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A Pilot Study to Determine the Impact on Dyslipidemia of Adding Tenofovir to Stable Background Antiretroviral Therapy: ACTG 5206

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Summary

Several studies have reported improvements in lipids after antiretroviral therapy (ART) switches to tenofovir disoproxil fumarate (TDF)-containing regimens. We assessed lipid-lowering effects of TDF by adding it to a stable ART regimen in this double-blind, placebo-controlled crossover study. We demonstrated that non-HDL-C, LDL-C and TC improved significantly over TDF vs. placebo treatment in HIV-infected individuals with dyslipidemia. Adding TDF to stable,

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virologically-suppressive ART regimens improved lipid parameters, supporting a lipid-lowering effect of TDF.

Keywords

Dyslipidemia; Tenofovir; Complications of Antiretroviral therapy

Research Letter

Coronary heart disease (CHD) and dyslipidemia have been associated with antiretroviral therapy (ART) and HIV itself in addition to traditional risk factors[1–4]. Current guidelines advocate managing dyslipidemia in HIV-infected individuals similar to the general population[5,6]. However, these recommendations often do not achieve lipid-lowering goals in HIV-infected individuals[7]. Antiretroviral guidelines advocate selecting regimens with less adverse lipid effects as one approach to modifying CHD risk[8].

Prior studies demonstrated that switching from other antiretroviral agents to tenofovir (TDF) improved most lipid parameters [9–13]. However, these improvements may be due to withdrawal of the offending agent or from TDF itself. Therefore, we designed a prospective study to evaluate the specific effect of TDF on lipids by adding TDF to a fully virologically suppressive antiretroviral regimen.

AIDS Clinical Trials Group (ACTG) A5206 was a double-blind, randomized, placebo-controlled, crossover pilot study. The Institutional Review Boards of all participating institutions approved the protocol. All subjects provided informed consent.

Inclusion criteria: HIV-infected individuals ≥ 18 years old, dyslipidemia [fasting triglycerides (TG) ≥ 150 and < 1000 mg/dL or non- high density lipoprotein cholesterol (HDL-C) ≥ 100 and < 250 mg/dL], virologically suppressed (HIV-1 RNA < 400 copies/mL) on stable ART for 90 days prior to study entry. Didanosine and “unboosted” atazanavir were not allowed due to concerns of drug-drug interactions. Exclusion criteria: CHD history, active hepatitis B, uncontrolled diabetes, untreated hypothyroidism, or hormonal anabolic therapy. Lipid lowering agents could not be changed or added.

Twelve-week treatment periods randomized to order of treatment (TDF and placebo, respectively) were separated by a 4-week washout period. Subjects were evaluated with fasting lipids [total cholesterol (TC), HDL-C, LDL-C, and TG] prior to the start of each treatment period and every 4 weeks. Lipid measurements were performed at the ACTG Central Metabolic Laboratory (Nicholls Institute, Quest Diagnostics, San Juan Capistrano, CA) by standard techniques as described elsewhere [14].

The primary endpoint was the change in non-HDL-C over 12 weeks of active TDF minus the change over 12 weeks of placebo. Because it was assumed there would be no period effect the primary analysis used the Wilcoxon Signed Rank test. As this was a pilot study, we used a one-sided significance test with a liberal type I error of 10.

Seventeen subjects enrolled: four (24%); female; six (35%) black; three (18%) Hispanic. Six subjects received protease inhibitors, thirteen received non-nucleoside reverse transcriptase inhibitors (NNRTIs), and fifteen received NRTIs (3 abacavir, 10 zidovudine, 2 both). One subject from each study arm did not complete the protocol, a third subject started a lipid-lowering agent in violation of the protocol, and a fourth did not have week 28 lipid results. As the primary analysis was a per protocol analysis, it and all other analyses were performed on the 13 subjects with complete data (6 in arm TDF→P and 7 in arm P→TDF).

At baseline, the median (IQR) fasting lipids (mg/dL) were 180 (142, 199) for non-HDL-C, 220 (185, 236) for TC, 109 (98, 151) for LDL-C, and 274 (178, 437) for TG. Table 1 details the outcomes. Non-HDL-C, LDL-C, and TC decreased significantly over the TDF period for all subjects in comparison to over the placebo period. HDL-C and TG did not significantly improve. However, the data did suggest a period effect ($p=0.07$) for TG which appears to be driven by the fact that the median changes while on placebo were -1 ($-83, 22$) mg/dL in P→TDF and -149 ($-221, 24$) mg/dL in TDF→P.

