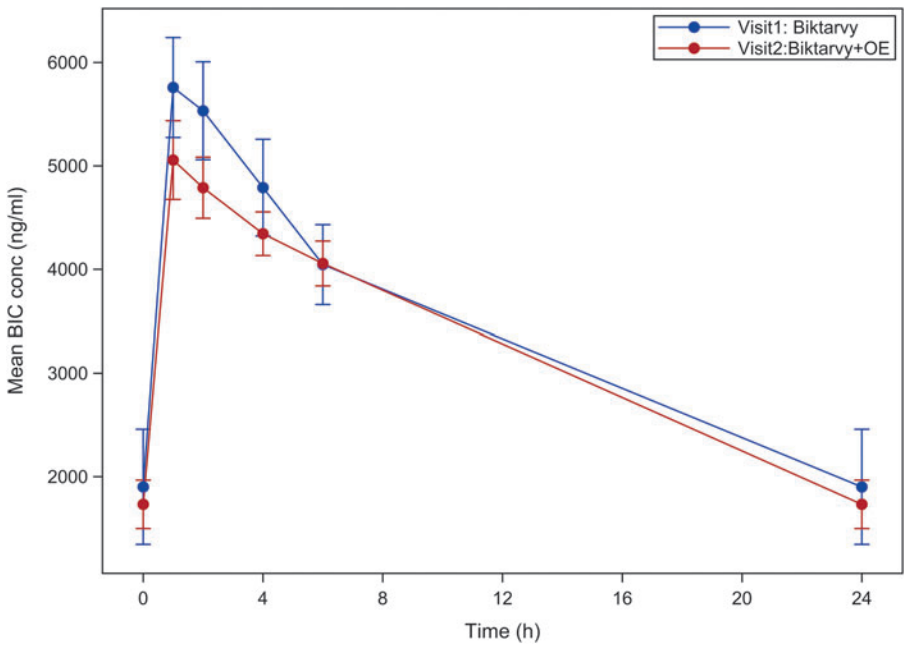

FIG. 3. Mean concentration-time curves for bictegravir (BIC) in Biktarvy.

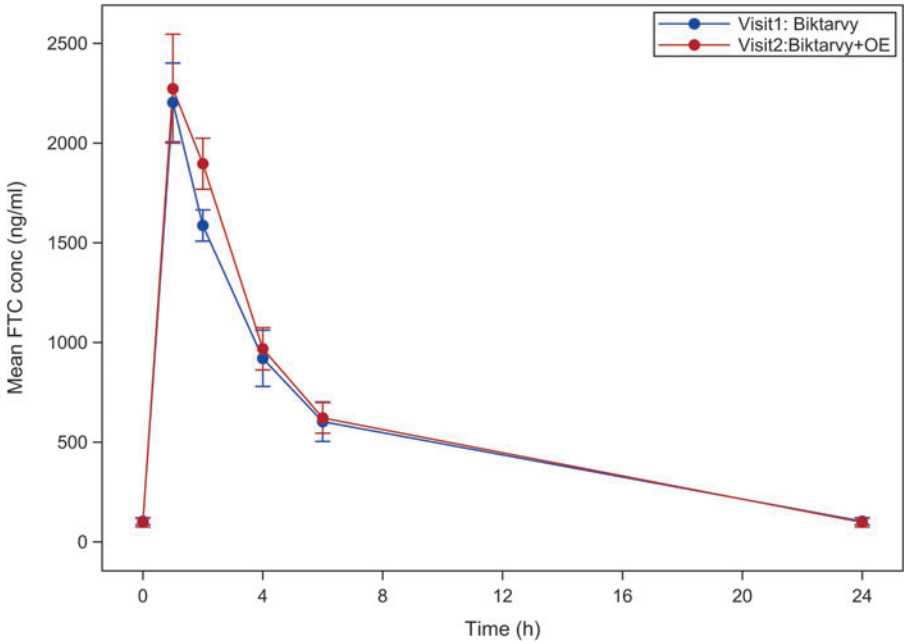

FIG. 4. Mean concentration-time curves for emtricitabine (FTC) in Biktarvy.

coencapsulation did not result in a clinically significant reduction in concentrations, assessed by Cmax and AUC. Although it is theoretically possible that coencapsulation could increase Cmax and AUC, our objective was not to assess such a change or to determine the exact mechanism of any reduction observed. Thus, we use one-sided *t*-test to test if there is a negative effect of coencapsulation on Cmax and AUC.

