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Detectable HIV RNA in late pregnancy associated with low tenofovir hair levels at time of delivery among women living with HIV in the United States

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Abstract

Objective: We evaluated peripartum tenofovir (TFV) exposure via hair measures among women living with HIV (WLHIV) in the United States.

Design: Observational cohort study

Methods: Hair samples were collected at or shortly after childbirth among mothers enrolled in the Surveillance Monitoring for ART Toxicities Study of the Pediatric HIV/AIDS Cohort Study (PHACS) between 6/2014–7/2016. Among mothers receiving tenofovir-disoproxil-fumarate (TDF)-based regimens during pregnancy, TFV hair concentrations were analyzed using liquid chromatography/tandem mass spectrometry. Weight-normalized TFV concentrations were $\log_{10}$ transformed. Multivariable linear regression assessed correlates of TFV concentrations.

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Results: Overall, 121 mothers on TDF-based ART during pregnancy had hair specimens tested for TFV concentrations and were included in the analysis. Median age at delivery was 31 years (IQR 26–36); 71% self-identified as non-Hispanic black, and 10% had unsuppressed viral loads (VL) in late pregnancy (HIV-RNA ≥400 copies/mL). Median time from birth to hair collection was 3 days (IQR 1–14) and median TFV hair concentration was 0.02 ng/mg (IQR 0.01–0.04). In multivariable models, an unsuppressed VL in late pregnancy was associated with 80% lower adjusted mean peripartum TFV concentrations than pregnancies with viral suppression (95% CI: −90% to −59%, p<0.001). Use of TDF only in the first trimester and attaining high school graduation were also associated with lower TFV hair concentrations.

Conclusions: Unsuppressed VL during late pregnancy was strongly associated with lower maternal TFV hair concentrations at birth, though viremia was rare. Efforts to improve maternal virological outcomes and eliminate vertical HIV transmission could incorporate drug exposure monitoring using hair or other metrics.

INTRODUCTION

Globally, 160,000 infants were newly infected with HIV in 2018, which is substantially above the global goal of 40,000 or fewer by 2018 to be on track to eliminate new pediatric HIV infections by 2030.[2] Adequate exposure to antiretroviral therapy (ART) is particularly important among women living with HIV (WLHIV) during the peripartum period. Higher ART exposure is associated with better virological outcomes[3–5] which has benefits for both mothers and infants because viremia in late pregnancy substantially increases risk of vertical HIV transmission.[6] Therefore, understanding and maintaining ART exposure among pregnant women continues to be a major public health concern for preserving maternal health and preventing vertical HIV transmission.[7]

Drug level monitoring in biomatrices provides objective data on ART exposure.[8–10] Prior studies examined objective biomarkers for ART exposure during pregnancy using blood concentrations (e.g., cord blood[11–14] and within erythrocytes[15]), which capture a short period of exposure. Hair concentrations of ART reflect cumulative systemic ART exposure and predict viral suppression in a number of settings.[16, 17] No prior studies have evaluated maternal ART exposure during pregnancy using hair measures among WLHIV in the United States (US). Using data from the Dynamic Cohort of the Surveillance Monitoring for ART Toxicities (SMARTT) Study, a prospective cohort of pregnant WLHIV conducted by the Pediatric HIV/AIDS Cohort Study (PHACS) network, we evaluated acceptability of hair collection during the peripartum period and measured TFV hair concentrations.

METHODS

Study population

The PHACS SMARTT study was designed to assess the safety of *in utero* antiretroviral exposure among perinatally HIV-exposed uninfected children born to mothers living with HIV.[18] The SMARTT Dynamic study enrolls children and their mothers living with HIV at 18 clinical sites in the US including Puerto Rico.[19] All pregnancies enrolled in the SMARTT Dynamic cohort with a delivery date between June 1, 2014 and July 1, 2016 were

eligible for the hair sub-study. Pregnancies with no reported maternal ART use during pregnancy, no maternal consent for hair collection, and lack of maternal scalp hair were ineligible. Eligible for the current analysis were pregnancies of women with reported use of tenofovir-disoproxil-fumarate(TDF)-based regimens at some point during pregnancy and who were approached for hair collection. Within this group, pregnancies with a maternal hair specimen tested for TFV were eligible for analyses of TFV drug levels.

The SMARTT protocol was approved by institutional review boards at each of the participating sites and the Harvard T.H. Chan School of Public Health; all participants provided written informed consent in their preferred language. Hair sub-study procedures were also approved by the University of Washington and the University of California, San Francisco (UCSF) Committees on Human Research.

