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The Lymphoid Tissue Pharmacokinetics of Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide in HIV-Infected Persons

Courtney V. Fletcher[1,*], **Anthony T. Podany**[1], **Ann Thorkelson**[2], **Lee C. Winchester**[1], **Timothy Mykris**[1], **Jodi Anderson**[2], **Siri Jorstad**[2], **Jason V. Baker**[2,3], **Timothy W. Schacker**[2]

[1]Antiviral Pharmacology Laboratory, University of Nebraska Medical Center, Omaha, Nebraska, USA;

[2]Division of Infectious Diseases, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA;

[3]Infectious Diseases, Hennepin Healthcare Research Institute (HHRI), Minneapolis, Minnesota, USA.

Abstract

The secondary lymphoid tissues (LT), lymph nodes (LN) and gut-associated lymphoid tissue are the primary sites of HIV replication and where the latent pool of virus is maintained. We compared the pharmacokinetics of tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) in LT of 13 HIV-infected persons receiving a TDF-containing antiretroviral regimen who subsequently switched to a TAF-containing regimen. Study participants were on stable antiretroviral therapy for ≥12 months with plasma HIV-RNA < 48 copies/mL for 6 months before enrollment and entry CD4 cell counts > 300 cells/μL. Intracellular concentrations of tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP) were quantified in PBMCs and in mononuclear cells obtained from LN, ileum and rectal tissues. With TAF, the TFV-DP concentrations in PBMCs and LN were 7.3-fold and 6.4-fold higher (ratios of geometric means of TAF to TDF), respectively, compared with TDF; ileal and rectal concentrations, however, were lower with geometric mean ratios of 0.14 and 0.18, respectively. A statistically significant relationship was observed between PBMC and LN concentrations of TFV-DP. During TDF-containing therapy, the expected effect of cobicistat to increase TFV plasma concentrations was observed, as were higher TFV-DP concentrations in PBMCs and mononuclear cells from LN, ileum and rectal tissues. The higher TFV-DP concentrations achieved with TAF in the LN provides the first human correlate of the observation in animals that TAF produced higher tenofovir LN concentrations. The ability to increase LN concentrations allows investigations of whether antiretroviral regimens with improved LN pharmacokinetics elicit a more complete virologic response in that compartment.

[*]Correspondence: Courtney V. Fletcher (cfletcher@unmc.edu).

AUTHOR CONTRIBUTIONS

C.V.F., A.T.P., J.V.B., and T.W.S. wrote the manuscript. C.V.F., J.V.B., and T.W.S. designed the research. C.V.F., A.T.P., A.T., J.A., L.C.W., S.J., J.V.B., and T.W.S. performed the research. C.V.F., A.T.P., S.J., and T.W.S. analyzed the data. A.T.P., L.W., T.M., and J.A. contributed new reagents/ analytical tools.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

In now the 5th decade of the HIV epidemic, combination antiretroviral therapy (ART) can achieve long-term suppression of plasma viral load to <50 copies/mL, decrease HIV transmission, reduce mortality and improve quality of life for people living with HIV. But, the ability to eradicate the virus from an infected individual still evades us. Furthermore, in persons with undetectable plasma viral loads immune reconstitution is incomplete and a state of immune activation linked with increased morbidity and mortality persists.[1] The reservoir of latent virus in resting CD4+ T cells is a major obstacle to virus eradication. The secondary lymph nodes (LN) and gut-associated lymphoid tissue (GALT) are the primary sites of HIV production and where the latent pool of virus is maintained.[2] Studies in HIV-infected persons and non-human primates (NHPs) have shown: low concentrations of some antiretroviral drugs (ARVs) in lymphoid tissue (LT); direct evidence of low-level ongoing virus production in the LN despite suppression of plasma viral load to <50 copies/mL; and an association between low ARV LN concentrations and measures of persistent viral production.[2–4] These findings inform the hypothesis that ARV concentrations in LT, particularly the LN, may be insufficient to suppress viral replication fully within that compartment and low-level production of HIV in LT could lead to re-seeding of the reservoir, contributing to inflammation and sustained immune activation.[5]