Over the 4-week washout period after TDF was discontinued, in arm TDF→P, TG (mg/dL) increased a median (IQR) 145.5 (35, 176) and 34% (28%, 51%) to 630 (365, 762) at week 16 suggesting a rebound after the discontinuation of TDF. For the subjects in arm P→TDF, the median increase over the washout period (weeks 28 to 32) was 63 (29, 115) and 32% (9%, 66%). For all subjects, TG increased significantly ($p=0.01$) over the 16 weeks of their TDF period and washout by a median of 80 (43, 158) mg/dL. In contrast over the 16 weeks of their placebo period and washout, TG increased by a median of 6.5 ($-71, 73$) ($p=0.97$).

Virologic suppression (< 400 copies/mL) was maintained in all subjects throughout the study. The median difference between the change in CD4+ cell count over 12 weeks of TDF vs. placebo was 49 ($-74, 146$) cells/mm³ and not statistically significant. Four grade 3 events were observed during the study. Of these, two were observed while the subject was receiving study drug: an elevation in bilirubin which was felt to be not study-related and an elevation in phosphorus level. No grade 4 events or graded creatinine elevations were reported during the study. For all subjects, the change in creatinine while on TDF was not significantly different than the change while on placebo.

We aimed to specifically assess whether TDF has direct lipid-lowering effects. Prior studies had suggested TDF may have a lipid lowering effect but it was not clear if this was due to the addition of TDF or due to the removal of an offending agent during a switch of nucleosides.

In this pilot study, adding TDF to existing virologically-suppressive ART regimens improved lipid parameters at 12 weeks of TDF study treatment, supporting an independent lipid-lowering effect of TDF. Also, the observation that TG increased over the washout period suggests a possible “rebound” effect after discontinuation of TDF. Although the potential mechanism is unclear, it is unlikely to be associated with viremia as virologic suppression was maintained throughout the study. This is the first prospective study to our knowledge to evaluate the specific effect of TDF on lipids by adding TDF to a stable ART regimen. Our findings support that TDF independently lowers lipids.

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Table 1

Median (Range) Fasting Lipid Values (mg/dL) (n=13)

	Non-HDL-C	TC	LDL-C	HDL-C	TG
TDF Week 0	198 (121 to 291)	230 (172 to 318)	106 (35 to 171)	40 (26 to 64)	342 (90 to 616)
TDF Week 12	164 (89 to 254)	195 (141 to 286)	103 (22 to 163)	34 (22 to 53)	264 (73 to 1308)
Placebo Week 0	206 (128 to 247)	236 (183 to 273)	109 (36 to 155)	41 (20 to 55)	275 (82 to 828)
Placebo Week 12	186 (119 to 344)	229 (183 to 368)	120 (27 to 168)	37 (23 to 64)	223 (56 to 1552)
ΔTDF	-32 (-90 to 89)	-39 (-101 to 81)	-12 (-61 to 10)	-2 (-17 to 7)	-14 (-288 to 871)
ΔPlacebo	-4 (-38 to 97)	-6 (-37 to 95)	-3 (-28 to 70)	2 (-9 to 9)	-36 (-377 to 724)
Estimated Median^a	-29.5	-36.5	-20.0	-5.0	39.5
p-value^b	0.01	<0.01	0.06	0.91	0.83
90% Exact CI Bound	-14 ^c	-16.5 ^c	-1 ^c	-9 ^d	81.5 ^c
% ΔTDF	-16% (-40 to 63)	-18% (-38 to 47)	-12% (-40 to 10)	-8% (-27 to 19)	-3% (-47 to 199)
% ΔPlacebo	-2% (-16 to 39)	-3% (-14 to 35)	-4% (-25 to 73)	4% (-18 to 20)	-13% (-63 to 87)
Estimated Median^a	-14%	-14%	-17%	-10%	16%
p-value^b	0.02	0.01	0.04	0.93	0.81
90% Exact CI Bound	-5% ^c	-7% ^c	-3% ^c	-19% ^d	36% ^c

^aHodges-Lehmann estimate of the median paired difference (Δ (%Δ) TDF - Δ (%Δ) Placebo)

^bOne-sided Wilcoxon Signed Rank test

^cUpper bound

^dLower bound