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CASE REPORT

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Pharmacokinetics of tenofovir alafenamide, emtricitabine, and dolutegravir in a patient on peritoneal dialysis

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Abstract

Introduction Peritoneal dialysis (PD) is an e□ective renal replacement modality in people with HIV (PWH) with end-stage kidney disease (ESKD), particularly those with residual kidney function. Data on pharmacokinetics (PK) of antiretrovirals in patients on peritoneal dialysis are limited.

Methods A single-participant study was performed on a 49-year-old gentleman with ESKD on PD and controlled HIV on once daily dolutegravir (DTG) 50 mg + tenofovir alafenamide (TAF) 25 mg / emtricitabine (FTC) 200 mg. He underwent serial blood plasma, peripheral blood mononuclear cell, and urine PK measurements over 24 h after an observed DTG + FTC/TAF dose.

Results Plasma trough (Cmin) concentrations of TAF, tenofovir (TFV), FTC, and DTG were 0.05, 164, 1,006, and 718 ng/mL, respectively. Intracellular trough concentrations of TFV-DP and FTC-TP were 1142 and 11,201 fmol/million cells, respectively. Compared to published mean trough concentrations in PWH with normal kidney function, observed TFV and FTC trough concentrations were 15.5- and 20-fold higher, while intracellular trough concentrations of TFV-DP and FTC-TP were 2.2-fold and 5.4-fold higher, respectively. TFV and FTC urine levels were 20 times lower than in people with normal GFR.

Conclusions In a single ESKD PWH on PD, daily TAF was associated with plasma TFV and intracellular TFV-DP trough concentrations 15-fold and 2-fold higher than those of people with uncompromised kidney function, potentially contributing to nephrotoxicity. This suggests that TFV accumulates on PD; thus, daily TAF in PD patients may require dose adjustment or regimen change to optimize treatment, minimize toxicity, and preserve residual kidney function.

Keywords HIV treatment, Peritoneal dialysis, Tenofovir, Emtricitabine, Nephrotoxicity, Trough concentration

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Introduction

People living with HIV (PWH) are at a higher risk for developing chronic kidney disease (CKD) than the general population. In North America, up to 1 in 10 individuals living with HIV has CKD, due to both HIV-related factors and traditional risk factors [1–4]. Peritoneal dialysis (PD) is a form of kidney replacement therapy that has been increasing in use globally and in the USA, where up to 10% of people needing dialysis are on PD [5]. However, data on antiretroviral pharmacokinetics (PK) and dosing in this population are scarce. Descovy™ (xed dose formulation of the nucleoside reverse transcriptase inhibitors emtricitabine (FTC) and tenofovir alafenamide (TAF) lacks an FDA label indication for people with severe kidney disease (creatinine clearance (CrCl)<30 mL/min) who are not yet on dialysis, but can be used in individuals with CrCl<15mL/min who are on hemodialysis (HD) without dose adjustment, with recommended dosing timed after HD [6–8].

TAF is a modi ed prodrug of tenofovir (TFV); it is administered at lower dosages than tenofovir disoproxil fumarate (TDF) and is associated with enhanced prodrug stability in plasma and lower systemic TFV exposures. Studies of healthy individuals switched from TDF to TAF showed 90% lower plasma TFV concentrations and 2- to 4-fold higher intracellular TFV-DP concentrations with TAF than with TDF [9]. e lower plasma TFV concentration is largely responsible for the improved kidney and bone toxicity pro le of TAF [10]. Studies in individuals with severe CKD (CrCl of 15 to 29 mL/min) given TAF have shown that plasma peak concentration (C_{max}) and area under the concentration-time curve extrapolated to in nity (AUC_{inf}) of TAF and TFV are 79% and 92% higher, and 2.8-fold and 5.7-fold higher, respectively, than in individuals with normal kidney function given TAF [11].