Pharmacologic sanctuary sites for ARVs include adipose tissue, the CNS, male and female reproductive tracts, GALT and LN.[6,7] The secondary LT are of particular interest because studies in humans and NHPs have shown these tissues are where >98% of the reservoir resides.[2] Tenofovir (TFV) is a nucleotide reverse transcriptase inhibitor (NRTI) available for oral administration as tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). Tenofovir, in either prodrug, is a recommended first-line drug for treatment of HIV-infection in ARV-naïve persons.[8] Studies in animals and HIV-infected persons have shown low penetration of TFV and its pharmacologically active moiety, TFV-diphosphate (TFV-DP) in LN when given as TDF.[3,9,10] Animal studies have shown 6- to 15-fold greater penetration (depending on anatomical location) of TFV in LN when given as TAF.[10] No data on LT penetration following TAF administration in HIV-infected individuals are available to confirm whether the finding of higher LN concentrations of TFV in animals translates to humans as higher LN concentrations of TFV-DP. Our objective was to compare the LT pharmacokinetics of TFV-DP following a switch from TDF to TAF in HIV-infected persons.

METHODS

Participants were HIV-infected adults enrolled in a study of immune reconstitution and LT compartments (NCT01852942). The clinical protocol and informed consent forms were approved by IRBs at the University of Minnesota and Hennepin Healthcare Research Institute, and all participants gave their written informed consent. Eligible participants were on stable ART for ≥12 months with plasma HIV-RNA < 48 copies/mL for 6 months before enrollment and CD4 cell counts > 300 cells/μL. Peripheral blood (including PBMCs) was collected every three months and excisional biopsies of inguinal LN, and colonoscopies with biopsies of the terminal ileum and rectum were planned at baseline and 12 and 30 months after enrollment. The protocol allowed changes to ART after the baseline visit.

PBMCs and mononuclear cells (MNCs) from the LN, ileum and rectum were all processed in the same laboratory using methods we have previously described.[3] Cell counts were obtained with the Countess II FL (ThermoFisher, Waltham, MA) using the cell counting chamber slides with trypan blue 0.4% for automated cell counting (Invitrogen). Intracellular concentrations of TFV-DP and emtricitabine-triphosphate (FTC-TP) were quantified by liquid chromatography–triple quadrupole mass spectrometry using published methods.[3] Briefly, TFV-DP and FTC-TP were quantified from lysed cellular matrix of PBMCs and MNCs on a Shimadzu Nexera ultra high-performance liquid chromatograph attached to an AB Sciex 5500 QTrap mass spectrometer. Quality control sample interbatch coefficients of variance averaged 7% and 4.9% for TFV-DP and FTC-TP, respectively. Absolute mean relative errors to the theoretical target quality control samples averaged −3% and 1.1% for TFV-DP and FTC-TP, respectively. The analytical range for the TFV-DP and FTC-TP assays was 2.5 to 1,000 fmol/sample and final results were expressed in fmol/10^6 cells. TFV-DP and FTC-TP concentrations were summarized and compared between TDF and TAF with descriptive statistics.

RESULTS

TFV-DP pharmacokinetic data were obtained from 13 HIV-infected persons who entered the study on a TDF-containing ART regimen and during the study switched to a TAF-containing regimen. These individuals (12 men, 1 woman) all had plasma HIV-RNA at entry < 48 copies/mL and all remained at this value except one who had a viral blip to 72 copies/mL but returned to and remained at < 48 copies/mL without any intervention. The median CD4 cell count at entry was 510 cells/μL. Concomitant ARVs were: FTC in all 13; efavirenz in four, rilpivirine in three, atazanavir/cobicistat in one, elvitegravir/cobicistat in four, raltegravir in one and dolutegravir in two. While continuing to receive TDF (and FTC) two participants changed their other ARVs before switching to TAF. After switching to TAF, all 13 continued receiving FTC; seven were also receiving elvitegravir/cobicistat, four rilpivirine, and one each dolutegravir and raltegravir. Participants received their TAF regimen for an average of 5.7 months before the first tissue samples were collected.

