Metabolic Effects of Pre-Exposure Prophylaxis with Co-Formulated Tenofovir Disoproxal Fumarate and Emtricitabine

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Summary: PrEP with TDF/FTC leads to small losses of body fat but does not appear to affect fat distribution or lean body mass. The lipid lower properties of TDF/FTC observed in HIV treatment are apparent in use as PrEP.

Running Title: Metabolic Effects of TDF/FTC for PrEP

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ABSTRACT

Background: Antiretroviral drugs have been associated with changes in fat metabolism including lipids, fat mass and fat distribution. In HIV treatment, tenofovir disoproxil fumarate (TDF) has been shown to have a more favorable metabolic profile than other drugs in its class. However, the metabolic effects of TDF used as PrEP have not been reported.

Methods: We evaluated the effects of TDF/FTC on lipids and body composition in participants in a blinded placebo controlled PrEP trial. Participants enrolled in a metabolic subcohort (N=251, TDF/FTC; N=247, placebo) consented to fasting lipid panels, dual-energy X-ray absorptiometry (DXA) scans for body composition and pharmacologic testing of plasma and intracellular tenofovir diphosphate levels at baseline and every 24 weeks thereafter.

Results: Lean body mass was stable and unaffected by TDF/FTC. Body weight increased in both groups but was lower on TDF/FTC through week 72. This difference was explained by lower fat accumulation on TDF/FTC. The net median percent difference (SE, p-value) for TDF/FTC v. placebo at week 24 was -0.8% (0.4%, p=0.02), +0.3% (0.4%, p=0.46), -3.8% (1.4%, p=0.009) for total, lean and fat mass, respectively. There was no apparent differential regional fat accumulation on TDF/FTC. Decreases in cholesterol, but not triglycerides, were seen in TDF/FTC participants with detectable drug levels compared with placebo.

Conclusions: TDF/FTC for PrEP showed cholesterol reductions and appeared to transiently suppress the accumulation of weight and body fat, compared to placebo. There was no evidence of altered fat distribution or lipodystrophy during daily oral TDF/FTC PrEP.

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Keywords: lipids; lipodystrophy; tenofovir/emtricitabine; PrEP; body composition

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INTRODUCTION

HIV prevention has been revolutionized by the use of antiretroviral drugs (ARV) for pre-exposure prophylaxis (PrEP). Multiple clinical trials have shown that oral tenofovir disoproxil fumarate (TDF) with and without emtricitabine (FTC) used as PrEP prevents HIV infection when taken as prescribed with an excellent safety profile [1-6] and is broadly acceptable for diverse populations at risk of HIV infection [7-12].

In people with HIV infection, some ARVs have been associated with metabolic changes including peripheral lipoatrophy, central adiposity, insulin resistance, hyperglycemia and dyslipidemia [13,14]. This is particularly apparent with thymidine analogues and some protease inhibitors. TDF appears to have a more favorable metabolic profile and use of TDF compared to stavudine or zidovudine has shown decreases in lipids and increases limb fat [15-20]. However, it has been difficult to evaluate the specific effects of TDF or TDF/FTC on metabolic parameters in isolation, given a constellation of other factors that may influence lipids and body composition including: HIV infection, the host response to HIV, and other drugs in the ARV regimen. PrEP trials provide an opportunity to study the effects of TDF/FTC on body composition and fat distribution in the absence of HIV infection and other confounders.

Further, rigorous documentation of safety is imperative in those taking a medication for prophylaxis and perceptions of ARV toxicity are an important barrier to PrEP uptake [7,21]. We provide the first report of metabolic effects of TDF/FTC PrEP on fasting lipids, body composition, and fat distribution in a cohort nested within a randomized placebo controlled trial of TDF/FTC as PrEP.

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METHODS

Study Design: The iPrEx trial was a randomized, double-blind placebo controlled trial of daily, oral TDF/FTC versus placebo for the prevention of HIV acquisition. Between July 2007 and December 2009, the trial enrolled 2,174 cisgender men and 325 transgendered women who have sex with men (MSM/TGW) in 6 countries. The study design and primary results have been described elsewhere [1]. All participants were followed monthly for HIV acquisition, and laboratory safety analyses were performed monthly for the first 16 weeks, week 24, and then every 12 weeks. Physical exams were performed every 6 months.

Metabolic Substudy: An opt-in metabolic substudy, which included whole-body dual-energy X-ray absorptiometry (DXA) scanning, was offered to all eligible iPrEx participants enrolled in Chiang Mai, Thailand; San Francisco, California; Cape Town, South Africa; and to participants in Lima, Peru and Rio de Janeiro, Brazil who enrolled in iPrEx after DXA scanning became available at those clinics [22]. The only additional eligibility criteria for the DXA substudy were weight <120 kg and no use of oral or inhaled glucocorticoids at entry. Substudy visits included venipuncture for an 8-hour fasting blood sample and spine, hip, and whole-body DXA scan. Visits were completed at baseline (prior to the first dose of study drug), at 24-week intervals during randomized treatment, at treatment discontinuation, and 24 weeks after stopping the study drug. Substudy participants gave written informed consent for the additional testing and visits. DXA scanning began in July 2008 and was completed in February 2011.