Conversely, the integrase strand transfer inhibitor (INSTI) dolutegravir (DTG) may be used for people with severe CKD (CrCl<30 mL/min) who tend to have lower plasma DTG concentrations for unexplained reasons [12], a small case series of the use of daily DTG in people on HD have found it to be safe and e ective without dose adjustment [13].

While some scant data on TAF dosing in people with ESKD on HD are available [14, 15], the pharmacokinetics of TAF in people on PD have not been characterized. ere is a single case report in the literature of a 46-year-old patient with HIV and HBV on PD who was taking TDF 245 mg once weekly+ritonavir-boosted atazanavir (r/ATZ). Plasma TFV concentrations were measured before and at 2 and 4 h into a peritoneal dialysis session with a 4-hour dwell; observed TFV trough concentrations were 510 ng/mL in serum and 200 ng/mL in the 24-hour dialysis uid, con rming that TFV is partially extracted by PD. In order to lower concentrations to achieve target steady state concentrations (50–300 ng/mL), TDF dosing was decreased to 245 mg every 2 weeks; post-dose adjustment, observed serum TFV concentrations were 200 ng/mL [16].

To our knowledge, the current report is the rst in the literature to describe the PK of TAF in a PWH on peritoneal dialysis.

Case presentation

A 49-year-old African American gentleman with past recovery from hepatitis B virus (HBV) infection and stably controlled HIV (CD4: 255 cells/mm^3 (13.5%); HIV RNA: < 20 copies/mL) developed ESKD in the past 2 years due to type 1 diabetes and hypertension (he denied ingesting any nephrotoxins over this period.) He had been initiated one year prior on continuous 4-cycler PD nightly via an abdominal peritoneal dialysis catheter. At the time of PD initiation, he was found to be a low average transporter with the peritoneal equilibration test (PET). He was consented and brought into the Clinical Research Unit for sampling on two consecutive days. Eleven months prior to the study visit he had a hospitalization for bacterial peritonitis related to his PD catheter. At the time of study visit, his eGFR was 6 mL/min/1.73 m^2 (eGFR CKD-Epi (2021) equation) and he was placed on the transplant list for a kidney-pancreas transplant. His overnight PD was followed by morning dosing of his ART. He had been on a TAF-containing regimen for 5 years and had initiated a regimen of once-daily 50 mg DTG/200 mg FTC/25 mg TAF 7 months prior to the described study visit. He was prompted daily to take his ART for 3 days prior to presenting to the clinical trials unit for pharmacologic sampling; pre-dose blood was collected, followed by his observed standard dose of DTG/FTC/TAF. Blood and urine were then collected over a 24-hour period.

Methods

e study was conducted at the Johns Hopkins University School of Medicine's Drug Development Unit under an institutional review board (IRB)-approved protocol (NA_00031939); the participant provided informed consent. e study included a screening visit to determine eligibility based on the participant taking one of the protocol's approved drugs, followed by the study visit. Blood was collected for plasma and PBMC isolation pre-dose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 h after the observed dose. Urine was collected cumulatively over two time periods, 0–10 h, and 10–24 h post-dose with urine volume totals recorded. e participant's plasma trough concentrations for all drugs were compared pre-dose and at 24 h after dose, to assess if he was at steady state on his ART. PK parameters were compared between the

person included in this case report and cohorts of PWH, both with normal kidney function and on hemodialysis (HD). (Table 1). e PK parameters compared included time until maximum plasma concentration (T_{max}), (C_{max}), minimum plasma concentration (C_{min}), and (AUC_{last}). Renal dose was calculated from the 24-hour cumulative urine volume and the urine drug concentration. Renal clearance was then calculated as described before [17, 18]. KT/V and urea clearance values were calculated in his Nephrology chart with an online calculator where K is urea clearance, T is time on dialysis, and V is the urea volume of distribution where K is urea clearance, T is time on dialysis, and V is the urea volume of distribution [19, 20].