The mechanism for the reduction in EVG Cmax and AUC by over encapsulation, although the test effect is marginal, is not known. A food effect may have contributed, as participants were given the coencapsulated ARV medications in the fasting state with breakfast provided 5–20 min after medication was taken. Food significantly enhances the oral bioavailability of EVG and forms the basis for the clinical recommendation that EVG be taken with food. The AUC of EVG can be decreased by up to 50% when taken on an empty stomach compared with food.[36] The small delay in the administration of food until after EVG was taken might have been sufficient to cause the reduction in Cmax and AUC. We believe the magnitude of the reduction seen (in comparison with historical average PK parameters where it was given with food although timing was not specified) is unlikely to be clinically significant. For example, coadministration of antacids 2 h after EVG (Genvoya tablet) reduces EVG Cmax and AUC $\sim$20% and that reduction is considered clinically acceptable.[37] Similarly, the cause of the reduced Cmax, but not

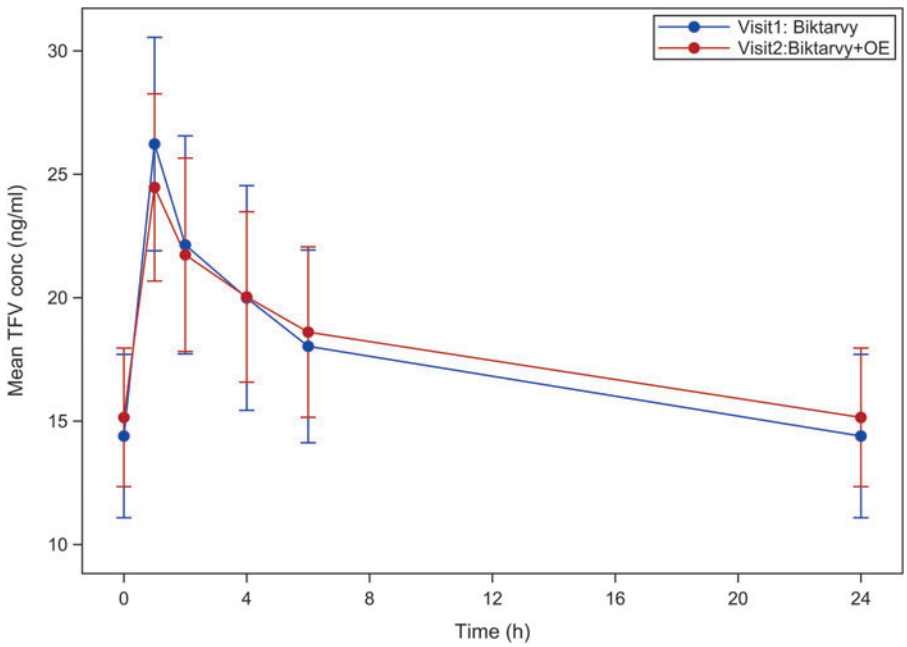

FIG. 5. Mean concentration-time curves for tenofovir (TFV) in Biktarvy.

AUC, for RPV in the RPV/FTC/TAF coencapsulated tablet is not known, but it is also most likely related to differences in the meals provided. RPV absorption is highly sensitive to the effect of food; exposure is reduced by 40% when taken in a fasted state (vs. a normal or high caloric meal) and this forms the basis for the recommendation that RPV be taken with a meal. As overall exposure (i.e., AUC) was not reduced, the reduction in RPV Cmax, if not due to the effect of a difference in meals between our study and the reference study, is unlikely to be clinically significant. For both EVG/COBI/FTC/TAF and RPV/FTC/TAF, it is noted that none of the other ARVs (FTC and TAF) was affected by coencapsulation, indicating the reduction observed for EVG and RPV is not a uniform effect on all components of their respective fixed dose tablets.

Coencapsulation reduced the Cmax of FTC and TDF and the AUC of FTC by 15%–22%; the mechanism of this reduction is not known. Our results are in contrast to those reported in a bioequivalence study of FTC/TDF conducted in 24 healthy subjects who received a single dose of FTC/TDF unencapsulated and coencapsulated with the same ingestible sensor (Proteus) and empty capsules (Capsugel DBcaps) used in our study.[24] That study and a recently published study found that the Cmax and AUC values for TFV and FTC were completely within the standard bioequivalence definition; a recently published bioequivalence evaluation in healthy-volunteers of TDF given as TDF/FTC/RPV coencapsulated with a different sensor also found bioequivalence for TDF.[24,38] There are some important differences between the Ibrahim and Chai studies and our present evaluation. The studies by Ibrahim and Chai enrolled healthy volunteers, while our study enrolled HIV-infected persons; PK differences have been observed between healthy volunteers and HIV-infected persons.[24,39] Ibrahim enrolled 24 participants and Chai enrolled 10 participants versus ours of 6. Ibrahim used a more complete sampling of the concentration-time curve by giving a single dose and collecting samples out to 72 h postdose; drug administration was in the fasting state and subjects remained fasting for 4 h after administration. In contrast, our study was conducted at steady-state, used more limited sample collection, could only collect blood samples within the 24 h of the once-daily dosing regimen for HIV-infected persons, and while drug administration was in the fasting state, a breakfast was given 5–20 min after administration. Thus, there are several potentially relevant differences that could account for the difference in results between our study and that of Ibrahim *et al.* Regardless, the magnitude of the difference in PK characteristics was small with the reduction in Cmax for TFV and FTC being 13% and 22%, respectively; the reduction in the AUC of FTC was only 15% (with a p value of .29 from one-sided two-sample t-test). We did not measure the pharmacologically active intracellular moieties of TFV and FTC (TFV-diphosphate and FTC-triphosphate) and thus do not know whether these reductions in plasma concentration translate into reductions in intracellular concentrations. We cannot exclude the possibility that these reductions in plasma concentrations are clinically significant. We believe that the most likely explanations for the difference between the Ibrahim study and ours are the difference in subjects (healthy volunteers vs. HIV-infected persons) and/or the difference in meal administration. For our subsequent studies in HIV-infected persons, we have modified our procedures to give coencapsulated FTC/TDF in the fasting state (as in the current study) and to maintain that fasting state for 2 h following drug administration.