Participants in San Francisco and Rio de Janeiro were scanned on Lunar Prodigy (Madison, Wisconsin) DXA instruments; those in Cape Town and Chiang Mai were scanned on Hologic Discovery (Waltham, Massachusetts) devices, and those in Lima were scanned on a Hologic

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Explorer. All clinics followed manufacturer-recommended calibration and maintenance procedures. A single study-specific spine phantom was circulated for scanning at all clinics for quality control. Each clinic's calibration and maintenance records were reviewed to assure consistency throughout the study. Scans were analyzed locally following a standardized protocol and reviewed centrally. With very few exceptions, all scans were analyzed by the same person at each DXA facility.

Lipid Testing: Fasting serum specimens from substudy visits were frozen and saved for centralized batch analysis (Quest Laboratories) for testing levels of triglycerides, total, high density and calculated low-density lipoprotein cholesterol (HDL-C, LDL-C).

Plasma and Intracellular Tenofovir and Emtricitabine Measurements: In previous reports, we found a substantial portion of the participants were using TDF/FTC less than daily, and half had no detectable PrEP drug in the active arm, indicating less than 1 tablet taken per week [23]. To fully understand the biological effects of the drugs, all DXA substudy participants assigned to TDF/FTC had tenofovir (TFV) and emtricitabine (FTC) concentrations at weeks 24, 48, and 72 measured in stored plasma. Intracellular TFV diphosphate (TFV-DP) concentrations at week 24 were measured in viably cryopreserved peripheral blood mononuclear cells (PBMC) [22,23]. These measurements permitted analysis by randomized assignment as well as time-varying drug exposure.

Data Analysis: Target enrollment in the DXA substudy was 500. Baseline characteristics were compared by an unequal-variance t-test for continuous variables and the Fisher exact test for

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categorical variables. The Fisher exact test was also used to compare categorical variables during follow-up. Percentage and absolute changes in parameters were calculated relative to baseline. We emphasize median changes, as have similar studies [17-20], to limit the influence of extreme values. Median differences in parameters by groups were compared by quantile regression [24] with a robust standard error to account for serial scans [25]. Median regression was also used to related week 24 lipids and body composition to TFV-DP at week 24 – the only timepoint at which is was measured. Results in seroconverters were censored beginning at the first visit with laboratory evidence of HIV infection. Outcomes were compared by randomized assignment as well as by drug detection result (detected v. BLQ) based on the pharmacology specimen collected at the visit at which the outcome was measured. All P values are 2-sided. Analyses were performed in STATA version 14.2 [26].

RESULTS

Participants: Four hundred ninety-eight (498) HIV-uninfected persons (247 TDF/FTC, 251 placebo) were enrolled in the metabolic study, 419 (n=214, 87%: TDF/FTC; n= 216, 86%: placebo) had at least one follow-up DXA scan, and 214 (87%) and 214 (85%) participants had at least one follow-up lipid value on TDF/FTC and placebo, respectively. The median number of lipid values was 4 in both groups. Of the 1638 lipids values during the study medication period, (1634, >99%) were reported by participants as fasting lipid values.

Baseline demographics did not differ by randomized treatment (Table 1). Participants had a median (IQR) age of 25 (21-33) and 24 (21-32) years on TDF/FTC and placebo, respectively (p=0.59). Most participants had baseline BMI in the normal range (≥ 18.5 to < 25 kg/m^2, 56% TDF/FTC, 65% Placebo, p=0.09). Total cholesterol was < 200 mg/dL in 86%.

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Observational duration and drug exposure were comparable between the arms. Median time on study was 64 and 61 weeks on TDF/FTC and placebo, respectively with an average of 3.2 DXA scans per participant in the metabolic substudy. Drug level testing data in TDF/FTC participants were complete in 425 of the 484 (88%) of post baseline scans through week 72. The metabolic cohort has been previously characterized and reported on in our analyses of bone mineral density [23].

Body Weight

Weight: Weight increased in the placebo group with median % change from baseline (SE) of +2.4% (0.7%) at 96 weeks (Figure 1). Weight decreased on TDF/FTC at week 24 by -0.1% (0.3%) with increases at later visits. The median net weight change on TDF/FTC compared with placebo was -0.8% (95 CI: -1.5% to -0.1%, P=0.02) at week 24 but by week 96, weights were similar, net difference +0.4% (95 CI: -1.6% to 2.4%, P=0.69). Net median differences compared to placebo ranged from -0.9% to -1.6% through week 72 at visits with plasma drug detected.

Nausea was reported more frequently in the TDF/FTC group compared to placebo in the overall trial cohort as reported previously [1]. To examine if the nausea was driving weight differences, we calculated the TDF/FTC weight difference at week 24 among participants stratified by reports of nausea though week 24. Median changes (SE) in weight at week 24 was -0.7% (0.5%) among those who reported nausea through week 24 and -1.2% (0.2%) among those who did not (P for interaction = 0.37).

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Data on the proportion of participants reaching weight loss thresholds were similar by group. This result is presented in the supplementary materials (Tables S1 and S2).