At SMARTT study entry, all infants were HIV-exposed, yet uninfected per SMARRT eligibility criteria[18] maternal ART exposure data, including start and stop dates, were abstracted from clinical records. Birth characteristics (gestational age and mode of delivery) and maternal HIV disease characteristics during pregnancy, including plasma HIV RNA concentration (viral load) and absolute CD4+ lymphocyte (CD4) cell counts, were also abstracted. Unsuppressed viral load was defined as HIV RNA ≥400 copies/mL. Demographic characteristics, including race/ethnicity and educational attainment, reasons for declining hair collection, as well as substance use during pregnancy, were obtained by interview.[20] Self-reported adherence (i.e., number of days HIV medicines were missed in the last 30 days) was added in March 2015.

Laboratory methods

Small hair samples (~100 strands) were collected at a single time point at or shortly after childbirth among willing WLHIV using previously described methods.[21] Among WLHIV with reported use of a TDF-based regimen during pregnancy, TFV hair concentrations in the proximal 1.5 centimeters of hair (representing ~6 weeks of exposure) were analyzed using validated liquid chromatography/tandem mass spectrometry (LC-MS/MS)-based methods at the UCSF Hair Analytical Laboratory (HAL).[22] The assay is validated from 0.002–0.400 ng TFV/mg hair and was peer-reviewed and approved by the National Institute of Health's Division of AIDS-supported Clinical Pharmacology and Quality Assurance (CPQA) program.[23]

Statistical analyses

We compared characteristics of eligible pregnancies in which women accepted vs. declined hair collection at delivery, as well as between pregnancies with vs. without maternal hair tested for TFV levels among those who had specimens collected. Reasons for not collecting maternal hair specimens were summarized. Among pregnancies with hair collected, we summarized the reasons for not assaying the hair. Wilcoxon rank-sum test and chi-square test were used for statistical comparisons across subgroups.

The weight-normalized TFV hair concentration outcomes were $\log_{10}$-transformed. Mean and median concentrations were estimated. We fit univariable linear regression models to evaluate associations of each covariate with TFV concentrations. Covariates with overall p-

value <0.25 in univariable analyses were included in multivariable models. We performed sensitivity analyses by restricting analyses to pregnancies with reported TDF use during all trimesters. For exploratory purposes, weight-normalized TFV hair concentrations were classified into categories according to dosing benchmarks from directly observed pharmacokinetic studies among non-pregnant women[22, 24] as benchmarks for pregnant women are unavailable. All analyses were conducted using SAS Version 9.4.

RESULTS

Overall, 335 pregnancies enrolled in the SMARTT Dynamic cohort between 2014 and 2016 reported use of TDF-containing ART and were approached to join the hair sub-study. Hair collection acceptability was high; only 65 (19%) women declined hair collection. The most frequently reported reason for declining hair collection was concern about disrupted hair appearance (32/65, 49%, Supplement Digital Content). Women who declined more frequently self-identified as non-Hispanic Black than women who accepted (83% vs. 61%, p=0.005) and were more frequently from southern US sites (85% vs. 35%, p<0.001). Other characteristics were similar between women who accepted and declined (Table 1).

Overall, 121 women had hair specimens tested for TFV levels and were included in the primary analysis. The most frequent reason for not testing hair specimens that were collected was insufficient amount of hair for analysis (90/149, 61%, Supplemental Digital Content).The most frequently used anchor drugs with TDF/emtricitabine-containing regimens included atazanavir/ritonavir (30%), rilpivirine (21%), and darunavir/ritonavir (16%). Among the 121 women, the median duration of TDF use during pregnancy was 33 weeks (IQR 20.1–38.3), 67% of women used TDF during all three trimesters, and 10% had unsuppressed VL in late pregnancy (Table 2). Compared to women who had hair specimens tested, women who had hair collected but not assayed were more frequently <25 years (26% vs. 17%, p=0.05), recruited from western US sites (28% vs. 17%, p=0.005), self-identified as Hispanic (41% vs 21%) and reported TDF use in the first and second trimesters only (7% vs. 1%, p=0.01); other characteristics were similar between groups (Supplemental Digital Content).

