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Short communication

Tenofovir disoproxil fumarate appears to disrupt the relationship of vitamin D and parathyroid hormone

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ABSTRACT

Background: Tenofovir disoproxil fumarate (TDF) increases serum parathyroid hormone (PTH) and 1,25 dihydroxy vitamin D (1,25-$(OH)_2$D), and decreases bone mineral density (BMD). Optimal treatment of TDF-associated BMD loss requires an understanding of the primary cause of these abnormalities.

Methods: Secondary review of data from two studies of TDF use in youth, comparing the relationship of PTH, 25-hydroxy vitamin D (25-OHD), and 1,25-$(OH)_2$D in 3 groups with varying exposures to TDF: Youth without HIV enrolled in a trial of TDF/emtricitabine (FTC) for HIV pre-exposure prophylaxis (PrEP) at baseline (no TDF exposure) and after 12 weeks of TDF (short-term TDF exposure); and youth with HIV treated with TDF-containing combination antiretroviral therapy (cART) for at least 6 months at study entry (long-term TDF exposure). Relationships were evaluated by correlation analyses.

Results: Participants ranged in age from 17-24 years and >50% were Black/African American. In persons not treated with TDF, PTH had the

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physiologically appropriate negative correlation with 25-OHD (r= -.3504, P=0.004). Correlations between PTH and 25-OHD in groups treated with TDF were weaker or absent. With longer-term TDF treatment in persons with HIV, 25-OHD and 1,25-$(OH)_2$D had the positive correlation similar to that found in vitamin D deficiency.

Conclusions: TDF changes the relationship of 25-OHD to PTH, suggesting that in persons using TDF for PrEP or cART, a higher than usual target for serum 25-OHD concentration might be needed to reduce PTH and optimize bone health.

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Running head: TDF-associated increased parathyroid hormone

INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is widely used in HIV treatment as a component of combination antiretroviral therapy (cART) and in HIV pre-exposure prophylaxis (PrEP) combined with emtricitabine (FTC). TDF-containing cART [1] and TDF/FTC PrEP both decrease BMD [2–4].

TDF increases serum parathyroid hormone (PTH) [5–7] and 1,25-dihydroxy vitamin D (1,25-$(OH)_2$D) concentrations [5]. It is not clear whether TDF directly affects PTH or 1,25-$(OH)_2$D or if these effects are due to other alterations in endocrine pathways that maintain calcium and phosphate homeostasis.

We utilized data from two trials involving TDF use in adolescents and young adults with [8] and without [3] HIV to explore the relationships among PTH, 25-hydroxyvitamin D (25-OHD), and 1,25-$(OH)_2$D, in the presence or absence of TDF.

METHODS

Data Sources

We used data from baseline and week 12 for participants in Adolescent Medicine Trials Network for HIV/AIDS Intervention (ATN) 117 [3], a metabolic sub-study of ATN 113 [2] (ages 15-17 years) and ATN 110 [4] (ages 18-22 years), prospective PrEP demonstration and safety studies in HIV uninfected men who have sex with men at United States ATN sites.

We also used baseline data from participants in ATN 109 [8], a randomized trial of vitamin D supplementation in youth ages 16-24 years with HIV, viral load <200 copies/mL, taking TDF-containing cART for >180 days at study entry.

All studies were approved by each center's institutional review board and required participants' written consent before enrollment.

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Participant Groups

These comparisons use three groups, differing by HIV infection status, reason for TDF use, and current TDF use and duration. Group 1 was ATN 117 participants at baseline: HIV uninfected and TDF-naïve [3]; Group 2, ATN 117 participants who had used TDF/FTC PrEP for 12 weeks (short-term TDF exposure), excluding those with red blood cell tenofovir diphosphate concentration below quantitation limits [3]; Group 3, ATN 109, HIV infected, TDF-containing cART >180 days at entry (long-term TDF exposure) [8]. We subdivided each group as vitamin D insufficient/deficient (VDD; 25-OHD<20 ng/mL) or sufficient (VDS, 25-OHD >=20 ng/mL) (Table 1). Race was categorized as Black/African American (AA) vs other.

Lab Data

Blood samples were collected after ≥8-hour fast, processed at study sites, and sent frozen for batch analysis [3,8].

Statistics

This analysis includes no cross-group comparisons. Spearman correlations and hypothesi testing of 25-OHD, 1,25-$(OH)_2$D, and PTH were evaluated within each of the three groups, and for the VDD or VDS subgroups of each group.