We acknowledge certain limitations of our study design. We used a sparse sampling strategy designed to accommodate the PK evaluations to be conducted in these persons living with HIV-infection in the course of an approximate 6-h study visit. In this design, we used the predose concentration (obtained $\sim$24 h before the dose given at the study visit) to represent the 24-h concentration following the observed dose at the study visit. This is a valid approach under the assumption of steady-state PK conditions. Our entry criteria, described in Methods, were designed to enroll persons stable on their ART regimen who were highly adherent. Although we hypothesized that coencapsulation would not affect Cmax or AUC, we reasoned that if there was an effect it would be on the process of drug absorption and not on drug elimination (renal excretion or hepatic metabolism). This assumption also informed our decision to use the 24-h predose concentration as the 24-h postdose concentration. If coencapsulation did reduce or delay Cmax, this choice could bias (minimize) an effect on AUC. We believe this effect would be minimal, however, based on the median time to maximum concentrations we observed across all formulations of 2 h (IQR 1–2 h), the 24-h dosing intervals, and the half-lives of the ARVs. Acknowledging these limitations, the data support that we obtained good approximations of the PK characteristics of the various ARVs. In addition to the Cmax and AUC values in Table 2, we have included a Supplementary Table S2 of the half-life values for the ARVs, all of which were in excellent agreement with literature values.

We did not use the traditional crossover design in this PK evaluation as the primary approach unless there were concerns in the initial analyses. The major reason behind this choice was based upon a number of other bioequivalence trials of coencapsulation of different drugs and the extensive experience with coencapsulation with the product used, indicating that the pretest likelihood of seeing a clinically relevant effect on PK was low.[24,26] Indeed, most of the components in the ARVs tested demonstrated PK characteristics when coencapsulated, which were comparable to those found in the FDA-approved package inserts or in available literature. Although not as powerful as a classical crossover design, using historical reference values for comparison is an efficient approach to identify any signals as to whether coencapsulation affects PK. Where we saw differences, two (EVG and RPV) we believe were a food effect, and while the effect of coencapsulation on TDF and FTC (in the Truvada formulation) might also be a food effect, it could be a difference in study participants indicating some potential pitfalls in extrapolating PK characteristics from one population to another.

With a limited sample size and sampling data points, we needed to use an efficient statistical approach to avoid more parameter estimation and conserve statistical power. The one-sided independent two sample t-test is robust (i.e., not sensitive) to the normal distribution assumption for the Cmax and AUC.[40] The two-sample t-test can still be used[41] when the sample size is small, the two groups have unequal sample sizes and unequal variances, and the distribution is transformed into normal (e.g., the lognormal distributions). The

statistical power of using the independent two-sample *t*-test when sample size is small is still comparable among non-normal distributions (e.g., exponential, logistic) for evaluation of means or location parameters.[40] The one-sided test is used because the main purpose of the PK trials was to confirm that there was no significant reduction in values of PK parameters. In this case, a two-sided test will not be appropriate.

The demonstration of acceptable PK of several commonly used ARVs coencapsulated with an ingestible sensor creates a digital medication that can be used to measure and track a patients' ARV adherence in real-time.[24,26,42] The findings from this study also provide some confidence that for those coencapsulated ARVs where PK characteristics did not meet our definition of no difference (e.g., EVG and RPV), the magnitude of differences in PK characteristics were unlikely to be clinically significant; our findings reinforce the recommendations that EVG and RPV must be administered with food. Collectively, the data from this study allow initiation of a planned randomized controlled trial to assess the feasibility, acceptability, and effectiveness of the ingestible sensor to investigate ARV adherence. Finally, the findings from this study will also enable researchers to conduct clinical trials with innovative behavioral interventions to improve adherence to ARV medications and enable clinicians to provide optimal care of HIV-infected individuals.

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Author Disclosure Statement

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

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Address correspondence to:
Honghu Liu, PhD
Public Health and Community Dentistry
Department of Medicine
Department of Biostatistics
University of California, Los Angeles (UCLA)
10833 Le Conte
Los Angeles, CA 90095-1668

E-mail: hhliu@mednet.ucla.edu