The median time from delivery to hair collection was 3 days (IQR 1–14). The median weight-normalized TFV hair concentration was 0.02 ng/mg (IQR 0.01–0.04). The mean $\log_{10}$ TFV hair concentration was −1.732 (standard deviation[SD]=0.602). In multivariable models, an unsuppressed VL in late pregnancy was associated with 80% lower adjusted mean peripartum TFV concentrations than pregnancies with viral suppression (95% CI: −90% to −59%, p<0.001, Table 2). The median weight-normalized TFV hair concentration was 0.005 ng/mg (IQR 0.002–0.008) and 0.02 ng/mg (IQR 0.01–0.04) among women with unsuppressed and suppressed VL, respectively. Using TDF-based ART only in the first trimester was associated with 92% lower peripartum TFV concentrations than pregnancies with TDF use beyond the 1st trimester (95% CI: −97% to −74%, p<0.001). Attaining high school graduation was associated with reduced TFV concentrations than lower education (adjusted % change: −43%, 95% CI: −64% to −8%, p=0.02). No other characteristics were associated with TFV hair concentrations (Table 2).

Sensitivity and exploratory analyses

Among 81 pregnancies that reported TDF use during all three trimesters, the median TFV hair concentration at delivery was 0.02 ng/mg (IQR 0.02–0.04) and mean $\log_{10}$ TFV hair concentration was −1.625 (SD=0.511). One-third (32%) of the 81 samples had TFV hair concentrations ≥0.038 ng/mg (equivalent to 7 doses/week in non-pregnant populations), 20% had TFV hair concentrations ≥0.023 and <0.038 ng/mg (4–6 doses/week), 26% had TFV concentrations between ≥0.012 and <0.023 ng/mg (2–3 doses/week), and 22% had TFV hair concentrations <0.012 ng/mg (<2 doses/week).

DISCUSSION

In this prospective cohort of women in the US on TDF-based ART, we found that hair collection at or near delivery was highly acceptable. Unsuppressed VL during late pregnancy was strongly associated with lower maternal TFV hair concentrations at birth, although viremia in late pregnancy was rare. Lower hair concentrations in the peripartum period could be a result of inadequate adherence[7, 25] or pharmacokinetic variability in pregnancy.[26] Our results add to the limited data on using objective metrics of ART exposure among maternal populations in the US and have implications for the “Ending the HIV Epidemic: A Plan for America” initiative[27], since maintaining sufficient ART exposure is critical for improving virological outcomes.

Acceptability of hair collection in previous ART exposure studies has generally been high (>95%)[17, 28, 29], although lower rates of acceptability are seen in studies among children and men-who-have-sex-with-men.[30, 31] The frequency of acceptability in our study was high (81%), with lower acceptability seen among non-Hispanic Black women and those living in the southern US. We found that concern about disrupted appearance was a frequent reason for declining hair collection. Qualitative studies could elucidate how hair collection acceptability can be improved, perhaps with less disruptive collection procedures.

Over two-thirds of WLHIV in our study who used TDF during all trimesters had low peripartum hair concentrations of TFV, suggestive of suboptimal exposure. Some studies among pregnant women show reduced plasma exposure to TFV and reduced TFV-diphosphate levels in dried blood spots[26, 32], though others do not.[33] In a recent study with near-perfect directly observed PrEP adherence, TFV-diphosphate levels among adolescent and young African women were 31–37% lower in pregnancy than postpartum suggesting lower exposure is a result of pharmacokinetic changes during pregnancy.[34] More directly observed pharmacokinetic studies, including among pregnant WLHIV, are needed to establish dosing thresholds of TFV exposure in hair, ideally by trimester. Future studies using rapid hair assays[35] and point-of-care urine assays[36] are also needed in addition to understand how objective measures can optimize clinical practice.[36, 37]

Previous studies among WLHIV in non-research settings of the US have found poor (52%) viral suppression at delivery[38], yet viremia was uncommon in our cohort. SMARTT enrollees may have more favorable HIV clinical outcomes due to enhanced follow-up and monitoring or highly effective concomitant medications. Participants who switched ART regimens could have viral suppression despite continued low TFV concentrations because of

a switching effect[39] or because they switched to a non-TDF containing ART regimen. However, 67% of women in our study used TDF during all three trimesters and results from analyses restricted to that subgroup were very similar to those of our primary models. We found that women who had graduated high school had lower TFV concentrations than women with lower educational attainment. This contrasts with results from prior studies from sub-Saharan Africa showing lower maternal education level is associated with poorer ART adherence.[40] Studies from other settings may be less applicable to the US, and more context-specific research is needed among WLHIV in the US to elucidate the association between education and ART exposure.[41, 42]