RESULTS

ATN 117 participants were younger, had lower percent Black/AA, and were male at birth, compared to participants in ATN 109, which included 15.7% females (Table 1). The majority of all participants had VDD (Table 1).

There were no differences in serum calcium or phosphate concentrations across the three groups or vitamin D-defined subgroups. Within each of the three groups, PTH was higher and fibroblast growth factor-23 lower in those with VDD than VDS. (Table 1).

25-OHD and PTH

In group 1, the only group with no TDF exposure, PTH had the physiologically appropriate [9–11] negative correlation with 25-OHD (r= -.3504, P=0.004). This relationship was less pronounced in Black/AA (r= -0.1675, P=0.44) and stronger in other races (r = -0.4819, P=0.0005). In contrast, correlations between PTH and 25-OHD in groups using TDF were weaker or absent (Table 2). For a given concentration of 25-OHD, PTH was higher in those using TDF, particularly among participants with longer-duration TDF exposure (group 3, HIV-infected taking TDF-containing cART [Figure 1])

1,25-$(OH)_2$D and PTH

Only group 2, using TDF PrEP for 12 weeks, showed a correlation between PTH and 1,25-$(OH)_2$D, strongest in the VDD subgroup (r=0.3590, P=0.0154; Table 2).

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25-OHD and 1,25-$(OH)_2D$

In group 1, 25-OHD and 1,25-$(OH)_2D$ showed the physiologically expected [12] positive correlation in the VDD subgroup (r=0.2956, P=0.0256) but not in the VDS subgroup (Table 2). This relationship was not found in group 2. A strong positive correlation was found between 25-OHD and 1,25-$(OH)_2D$ in group 3 overall (r=0.3189, P<0.001) and in the VDD subgroup (Table 2).

DISCUSSION

25-OHD and PTH

These analyses suggest that TDF disrupts the 25-OHD and PTH relationship, since the physiologically appropriate negative correlation of 25-OHD and PTH [9–11], seen in the group not using TDF, was weaker or absent in groups receiving TDF-containing cART or PrEP.

Insufficient 25-OHD is known to cause low serum calcium due to lower 1,25-$(OH)_2D$ synthesis and associated decreased intestinal calcium absorption [10]. PTH secretion then increases to maintain serum calcium by drawing calcium from bone, which may ultimately lead to a low BMD [10]. As 25-OHD increases, the PTH concentration declines and then plateaus [11], suggesting a 25-OHD concentration above which further 25-OHD increases will not lead to continued PTH decline. The 25-OHD concentration at which PTH plateaus is debated [9] and differs by race [13]. This analysis did not identify a PTH “plateau” even at higher 25-OHD concentrations, although we observed a weaker association between 25-OHD and PTH in Black/AA compared to other races. This analysis showed that for a given 25-OHD concentration, participants using TDF had higher PTH than those not using this medication, suggesting a state of relative physiologic vitamin D insufficiency.

These analyses do not illuminate the mechanism underlying this altered relationship between 25-OHD and PTH. While PTH increases in response to small changes in serum calcium [10], detecting such a change would be unlikely, given the tight regulation of circulating calcium, which was not different across groups. While other studies have shown that TDF raises PTH [6,7,14], the TDF-associated PTH increase does not appear to be mediated by increased urinary calcium excretion [5,6]. While hyperphosphatemia increases PTH [10], this would not pertain here, since TDF causes renal phosphate loss [5]. Increased vitamin D binding protein, found at TDF- containing cART initiation [7,14], and with higher plasma tenofovir concentrations [5], may decrease free 25-OHD and lead to “functional” vitamin D deficiency.

Our findings differ from those of a previous study examining the relationship of TDF with 25-OHD and PTH in participants with mean (SD) age 47 (9.8) years, who were 94% White [15]. That study found no difference in the 25-OHD and PTH relationship in persons treated with TDF-containing cART versus cART without TDF. Our study included over 50% Black/AAs, who in general have lower 25-OHD concentrations, and higher PTH and BMD for a given 25-OHD concentration [13], and also included

younger participants, who generally have higher 25-OHD concentrations and lower PTH for a given 25-OHD concentration [16]. It is possible that differences in the racial and age-related composition of the cohorts explain the disparate findings.