Concentrations of TFV-DP and FTC-TP in PBMCs and MNCs from LN, ileal and rectal biopsies associated with the TDF- and TAF-containing regimens are given in Tables 1 and 2. Concentrations of TFV-DP in PBMCs and LN with TAF were 7.3-fold and 6.4-fold greater (ratio of geometric means of TAF to TDF), respectively. TFV-DP concentrations in the ileum and rectum, however, were lower for TAF compared with TDF, with geometric mean ratios of 0.14 and 0.18, respectively. TFV-DP concentrations in PBMCs, LN, ileum and rectum in the only female were as follows. Her TFV-DP concentrations (fmol/10^6 cells) on TDF were PBMCs, 81; LN, below limit of quantitation; ileum, 1170; and rectal, 184. With TAF, TFV-DP concentrations were: PBMCs, 607; LN, 229; ileum, 703; and rectal, 49 fmol/10^6 cells. LN and PBMC concentrations of TFV-DP were related described by the equation: $Y = 0.1474X + 15.25$; $r^2 = 0.58$; $P < 0.001$. No other relationships were observed for TFV-DP, or for FTC-TP in PBMCs compared with LN, ileal or rectal concentrations.

DISCUSSION

We show that TFV-DP concentrations in PBMCs and LN were 7.3-fold and 6.4-fold higher, respectively, in HIV-infected persons who switched from TDF to TAF. The higher PBMCs concentrations of TFV-DP with TAF agree with published literature.[11] Our finding that LN TFV-DP concentrations were higher with TAF provides the first evidence that the higher LN concentrations of TFV following oral TAF administration to dogs translates to humans as higher intracellular concentrations in the LN of the pharmacologically active moiety, TFV-DP. We also found that TFV-DP concentrations in MNCs from the ileum and rectum were lower with TAF compared with TDF. This finding agrees with reports from others of lower TFV-DP concentrations with TAF in rectal tissue homogenates from NHPs and women.[12,13]

Penetration of drugs into LTs depends on several physicochemical characteristics including molecular weight, ionization, dissociation constant (pKa), lipophilicity (logP), protein binding and particle size; higher molecular weight, lipophilicity and particle size have been associated with greater intestinal lymphatic system absorption.[14] These physicochemical characteristics of TAF, TDF and TFV do not completely discriminate differences in LT penetration. However, TAF has greater stability than TDF in human plasma and more efficiently delivers TFV to lymphoid cells and tissues that is facilitated also by efficient metabolism of TAF by cathepsin A, which is highly expressed in lymphoid cells.[15] These properties provide a mechanism for the higher levels of TFV-DP seen in PBMCs, and as we have now shown in LN with TAF. Both TAF and TDF achieve lower concentrations of TFV-DP in the LN than their corresponding values in PBMCs. This finding and magnitude of restricted LN bioavailability is consistent with the work of others who used different techniques including administration of radiolabeled drug and positron emission tomography in rats,[9] tissue distribution studies after oral administration of radiolabeled TDF and TAF to dogs,[10] and isolation of MNCs from LNs after oral administration of TDF and TAF to NHPs.[16,17] The lower concentrations of TFV-DP in the ileum and rectum seen with TAF may be a combination of several factors. The bioavailability of TAF is estimated at 40% compared with 25% for TDF. TAF and TDF are substrates for the efflux transporters P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) both expressed in gastrointestinal tissues.[15] While TAF has greater stability in plasma than does TDF, it is unstable in intestinal and hepatic cytoplasmic extracts. The combination of the higher bioavailability of TAF, the low oral dose administered to humans and intestinal efflux that prolongs its residence time in intestinal tissues allowing increased intestinal metabolism, may collectively lead to low luminal concentrations. Clinically, studies of TAF- vs. TDF-containing regimens for treatment of HIV infected persons have shown equally high-rates of suppression to or maintenance of undetectable levels of plasma HIV-RNA.[18,19] Additionally, TAF/FTC has been shown noninferior to TDF/FTC for preexposure prophylaxis (PrEP) of HIV transmission in men who have sex with men and transgender women at high risk for acquiring HIV.[20]