Our study has limitations. We are unable to assess the contribution of pharmacokinetic variability versus adherence to low TFV concentrations among women in this study. Over half of specimens collected from participants could not be tested for TFV concentrations, mainly due to insufficient amount of hair, which may result in potential bias. To address this limitation, we evaluated differences between pregnancies with vs. without maternal hair tested. Future studies should improve real-time quality control procedures and ongoing training to ensure quality sample collection, including sufficient amounts of hair for analysis. Our study only assessed TFV hair levels at one time point. Future studies should examine newer ARVs used in pregnancy to evaluate whether patterns of TFV exposure are the similar with other drugs and if exposure changes over time. Self-reported adherence data were incomplete and we did not collect reasons for non-adherence. We are unable to comprehensively associate hair metrics with adherence. Future studies should gather information on adherence barriers and facilitators in relation to hair concentrations of ARV among WLHIV in the US.

In conclusion, unsuppressed VL among WLHIV in the US during late pregnancy was strongly associated with low maternal TFV hair levels at birth. Efforts to improve maternal HIV outcomes and reach elimination of vertical HIV transmission could incorporate drug exposure monitoring using hair or other metrics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Characteristics of women accepting vs. declining maternal hair specimen collection at time of delivery, among pregnancies with TDF exposure during pregnancy (n=335)

	N (%) or Median (IQR)			
		Hair Specimen Collection		
Characteristics	**Total (N=335)[4]**	**Accepted (N=270)**	**Declined (N=65)**	**p-value[1]**
Age at delivery (years)	29.3 (25.5–34.3)	30.0 (25.5–34.6)	28.1 (25.0–33.0)	0.05
Age category at delivery (years)				
< 25	76 (23%)	59 (22%)	17 (26%)	0.20
25 – 34	185 (55%)	146 (54%)	39 (60%)	
≥ 35	74 (22%)	65 (24%)	9 (14%)	
Race/Ethnicity				
Black Non-Hispanic	220 (66%)	166 (61%)	54 (83%)	**0.005**
White Non-Hispanic	18 (5%)	14 (5%)	4 (6%)	
Other Non-Hispanic	2 (1%)	2 (1%)	0 (0%)	
Hispanic	94 (28%)	87 (32%)	7 (11%)	
Achieved at least high school graduation	231 (69%)	182 (67%)	49 (75%)	0.11
Research site region				
Puerto Rico	19 (6%)	18 (7%)	1 (2%)	**<0.001**
West	68 (20%)	63 (23%)	5 (8%)	
South	150 (45%)	95 (35%)	55 (85%)	
Midwest	28 (8%)	27 (10%)	1 (2%)	
Northeast	70 (21%)	67 (25%)	3 (5%)	
Recreational drug use during pregnancy[2]	41 (12%)	33 (12%)	8 (12%)	0.98
Gestational age at delivery (weeks)	38 (37–39)	38 (37–39)	38 (38–39)	0.55
Mode of delivery: C-section	177 (53%)	146 (54%)	31 (48%)	0.34
BMI at delivery (kg/m^2)				
18.5 – 24.9	22 (7%)	21 (8%)	1 (2%)	0.12
25.0 – 29.9	65 (19%)	49 (18%)	16 (25%)	
≥ 30	162 (48%)	125 (46%)	37 (57%)	
Missing	86 (26%)	75 (28%)	11 (17%)	
Latest RNA (copies/mL) during pregnancy				
< 400	302 (90%)	247 (91%)	55 (85%)	0.23
400 – 1000	9 (3%)	7 (3%)	2 (3%)	
>1000 – 10000	8 (2%)	6 (2%)	2 (3%)	
> 10000	12 (4%)	7 (3%)	5 (8%)	
Duration of ARV use in pregnancy (weeks)	34.1 (23.3–38.4)	35.1 (23.3–38.4)	30.4 (23.0–37.9)	0.22
Duration of TDF use in pregnancy (weeks)	31.2 (18.9–38.3)	32.1 (18.9–38.3)	28.7 (19.8–37.8)	0.64
Missed any ART pills in the last 30 days[3]				
No	144 (43%)	126 (47%)	18 (28%)	0.60
Yes	45 (13%)	38 (14%)	7 (11%)	

Characteristics	N (%) or Median (IQR)			
	Hair Specimen Collection			
	Total (N=335)[4]	Accepted (N=270)	Declined (N=65)	p-value[1]
Don't know	2 (1%)	1 (0%)	1 (2%)	
Missing	144 (43%)	105 (39%)	39 (60%)	

[1] Chi-Square tests for proportions and Wilcoxon tests for continuous measures

[2] Recreational drugs included: marijuana, cocaine, heroin, sedatives, methamphetamines, PCP, opium, stimulants, barbiturates, amphetamines, inhalants, LSD, and other hallucinogens.