1,25-$(OH)_2$D and PTH

This analysis suggests that TDF primarily causes increased PTH, since those treated with TDF had a stronger positive correlation between PTH and 1,25-$(OH)_2$D, suggesting a normal 1,25-$(OH)_2$D counter-regulatory response to increased PTH [10]. If TDF primarily increased 1,25-$(OH)_2$D, that could cause a low PTH [10], manifesting as a negative correlation. The lack of a positive correlation between PTH and 1,25-$(OH)_2$D in group 3 suggests a return to the baseline relationship of PTH and 1.25-OHD with chronic TDF exposure, but at higher PTH concentrations.

25-OHD and 1,25-$(OH)_2$D

The expected relationship between 25-OHD and 1,25-$(OH)_2$D is a positive correlation in persons with VDD, and a weak or absent correlation when 25-OHD reaches adequate concentrations [12]. This pattern was seen in Group 1, where there was a positive correlation in those with VDD, but not VDS. However, the correlation was absent with short-term TDF exposure (group 2). The positive correlation between 25-OHD and 1,25-$(OH)_2$D (physiologically appropriate for vitamin D deficiency) was again seen in participants with longer-term TDF treatment (group 3) suggesting that longer-term TDF treatment causes ongoing stress to calcium and phosphate homeostasis, similar to vitamin D deficiency [12].

While we avoided cross-study comparisons, the results of this secondary analysis of two separate studies should be interpreted with caution. These studies were performed in youth with normal renal function, and findings may be different in older persons receiving TDF-containing regimens, or in persons using TDF for longer periods.

IMPLICATIONS FOR TREATMENT

These data suggest that a higher 25-OHD concentration may be needed to control the high PTH concentration associated with TDF treatment, supporting the 25-OHD target of >30 ng/mL recommended by the Endocrine Society for persons whose clinical profile includes a threat to bone health [17]. This slightly higher 25-OHD threshold is in contrast to a minimum serum 25-OHD target of 20 ng/mL recommended by the Institute of Medicine for maintenance of bone health in healthy populations [18]. In youth with HIV treated with TDF- containing cART, this target was reached within 12 weeks using vitamin D3 50,000 International Units (IU) monthly [19], resulting in a PTH decrease [19] and lumbar spine BMD increase [8], in persons both with and without a baseline 25-OHD <20 ng/mL. Similar improvements have been seen in youth with HIV treated with TDF-containing cART using vitamin D3 2,000 or 4,000 IU daily [20].

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In summary, these findings suggest that TDF changes the relationship of 25-OHD to PTH, resulting in a physiologic state similar to 25-OHD insufficiency. A higher than usual target for 25-OHD serum concentration may be needed to reduce PTH and PTH-associated bone resorption, to optimize bone health in persons treated with TDF- containing cART or TDF/FTC PrEP.

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Disclosures

No author has a conflict of interest.

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Figure 1 Relationship of Parathyroid Hormone and 25- hydroxy Vitamin D in the Presence and Absence of Tenofovir Disoproxil Fumarate

Circles/solid line = group 1, HIV-uninfected, no TDF; Triangles/dashed line = group 2, HIV-uninfected, short-term TDF exposure; Plus sign/dotted line = group 3, HIV-infected, longer-term TDF exposure. The group 1 relationship is described by the equation $PTH_{predicted}$ = 36.24-0.41*25-OHD. Only group 1 shows statistically significant relationship between PTH and 25-OHD. Between group 1 and group 2 the slopes of the lines are different, and between group 1 and group 3 the intercepts of the lines are different

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Table 1 Cohorts studied.