Body Composition

Lean Body Mass: Lean body mass (LBM) was stable in both groups through the follow-up period (Figure 2a). Median changes (SE) at week 48 were +0.5% (0.3%) on TDF/FTC v. +0.1% (0.3%) on placebo, p=0.42 compared to baseline LBM — a net median difference of +189g, (0.95 CI: -303g to +681g). Among those with plasma drug detected at week 48, the median (SE) change was +0.0% (0.5%) compared to +0.4% (0.5%) without detection, p=0.58. Changes between groups defined by randomization or drug detection were not significant at any timepoint.

Overall Fat Mass: The increases in body weight were accounted for by increases in fat mass (Figure 2b). Participants on placebo steadily gained total body fat during the follow-up period with median percent increase from baseline (SE) of 6.4% (2.0%) at week 72. Participants randomized to TDF/FTC showed no median change overall at weeks 24 and 48, with increases at weeks 72 and 96. Median net differences between randomized groups were -3.8% (95 CI: -6.6% to -0.9%, P=0.009) at week 24 and narrowing to +1.0% (95 CI: -7.0% to +9.1%, P=0.80) at week 96.

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The pattern of differential fat changes was sharper when drug detection by plasma was taken into account with a net median decrease in those on TDF/FTC with drug detected v. placebo of -4.9% (-644g) at week 24 (p=0.003, compared to placebo) rebounding to -0.9% (-368g) at week 72 (p=0.83 drug detected at week 72 v. placebo).

At week 48, there was also less fat gain on TDF/FTC (p=0.025) compared to placebo and fat loss among those with plasma drug detected at the visit (P < 0.001 compared to placebo and TDF/FTC without detection). In a multivariate model, week 48 fat changes were not associated with enrolling clinic (P=0.54), age (P=0.59), race (P=0.62), trans identity (P=0.17), baseline BMI (P=0.57) or baseline fat mass (P=0.76). Fat loss was also no greater among those who reported diarrhea (P=0.33) or nausea (P=0.70) within the first 12 weeks after randomization, compared with those who did not. The only significant predictor was detection of TFV in plasma at week 48 (p=0.004).

Regional Fat Mass: Trunk fat tended to accumulated slower among people in the active arm overall due to a decline in trunk fat among those with drug detected at visits through week 48 (Figure 3a). Trunk fat between randomized groups was statistically significantly lower only at week 48. The median (SE) change in trunk fat at week 48 was +6.4% (1.6%) on placebo, +6.3% (2.3%) in the TDF/FTC group who had no plasma TDF/FTC detected, and -3.6% (2.5%) on TDF/FTC with drug detected at week 48 (p=0.98 for no drug detected and p = 0.001 for detected drug v. placebo, respectively). The change in limb (arm + leg) fat (Fig 3b) at week 48 was a median (SE) at +3.9% (1.5%) on placebo with -3.0% (2.3%) and +6.5% (2.2%) on TDF/FTC with and without plasma drug detected (p=0.33 for no drug detected v. placebo and p = 0.01 for detected drug v. placebo).

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There was no evidence of differential TDF/FTC effect on changes in body fat by region (trunk v. limbs, P for interaction, 0.69, 0.29, 0.62, 0.53 at weeks 24, 48, 72 and 96). There was also no evidence of interaction by drug detection at any visit.

Lipids

Median values of LDL-C, HDL-C and total cholesterol tended to decrease on TDF/FTC from baseline. These changes were non-significant for total cholesterol (Fig 4a) and LDL-C (Fig 4b) between randomized groups overall but were significant for HDL-C (Fig 4c). Median (SE, P-value) changes from baseline for HDL-C were -6.1% (1.6%, P=0.003) on the relative scale and –3.9mg/dL (1.2, P=0.006) on the absolute scale at week 48 on the TDF/FTC arm.

Lipid effects were statistically significant comparing visits with plasma drug detected to the placebo group. Median percent changes (SE) at week 24 for visits with plasma drug detected on TDF/FTC v. placebo were -7.5% (1.5%) v. -1.1% (1.2%), $p < 0.001$ for total cholesterol, -7.9% (1.8%) v. 0.0 (1.3%), $P < 0.001$ for LDL-C and -7.7% (2.0%) v. 0.0% (1.4%), p=0.002 for HDL-C, respectively. On the absolute scale, the changes (on TDF/FTC with TFV detected v. placebo, respectively) at week 24 translated to -11.6 mg/dL (2.3) v. -1.9 (1.8), $p = 0.001$ for total cholesterol, -7.3mg/dL (1.7) v. 0.0 (1.3), $p < 0.001$ for LDL-C and -3.9mg/dL (0.9) v .0.0 (0.5), $p < 0.001$ for HDL-C, respectively. The results for non HDL-C were similar to LDL-C. On placebo, 20% ever had HDL-C levels below 40 mg/dL compared to 26% on TDF/FTC (p=0.17). HDL-C values less than 40 mg/dL were not more common among those with drug detected (p=0.18; detected v. placebo).

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At week 48, the HDL: cholesterol ratio tended to be increased more on TDF/FTC +5.7 (2.1) than placebo + 0.13 (2.2) but the difference was not significant (p=0.07) and there was no trend at other timepoints There were no significant changes in triglyceride values (Fig 4d, Supplementary material, Table S3).