The low sample size precludes comparing TFV-DP concentrations between male and female sex at birth. This gap in our knowledge of sex differences should be addressed in future investigations. This need is emphasized as TAF/FTC has not yet been FDA-approved for PrEP in cisgender women at risk for HIV acquisition from receptive vaginal sex due in part

to insufficient tissue pharmacokinetic data. We note other studies in HIV-infected and not HIV infected persons have found that females have higher TFV-DP concentrations in PBMCs compared with males.[21] Acknowledging the sample size limitation, we compared TFV-DP concentrations in those receiving a regimen with or without cobicistat, an inhibitor of cytochrome P450 3A, Pgp and BCRP.[22] During TDF-therapy, the expected effect of cobicistat to increase plasma TFV concentrations was observed, as were increased TFV-DP PBMC, LN, ileal and rectal concentrations. Effects of other concomitant ARVs should not be excluded, as in vitro studies have reported an interaction with the combination of TFV, FTC and efavirenz, apparently modulated by multidrug resistance-associated proteins, which resulted in higher intracellular concentrations of TFV and FTC.[23] Contemporary ART commonly involves combinations of drugs that are substrates, inducers and/or inhibitors of drug metabolizing enzymes and transporters, which can result in drug-drug interactions, such as antagonism of NRTI phosphorylation that manifest intracellularly but not in plasma.[24] The optimal selection of ARVs to be given in combination may benefit from a more careful study of intracellular as well as systemic pharmacology.

The key finding of this investigation of intracellular TFV-DP concentrations in LT was that LN concentrations were 6.4-fold higher with TAF compared with TDF. TAF produced TFV-DP concentrations in the LN (median, 130 fmol/10^6 cells) greater than those achieved by TDF in PBMCs (median, 57 fmol/10^6 cells) and in the LN (median, 26 fmol/10^6 cells). These data show that drug concentrations in the LN compartment, where evidence of persistent viral production and associations between low ARV concentrations and measures of persistent viral production have been reported, can be increased.[2–5] This has previously been shown with parenteral administration of an ARV nanoformulation in NHPs, but not with an oral drug in humans.[25] The lower ileal and rectal TFV-DP concentrations with TAF could raise questions about whether they are sufficient to fully suppress replication in those tissues. The demonstration, however, that TAF is non-inferior to TDF for PrEP in men who have sex with men offers some reassurance of activity in the rectum. The complete suppression of HIV viral replication is a prerequisite for eradication of HIV from tissue reservoirs. The ability to improve pharmacokinetic conditions in the LN allows investigations of whether ARV regimens with enhanced LN concentrations elicit a more complete virologic response, although a focus on all lymphoid tissues is warranted, given they are where >98% of the reservoir resides.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

- The secondary lymphoid tissues (LT), lymph nodes (LN) and gut-associated lymphoid tissue (GALT), are the primary sites of HIV replication and where the latent pool of virus is maintained. Studies in HIV-infected persons have shown low LN concentrations of some antiretroviral drugs and an association between low antiretroviral concentrations in LN and measures of persistent viral production.

WHAT QUESTION DID THIS STUDY ADDRESS?

- A comparison of the LT pharmacokinetics of the intracellular pharmacologic-active moiety, tenofovir-diphosphate, in HIV-infected persons following oral administration of tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

- Tenofovir-diphosphate concentrations in PBMCs and LN were 7.3-fold and 6.4-fold higher, respectively, with TAF. Our finding that TAF achieved higher LN concentrations of tenofovir-diphosphate provides the first human correlate of the observation in animals that TAF produced higher tenofovir LN concentrations. TFV-DP concentrations in the ileum and rectum, however, were lower with TAF compared with TDF.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

- The ability to increase LN concentrations allows investigations of whether ARV regimens with increased LN concentrations can achieve a more complete virologic response.