[3] Assessment of self-reported ART adherence was added to the SMARTT cohort study starting in May 2015

[4] Variables with missing data not presented in table included: race/ethnicity (n=1, 0.3%), high school graduation (n=2, 1%), mode of delivery (n=1, 0.3%), last RNA during pregnancy (n=4, 1%).

Table 2.

Correlates of mean $\log_{10}$ maternal TFV hair concentrations at delivery among women on TDF-containing ART (n=121)

Maternal characteristics	N (%) or Median (IQR)	Mean $\log_{10}$ TFV concentration	Univariable linear regression			Multivariable linear regression[3]		
			Absolute Difference[1] (95% CI)	% Change[2] (95% CI)	p-value	Absolute Difference[1] (95% CI)	% Change[2] (95% CI)	p-value
Age at delivery (years)								
≥ 35	37 (31%)	−1.698	0.021 (−0.307, 0.349)	4.9 (−50.7, 123.3)	0.90			
25 – 34	63 (52%)	−1.756	−0.038 (−0.340, 0.265)	−8.3 (−54.3, 83.9)	0.80			
< 25	21 (17%)	−1.719	Ref.					
Race/Ethnicity								
White/Other Non-Hispanic	9 (7%)	−1.932	−0.221 (−0.640, 0.199)	−39.8 (−77.1, 57.9)	0.30			
Hispanic	26 (22%)	−1.729	−0.017 (−0.285, 0.251)	−3.9 (−48.1, 78.1)	0.90			
Black Non-Hispanic	86 (71%)	−1.712	Ref.					
Completed education								
Graduated high school	86 (71%)	−1.791	−0.203 (−0.440, 0.034)	−37.4 (−63.7, 8.1)	0.09	−0.241 (−0.448, −0.034)	−42.6 (−64.4, −7.6)	**0.02**
Less than high school	35 (29%)	−1.587	Ref.					
Any recreational drug use in pregnancy								
Yes	15 (12%)	−1.686	0.052 (−0.277, 0.382)	12.8 (−47.2, 141.2)	0.75			
No	106 (88%)	−1.738	Ref.					
Any pain medication use in pregnancy								
Yes	5 (4%)	−2.059	−0.341 (−0.884, 0.202)	−54.4 (−86.9, 59.2)	0.22	−0.258 (−0.729, 0.213)	−44.8 (−81.3, 63.5)	0.28
No	116 (96%)	−1.718	Ref.					
Any antidepressant use in pregnancy								
Yes	4 (3%)	−1.842	−0.114 (−0.722, 0.494)	−23.1 (−81.0, 211.8)	0.71			
No	117 (97%)	−1.728	Ref.					
Any tobacco use in pregnancy								
Yes	18 (15%)	−1.738	−0.008 (−0.313, 0.298)	−1.8 (−51.4, 98.6)	0.96			
No	103 (85%)	−1.731	Ref.					
Any alcohol use in pregnancy								