DISCUSSION

Short-term metabolic effects of TDF in HIV-uninfected persons have been previously reported [27]; however, we report the first long-term metabolic evaluation of TDF/FTC in healthy, HIV-uninfected persons against a blinded placebo.

We find modest cholesterol-lowering effects of TDF/FTC. While ARV switch studies have found decreases with substitution of TDF [15-20], initiation studies found no decrease in lipids with starting a TDF/FTC based regimen [15]. In two randomized studies, addition of TDF to existing stable regimens in persons with dyslipidemia decreased total, LDL, and HDL cholesterol over 12 weeks [28,29]. The magnitude of our observed cholesterol decreases, even after correcting for adherence, appears smaller than previous reports and the clinical significance of these changes is unclear, particularly given their transient nature. Unlike many studies in HIV-infected persons [15-20], we found no decrease in triglycerides (TG) with TDF/FTC. However, TG decrease with TDF was seen neither in healthy volunteers [27] nor in placebo controlled studies of HIV-positive persons on a suppressive regimen [28, 29]. This may suggest that reductions in triglycerides may be related to improved virologic control, rather than a direct effect of TDF. The

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observed reductions in cholesterol are also of interest given the modest increases in lipids seen in HIV-infected persons initiating or switching to regimens containing tenofovir alafenamide (TAF), which some have speculated may be attributable to the absence of high plasma TDF concentrations [30-32].

Weight increased in the placebo group while decreasing transiently in the TDF/FTC group. Modest weight gain is expected in healthy populations throughout early adulthood [33,34], and the selective accumulation of adipose tissue is striking. Unfortunately, we lack dietary or physical activity data on our participants. The apparently suppressive effect of TDF/FTC on fat accumulation in the early stages of treatment could not be explained by transient nausea and requires further study.

The DXA scans demonstrate that LBM appears unaffected by TDF/FTC and that total weight differences are driven by changes in fat. There was clear gain of fat mass in association with weight gain in the placebo group, whereas it appears that TDF/FTC may lead to a short-term decrease in weight and fat mass. Fat loss with TDF/FTC appears to occur proportionally between trunk and limbs. Further, the effect is transient even at visits with drug detected, so falling adherence is a less likely explanation. Overall, our data provide no evidence of selective peripheral fat loss. However, with few scans after week 48, long-term trends are difficult to discern. The data do not suggest that fat loss is associated with the transient nausea reported with TDF/FTC. Our DXA results do not allow assessment of more subtle fat changes such as changes in facial fat or subcutaneous versus visceral abdominal fat.

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Differences in body fat and lipids between groups became more pronounced when plasma drug detection was considered. At week 24, intracellular levels of tenofovir diphosphate (TFV-DP) were also tested. Quantitative TFV-DP levels at week 24 were not significantly more associated with metabolic parameters than plasma detection at week 24. In previous work, TFV-DP was tightly, associated with HIV seroconversion risk [23] and bone mineral density [22]. The lack of a quantitative association of metabolic changes with TFV-DP suggests that daily use of TDF/FTC may not lead to larger body composition or lipid changes (Supplementary material, Table S3).

Leading concerns for TDF/FTC PrEP uptake in populations have been side effects and long-term toxicity [21]. Body composition changes from some ARVs have been shown to be stigmatizing in ways which inhibit adherence and uptake [16] and dyslipidemia can elevate the risk of cardiovascular disease [14]. TDF/FTC has not been linked with these phenomena; however, these data provide additional reassurance on the modest, apparently benign and possibly transient metabolic effects of TDF/FTC as PrEP. However, our cohort is limited to a relatively young MSM/TGW population over a 1 to 2-year period. Longer term effects in older populations merit further evaluation.

Taken together, these results in a healthy seronegative population are consistent with results of randomized ART initiation [15] and switch studies [16-20] suggesting that TDF has no selective effect on regional fat distribution and leads to modest decreases in lipids.

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FIGURE LEGENDS

Figure 1. Median Percentage Increase in Body Weight in the Metabolic Cohort. Curves are stratified by randomized treatment (Placebo v. TDF/FTC) with the TDF/FTC group further stratified by detection of either TFV or FTC in a plasma sample ("Detected") from that visit or not ("BLQ"). Drug level testing was conducted through week 72. Bars indicate one standard error. The table below the axis gives the number of participants per group with available at least one DXA scans in each visit window. Multiple scans by individuals in windows were averaged.

X-axis (Panels a-b): Weeks Since Randomization

Y-axis (Panels a-b): Median Percent Change in Body Weight from Baseline

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Figure 2a. Median Percentage Increase in Lean Body Mass as Measured by Dual X-ray Absorptiometry in the Metabolic Cohort. Curves are stratified by randomized treatment (Placebo v. TDF/FTC) with the TDF/FTC group further stratified by detection of either TFV or FTC in a plasma sample ("Detected") from that visit or not ("BLQ"). Drug level testing was conducted through week 72. Bars indicate one standard error. The table below the axis gives the number of participants per group with available at least one DXA scans in each visit window. Multiple scans by individuals in windows were averaged.