Drug concentrations were determined via liquid chromatographic-mass spectrometric (LC-MS/MS) analysis using previously described methods by the Clinical Pharmacology Analytical Laboratory (CPAL) within the Johns Hopkins University School of Medicine [23–25]. Assay lower limits of quanti cation (LLOQ) were as follows: plasma TAF, 0.03 ng/mL; plasma TFV: 1 ng/mL; plasma FTC: 5 ng/mL; plasma DTG: 100 ng/mL; urine TFV, 50 ng/mL; urine FTC, 50 ng/mL; PBMC tenofovir diphosphate (TFV-DP), 5 fmol/sample; PBMC emtricitabine triphosphate (FTC-TP), 50 fmol/sample. Intracellular anabolite concentrations were normalized to cell counts and reported as fmol/million cells.

Results

e participant was initially non-oliguric and continued to produce urine throughout the 24-hour study visit. Dialysis dose delivered was quanti ed by the KT/V ratio and residual kidney function was quanti ed by the urea clearance (for reference, normal kidneys clear urea at a rate of 65 mL/min, equating to 655 L of blood per week). KT/V ratio and residual renal urea clearance were 1.82 and 0.58 L/week six weeks before the study visit, 1.84 and 0.07 L/week one month after the study visit, 1.84 and 0.43 L/week 4 months after the study visit, and 1.62 and 0.18 L/week six months after the study visit, respectively [19, 20]. Viral suppression was maintained.

Plasma concentration time pro les were plotted in relation to PK values in those with normal renal function (Fig. 1). Plasma pre-dose and 24-hour post-dose trough concentrations were 670 and 718 ng/mL for DTG, 147 and 164 ng/mL for TFV, and 888 and 1006 ng/mL for FTC, respectively, indicating that the participant may not have been at steady-state for his ART medications. e TAF C_{min} was below the limits of quantitation of 0.05 ng/mL. When compared with concentrations in PWH with normal kidney function, (Tables 2 and 1) TAF C_{max} and AUC_{last}, were 1.92 and 1.40 times higher respectively; elevations were more pronounced for TFV, as C_{max} and AUC_{last} were 11.1 and 13.3-fold higher in the participant undergoing PD than in PWH with normal renal function. FTC C_{max} and AUC_{last} were 1.74 and 5.56-fold higher. C_{min} was 15.5-fold and 20- fold higher for TFV and FTC, respectively. Lastly, DTG $C_{min,}$ C_{max} and AUC_{last} were 0.90-, 0.51-and 0.60-fold lower, respectively.

Intracellular TFV-DP and FTC-TP concentrations were compared with historical and published data (Table 2); TFV-DP C_{max}, AUC_{last}, and C_{min} were 1.74 times, 2.04 times, and 2.18 times higher in the participant receiving PD (Table 2). TFV-DP C_{max} and AUC_{last} were still within the range of concentrations observed in those with non-compromised renal function. For FTC-TP, C_{max} was 4.68 times higher but within normal range, while AUC_{last}, and C_{min} were 4.17 and 5.44 times higher, respectively, and out of range when comparing his measurements with the

Table 1 Plasma and intracellular PK parameters for TAF, TFV, FTC, and DTG from a participant with HIV on PD & Comparison (ratio) of parameters to those in PWH with normal kidney function (normal CrCl)

Drug	Matrix	T_{max} (hours)	C_{max} (ng/mL)	C_{max} Ratio PD/Normal CrCl	AUC_{last} (h*ng/mL)	AUC_{last} Ratio PD/Normal CrCl	C_{min} (ng/mL)	C_{min} Ratio PD/Normal CrCl
TAF	**Plasma**	0.5	311.3	1.92	289.8	1.40	0.05	–
TFV	**Plasma**	4	169.4	11.14	3,905.6	13.33	164.4	15.51
FTC	**Plasma**	2	2991	1.74	44,522	5.56	1,006	20.12
DTG	**Plasma**	4	1719	0.51	26,401	0.60	717.8	0.86
TFV–DP	**PBMC**	5.6	1,554.10	1.74	27,172.61	2.04	997.91	2.18
FTC–TP	**PBMC**	5.6	21,068.61	4.68	294,599.8	4.17	9,789.94	5.44