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Table 1

TFV (ng/mL) and TFV-DP (fmol/10^6 cells) concentrations by tenofovir formulation, compartment and antiretroviral regimen

	Matrix and concentrations (median (interquartile range) geometric mean)				
Drug and regimen	**Plasma**	**PBMC**	**Lymph Node**	**Ileum**	**Rectum**
TDF					
All regimens (*n* = 15)	126 (74, 240) 133	57 (44, 96) 76	26 (7, 78) 22	641 (448, 1,501) 753	456 (194, 909) 296
NNRTI or INSTI (*n* = 10)	110 (70, 211) 116	53 (37, 80) 63	25 (8, 66) 23	632 (372, 1,280) 641	204 (142, 340) 142
PI or INSTI with cobicistat (*n* = 5)	180 (89, 292) 170	57 (54, 249) 112	70 (48, 92) 55	2,063 (1,321, 2,805) 1,434	1,326 (1,154, 1,498) 1,281
TAF					
All regimens (*n* = 13)	14 (8, 21) 14	595 (432, 662) 560	130 (102, 151) 139	151 (26, 385) 102	49 (33, 107) 54
NNRTI or INSTI (*n* = 6)	14 (7, 21) 12	683 (589, 914) 699	143 (125, 160) 135	248 (87, 466) 146	44 (38, 85) 53
INSTI with cobicistat (*n* = 7)	16 (13, 21) 16	483 (415, 592) 448	106 (98, 132) 143	66 (18, 151) 67	54 (29, 116) 55

NNRTI, Non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor. Samples collected during TDF/FTC therapy were obtained at the following average times post dose: plasma, 14.37 hours; LN, 13.23; ileum, 12.43; and rectum, 12.23. During TAF/FTC therapy, samples were obtained at average post dose times of: plasma, 11.26 hours; LN, 13.87 hours; ileum, 12.72; and rectum, 12.85 hours. Processing of plasma, PBMC and tissue samples was initiated within 30 minutes after collection. Usual times to complete processing are: plasma, 20 minutes; PBMC, 75 minutes; LN, 40 minutes; and ileal and rectal samples, 80 minutes. During TDF/FTC therapy, a total of 190 plasma samples were obtained and each was analyzed for both TFV and FTC; TFV and FTC were each below the limit of quantitation (BLQ) in 1 (the same) sample. 165 PBMC, LN, ileal and rectal samples were collected during TDF/FTC therapy and each was analyzed for TFV-DP and FTC-TP; 36 analytes (10.9%) were BLQ. During TAF/FTC therapy, 54 plasma samples were obtained, and each analyzed for TFV and FTC; TFV was BLQ in 1 sample. A total of 97 PBMC, LN, ileal and rectal samples were collected during TAF/FTC therapy and analyzed for TFV-DP and FTC-TP; 3 analytes (1.5%) were BLQ. BLQ values were excluded (i.e., no value was imputed) for calculation of the summary statistics in **Tables 1** and 2.

Table 2

FTC (ng/mL) and FTC-TP (fmol/10^6 cells) concentrations by tenofovir formulation, compartment and antiretroviral regimen

	Matrix and concentrations (median (interquartile range) geometric mean)				
Drug and regimen	**Plasma**	**PBMC**	**Lymph Node**	**Ileum**	**Rectum**
FTC with TDF					
All regimens (*n* = 15)	463 (147, 997) 384	4,769 (3,570, 6,780) 4,969	1,710 (1,484, 2,238) 1,148	366 (232, 901) 364	292 (160, 818) 323
NNRTI or INSTI (*n* = 10)	351 (118, 944) 341	4,277 (3,614, 5,297) 4,736	1,721 (781, 2,194) 840	371 (236, 606) 394	390 (288, 976) 436
PI or INSTI with cobicistat (*n* = 5)	531 (247, 1,088) 471	5,054 (2,794, 9,703) 5,471	1,699 (1,528, 2,253) 2,017	361 (141, 1,000) 315	126 (121, 259) 178
FTC with TAF					
All regimens (*n* = 13)	323 (140, 1,186) 371	7,580 (4,902, 10,951) 6,964	3,469 (2,222, 5,437) 3,419	348 (207, 568) 380	206 (101, 438) 200
NNRTI or INSTI (*n* = 6)	197 (89, 1,067) 265	6,300 (4,902, 10,517) 6,901	3,469 (2,276, 5,249) 3,513	434 (187, 771) 448	261 (141, 414) 212
INSTI with cobicistat (*n* = 7)	577 (286, 1,223) 566	9,165 (4,882, 10,951) 7,027	3,608 (2,252, 5,419) 3,297	256 (227, 464) 306	121 (83, 429) 186

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