Maternal characteristics	N (%) or Median (IQR)	Mean log_{10} TFV concentration	Univariable linear regression			Multivariable linear regression[3]		
			Absolute Difference[1] (95% CI)	% Change[2] (95% CI)	p-value	Absolute Difference[1] (95% CI)	% Change[2] (95% CI)	p-value
Yes	13 (11%)	−1.906	−0.195 (−0.545, 0.154)	−36.2 (−71.5, 42.7)	0.27			
No	108 (89%)	−1.711	Ref.					
Gestational age at birth (weeks)	38 (38–39)	-	−0.057 (−0.138, 0.025)	−12.2 (−27.2, 5.9)	0.17	−0.034 (−0.105, 0.036)	−7.6 (−21.4, 8.7)	0.34
Mode of delivery[4]								
C-section	71 (59%)	−1.758	−0.056 (−0.278, 0.167)	−12.0 (−47.3, 46.9)	0.62			
Vaginal	49 (41%)	−1.702	Ref.					
BMI at delivery (kg/m^2)[4]								
≥ 30	54 (64%)	−1.819	−0.124 (−0.587, 0.340)	−24.8 (−74.1, 118.5)	0.60			
25.0 – 29.9	22 (26%)	−1.756	−0.061 (−0.570, 0.449)	−13.0 (−73.1, 180.9)	0.81			
18.5 – 24.9	9 (11%)	−1.695	Ref.					
Latest CD4 count (cells/mm^3) in pregnancy[4]								
<350	32 (27%)	−1.725	0.008 (−0.237, 0.253)	1.9 (−42.0, 78.9)	0.95			
≥350	85 (73%)	−1.733	Ref.					
Latest HIV RNA (copies/mL) in pregnancy[4]								
≥400	12 (10%)	−2.328	−0.665 (−1.000, −0.331)	−78.4 (−90.0, −53.3)	< 0.001	−0.696 (−1.010, −0.382)	−79.9 (−90.2, −58.5)	**< 0.001**
<400	107 (90%)	−1.663	Ref.					
Missed any HIV medicines (last month)[4]								
≥2 days	17 (22%)	−1.651	0.046 (−0.257, 0.349)	11.1 (−44.7, 123.4)	0.76			
<2 days	60 (78%)	−1.697	Ref.					
Hair color								
Black	99 (82%)	−1.707	0.136 (−0.145, 0.417)	36.8 (−28.4, 161.3)	0.34			
Other/mixed	22 (18%)	−1.843	Ref.					
NNRTI use during pregnancy[4]								

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Maternal characteristics		N (%) or Median (IQR)	Mean log_{10} TFV concentration	Univariable linear regression			Multivariable linear regression[3]		
				Absolute Difference[1] (95% CI)	% Change[2] (95% CI)	p-value	Absolute Difference[1] (95% CI)	% Change[2] (95% CI)	p-value
	Yes	35 (30%)	−1.718	0.022 (−0.222, 0.266)	5.2 (−40.0, 84.4)	0.86			
	No	83 (70%)	−1.740	Ref.					
PI use during pregnancy[4]									
	Yes	69 (58%)	−1.764	−0.073 (−0.299, 0.152)	−15.5 (−49.8, 42.0)	0.52			
	No	49 (42%)	−1.691	Ref.					
INSTI use during pregnancy[4]									
	Yes	46 (39%)	−1.666	0.111 (−0.117, 0.338)	29.0 (−23.6, 117.8)	0.34			
	No	72 (61%)	−1.776	Ref.					
TDF use in all trimesters[4]									
	Yes	81 (68%)	−1.625	0.345 (0.114, 0.577)	121.4 (29.9, 277.4)	0.004	0.105 (−0.110, 0.321)	27.5 (−22.3, 109.2)	0.33
	No	37 (32%)	−1.970	Ref.					
TDF use in 1st trimester only									
	Yes	5 (4%)	−2.769	−1.082 (−1.592, −0.572)	−91.7 (−97.4, −73.2)	< 0.001	−1.072 (−1.555, −0.589)	−91.5 (−97.2, −74.3)	**< 0.001**
	No	116 (96%)	−1.687	Ref.					

ART=antiretroviral therapy (ART); NNRTI=non-nucleoside reverse transcriptase inhibitors; PI=protease inhibitor; INSTI=integrase strand transfer inhibitor; TDF=tenofovir disoproxil fumarate; TFV=tenofovir

[1] Estimated absolute difference in adjusted mean log_{10}-transformed TFV concentration: 1) per one unit increase in continuous covariate measures; or 2) between pregnancies with specific characteristic vs the reference group for categorical covariate measures.

[2] Estimated percent change in adjusted mean TFV concentration: 1) per one unit increase in continuous covariate measures; or 2) between pregnancies with specific characteristic vs the reference group for categorical covariate measures.

[3] Covariates with p-value < 0.25 in univariable analysis were included in the multivariable model.

[4] Variables with missing table not presented in the table: C-section delivery (n=1, 1%), BMI (n=36, 30%), latest CD4 count during pregnancy (n=4, 3%), latest HIV RNA during pregnancy (n=2, 2%), missed any HIV medicines on ≥2 days (n=44, 36%), ART regimen containing 3 or more classes (n=3, 2%), PI use (n=3, 2%), NNRTI use (n=3, 2%), INST use (n=3, 2%), and TDF use in all trimesters (n=3, 2%)