Figure 2b. Median Percentage Increase in Total Fat Mass as Measured by Dual X-ray Absorptiometry in the Metabolic Cohort. Curves are stratified by randomized treatment (Placebo v. TDF/FTC) with the TDF/FTC group further stratified by detection of either TFV or FTC in a plasma sample ("Detected") from that visit or not ("BLQ"). Drug level testing was conducted through week 72. Bars indicate one standard error. The table below the axis gives the number of participants per group with available at least one DXA scans in each visit window. Multiple scans by individuals in windows were averaged.

X-axis (Panels a-b): Weeks Since Randomization

Y-axis (Panel a): Median Percent Change in Lean Body Mass from Baseline

Y-axis (Panel b): Median Percent Change in Fat Mass from Baseline

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Figure 3a. Median Percentage Increase in Fat Mass in the Trunk as Measured by Dual X-ray Absorptiometry in the Metabolic Cohort. Curves are stratified by randomized treatment (Placebo v. TDF/FTC) with the TDF/FTC group further stratified by detection of either TFV or FTC in a plasma sample ("Detected") from that visit or not ("BLQ"). Drug level testing was conducted through week 72. Bars indicate one standard error. The table below the axis gives the number of participants per group with available at least one DXA scans in each visit window. Multiple scans by individuals in windows were averaged.

Figure 3b. Median Percentage Increase in Fat Mass in the Limbs (Arms+Legs) as Measured by Dual X-ray Absorptiometry in the Metabolic Cohort. Curves are stratified by randomized treatment (Placebo v. TDF/FTC) with the TDF/FTC group further stratified by detection of either TFV or FTC in a plasma sample ("Detected") from that visit or not ("BLQ"). Drug level testing was conducted through week 72. Bars indicate one standard error. The table below the axis gives the number of participants per group with available at least one DXA scans in each visit window. Multiple scans by individuals in windows were averaged.

X-axis (Panels a-b): Weeks Since Randomization

Y-axis (Panel a): Median Percent Change in Trunk Fat Mass from Baseline

Y-axis (Panel b): Median Percent Change in Limb Fat Mass from Baseline

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Figure 4a. Median Percentage Increase in Fasting Total Cholesterol in the Metabolic Cohort+. Curves are stratified by randomized treatment (Placebo v. TDF/FTC) with the TDF/FTC group further stratified by detection of either TFV or FTC in a plasma sample ("Detected") from that visit or not ("BLQ"). Drug level testing was conducted through week 72. Bars indicate one standard error. The table below the axis gives the number of participants per group with available with lipid results in each visit window. Multiple results by individuals in windows were averaged.

Figure 4b. Median Percentage Increase in Fasting Low Density Lipoprotein (LDL) in the Metabolic Cohort+. Curves are stratified by randomized treatment (Placebo v. TDF/FTC) with the TDF/FTC group further stratified by detection of either TFV or FTC in a plasma sample ("Detected") from that visit or not ("BLQ"). Drug level testing was conducted through week 72. Bars indicate one standard error. The table below the axis gives the number of participants per group with available with lipid results in each visit window. Multiple results by individuals in windows were averaged

Figure 4c. Median Percentage Increase in Fasting High Density Lipoprotein (HDL) in the Metabolic Cohort. Curves are stratified by randomized treatment (Placebo v. TDF/FTC) with the TDF/FTC group further stratified by detection of either TFV or FTC in a plasma sample ("Detected") from that visit or not ("BLQ"). Drug level testing was conducted through week 72.Bars indicate one standard error. The table below the axis gives the number of participants per group with available with lipid results in each visit window. Multiple results by individuals in windows were averaged

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Figure 4d. Median Percentage Increase in Triglycerides in the Metabolic Cohort. Curves are stratified by randomized treatment (Placebo v. TDF/FTC) with the TDF/FTC group further stratified by detection of either TFV or FTC in a plasma sample ("Detected") from that visit or not ("BLQ"). Drug level testing was conducted through week 72. Bars indicate one standard error. The table below the axis gives the number of participants per group with available with lipid results in each visit window. Multiple results by individuals in windows were averaged

X-axis (Panels a-d): Weeks Since Randomization

Y-axis (Panel a): Median Percent Change in Total Cholesterol from Baseline

Y-axis (Panel b): Median Percent Change in LDL-C from Baseline

Y-axis (Panel a): Median Percent Change in HDL-C from Baseline

Y-axis (Panel d): Median Percent Change in Triglycerides from Baseline

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Table 1: Baseline Demographics of the 498 HIV Negative Participants in the Metabolic Cohort