Variable	Group 1			Group 2			Group 3		
Study /Week	117 BL	117 BL	117 BL	117 wk12	117 wk12	117 wk12	109 BL	109 BL	109 BL
N	99	57	42	77	45	32	209	130	79
HIV status	neg	neg	neg	neg	neg	neg	pos	pos	pos
ARVs	none	none	none	TDF PrEP	TDF PrEP	TDF PrEP	TDF cART	TDF cART	TDF cART
TDF duration[a]	-	-	-	12 weeks	12 weeks	12 weeks	20.8 (10.0, 28.7) months	20.6 (9.9, 28.2) months	21.1 (10.1, 28.7) months
Vitamin D category	all	25-OHD <20	25-OHD >=20	all	25-OHD <20	25-OHD >=20	all	25-OHD <20	25-OHD >=20
Age	20 (18, 21)	20 (19, 21)	19 (17, 21)	20 (19, 21)	20 (19, 21)	19 (17.5, 21)	22 (21, 23)	22 (20, 23)	22 (21, 24)
Sex (%F)	0	0	0	0	0	0	15.7%	16.8%	13.9%
Race (% Black/AA)	52.5%	70.2%	28.6%	53.2%	68.9%	31.3%	73.3%	78.6%	64.6%
BMI	22.8 (20.7, 26.5)	23.8 (21.7, 29.1)	22.4 (20.7, 25.1)	23.7 (21.6, 27.6)	25.3 (21.9, 29.7)	22.5 (20.9, 25.3)	23.5 (21.2, 28.8)	23.7 (21.3, 29.8)	23.3 (21.4, 27.4)
Serum Calcium	9.8 (9.6, 9.9)	9.8 (9.6, 9.9)	9.8 (9.6, 10.0)	9.8 (9.5, 9.9)	9.8 (6.5, 10.1)	9.8 (9.6, 9.9)	9.4 (9.2, 9.6)	9.3 (9.1, 9.6)	9.4 (9.3, 9.7)
Serum Phosphate	3.6 (3.3, 4.0)	3.6 (3.4, 3.9)	3.6 (3.2, 4.0)	3.5 (3.2, 3.8)	3.6 (3.2, 3.8)	3.4 (3.2, 3.8)	3.5 (3.2, 3.9)	3.5 (3.2, 3.9)	3.5 (3.2, 3.9)
25-OHD	18.4 (12.0, 23.7)	13.1 (9.3, 16.7)	24.2 (22.5, 26.3)	21.0 (16.3, 28.2)	17.7 (12.3, 22.0)	27.9 (20.8, 31.5)	16.4 (11.4, 23.9)	13.3 (9.5, 15.4)	26.6 (22.5, 31.4)
1,25-$(OH)_2D$	67.2 (49.3, 85.2)	69.1 (48.7, 84.0)	66.4 (52.0, 88.8)	77.9 (56.2, 99.5)	76.3 (57.6, 98.1)	83.0 (53.8, 101.2)	71.1 (57.9, 93.0)	68.6 (54.7, 87.5)	80.8 (61.3, 109.6)
PTH[b]	26.9 (20.5, 34.8)	29.6 (24.3, 40.2)	25.0 (19.2, 28.4)	29.2 (25.1, 35.7)	30.5 (25.9, 42.5)	26.9 (22.4, 31.7)	37.5 (28.8, 47.4)	39.1 (30.2, 48.4)	35.8 (27.3, 45.7)
FGF23[c]	38.7 (32.7, 44.5)	36.6 (32.4, 44.5)	40.5 (36.9, 45.6)	35.1 (30.6, 44.3)	34.9 (28.8, 42.5)	36.8 (32.8, 45.0)	33.8 (26.7, 42.6)	32.7 (25.4, 41.8)	35.1 (30.1, 43.1)

Abbreviations: BL = baseline; wk = week; TDF = tenofovir disoproxil fumarate; BMI = body mass index; 25-OHD = 25 hydroxy vitamin D; 1,25-$(OH)_2D$ = 1,25 dihydroxy vitamin D. PTH = parathyroid hormone; FGF23 = fibroblast growth hormone 23;

a. Continuous data are presented as median (Q1, Q3);

b. P values for difference in PTH between VDS and VDD: Group1, p=0.002; Group 2, p=0.051; Group 3 p=0.057.

c. P values for difference in FGF23 between VDS and VDD: Group 1, p=0.09; Group 2, p=0.38; 109: Group 3, p=0.015)