Data from individuals with normal creatinine clearance based on results from:

a) Two phase III trials (GS-US-292-0104 and GS-US-292-0111) for TAF and TFV [6, 8]

b) Data from Phase III trial FTC-101 for FTC [6, 8]

c) Data from Min et al. for DTG [21]

d) Data from Thurman et al. for TFV-DP and FTC-TP [22]

CrCl=creatinine clearance; TAF=tenofovir alafenamide; FTC=emtricitabine; TFV=tenofovir; DTG=dolutegravir; T_{max}=time of maximal concentration; C_{max}=maximal concentration; AUC_{last}=area under the concentration-time curve from time 0 until the last observed concentration; C_{min}=trough concentration at 24 hours (the end of the dosing interval) PBMC=peripheral blood mononuclear cells; TFV-DP=tenofovir-diphosphate (active intracellular metabolite of tenofovir); FTC-TP=emtricitabine triphosphate (active intracellular metabolite of emtricitabine)

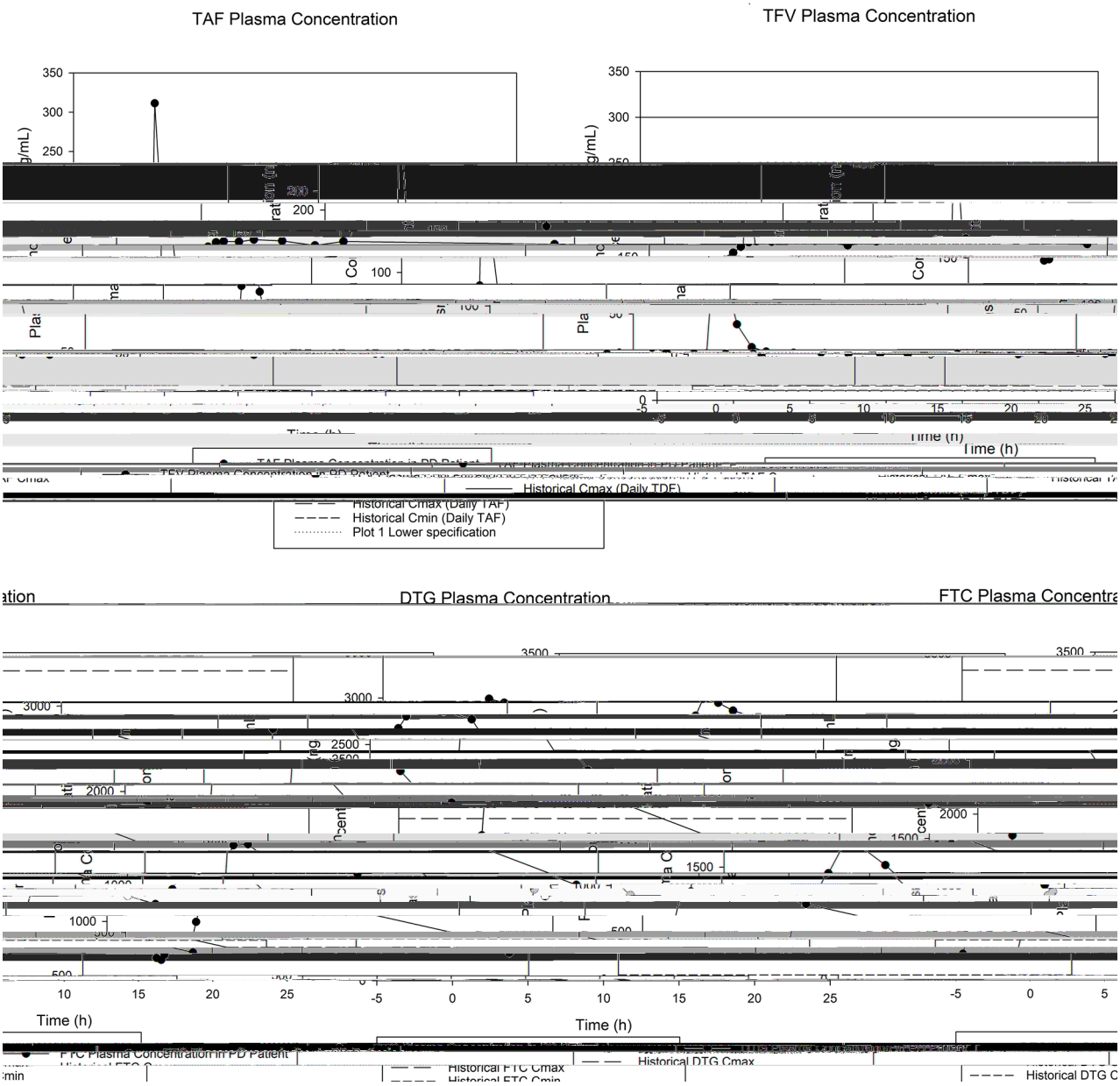

Fig. 1 Plasma concentration: time plots of TAF, TFV, FTC, and DTG. Plasma drug concentration versus time plots for each of the four analytes related to the three drugs studied. Dotted reference lines indicate historical C_{max} (long dash) and C_{min} (short dash) for TAF, TFV, FTC, and DTG historical data. TFV plot includes additional historical C_{max} (solid line) and C_{min} (dotted line) from TDF dosing

median FTC-TP exposures of people with normal kidney function.

e participant produced 615 mL of urine over a 24-hour period. Total urine concentrations for FTC and TFV were 56,380 ng/mL and 6,743 ng/mL, respectively, for the rst (0–10 h) period, and 27,970 ng/mL and 4,524 ng/mL, respectively, for the 10-24-hour period. Dose and renal clearance were calculated for both drugs. For TFV, the cumulative amount excreted (A_{0-24}) was 3.3 mg, which makes up 22% of the 15 mg of TFV provided by 25 mg of TAF [26]. e TFV renal clearance was 14.1 mL/min. For FTC, (A_{0-24}) was 23.86 mg, which is 11.9% of total 200 mg dose, with renal clearance 8.93 mL/min.

Discussion

We present the rst report on TAF PK in a person with HIV with ESKD on chronic PD. Both C_{max} and AUC of TAF in this participant were comparable with TAF concentrations in individuals with normal kidney function, likely due to the fact that TAF is not renally cleared to a signi cant degree [11, 27]. However, plasma TFV concentrations were higher in the setting of PD, ranging from

Table 2 Comparison of Plasma and Intracellular PK parameters for TAF, TFV, FTC, and DTG between the participant with HIV on PD and other populations with and without HIV and renal impairment