		Placebo (N=247)	TDF/FTC (N=251)	P-Value
Age+	At entry (years)	24 (21 - 32)	25 (21 - 33)	0.59
Race (Self-Reported)*	Black/African American	25 (10%)	37 (15%)	0.30
	White	43 (17%)	45 (18%)	
	Mixed/Other++	133 (53%)	115 (47%)	
	Asian	50 (20%)	50 (20%)	
Country of Enrollment				0.94
	Peru	106 (43%)	114 (45%)	
	Brazil	29 (12%)	25 (10%)	
	South Africa	31 (13%)	28 (11%)	
	Thailand	47 (19%)	47 (19%)	
	United States	34 (14%)	37 (15%)	
Trans Identity*		26 (10%)	26 (11%)	1.00
Time on Study Drug+	Weeks	61 (40 - 87)	64 (43 - 88)	0.94
Height+	cm	170 (165 - 177)	169 (165 - 176)	0.41
Weight +	kg	66.1 (59.5 – 76.0)	66.4 (58.6 – 76.5)	0.46
Lean Mass+	kg	50.6 (46.2 – 55.8)	50.6 (45.8 – 55,2)	0.46
Fat Mass+	kg	12.4 (9.1 – 17.5)	12.4 (8.3 – 18.3)	0.44
Percent Body Fat	%	19 (15-24)	19 (14-24)	0.46
BMI+	kg/m^2	23 (21 - 26)	23 (20 - 25)	0.65
BMI Category*	< 18.5	20 (8%)	29 (12%)	0.09
	18.5 to < 25	163 (65%)	138 (56%)	
	25 to 30	54 (22%)	70 (28%)	
	≥ 30	14 (6%)	10 (4%)	
Total Cholesterol+	mg/dL	162 (137 - 186)	160 (137 - 182)	0.75
Total Cholesterol*	≥ 200 mg/dL	31 (13%)	35 (15%)	0.69
HDL Cholesterol+	mg/dL	44 (37 - 54)	44 (39 - 52)	0.96
LDL Cholesterol+	mg/dL	93 (74 - 114)	92 (75 - 112)	0.72
Triglycerides+	mg/dL	87 (62 - 122)	85 (66 - 126)	0.29

+ summary is median (interquartile range) with p-value by unequal variance t-test
* summary is n (%) with p-value by the Fisher exact test.
++ Participants in Peru and Brazil frequently identified as being of mixed race

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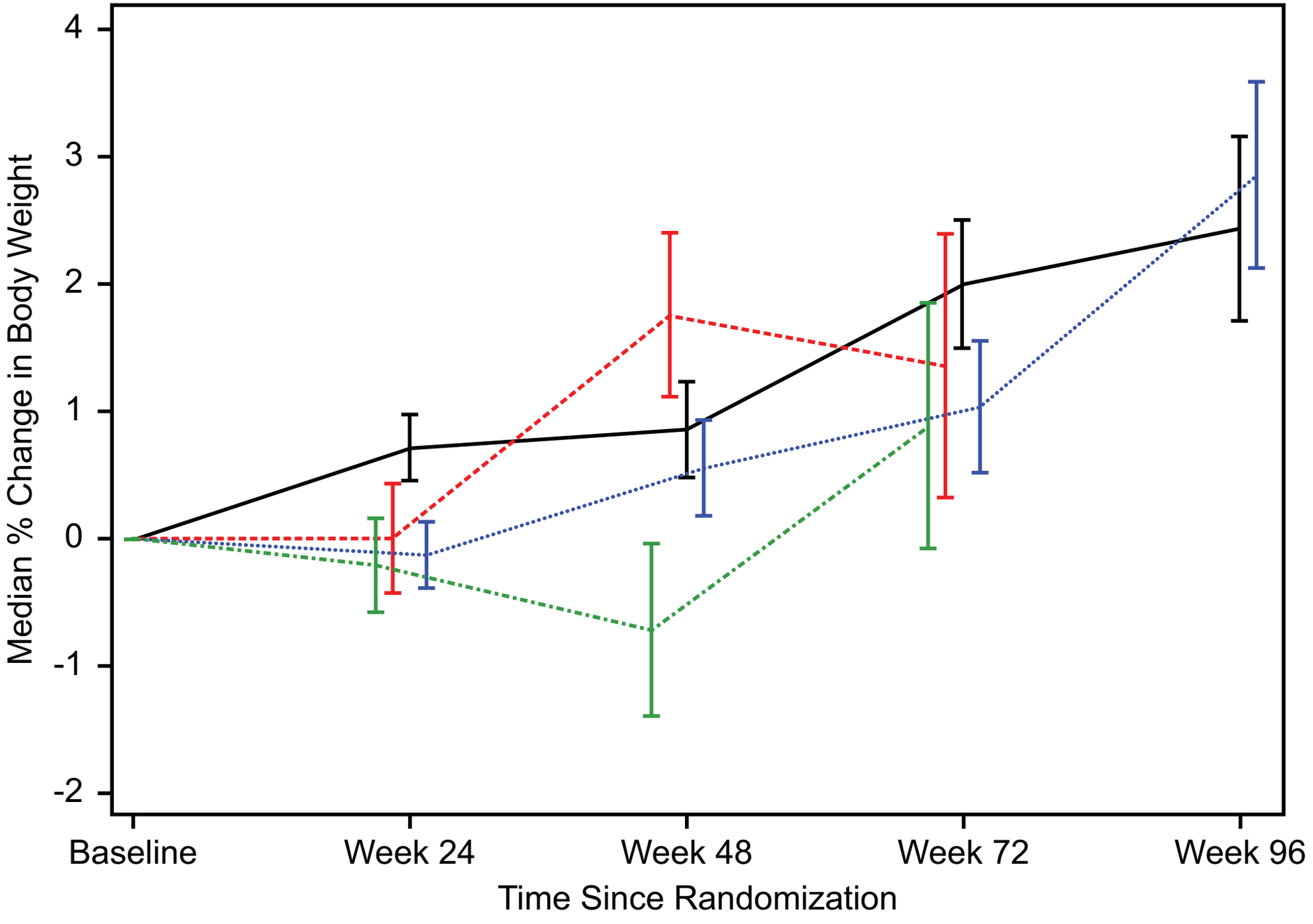