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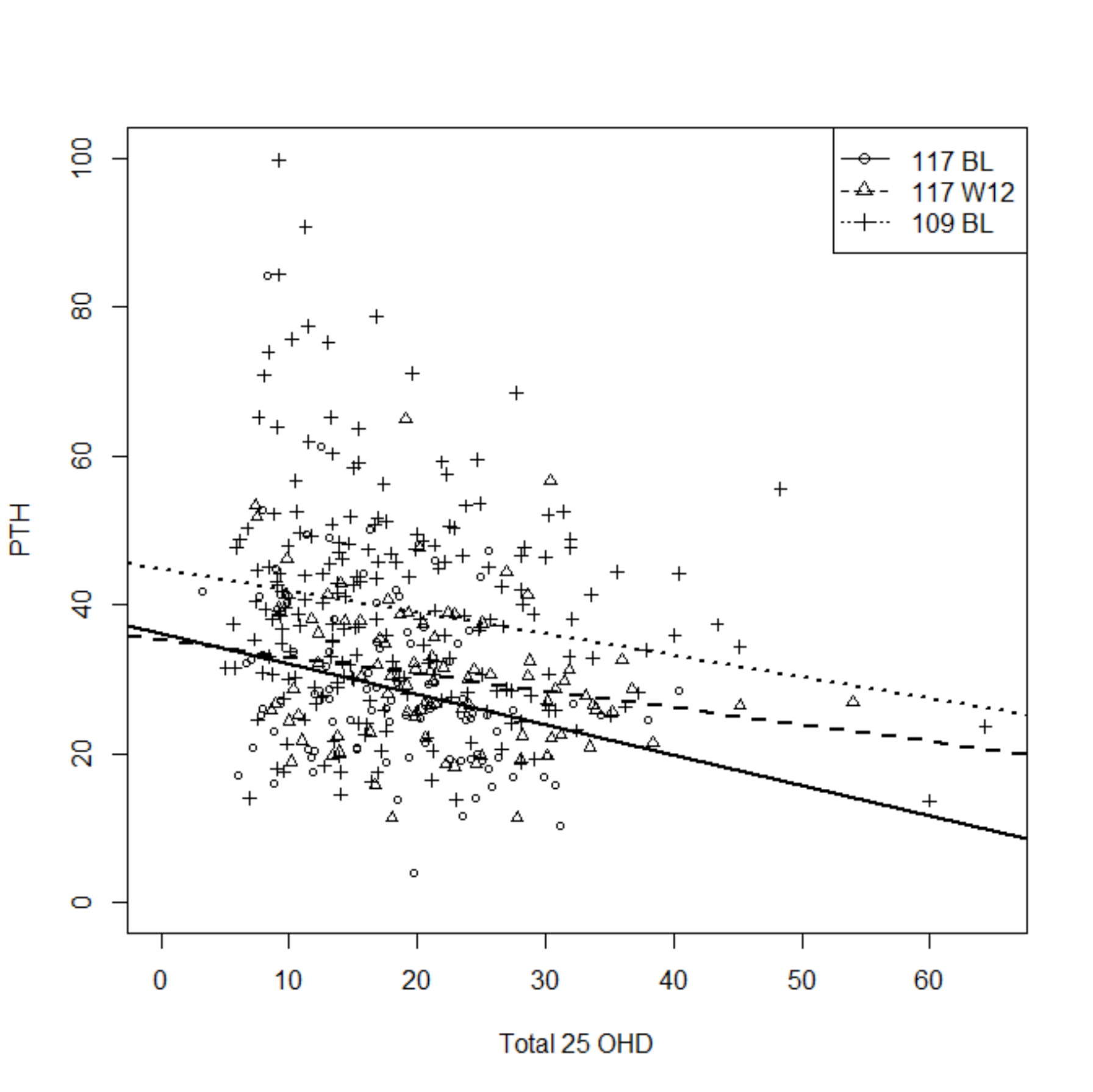
Table 2. Correlations by Group and Vitamin D status

Variable	Group 1			Group 2			Group 3		
Study and Week	117 BL	117 BL	117 BL	117 wk12	117 wk12	117 wk12	109 BL	109 BL	109 BL
Vitamin D category	all	VDD	VDS	all	VDD	VDS	all	VDD	VDS
25-OHD x PTH	-0.3504 0.0004	-0.0650 -	-0.3863 0.0115	-0.1232 -	0.0791 -	-0.2049 -	-0.1545 0.0258	-0.0791 -	-0.0665 -
1,25-$(OH)_2D$ x PTH	0.1133 -	0.2337 -	0.0904 -	0.2410 0.0350	0.3590 0.0154	0.0700 -	-0.0603 -	-0.0332 -	-0.0227 -
25-OHD x 1,25-$(OH)_2D$	0.1886 -	0.2956 0.0256	0.0109 -	0.0407 -	-0.0564 -	0.1796 -	0.3189 <0.0001	0.3078 0.0004	-0.0001 -

Abbreviations: BL = baseline; wk = week; 25-OHD = 25 hydroxy vitamin D; 1,25-$(OH)_2D$ = 1,25 dihydroxy vitamin D. PTH = parathyroid hormone; VDD = vitamin D deficient, 25-OHD <20 ng/mL; VDS = vitamin D sufficient, 25-OHD $\geq$20 ng/mL

Cells with statistically significant correlations by Spearman show r and p value. Cells with "-" had P value > 0.05


117 BL
117 W12
109 BL
PTH
0
20
40
60
80
100
0
10
20
30
40
50
60
Total 25 OHD