Drug	Population	Sample size (# individuals)	T_{max} (hours)	C_{max} (ng/mL)	C_{max} Ratio PD/Normal CrCl	AUC_{last} (h*ng/mL)	AUC_{last} Ratio PD/Normal CrCl	C_{min} (ng/mL)	C_{min} Ratio PD/Normal CrCl
TAF	**HIV+, Normal CrCL**[a][b]	*N* = 539	1	162		206			
	HIV-, Renal impairment[b, c]	*N* = 13		364 (65.7)		513 (47.3)			
	HIV+, PD	1	0.5	311.3	**1.92**	289.8	**1.40**	0.05†	
	HIV+, HD[b, d]	*N* = 12		246 (75%)	**1.26‡**	232 (53)	**1.25‡**		
TFV	**HIV+, Normal CrCL**[a, b, e]	*N* = 841	1	15.2 (26.1)		293 (27.4)		10.6 (28.5)	
	HIV-, Renal impairment[b, c]	*N* = 14		26.4 (32.4)		2,070 (47.1)			
	HIV+, PD	*N* = 1	4	169.4	**11.14**	3905.6	**13.33**	164.4	**15.51**
	HIV+, HD[b, d]	*N* = 10		443 (41)	**0.38‡**	8,720 (39)	**0.45‡**	265 (73)	**0.6‡**
FTC	**HIV+, Normal CrCL**[a, b, e]	*N* = 8	1 (1, 2)	1,720 (53)		8,000 (15)		50 (24)	
	HIV+, PD	*N* = 1	2.0167	2,991	**1.74**	44,522.08	**5.56**	1,006	**20.12**
	HIV+, HD[b, e]	*N* = 11		4,880 (41)	**0.61‡**	62,900 (48)	**0.71‡**	1280 (59)	**0.79‡**
DTG	**HIV+, Normal CrCL**[g, b]	*N* = 10	2	3,340 (16)		43,400 (20)		830 (26)	
	HIV+, PD	*N* = 1	4	1,719	**0.51**	26,401.27	**0.60**	717.8	**0.86**
	HIV+, HD[h]			1,894	**0.91‡**				
PBMC TFV-DP	**HIV-, normal CrCl**[i, j] Median (range)	*N* = 24	2 (1, 48)	892.35 (388.06, 5,004.52)		13,297.91 (7,603.8, 37,310.19)		457.1 (238.6, 813.69)	
	HIV + on PD[k]	*N* = 1	5.6	1,554.10	**1.74**	27,172.61	**2.04**	997.91	**2.18**
PBMC FTC-TP	**HIV-, normal CrCl**	*N* = 24	2 (1, 8)	4,500.23 (2,793.30, 23,531.58)		70,695.24 (50,554.78, 151,745.63)		1,800.44 (1,147.562, 3,443.56)	
	HIV + on PD	*N* = 1	5.6	21,068.61	**4.68**	294,599.8	**4.17**	9,789.94	**5.44**

HD = hemodialysis; PD = peritoneal dialysis; CrCl = creatinine clearance; TAF = tenofovir alafenamide; FTC = emtricitabine; TFV = tenofovir; DTG = dolutegravir; T_{max} = time of maximal concentration; C_{max} = maximal concentration; AUC_{last} = area under the concentration-time curve from time 0 until the last observed concentration; C_{min} = trough concentration at 24 h (the end of the dosing interval) PBMC = peripheral blood mononuclear cells; TFV-DP = tenofovir-diphosphate (active intracellular metabolite of tenofovir); FTC-TP = emtricitabine triphosphate (active intracellular metabolite of emtricitabine); CrCl = creatinine clearance; PD = peritoneal dialysis

a) Based on data from two pivotal phase III trials (GS-US-292-0104 and GS-US-292-0111). [6, 8]

b) Data represented in Mean (CV%)

c) Based on data by Custodio et al. [11]

d) Based on data by Eron et al. [14, 15]

e) Based on data from Phase III trial FTC-101 [8]

f) Based on data from Min et al. [21]

g) Concentration is average of 5 patients' levels post hemodialysis. Dialysis was performed ~ 5.9 h post dose. Data by Molto et al. [13]

h) Based on data by Thurman et al. [22]

i) Data represented in Median (range)

j) eGFR -CKD-EPI Creatinine for patient = 6 mL/min/1.73 m^2

† C_{min} for TAF was below the limit of quantification for the assay (BLQ < 0.03 ng/mL). This value represents the C_{last} that was detected 10 h

‡ Ratio of PD/HD data

11-fold (C_{max}) to 15-fold (C_{min}) higher compared to individuals with normal kidney function. e elevated TFV trough observed in the participant on TAF in the setting of PD likely indicates plasma accumulation. Notably, the TFV trough concentration was also 3-fold higher than what would be expected with steady-state TDF dosing in someone with normal renal function (median trough concentration of ~ 50 ng/mL (IQR 35–77) [28–30].