Number of Scans	Week 24	Week 48	Week 72	Week 96
Placebo ——	211	168	112	56
TDF/FTC	210	166	108	55
Plasma BLQ -----	86	80	34	
Plasma Detect	116	70	39	

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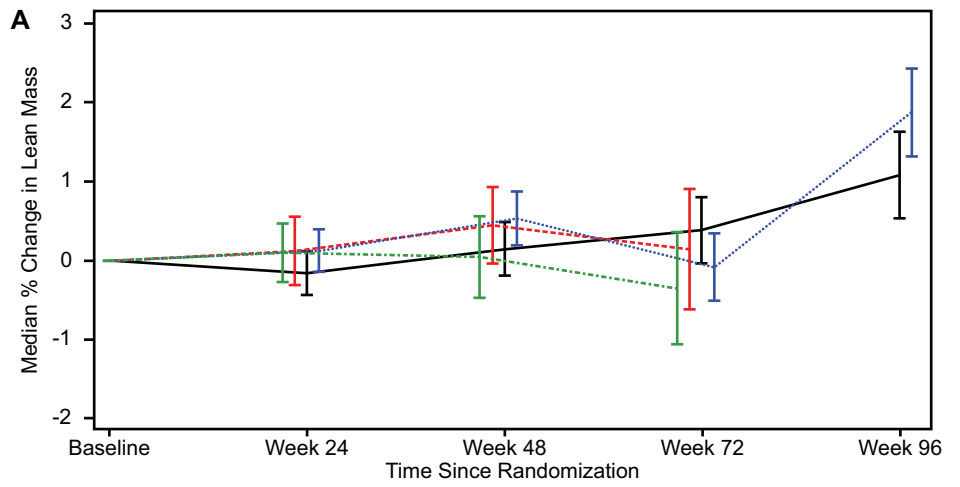

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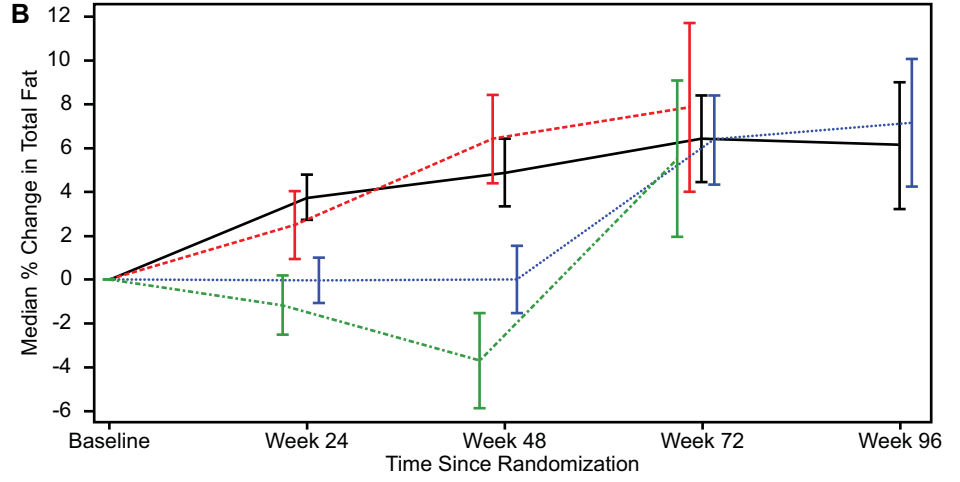

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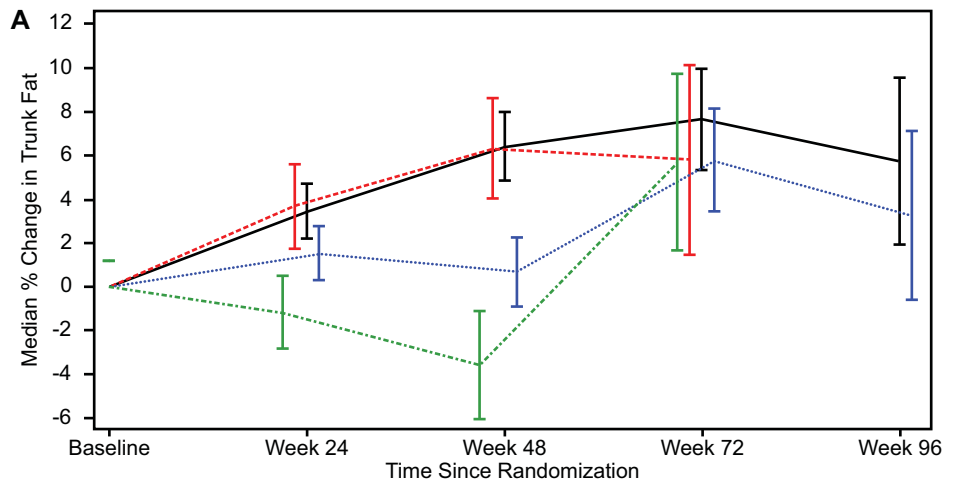

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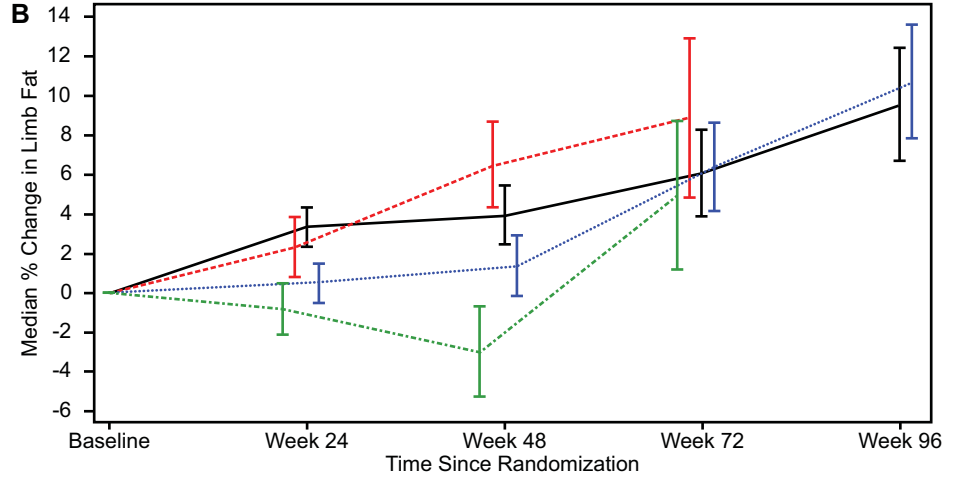

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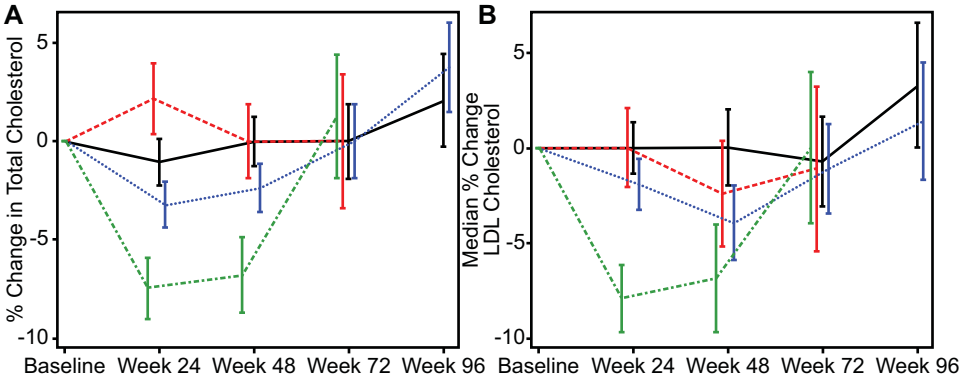
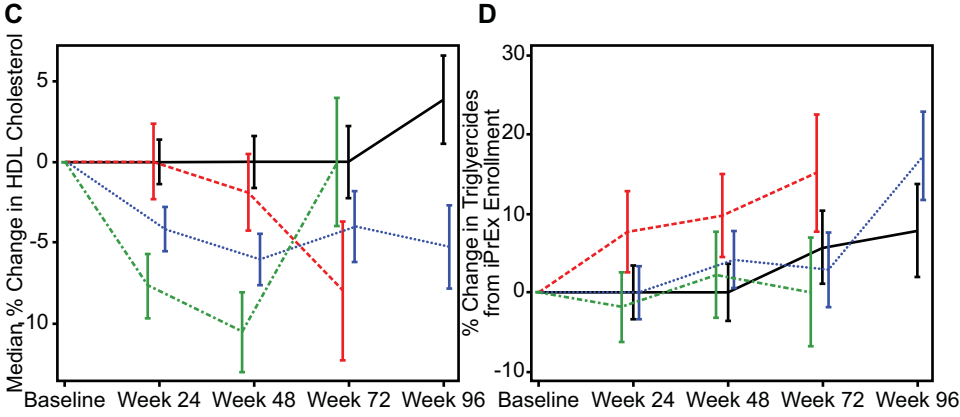


Number of Scans	Week 24	Week 48	Week 72	Week 96
Placebo —	194	174	116	58
TDF/FTC ·····	199	176	114	63
Plasma BLQ - - -	83	83	36	
Plasma Detect - - -	114	79	42	

Number of Scans	Week 24	Week 48	Week 72	Week 96
Placebo —	192	172	116	56
TDF/FTC ·····	198	175	114	63
Plasma BLQ - - -	83	83	36	
Plasma Detect - - -	113	78	42	



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