While FTC C_{max} was modestly higher in our PD patient compared to patients with normal renal function, both FTC AUC_{last} and FTC trough (C_{min}) were many-fold higher—6-fold and 20-fold higher, respectively. is suggests FTC accumulation in the plasma, however, this may not add substantial toxicity risk given the overall tolerability of FTC [31]. Lastly, DTG peak, trough, and AUC_{last}, measurements were lower in this participant than in people with normal kidney function. is might indicate that

DTG is either (1) better cleared by PD (compared to HD where it is only minimally cleared, with a median extraction ratio of 7%) or (2) not being absorbed as well, or (3) another mechanism that is not yet characterized [13]. Regardless, the DTG trough concentrations, while low, are above the protein-adjusted in vitro IC90 of 64 ng/mL and also above 300 ng/mL, the median plasma trough concentrations established to be su cient for viral suppression from 10 mg DTG once daily,, which showed equivalent viral suppression to recommended 50 mg once daily in the phase 2 e cacy trial SPRING-1) [32].

Despite the high plasma TFV concentrations, TFV-DP C_{max} and AUC_{last} were within the normal range, while C_{min} was slightly above the range, 2.18 times the average historical data. For FTC-TP, C_{max} was within range, while AUC_{last} and C_{min} were higher compared with historic data, with C_{min} being 5.44-fold higher than the historical average. e molar relationship between plasma FTC and intracellular FTC-TP (0.1) is higher than previously reported (0.034) [33, 34, 22] and may be attributed to the 20-fold higher plasma FTC trough concentrations, or the saturation of one of the molecular mechanisms responsible for the conversion of FTC to FTC-TP [8, 35, 36].

Comparing the participant's urine data to a recent study of people with normal renal function taking FTC/TDF [37], the TFV A_{0-24} was 38 mg, which made up 28% of the 136 mg TFV provided by 300 mg TDF, while the clearance was 289 mL/min, which is 20-fold higher than the clearance in the participant. is supports that TFV is not getting su ciently cleared in the participant by his kidneys nor by his PD, causing the accumulation. As for FTC, in those with normal renal function, the A_{0-24} was 114 mg, making up 57% of the 200 mg dose of the FTC. Clearance was 216 mL/min, 24-fold the clearance in the participant.

e factors that determine whether a given drug is likely to be removed via PD include drug speci c factors like molecular weight, protein binding, water solubility, and volume of distribution, as well as patient speci c factors like their peritoneal membrane transport function [38, 39]. TFV it is cleared by HD, with an extraction ratio of around 54%, and has factors that suggest it should be easily dialyzable via PD [14, 40]. However, since plasma TFV concentrations were quite elevated in this participant on PD, the amount of TFV removed with PD is likely insu cient to overcome the accumulation that occurs in the absence of renal elimination. And although the TFV concentrations were lower compared with historical HD data, those were from people dosed with TDF. Bloodstream TFV concentrations in the setting of daily adherence to TAF might be even higher, given that this individual was not at steady state. Further, the TFV accumulation observed in our PD patient led to TFV plasma trough concentration threefold those seen with daily TDF dosing, possibly mitigating any renal safety advantages conferred by TAF compared to TDF, as concentrations in this range have previously been linked to potential nephrotoxicity [41, 42].

Between the time of the study visit and the publication of this report, the patient's residual kidney function had declined further, uctuating around a low baseline. We do not know if this resulted from continued progression of his underlying renal disease or elevated plasma TFV concentrations. Regardless, based on data from this single individual on PD, we conclude that once daily TAF dosing results in plasma trough TFV concentrations 15-fold higher than those in individuals with normal kidney function, and 3-fold higher than trough TFV concentrations in individuals with normal kidney function on TDF. Notably, we do not judge any of the observed PK changes in the participant on PD to have resulted in any loss of antiviral e cacy; he has remained suppressed. But while more research is needed, it may be reasonable at present to avoid daily TAF in people with ESKD receiving PD where preservation of residual kidney function is strongly desired.

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Author contributions
SAM, EJF, and RPB performed the research. SAM, EJF, EDW, CWH, and MAM designed the research study. RPB and MAM contributed essential reagents and tools. SAM and EDW analyzed the data. All authors contributed equally in writing the paper.

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Data availability
The deidenti ed data that support the ndings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Competing interests
MGA is involved in litigation involving Gilead Sciences Inc.

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